Logan University Symposium 2026

Health Longevity Function Wellness

Two Hours

Dan Murphy, DC

Health Wisdom

Allopathic providers (medical doctors) are primarily chemical providers of care (pharmacology). Government gives drug companies patents for their products, allowing for hundreds of billions of dollars in profits. Government does not grant patents on natural products, even if they work great, which is one of the reasons we hear much less about them.

Chiropractors are primarily mechanical providers of care (adjustments, exercise, tissue work, etc.) The chiropractic approach was awarded the Nobel Prize in 2021 (mechanoreceptors, sorry Al, from UCSF). This is in part why all major sports teams have a handful of mechanical providers (chiropractors, physical therapists, trainers, etc.).

Chiropractic education stresses mechanical interventions, and it also stresses evolutionary biology. Most chiropractors, including me, consider themselves to be evolutionary biologists, which is the point.

Evolutionary biology cares about only one thing, perpetuating the species by making the next generation. For nearly all humans, for millennia, our babies are made prior to age 50. Evolution and biology pretty much do not care about what happens to us after about age 50 because we have already had our babies.

To help the younger crowd to make babies, humans are blessed with a lot. Youngsters are stronger, faster, quicker, greater endurance, better brain (less wisdom), more and stronger sperm, healthy release of eggs, hormones that increase sex drive and fertility, healthy joints and blood vessels and nerves and organs and immunity, including teeth, hearing, and vision. Critical molecules that are abundant in youth are scarce after age 50, like CoQ10, melatonin, glutathione, and many more.

Youth blessings quickly begin to disappear after age 50. The best longevity experts state that if one wants an additional 50 years of living after age 50, one must supplement with a handful of molecules to replenish that what we had in abundance in youth.

A favorite go-to for what these supplements should be is the work of Bruce Ames.

Top researchers will boast about having 100 articles indexed in the National Library of Medicine of the USA. Ames had more than 400. Ames died last year at age 95, just short of his 96th birthday. He did not die from disease; he died from a complication following a fall. That put him in good company with the cancer-mitochondria-fermentation-respiration Nobel Prize winner Otto Warburg. Warburg died in 1970 at the age of 87, also from a fall; he was on a ladder getting a high book off the shelf. History acknowledges that Warburg should have won 3 Nobel Prizes.

Ames' longevity article, published in the journal of the *Proceedings of the National Academy of Sciences of the USA* (my review is attached), is the gold standard. I believe that this is, in part, what we should all do if we want that additional 50 years of healthy living.

Although evidence and consensus always (and should) change as more is learned, at present it points to all people needing 5 supplements, including our children and now our grandchildren. This is mostly because we subsidize the wrong stuff, we allow toxic ultra-processed dopamine addicting chemicals into the food chain, and deplete our soils of what we need, etc. The 5 are:

- Omega-3s
- Vitamin D3
- Vitamin K2-4 and K2-7
- Magnesium
- B complex, often supplied in a multiple mineral/vitamin supplement

Then there is a handful stuff that our kids do not need, but we, being over 50 years old, do need, to hit 100 years of age (or 95 if we fall), doing well mentally and physically:

- CoQ-10
- PQQ
- acetyl-l-carnitine
- alpha-lipoic acid
- ergothioneine (H_2S precursor)
- taurine
- resveratrol
- curcumin
- glutathione

There are also a few more do's and don'ts if one is getting dementia.

Chiropractors are not trained in pharmacology and drugs are outside of their scope of license. Yet chiropractors are trained in the chemistry of supplements and they are allowed to integrate them into their clinical approach. That's why I know this stuff.

Also, read the lifestyle advice from the top nutrition journal in the world, the *American Journal of Clinical Nutrition* from last year (2024), my review is also attached.

The importance of exercise cannot be underestimated.

Murph

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...or cooks
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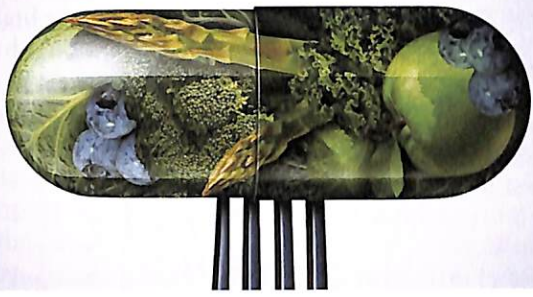
Our Experts Agree:

Nearly Everyone Should Take These 5 Vitamins



Are there nutritional supplements that everyone should consider taking? We posed that question to five nutrition-savvy doctors who have served as experts for *Bottom Line Personal* for years. Surprisingly, they not only all said "yes," but they all generally agreed on what these nutritional supplements are.

That consensus is even more surprising given the negative attention that multivitamin/mineral supplements have gotten lately. Some studies have failed to find that they protect against heart disease, for example. But that's not why most people even take multis—or should, our experts say. *Better reason:* To ensure that you are getting adequate amounts of essential nutrients to function at your best day to day.

Many Americans don't get enough. According to the latest Dietary Guidelines report, common nutritional shortfalls include the B vitamin folate, vitamin D and magnesium. And deficiencies become more common for certain nutrients after age 50, when nutrient absorption often declines.

Important: Our experts agreed that in addition to the specific recommendations below, everyone should take a multivitamin/mineral supplement that supplies 100% of the Recommended Daily Intake (RDI) for most vitamins, minerals and trace elements (especially selenium, chromium and iodine). *Exception:* Iron deficiency is rare in people over age 50, so iron should be part of your multi only if a doctor-ordered test shows that you are iron-deficient. Why? Too much acts as an unhealthy oxidant.

A healthy diet always comes first, our experts agree. *Example:* Fruits, vegetables and beans provide fiber and potassium that supplements generally don't provide.

Does everyone *need* all these supplements? No. If you eat fatty seafood at least twice a week, for example, you could safely skip omega-3 supplements. But most of us would benefit from >>

SecretsInside

>> taking *all* of these supplements.

What follows are the amounts that our experts agree are safe and beneficial for everyone. They often prescribe higher amounts for certain patients. *Important:* Share your supplementation plan with your health-care provider, who can offer individual guidance.

A good multi is just the beginning, our experts told us. Here are four additional daily supplements that benefit nearly everyone...

MAGNESIUM

Magnesium strengthens muscles, builds bone, energizes the brain, regulates the heart, reduces high blood pressure, balances blood sugar, aids sleep, eases pain, improves digestion, helps your body utilize calcium and more. Before processed food dominated the diet, Americans consumed 600 milligrams (mg) of magnesium a day on average. Today, that number is about 275 mg—well below the RDI of 420 mg for men and 320 mg for women.

Recommended daily dose: Our experts most often prescribe 200 mg twice a day—once in the morning, once in the evening—for a daily total of 400 mg. *Avoid:* Magnesium oxide, which can sometimes cause loose stools. *Best:* Magnesium glycinate.

B VITAMINS

B vitamins play important roles in the health of your brain and nerves, blood, digestive tract, muscles, skin and eyes. They help power every cell in the body. Our experts put a special emphasis on folate, B-6 and B-12.

Recommended daily dose: Take a "B-50-complex" supplement either once a day or in divided doses twice a day. This formulation, sold under a number of different brands, includes all the Bs. The name refers to the fact that the daily dosage is 50 mg or 50 micrograms (mcg) for many of the Bs. Those levels exceed the RDI in most cases but are safe to take daily.

Additional recommendation: If you are a vegetarian or a vegan or are over age 50, also take a separate B-12 supplement. While a B-50-complex supplement will have a small amount of B-12 (typically 50 mcg), taking an additional B-12 supplement is important because B-12 deficiency is particularly common as we age, in part because we produce less of the stomach acid needed to absorb it from food. *Tip:* Look for a sublingual (under-the-tongue) product providing the most active form—methylcobalamin—at a daily dose of 1,000 mcg.

VITAMIN D

Vitamin-D deficiency is disturbingly common in the US. Indeed, *most* Americans have blood levels below a minimally healthy level of 30 nanograms per milliliter (ng/mL). Our experts agreed that blood levels above 50 ng/mL (but not higher than 80 ng/mL) are best for peak functioning of muscles, bones, digestion, immunity, hormones and circulation. Vitamin D also may help prevent breast and colon cancers.

Recommended daily dose: 2,000 international units (IU) of D-3, the form that's best absorbed. That supports a blood level of 50 ng/mL for most people and is safe to take daily long-term. *Important:* Get your vitamin-D level tested. If it's very low, your doctor may prescribe higher doses, up to 10,000 IU daily.

FISH OIL

Fatty fish such as salmon and sardines are rich in the omega-3 fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). If you don't eat fatty fish at least twice a week, consider a daily omega-3 supplement.

It's true that recent studies have failed to find that these supplements prevent heart disease in healthy people. But omega-3s are key nutrients for every cell in the body, and most Americans don't get enough. And there is evidence that they are key to lifelong health. *Example:* In a study from Harvard Medical School and several other leading institutions, researchers looked at 15 years of health data on more than 6,500 postmenopausal women and found that those with the highest levels of EPA and DHA were 11% less likely to die from any cause during the study than those with the lowest levels. Another recent study conducted at Tufts University on men and women found that higher blood levels of omega-3s were linked to healthier aging.

Reason: Omega-3 fatty acids make all cell membranes more flexible and youthful—and every part of the body benefits. They can ease arthritis, improve mood and ward off depression, protect against dementia, reduce high triglycerides (blood fats) and even slow skin aging.

Recommended daily dose: A supplement that supplies 1,000 mg of EPA and DHA combined. Higher doses may be prescribed to reduce high triglycerides. *Caution:* Omega-3 supplements act as anticoagulants, so talk to your doctor before taking one if you already are taking a prescription anticoagulant.

Bottom Line Personal interviewed...

Hyla Cass, MD, integrative physician in private practice in Los Angeles, natural supplement formulator and consultant, and coauthor of several books including *8 Weeks to Vibrant Health.* CassMD.com

Joshua Levitt, ND, naturopathic physician in private practice in Hamden, Connecticut, a clinical preceptor for Yale School of Medicine and author of *The Honey Phenomenon: How This Liquid Gold Heals Your Ailing Body.* WholeHealthCT.com

Michael Murray, ND, author or coauthor of more than 30 books featuring natural approaches to health, including *The Encyclopedia of Nutritional Supplements* and *Bottom Line's Encyclopedia of Healing Foods.* He is based near Scottsdale, Arizona. DoctorMurray.com

Andrew Rubman, ND, director of Southbury Clinic for Traditional Medicines in Southbury, Connecticut, and author of the blog "Nature Doc's Patient Diary" at BottomLineInc.com. SouthburyClinic.com

Jacob Teitelbaum, MD, holistic fibromyalgia and pain specialist in private practice in Kailua Kona, Hawaii, and coauthor of *Real Cause, Real Cure.* EndFatigue.com

Title photo: Gettyimages/triloks

The Minimum Eight Supplements

1) A quality multiple vitamin/mineral supplement, without copper, daily

The vitamin/mineral content of food is linked to the quality of the soil the food is grown in. Not only is our soil depleted of critically important minerals, our crops/soil are exposed to huge amounts of chemicals that bind to minerals, making them unavailable for human nutritional requirements. This is called nutritional inflation, and the entire world is suffering from it. A quality multiple vitamin/mineral supplement is now necessary for the majority of people on the planet. Importantly, the supplement should not contain copper, as supplemental copper has been linked to an increased risk of Alzheimer's Disease for more than a dozen years.

2) 3,000 mg/day of EPA+DHA omega-3s from purified fish oil per day

The Theory of Everything: the majority of chronic incurable degenerative diseases are linked to inflammation. The most critical driver of inflammation is the ratio of omega-6 to omega-3 fats. Americans consume far too many inflammatory omega-6s, and far too few anti-inflammatory omega-3s.

3) Vitamin D3, 5000 IU per day

Vitamin D does a lot more than build healthy bones. It is critical for immune system function and for brain physiology. Most Americans are significantly low in vitamin D levels and supplementation is necessary for almost everyone.

4) Magnesium (Mg++), about 500 mg/day

Magnesium is a cofactor for the activity of 700-800 human enzymes. Magnesium is the most important mineral for accessing human energy; it also protects the heart, blood vessels, and brain. Most Americans are significantly low in magnesium and supplementation is necessary for almost everyone.

5) Vitamin K2-4 and K2-7

Without vitamin K2-4 and K2-7, calcium is deposited into arteries, joints and kidneys. This is why most people who take vitamin D should also take vitamin K. Individuals with blood clotting disorders should talk to their doctor before taking vitamin K. Individuals taking statin drugs often need to double vitamin K supplementation, but again should ask their doctor.

6) CoQ-10

CoQ-10 is required for mitochondrial energy production. The mitochondria is the biological epicenter of aging; one is only as young as their mitochondria. CoQ-10 production drops off significantly with age, and everyone over 40 or 50 years should supplement with CoQ-10.

7) Iodine

The most sensitive and susceptible human tissue to toxins is the thyroid gland. The thyroid is the "canary in the coal mine." Iodine is required for thyroid health. Iodine levels are under attack by halogenated industrial chemicals such as fluorine, chlorine, and bromine, which are everywhere. "If you are not deficient at the start, iodine is still worth supplementing because it provides a protective effect against many industrial chemicals and will prevent future deficiency."

8) Probiotics with Prebiotics

The microbiome is critical for health, immunity, neurology, blood vessels, etc. The microbiome is under assault from so many different reasons: antibiotics, pain drugs, chemicals including Roundup, birth control pills, dietary lectins, etc. Consumption of Probiotics with Prebiotics is not necessary.

Required Supplements
(Nutri-West: 800-443-3333)

Infants / Children / Pre-puberty

Omega-3 Fatty Acids:
The DHA should be greater than the EPA (2.6/1)
The formula should have an ideal ratio of ALA, EPA, DHA, and GLA with vitamin E

Complete Children's EPA/DHA
One capsule per day per year of age (a 5-year old would take 5/day)

Omega-3 double bond protectors (anti-oxidants):
Vitamin C, B6, B12, Folate, Riboflavin

Complete Children's Co-Factors
One capsule per day per day

Vitamin D3
(Contraindicated in those with sarcoidosis and other granulomatous diseases)

Infants: 400 IU per day for infants (1 *Vitamin D 400*)

Pre-Puberty: 2,500 IU per day for children (1 *Complete Immuno D3*)

Required Supplements
(Nutri-West: 800-443-3333)

Adults

Multiple Vitamin-Mineral
Should be copper free (less than 100 micrograms) and iron free
Core Level Health Reserves 1 daily

Omega-3 Fatty Acids
The EPA should double the DHA (2:1 ratio)
The formula should have an ideal ratio of ALA, EPA, DHA, and GLA with vitamin E
3,000 mg of EPA + DHA per day (*6 Complete Omega-3 Essentials*)
or 1 ***table***spoon of *Complete Hi-Potency Omega-3 Liquid*

Omega-3 Double Bond Protectors (Anti-Oxidants):
Vitamin C, B6, B12, Folate, Riboflavin
1 *Complete Omega-3 Co-Factors per* ***3*** *grams of EPA + DHA*

Vitamin D3
(Contraindicated in those with sarcoidosis and other granulomatous diseases)
5,000 IU per day (1 *Complete Hi D3*)
10,000 IU for some in northern latitudes, depending on skin pigmentation and labs

Magnesium
(Contraindicated in those with kidney failure, myasthenia gravis, excessively slow heart rate, bowel obstruction (reference below)
(dosage as per Carolyn Dean, MD, reference below)
3-4.5 mg/pound of body weight (300-900 mg per day, 1-3 per day)
Complete Magnesium
(this product is highly absorbed and 1 daily is often sufficient)

Vitamin K 2-4 and K 2-7
(may be contraindicated in those with blood clotting problems or on blood thinning pharmacology)
Complete K 1 daily

CoQ-10
Complete Energy 2 daily
Adds sufficient *CoQ-10*, *75 mg per capsule* with 10 added enhancing couplers

Iodine
Iodine Rescue 1 ***weekly*** is sufficient for most without thyroid dysfunction

Probiotics with Prebiotics
Total Probiotic 1 per ***meal***

Optimizing Supplements

(adults only)

(Nutri-West: 800-443-3333)

Mitochondrial Health: (4 *Complete AG*)

A)	Acetyl-l-carnitine	680 mg per day
B)	Alpha-lipoic acid	240 mg per day
C)	CoQ-10	10 mg per day

Detoxification / Endogenous Anti-oxidation
Increase Glutathione

- **Undenatured Whey Protein**: (*Complete Whey-G*)
  Children 7 grams per day = 1 scoop per day
  Adults 21 grams per day = 3 scoops per day

- **N-Acetyl Cysteine, or NAC**: (*Complete Glutathione*)
  Children 120 mg per day 2 per day
  Adults 240 mg per day 4 per day

- **Sublingual Glutathione** (*Complete Sublingual Glutathione*)
  2 daily

Brain Anti-Inflammation; Brain Protection (4 *Complete Neuro*)
(adults only) (Post-Concussion Syndrome, 8 daily)

- **Resveratrol** 100 mg per day

- **Curcumin (Tumeric)** 200 mg per day

Enhance Production of Acetyl-Choline

Complete Brain Charge (1 daily)

Complete Synapse (1 daily)

Nutri-West Magnesium Product Specifications
Complete Magnesium

Elemental Magnesium	as malate	250 mg
	as citrate	45 mg
	as glycinate	5 mg
MCT Medium Chain Triglycerides:		25 mg
Inulin (soluble fiber):		25 mg
Taurine		25 mg
Coconut fiber		10 mg

The Magnesium Miracle
Carolyn Dean, MD
Ballantine Books, 2014

"To individualize your magnesium dosage, the rule of thumb for men and women is 3.0 to 4.5 mg/lb of body weight per day. That translates into a total dietary and supplemental magnesium of 600 to 900 mg per day for a 200-lb man." p. 240

"Serial testing of Magnesium RBC levels and seeking the optimum blood level of 6.5 mg/dL may be the only way to ensure magnesium repletion." p. 240

"For the average person, oral magnesium, even at high dosages, has no side effects except loose stools, which is a mechanism to release excess magnesium." p. 240

"Magnesium can be taken with or without meals, but it's preferable to take it between meals for better absorption. Magnesium requires stomach acid to be absorbed." p. 247
[we like Nutri-West's product Hypo-D for this]

"Take your first dose of magnesium when you wake up in the morning and the last dose at bedtime." p. 250

Magnesium and malic acid "are both critical to the body's energy production." p. 179

In *magnesium malate*, the weak double bond "makes it readily soluble in the body." P. 246

Magnesium citrate is the most widely used magnesium supplement because it's inexpensive." P. 242

Magnesium glycinate is another "highly absorbable form of magnesium." p. 250

"Taken together in this combination, magnesium and taurine have a synergistic effect, stabilizing cell membranes, calming the nervous system, and inhibiting nerve excitation." P. 245

"Vitamin B6 increases the amount of magnesium that can enter the cells; as a result, these nutrients are often taken together." We also know that magnesium and the essential fatty acids (EFAs, found in fish) are interdependent; each works much more efficiently when the other is present in sufficient amounts." pp. 252-253
[take you fish oil and co-factors with your magnesium]

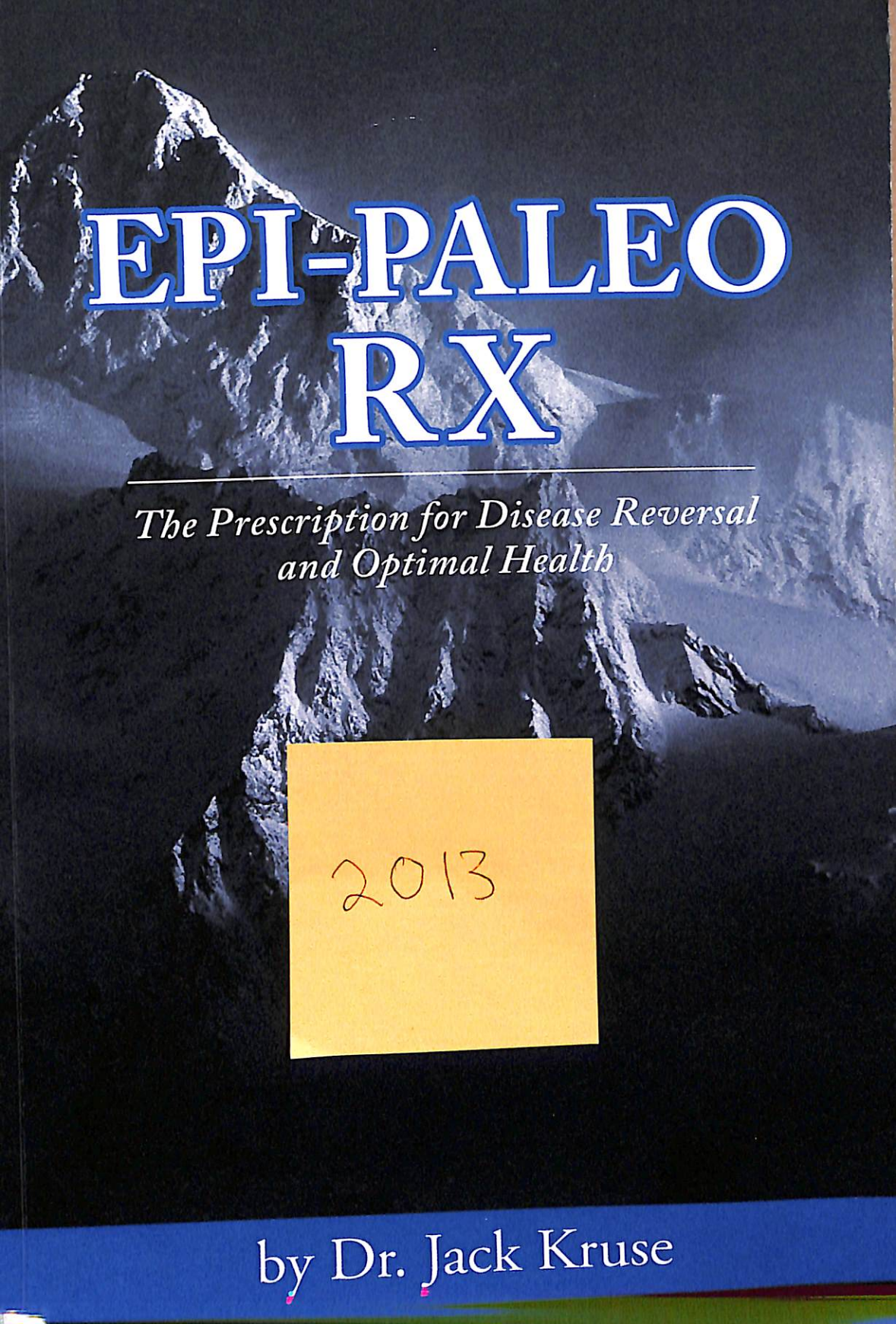
Contraindications to Magnesium Therapy, p. 240

Kidney Failure

Myasthenia gravis

Excessively slow heart rate

Bowel Obstruction


EPI-PALEO
RX
The Prescription for Disease Reversal
and Optimal Health
2013
by Dr. Jack Kruse

and enhances insulin sensitivity to protect our bones. It also increases testosterone, which increases bone density in both men and women.

Osteocalcin is vital in forming bone and directing calcium deposition in bone, dentin (teeth), and the arteries of our body. There is even scientific evidence of a hypothalamic pituitary axis that controls our susceptibility to tooth decay and dental plaque and the mineralization of teeth. This was work done 25 years ago by Dr. John Lenora of Loma Linda University.

Osteocalcin is also tied to a vitamin found in food called vitamin K2. Vitamin K2 is not like the vitamin K1 with which most physicians are familiar. In fact, many do not know that vitamin K has three isoforms, and all three do different things. Vitamin K2 has been removed from the modern food supply by food processing. Vitamin K2 and osteocalcin are key factors in saliva to help maintain optimal dental health.

In essence, osteocalcin sends absorbed calcium to the correct tissues in our body. This is important because the conventional wisdom treatment for osteoporosis usually involves only calcium and vitamin D supplementation. Recent studies have linked calcium supplementation to adverse cardiac outcomes. The reason for this link is not well known, but it is likely secondary to a co-morbid lack of vitamin K2 in people, perhaps causing calcium to be sent to our coronary and carotid arteries instead of our bone. Vitamin K2 is the calcium traffic cop in our bodies, and osteocalcin tells us whether we are deficient in this vitamin. You can order this test yourself off the internet without a prescription and bring it to your doctor's attention.

In order to become active, osteocalcin has to be carboxylated, a chemical reaction that adds carbon dioxide or bicarbonate to form a carboxyl group. When someone has insulin resistance or type 2 diabetes, they have a lot of un-carboxylated osteocalcin, which won't allow calcium into the bone collagen matrix. This is another reason diabetics are at high risk for bone diseases. Instead, the calcium is placed in tissues where it doesn't belong, such as heart valves and in many different arteries of our body. Most aortic valves in this country are replaced because they are calcified and don't work. Why? They are vitamin K2 deficient. This link is not well known by vascular surgeons. I have alerted my colleagues about this link so they can help patients who have arterial calcification. I often see this risk when I see X-rays that show calcification of arteries. Most people with bad atherosclerosis also suffer from this. This can be followed up and measured with a calcium index score of your heart or vessels-a high calcium index

score is not a good sign for your long-term health. This is particularly true for your heart.

We want this calcium to be directed to our bone and not the soft tissues in our vascular tree. This is why studies have found excessive calcium supplementation to be harmful. The answer is to stop the calcium supplementation and take K2 through diet or supplementation. Most people who have had their gallbladders removed also have a vitamin K2 deficiency because the body recycles K2 using the gallbladder. I have an entire blog on my website that covers the K2 recycle steps if you would like to learn more about how this might effect your health.

So what carboxylates osteocalcin to make it active in humans? Vitamin K2! K2 carboxylates osteocalcin to make it an active hormone to direct calcium to the right tissues. When K2 levels are low, we see calcification in the arteries, the spine, or as tartar build up on your teeth. This is information few physicians and dentists are aware of. I learned about it in piecemeal fashion because I was a dentist before I was a neurosurgeon, and I put those pieces together about seven years ago. My teeth used to build up a lot of tartar until I increased my K2 levels in my diet and in supplement forms.

People with diabetes and insulin resistance are deficient in vitamin K2, as are most people who eat a SAD. Because osteocalcin helps modulate insulin release, vitamin K2 can also be used to treat type 2 diabetes; there are several published studies on this, although they are also not well known in this country. The Japanese use vitamin K2 in the form of natto to treat osteoporosis.

I first discovered the link between K2 and osteoporosis while doing research related to my young patient with the broken neck I mentioned earlier. While looking for answers I tripped over this data. Like most physicians, I did not know what K2 was at that time, much less what it did. If you go into most pharmacies or supplement stores you will be hard pressed to find vitamin K2 even today. Allopathic medicine recognizes vitamin D3 deficiency, but in my opinion vitamin K2 deficiency is a bigger and more costly public health mess because it is common in three epidemic diseases: Diabetes, atherosclerosis, and osteoporosis. The cost of treating these diseases in our country is staggering. This is clearly an area where an ounce of prevention saves a pound of cures.

I use K2 frequently in my practice because most who come to see me have a spine disease. Vitamin K2 is on my top-ten Paleo supplement list

on my blog. Most vascular surgeons are unaware of what vitamin K2 is and how it can prevent atherosclerosis. I run a lab on osteocalcin to quantify how much a patient's diet is depleted in vitamin K2. Most of our endogenous (made in the body) vitamin K1 and K2 is made from gut bacteria when we are healthy. But if you have a leaky gut or gut dysbiosis, you might not be able to recapture your vitamin K2 and will need a bigger dietary source on a regular basis. I think the SAD selects for a gut microflora that ensures vitamin K2 depletion, and that this is the reason we have a pandemic in vitamin K2 losses and see a lot of unhealthy bone. I also think it is why cardiovascular disease is so prevalent these days. Going with a Paleolithic diet solves this issue for most.

So if one has leptin resistance, leaky gut, or dysbiosis, we should expect a major problem with osteocalcin and K2 if we follow our own labs. I always look at the patient's HDL level to see if the gut may be leaky. I covered this extensively on the chapter on lab tests. Here is another thing to remember about Vitamin K-if the patient is on Coumadin, the problem is a bigger deal. Coumadin is a very common prescription and blocks the body's ability to recycle vitamin K, making it a very potent blood thinner, but also depleting cells of K2.

Vitamin K2 is important not only for diabetics, patients with heart disease, and patients with peripheral artery disease from atherosclerosis, but also for those with osteopenia or osteoporosis. Vitamin K2 is used as a first-line treatment of osteoporosis in Japan in doses of up to 45 mg a day. Unlike the SAD, the Japanese diet has a major source of Vitamin K2 in natto, which is fermented soybeans. Yes, I have tried it, and it tastes terrible. None of my patients will eat natto! The best source of Vitamin K2 in the SAD is pastured butter, which, ironically, most physicians advise their patients not to eat. Pastured butter is grass-fed butter. Vitamin K2 is also found in many green leafy plants, but with newer farming techniques and the advent of many pesticides, vitamin K levels have dropped in most non-organic foods.

Gut dysbiosis and leaky gut are the major causes of osteocalcin problems because K2 also comes from gut bacteria. If the gut flora mix is not optimal, we lose our ability to recycle endogenous vitamin K. This creates an overall depletion of Vitamin K that must be compensated for in our diet. In the United States, our diets have been stripped of vitamin K2, partly because pasteurization robs dairy products of their vitamin K content.

Raw dairy, on the other hand, contains plenty of vitamin K2. This is why I tell my osteopenic patients to seek raw milk and raw milk cheeses.

If we can't recycle our vitamin K2 and we have poor dietary sources of K2, it means the proteins that depend on K2 are not going to work optimally. We see the effects in the heart, arteries, and in our bones. So people who are deficient in K2 cannot activate osteocalcin. Moreover, the data from the experiments at Columbia University made it clear that osteocalcin tells our pancreatic beta cells to produce more insulin and our pituitary gland to make more testosterone. These two mechanisms help us form bone. This is exactly why the Primal Rx employs these techniques for treatment.

WHY POSTMENOPAUSAL WOMEN STRUGGLE WITH FAT LOSS

Osteocalcin has another little-known function important for diabetics and the obese. Osteocalcin instructs fat cells to release adiponectin, a hormone that increases our insulin sensitivity. Adiponectin is inversely correlated with body weight. It is highest in thin patients and lowest in the obese. This hormone plays a role in the metabolic derangements that result in type 2 diabetes, obesity, atherosclerosis, and fatty liver disease. Women also have higher levels of adiponectin than men, as well as higher levels of leptin. When adiponectin is released from fat cells, so is leptin.

These facts are important when one considers weight loss patterns in men and women and why they differ, and why women struggle with their weight after menopause. Another factor is declining dopamine levels, which control the release of hormones from the pituitary gland. This in turn affects the levels of dopamine in the reward tracts of the frontal lobes, causing people to seek foods that make them gain weight.

WHERE DOES LEPTIN FIT INTO THE OSTEOPOROSIS STORY?

Leptin is a hormone secreted by fat cells, and leptin inactivates osteocalcin via the sympathetic nervous system. Fat cells also release leptin when inflammation is high. Here is where I made the link between leptin resistance and osteoporosis about seven years ago. Leptin is very similar in chemical structure to IL-6, which is the main inflammatory cytokine behind many Neolithic diseases. This is the chemical that causes a person's

Longevity Supplements

Nutri-West Specialty formulated Longevity Supplements

Complete Longevity:

Complete Longevity is recommended for longevity because, well, the ingredients were hand-picked to best support longevity. Ergothioneine was noted in the Journal of Nutritional Sciences (Cambridge) to be a 'longevity vitamin' that is limited in the American diet. Nutrients that affect cellular repair, function, replication etc. along with mitochondrial and telomere integrity are considered in any longevity protocol, and Complete Longevity was formulated with that in mind. Taurine, pyrroloquinoline quinone (PQQ) lutein, zeaxanthin, lycopene and astaxanthin are all superstars that boost the formula.

Complete A-G:

Complete A-G was formulated to be part of a healthy aging protocol. Specifically, the combination of acetyl-L-carnitine and alpha lipoic acid with co-Q-10 is reported by the famous researcher Bruce Ames to be one of the best combinations for support, and the synergy included in the formula further optimizes that support.

Complete Energy:

Complete Energy is a super combo of all the nutrients best known to rev up energy levels. Co-Q 10, PQQ, quercetin, alpha lipoic acid, broccoli powder, rhodiola, parsley, etc. all synergize for support of energy production, mitochondrial health, healthy aging/cognition, nerve, brain & heart health, muscular strength/coordination, antioxidant function, nociceptive pathways… all the things to watch for in a longevity protocol.

Complete Gluco-D:

Complete Gluco-D has research-based nutrients to optimally support blood sugar. Alzheimer's these days is referred to as a "diabetes of the brain", so it is extremely important to support healthy blood sugar levels as much as we can. The brain's elasticity and integrity is critical for leading a long, quality filled life. Chromium, gymnema sylvestre, benfotiamine, fenugreek, etc. and a long list of synergistic nutrients contribute to the success of Complete Gluco-D.

Prolonging Healthy Aging: Longevity Vitamins and Proteins

Proceedings of the National Academy of Science (PNAS)
October 23, 2018; Vol. 115; No. 43; pp. 10836–10844

Bruce N. Ames: From the Nutrition and Metabolism Center, Children's Hospital Oakland Research Institute, CA. This study cites 148 references.

A recent (May 1, 2020) PubMed literature search using "Ames BN" locates 400 articles.

V/M = Vitamins and minerals

KEY POINTS FROM THIS ARTICLE:

1) Proteins/enzymes are classified into two classes according to their essentiality for immediate survival/reproduction and their function in long-term health:

- **Survival proteins**

versus

- **Longevity proteins**

2) ***The Triage Theory***:

- "A modest deficiency of one of the nutrients/cofactors triggers a built-in rationing mechanism that favors the proteins needed for immediate survival and reproduction (survival proteins) while sacrificing those needed to protect against future damage (longevity proteins)."

- Many nutrients "play a dual role for both survival and longevity."

3) "Impairment of the function of longevity proteins results in an insidious acceleration of the risk of diseases associated with aging."

- "Nutrients required for the function of longevity proteins constitute a class of vitamins that are here named 'longevity vitamins'."

- **Taurine** [details below] should be considered as a *conditional vitamin*.

- These 10 compounds should be considered as putative longevity vitamins:

  - The fungal antioxidant ergothioneine
  - The bacterial metabolites pyrroloquinoline quinone (PQQ) and queuine

- The plant antioxidant carotenoids lutein, zeaxanthin, lycopene, α- and β-carotene, β-cryptoxanthin

- The marine carotenoid astaxanthin

4) "Because nutrient deficiencies are highly prevalent in the United States (and elsewhere), appropriate supplementation and/or an improved diet could reduce much of the consequent risk of chronic disease and premature aging." **[Key Point]**

5) Dr. Ames proposes that an "optimal level of many of the known 30 vitamins and essential minerals/elements (V/M), plus that of 10 new putative vitamins described herein, is necessary for promoting healthy aging." **[Important]**

6) The "triage theory" states that when there is a V/M shortage, the proteins/enzymes that are sacrificed are the ones necessary for supporting long-term health. **[Important]**

- Many V/M are necessary for supporting long-term health.

- Many V/M deficiencies "increase the risk of future disease and shortens the lifespan."

  - These V/M are "**longevity vitamins**," and the proteins associated with them are "**longevity proteins**."

7) "Approximately 30 V/M are cofactors necessary for metabolism to function properly and were discovered because severe dietary deficiencies were linked to serious adverse health effects."

- Vitamins A, B1, B2, B6, B12, biotin, C, choline, D, E, folic acid, K, niacin, pantothenate; and minerals/elements calcium, chloride, chromium, cobalt, copper, iodine, iron, manganese, magnesium, molybdenum, phosphorus, potassium, selenium, sodium, sulfur, and zinc.

- The marine omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentanoic acid (EPA) are also essential but they are not vitamins.

- Nine essential dietary amino acids are also important for the synthesis of proteins and hormones.

8) Most of the world's population, including developed countries, consume many of the V/M below recommended levels.

9) The estimated average requirement (EAR) values are the intake level for a nutrient at which the needs of half of the healthy population is adequate and half is inadequate. The United States population ingesting V/M quantities below the EAR (including fortifications and supplements) are:

- Vitamin D 70%
- Vitamin E 60%
- Magnesium 45%
- Calcium 38%
- Vitamin K 35%
- Vitamin A 34%
- Vitamin C 25%
- Zinc 8%
- Vitamin B6 8%
- Folate 8%

- "Intakes of the marine omega-3 fatty acids DHA and EPA are also remarkably low in the United States population."

10) "A diet containing much of its calories as refined foods and sugar is deficient in V/M and leads to an unhealthy and shorter life." **[Key Point]**

11) The triage theory notes, "modest V/M deficiencies—insufficient to elicit overt symptoms of severe deficiency—might contribute significantly to the aging process and the diseases of aging." **[Key Point]**

- "A strategic rationing response has been selected through evolution, which ensures that when a moderate shortage of a V/M is encountered, the scarce V/M is preferentially retained by those V/M-dependent proteins/enzymes that are essential for survival and reproduction, such as proteins essential for early development and immediate survival (survival proteins)."

- "Proteins/enzymes needed for maintaining long-term health by preventing insidious damage are starved for that V/M and become increasingly inactive, thus leading to an increase in diseases of aging."

12) "A major aspect of degenerative aging is that the damage is insidious and clinically not obvious because it accumulates slowly over time and is apparent only later in life. The connection to V/M shortages is underappreciated." Example:

- Some vitamin K-dependent proteins are required for short-term survival (like blood-clotting).

- Other K-dependent proteins are involved in long-term health.

13) Adequate V/M throughout life plays an important role in healthy aging.

14) *Longevity proteins* are sacrificed to allow for survival during triage rationing, but they also protect against diseases of aging.

- Longevity V/M are needed for the function of longevity proteins, and a shortage of which results in damage that is cumulative and insidious.

15) *Survival enzymes/proteins* are needed for short-term survival and reproduction, and are preferentially supplied with a V/M necessary for their function.

- Survival V/M are needed for the function of short-term survival proteins.

16) V/M that support both survival and longevity proteins are subject to triage rationing favoring survival. **[Key Point]**

- Hence, their shortage leads continuously to accelerated aging. **[Key Point]**

17) There are some compounds that are needed only for longevity, and therefore are *not* essential for short-term survival. These compounds have *not* been recognized as V/M, but effectively *function* as longevity V/M (the 10 listed above).

18) Most V/M necessary for the proper function of longevity proteins/enzymes are also survival V/M. These include:

- Vitamin K
- Selenium
- Vitamin D
- Marine omega-3 fatty acids DHA and EPA
- Magnesium
- Taurine

    - "The levels of each of these are inadequate in a large percentage of the American population, and these deficiencies are a major contributor to unhealthy aging."

19) "Vitamin D levels are inadequate in 70% of the United States population."

- "Almost all dark-skinned people residing in northern latitudes are particularly deficient."

- About 2,700 binding sites have been found in the human genome as interacting with the vitamin D receptor protein (14).

- Vitamin D deficiency causes or is associated with a large number of diseases that affect healthy aging, including all-cause mortality, cancer, cardiovascular disease, diabetes, and brain function.

- "It is particularly important to tune up metabolism with respect to vitamin D."

- There is no increased risk of vitamin D toxicity even when blood levels of 25(OH)D were as high as 100 ng/mL.

- Vitamin D is "important for a healthy long life, and thus it is a longevity vitamin."

20) The intake of **DHA** and **EPA** is inadequate in most of the US population.

- Low EPA and DHA levels in red blood cells is associated with increased all-cause mortality.
- Each 1% increase in plasma DHA/EPA was linked with a 20% decreased risk in all-cause mortality. **[Very Important]**
- DHA/EPA are present in high levels in the central nervous system and are important for brain.
- Omega-3 fatty acids supplementation is a promising treatment for schizophrenia.
- Low blood levels of DHA/EPA are associated with a faster rate of telomere shortening, a marker of cell aging.
- DHA/EPA are important for vitamin D steroid hormone effectiveness.
- DHA/EPA are inefficiently made from linolenic acid [plant-based omega-3].

21) **Magnesium** (Mg) is present in the center of the chlorophyll molecule, with plants being a major dietary source.

- "Mg deficiency affects about 45% of the United States population and has been associated with increased all-cause mortality, poor DNA repair capacity, increased risk of lung cancer and various other kinds of cancer, heart disease, telomere shortening, and risk of stroke."
- Mg deficiency is a principal driver of CVD, "a worldwide under-recognized problem, and thus that it is a major public health crisis."
- Mg is required to convert vitamin D to its active steroid hormone form.

22) Conditional Vitamins are synthesized by the body, but not at a level that is sufficient to optimize metabolism.

23) **Choline** is a conditional vitamin

- Only 11% of women achieve the recommended intake of choline.
- Choline deficiency results in DNA strand breaks and affects brain development.

24) **Taurine** is also a conditional vitamin; it is synthesized in humans, but not in sufficient amounts.
[Taurine is an organic compound that is widely found in animal tissues, especially in fish and meat. It can be synthesized from cysteine. It may be low or negligible in a strict vegetarian diet {**important**}.]

- Taurine is important in preventing numerous health problems, such as CVD, brain function, diabetes, and mitochondrial diseases.
- Taurine functions as *both* a survival vitamin and a longevity vitamin.
- Taurine is located in the cytosol and in mitochondria and it is present in virtually all human tissues at millimolar concentrations.
- Good dietary sources of taurine include fish and other seafood, seaweed, eggs, and dark-meat poultry.
- Taurine is particularly important in the mitochondria and deficiencies are associated with mitochondrial diseases.
- Taurine improves mitochondria energy production, reducing exercise-induced fatigue and improved recovery.
- Taurine is the main buffer against mitochondrial oxidant production.
- Taurine supplementation lowers blood pressure and improves vascular function. "Taurine consumption was the most significant factor associated with reduced risk of ischemic heart disease (IHD)."
    - "Japanese people in Okinawa had the highest taurine dietary intake and the lowest incidence of IHD and longest lifespan."
- "Taurine plays an important role in brain development, including neuronal proliferation, stem cell proliferation, and differentiation."
- Taurine has no toxic effects in humans.
- Taurine is a neuromodulator in the central nervous system.
- Taurine inhibits the N-methyl-D-aspartate receptor [NMDA]. **[Important]**
- In diabetics, taurine supplementation remediates retinopathy, neuropathy, nephropathy, cardiopathy, atherosclerosis, altered platelet aggregation, and endothelial dysfunction.
- Taurine is important for fetal development, and because the human fetus cannot synthesize taurine it must be provided by the mother.

- "Taurine is well established as an important conditional vitamin for survival functions and for healthy longevity."

25) Dr. Ames believes that other conditional vitamins include lipoic acid, ubiquinone, and carnitine.

26) Dietary biochemicals that are not officially recognized as vitamins but have a positive age-delaying effect are called *Putative Longevity Vitamins*. They reduce the accumulation of long-term oxidative damage. They are *not* classified as "survival vitamins":

- Ergothionine (ESH)
  A fungal antioxidant
- Pyrroloquinoline Quinone (PQQ)
  A bacterial compound pyrroloquinoline quinone (PQQ)
- Queuine
  A bacterial compound
- Carotenoids (seven plant compounds, one marine compound)

27) "Vitamin C is categorized as a survival vitamin because, in addition to being an antioxidant, it also functions as a cofactor for survival proteins."

28) "Vitamin E is a fat-soluble, free-radical scavenger/chain-breaking antioxidant, and is not required for any known protein/enzyme functions."

29) **Ergothioneine** (ESH)

- Synthesized by most mushrooms (highest in oyster and king boletus mushrooms, lowest in white-button commercial mushrooms), cyanobacteria, and many types of soil bacteria, but not by plants or animals.

- Also found in beef, pork, lamb, and chicken.

- Present in almost all human cell and tissue types and plays a significant role as an antioxidant.

- Levels decrease significantly with age, especially after past 80 years.

- Acts as an adaptive antioxidant for the protection of injured tissues.

30) **Pyrroloquinoline Quinone** (PQQ)

- "PQQ is made by many species of bacteria, but not by animals or plants."

- PQQ is "synthesized by soil bacteria, enters plants from the soil, and thus enters human diets; it was detected in every sample of fruits and vegetables tested."

- "PQQ is a powerful antioxidant and is much more stable than ascorbic acid."
    - "In redox cycling, PQQ has 20,000 potential catalytic cycles, compared with 4 for ascorbic acid."
- The health benefits of PQQ in humans include antioxidant activity, neuroprotection, cognition, and lowering the level of inflammatory C-reactive protein.
- PQQ improves mitochondrial efficiency and induces mitochondrial biogenesis.
- "PQQ is promising as a longevity vitamin in humans. It is necessary for mitochondrial health."

31) **Queuine**

- Queuine is an evolutionarily ancient compound that is derived from bacteria.
- All eukaryotic organisms, including humans, convert queuine to queuosine.
- Queuine is required to convert:
    - Phenylalanine to tyrosine, tyrosine to DOPA, and DOPA to epinephrine and norepinephrine
    - Tryptophan to serotonin
    - Arginine to nitric oxide (NO)

32) **Carotenoids**

- There are ~600 carotenoids synthesized by plants, but not by animals.
- They act as antioxidant pigments in all plants and usually contain 11 conjugated double bonds, which accounts for their yellow/orange/red colors.
- All photosynthetic plants synthesize carotenoids to quench singlet oxygen, a highly energetic and toxic form of oxygen created in cells by strong light.
- These six carotenoids account for 95% of the carotenoids found in the blood and brains of North Americans:
    - Lutein
    - Zeaxanthin
    - Lycopene
    - α- and β-carotene (a precursors of vitamin A)
    - β-cryptoxanthin (a precursors of vitamin A)
- A seventh carotenoid, the powerful marine carotenoid astaxanthin, contains 13 conjugated double bonds.

- "There is good evidence that these carotenoids help optimize a healthy lifespan."

- "Carotenoids are included among putative longevity vitamins because of the evidence that they protect long-term health."

33) "Prolonging good health while aging is an important issue in a world with large increases in life expectancy."

34) "The relatively simple approach of securing sufficient intake of well-known dietary V/M, plus taurine, plus the 10 putative longevity vitamins introduced here, could lead to healthy aging by 'tuning-up metabolism' and promoting metabolic harmony and health." **[Key Point]**

35) "By optimizing survival and longevity V/M intake throughout life, premature, insidious, and increased risk of degenerative diseases may in large part be preventable." **[Key Point]**

36) "V/M deficiencies, as indicated by intakes below the EAR, are common in the United States and around the globe, especially among the poor, children, adolescents, the obese, and the elderly."

37) "Evidence is accumulating that lack of foods that are particularly nutrient-rich is a contributor to diseases of aging." **[Important]**

38) "Healthy foods are nutrient-dense, containing high levels of V/M, fiber, and longevity vitamins, relative to calories."

- "Humans should be able to stay healthier longer during old age if nourished appropriately."

39) "Some of the insidious damage due to a nutrient shortage may be reversible once the V/M intake is increased." **[Important]**

40) "Obese individuals are particularly deficient in V/M, which is a likely explanation, among others, for a decrease in longevity through an increased frequency of every age-associated disease that has been examined, including cancer, heart disease, brain decay, and immune decay."

- "The health and longevity of the obese would benefit greatly from an improvement in their V/M intake."

41) "An important concept relative to the use of vitamins for health is the fact that over 50 human genetic diseases can be ameliorated by the administration of high doses of supplements." **[Important]**

- "Supplementation raises the concentration of the needed coenzyme to levels that overcome a defect in the enzyme-binding site (which is likely to be deformed by mutation or aging-related membrane rigidity) besides possibly affecting the abundance and stability of some proteins." **[Key Point]**

42) "Eventually, the age of preventive medicine will take into consideration the major effects of V/M components."

43) "Two examples of consequences of V/M insufficiency, which are measurable, are increased DNA damage and mitochondrial decay."

44) The benefits derived from an improved V/M utilization is:

- Prevention of the degenerative diseases of aging
- Lowering medical costs
- Increases savings

45) "In conclusion, in addition to keeping physically fit, the low hanging fruit in prolonging a healthy aging lies in optimizing V/M intake." **[Key Point]**

COMMENTS FROM DAN MURPHY:

This article is validating and consistent with our message for more than 20 years.

We take Nutri-West Supplements: (800) 443-3333

Our dietary habits are consistent with this article by Dr. Ames.

Our supplements, consistent with this article, are attached below.

Longevity Supplements
Nutri-West: 800-443-3333

Multiple Vitamin-Mineral: *Core Level Health Reserves*
Contains the complement of B vitamins and selenium. It is copper and iron free.

Omega-3 Fatty Acids

Infants, children, pre-puberty: *Complete Children's EPA/DHA*
The DHA should be greater than the EPA (2.6/1)
1 per day per year of age (i.e., a 5-year old would take 5)

Adults:
An ideal ratio of ALA, EPA, DHA, and GLA; EPA should be double DHA
3,000 mg of EPA + DHA per day (*6 Complete Omega-3 Essentials*)
or 1 teaspoon of *Complete Hi-Potency Omega-3 Liquid*

Omega-3 Antioxidants: *Complete Omega-3 Co-Factors per gram of EPA+DHA*)
To protect Omega-3 double bonds from oxidation.
Also contains a compliment of B vitamins and vitamin C.

Vitamin D3

Infants:	400 IU per day for infants	(1 *Vitamin D 400*)
Pre-Puberty:	2,500 IU per day for children	(1 *Complete Immuno D3*)
Adult:	5,000 IU per day	(1 *Complete Hi D3*)

Magnesium: *Complete Magnesium*: 300/mg of Mg++/per tablet (mostly malate)
Also contains Taurine

Vitamin K 2-4 and K 2-7 *Complete K* (1 daily)

CoQ-10 (ubiquinone, conditional vitamin) and **Pyrroloquinoline Quinone** (PQQ)
4 *Complete Energy*

Mitochondrial Health: (4 *Complete AG*)
Contains conditional vitamins "lipoic" acid" and "carnitine"

A)	Acetyl-l-carnitine	680 mg per day
B)	Alpha-lipoic acid	240 mg per day
C)	CoQ-10	10 mg per day

Choline Enhancement:

Complete Brain Charge (1 daily)

Complete Synapse (1 daily)

How to Add 20 Years to Your Life and Life to Your Years with 12 Simple Lifestyle Changes

THE H* FACTOR SOLUTION

2003

*(Homocysteine, the Best Single Indicator of Whether You Are Likely to Live Long or Die Young)

JAMES BRALY, M.D.
& PATRICK HOLFORD

The H Factor Solution

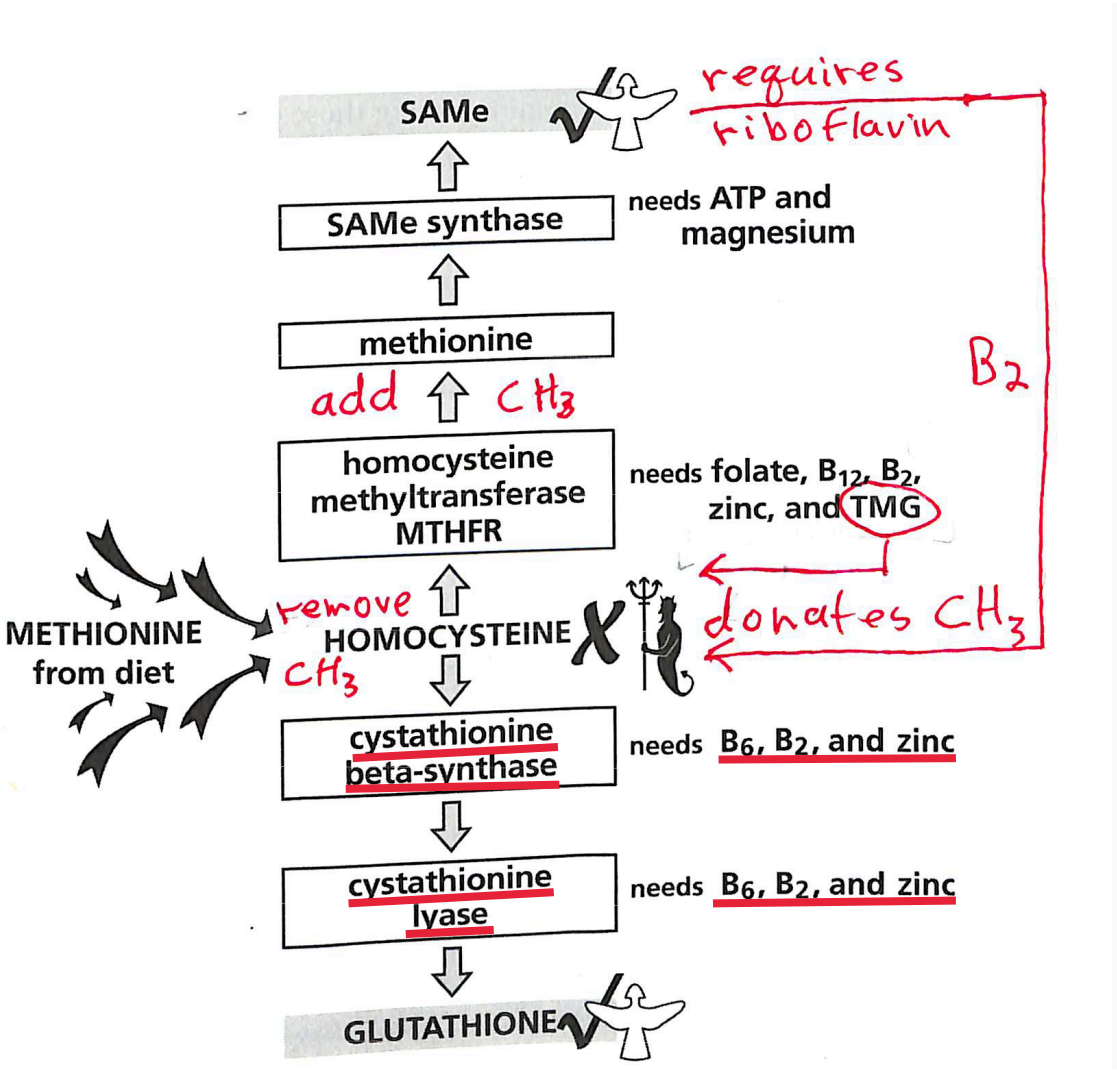
Homocysteine, the Best Single Indicator of Whether You Are Likely to Live Long or Die Young

James Braly, MD
2003

"The reason homocysteine accumulates in the body is because enzymes aren't working properly."

"Enzymes don't work alone. They have helpers, called cofactors: primarily B-complex vitamins folic acid (folate), pyridoxine (vitamin B6), cobalamin (vitamin B12), and riboflavin (vitamin B2), and the minerals zinc and magnesium."

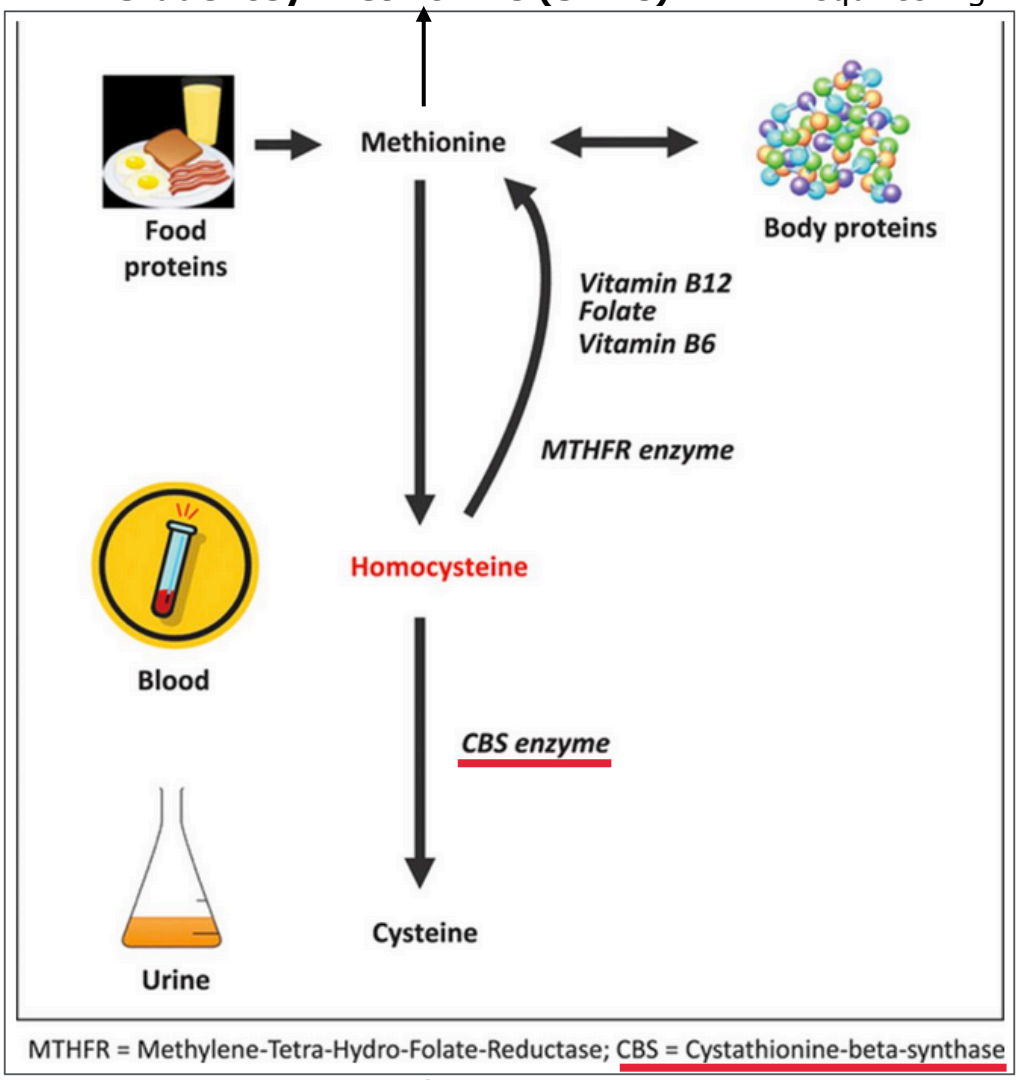
TMG = trimethylglycine: "TMG is the single best and most affordable methyl donor discovered so far,"... "in combination with the big-four B vitamins, it's the best homocysteine buster."



Homocysteine and MTHFR Mutations

Circulation
July 7, 2015; Vol. 132; No. 1; pp. e6-e9
Stephan Moll, MD and Elizabeth A. Varga, MS: from the University of North Carolina School of Medicine, and Ohio State University College of Medicine.

S-adenosyl Methionine (SAMe) Requires Mg++ and ATP



Requires B6, B2, zinc

Reduced Glutathione
GSH

Glutathione Reductase
Requires Riboflavin (B2)

Oxidized Glutathione
GSSG

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Review

Black gas, bright future: H_2S based therapeutics for neurodegenerative disorders

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ABSTRACT

From shaping Earth's earliest anoxic seas to quietly orchestrating cellular life today, hydrogen sulfide (H_2S) has journeyed from ancient toxin to modern therapeutic candidate. Once abundant in Earth's primordial environment, H_2S has reemerged as a critical endogenous gasotransmitter in modern biology. Within the central nervous system, H_2S regulates redox homeostasis, mitochondrial bioenergetics, inflammatory signalling, and neuronal excitability. A key mechanism involves post-translational modification of protein cysteine residues (persulfidation), reactions with metal centres, and scavenging of reactive oxygen and nitrogen species, thereby influencing diverse cellular processes. Dysregulation of H_2S metabolism, whether deficient or excessive, is increasingly implicated in neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's disease, Down syndrome, and in stroke and traumatic brain injury. This review focuses on neuronal aspects of H_2S biology and therapeutic relevance in these conditions. Restoration of H_2S signalling in preclinical models improves cognitive and motor function, reduces neuropathology, and preserves mitochondrial integrity. Therapeutic innovation has produced a variety of H_2S donors, including slow-releasing compounds, organelle-targeted agents, and emerging nanomaterial platforms such as polymer-based and metal–organic frameworks for precision CNS delivery. Natural compounds such as ergothioneine, a sulfur-containing antioxidant, are also gaining attention as potential modulators of endogenous H_2S pathways. Future directions include integration of H_2S therapies with genetic targeting tools and elucidation of their interactions with other gasotransmitters and gut–brain axis signalling. Although clinical trials remain limited, the convergence of donor chemistry, molecular biology, and delivery technologies positions H_2S-based therapeutics as a promising frontier for treating neurodegeneration and acute neural injuries.

Introduction: H_2S, A homeostatic regulator in disguise

Cells exist in a state of dynamic equilibrium, continuously sensing and responding to fluctuations in their internal and external environments. This homeostatic balance is maintained through tightly regulated networks of signalling molecules that coordinate redox status, energy metabolism and adaptive gene expression [1–3]. Among these modulators is hydrogen sulfide (H_2S), a small gaseous molecule that once billowed like black smoke from ocean bedrock during Earth's early history, shaping the euxinic environments from which life itself emerged [4]. Despite this primordial legacy, H_2S was long dismissed as merely a toxic and foul-smelling chemical until its rediscovery as a key endogenous signalling molecule in modern biology. H_2S is now recognised as a *bona fide* gasotransmitter alongside nitric oxide (NO) and carbon monoxide (CO), as these molecules permeate the cell membrane *via* passive diffusion without the requirement of a specific transporter [5–7]. H_2S manifests its diverse biological effects through mechanisms such as posttranslational modification (PTM), reactions with metalloproteins, modulation of ion channels and redox buffering [8,9]. Its pleiotropic roles in stress adaptation, mitochondrial function and inflammation have positioned H_2S as a compelling candidate for therapeutic exploitation, particularly in the context of neurological disease, where redox imbalance and metabolic dysfunction are prominent pathological features [10].

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In mammals, enzymatic production of H_2S occurs *via* two main distinct pathways (Fig. 1). The transsulfuration pathway, located primarily in the cytosol, involves cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE), which convert homocysteine and cysteine into H_2S in a pyridoxal 5′-phosphate (PLP)-dependent manner. Separately, in the mitochondrial-associated pathway, cysteine aminotransferase (CAT) converts cysteine into 3-mercaptopyruvate (3-MP), which is then used by 3-mercaptopyruvate sulfurtransferase (3-MST) to generate H_2S [11]. CBS is highly expressed in the brain (astrocytes and neurons of cortex, hippocampus, etc.), whereas CSE predominates in peripheral tissues but is also present in the CNS [12]. 3-MST, often working with cysteine aminotransferase (CAT), contributes to mitochondrial H_2S production in neurons. A third minor pathway uses D-cysteine with D-amino acid oxidase and 3-MST [13–15]. These enzymes are regulated allosterically and transcriptionally, for instance CBS by S-adenosylmethionine and CO, and CSE by intracellular Ca^{2+} and transcription factors [16–19]. An additional enzymatic route for H_2S production has been recently identified involving human selenium-binding protein 1 (SELENBP1), which exhibits methanethiol oxidase activity analogous to that observed in methylotrophic bacteria. SELENBP1 catalyses the oxidative degradation of methanethiol, resulting in the formation of H_2S, hydrogen peroxide (H_2O_2), and formaldehyde [20]. Alternatively, H_2S can be generated through a non-enzymatic reaction involving L-cysteine, ferric iron (Fe^{+3}), and vitamin B_6, as shown in a study investigating this alternative pathway [21]. However, the actual contribution of this non-enzymatic route to the total circulating H_2S pool remains uncertain and is open to question, particularly in light of the slow kinetics of the reaction and the low amounts of H_2S detected even under supraphysiological or physiological substrate conditions. Finally, gut microbiota constitutes the important source of H_2S in mammals, contributing to both systemic and local sulfide pools [22,23]. Recent studies have highlighted the microbial production of H_2S not only as a modulator of intestinal homeostasis but also as a potential driver of pathological processes, including tumorogenesis and neurodegeneration [24–26].

In biological systems, H_2S exists in equilibrium with its deprotonated form, hydrosulfide (HS^-), with a pKa of ~6.9 and at physiological pH (~7.4), HS^- is the dominant species, while some H_2S remains in its neutral, membrane-permeable form [27]. The fully deprotonated sulfide ion (S^{2-}), with a pKa >12, is not present under normal conditions and only forms in highly alkaline environments. The hydrosulfide anion (HS^-) is primarily responsible for the biological actions of H_2S, which can be broadly categorised into three main mechanisms: redox-dependent post-translational modifications; interactions with metal centres and metalloproteins; and the scavenging of reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) [27].

The primary route for H_2S catabolism is mitochondrial oxidation [28,29]. This process begins with oxygen-independent activity of sulfide: quinone oxidoreductase (SQR), a mitochondrial inner membrane protein, which initiates the oxidation of H_2S by transferring electrons from H_2S to the oxidised form of coenzyme Q (CoQ), thereby feeding electrons into the respiratory chain and contributing to ATP synthesis [30]. During this reaction, SQR converts H_2S into a protein-bound persulfide intermediate (SQR-SSH). The persulfide generated on SQR can then follow transfer of sulphur atoms from SQR-SSH to sulphite (SO_3^{2-}), leading to the formation of thiosulfate ($S_2O_3^{2-}$) in a reaction involving thiosulfate sulfurtransferase (TST), which can further transfer sulphur to glutathione (GSH), producing glutathione persulfide (GSSH) and regenerating SO_3^{2-} [31,32]. Alternatively, sulphur atom from SQR-SSH can be transferred directly to GSH to form GSSH, which is subsequently oxidised by persulfide dioxygenase (ETHE1) to yield SO_3^{2-} [33]. The resulting SO_3^{2-} is then oxidised to sulphate (SO_4^{2-}) by sulphite oxidase (SO) and excreted renally [34]. Additionally, rhodanese (Rhd) can catalyse the transfer of sulphur atom from GSSH to SO_3^{2-} producing $S_2O_3^{2-}$, much of which is ultimately converted to SO_4^{2-} by the sequential action of thiosulfate reductase (TR) and SO [35].

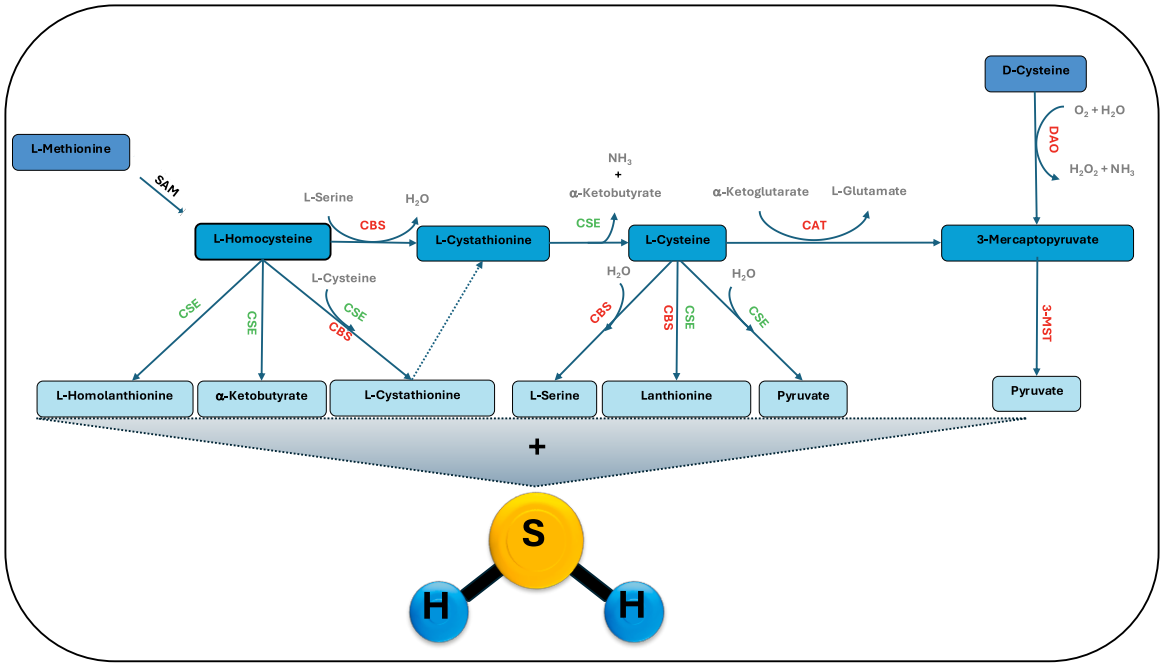

Fig. 1. Canonical enzymatic pathways for endogenous hydrogen sulfide (H_2S) production in mammals. The transsulfuration pathway involves the conversion of L-methionine to L-homocysteine *via* methionine recycling pathway and subsequently to L-cystathionine and L-cysteine *via* the enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). L-cysteine serves as a substrate for both CBS and CSE, contributing directly to H_2S generation. The alternative pathway involving cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3-MST) utilizes L-cysteine or D-cysteine (following deamination by D-amino acid oxidase, DAO) to produce 3-mercaptopyruvate, a key intermediate for mitochondrial H_2S production. The diagram illustrates the interconnected routes of transsulfuration and the contribution of each enzymatic step to H_2S biosynthesis, emphasizing the roles of CBS, CSE, CAT, 3-MST, and DAO.

Regulation of canonical pathways

One of the principal mechanisms by which H_2S exerts its biological effects is through protein persulfidation (also known as *S*-sulfhydration), a post-translational modification involving the addition of a sulphur atom (S) to the thiol group (-SH) of cysteine residues, forming a persulfide (-SSH). This redox-based modification, often compared to *S*-nitrosylation (nitric oxide-dependant PTM), can significantly influence protein activity, stability, and cellular signalling dynamics [27,36]. Persulfidation often enhances enzyme or protein activity or modifies how proteins interact with partners [37]. For example, sulfhydration of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) has been shown to greatly increase its activity, and persulfidation of actin promotes actin polymerisation, affecting cytoskeletal dynamics [36].

Early work by Kimura and colleagues established that H_2S enhances N-methyl-D-aspartate receptor (NMDAR) currents and promotes hippocampal long-term potentiation (LTP), a cellular correlate of learning and memory [38]. More recent studies have revealed that H_2S can induce persulfidation of serine racemase (SR), an enzyme critical for the synthesis of D-serine, a co-agonist of NMDARs. This modification upregulates SR activity, thereby potentiating NMDAR signalling and further promoting LTP [39]. In addition, H_2S and polysulfides have been shown to increase the release of neurotransmitters including γ-aminobutyric acid (GABA), D-serine, and glutamate, leading to transient inhibition of NMDAR activity. These effects were found to depend on the activity of transient receptor potential ankyrin 1 (TRPA1) channels and 3-MST, providing further mechanistic insight into how sulphur signalling modulates synaptic plasticity. Notably, this pathway has emerging implications in behavioural regulation and psychiatric phenotypes [40].

In parallel, H_2S modulates various ion channels, which alters neuronal and glial excitability as well as vascular tone. A well-characterised target is the ATP-sensitive K^+ channel (K_ATP) found in many cell types. H_2S reacts with a conserved cysteine on the channel's Kir6.x subunits (e.g., Cys43 on Kir6.1), persulfidating that site [41]. This prevents ATP from binding and closing the channel, thereby keeping the K^+ channel open. The result is an efflux of K^+ ions that hyperpolarises the cell membrane. In neurons, this hyperpolarisation can reduce firing rates, and in smooth muscle (such as in cerebral arteries) causes relaxation and vasodilation [42]. H_2S similarly activates certain Ca^{2+}-activated K^+ channels, which can modulate calcium-dependent electrical activity and signalling in both neurons and astrocytes [43,44]. Additionally, application of H_2S, either as sodium hydrosulfide (NaHS) or *via* the slow-releasing donor GYY4137 to primary cultured rat hippocampal neurons was shown to induce persulfidation of a critical cysteine residue (Cys73) on the voltage-gated potassium channel Kv2.1, resulting in channel inhibition and a consequent enhancement of neuronal excitability [45]. Through these actions on ion channels, H_2S generally has an inhibitory effect on over-excitation, though in some contexts (for example, by modulating Ca^{2+} flux in astrocytes) it may indirectly facilitate excitatory signalling. H_2S also affects the varieties of voltage dependant Ca^{2+} channels (VDCC) [46,47], such as L-type Ca^{2+} channel (LTCC) in heart and muscle [48,49], N, P/Q and T-type Ca^{2+} channels expressed in neuronal tissue [46,50]. Importantly, these canonical signalling mechanisms of persulfidation of proteins and the gating of ion channels are unique to H_2S, even as they conceptually parallel the mechanisms used by NO and CO [8,51].

Redox regulation and non-canonical pathways

Beyond its direct effects on proteins and channels, H_2S profoundly influences cellular redox pathways and survival signalling. One key role of H_2S is as an antioxidant. It can directly scavenge ROS and RNS (e.g. peroxynitrite), whilst also elevating the cell's endogenous antioxidant capacity [52,53]. A prime example of the latter is H_2S's interaction with the Keap1 Nrf2 system. Under basal conditions, the transcription factor Nrf2 is kept inactive in the cytosol by its inhibitor Keap1. H_2S can persulfidate Keap1 (for instance at cysteine-151), which weakens the Keap1 Nrf2 binding [54]. This allows Nrf2 to translocate into the nucleus and induce a suite of cytoprotective genes including those coding for glutathione synthesis (e.g., glutamate-cysteine ligase), NAD(P)H: quinone oxidoreductase 1 (NQO1), and haeme oxygenase-1 (HO-1). Through Nrf2 activation, H_2S ramps up the production of glutathione and other antioxidants, thereby fortifying neurons against oxidative stress and ischemic injury [55,56].

H_2S also modulates signalling pathways involved in inflammation and cell survival, acting in what might be considered "non-canonical" fashions (i.e., not purely through persulfidation). For example, during inflammatory stress, H_2S can influence the NF-κB pathway. Tumour necrosis factor-α (TNF-α) stimulation is known to increase Sp1-mediated transcription of CSE, leading to higher H_2S production[45]. The additional H_2S then persulfidates the p65 subunit of NF-κB. Persulfidation of p65 enhances its binding to the coactivator RPS3, which skews NF-κB towards activating gene programs that are anti-apoptotic and pro-survival, rather than pro-inflammatory [57]. In essence, H_2S can tip the balance of NF-κB signalling to favour cell survival under stress conditions. This is one example of how H_2S intersects with major regulatory networks. Other studies have shown H_2S can modulate pathways like PI3K/Akt and MAPK/ERK [58,59], further pointing its potential in neural cells.

Epigenetic interactions

Emerging evidence indicates that H_2S signalling can extend to epigenetic regulation of gene expression [60,61]. One avenue is *via* modification of chromatin-modifying enzymes. H_2S or H_2S-donating molecules have been found to inhibit certain DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) in experimental systems[48]. By modulating these enzymes, H_2S can lead to changes in DNA methylation patterns and histone acetylation status, resulting in the upregulation of protective genes or the silencing of deleterious ones. For instance, H_2S donor treatment in neuronal cultures has been associated with decreased global DNA methylation and increased acetylation of histone tails, changes that correlate with the expression of genes promoting cell survival and neuroplasticity [62]. Recent evidence suggests that H_2S may influence epigenetic regulation in neurodegeneration. In a rat model of Parkinson's disease (PD) induced by 6-hydroxydopamine (6-OHDA), H_2S treatment attenuated disease-associated phenotypes, including reductions in dopamine, its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC), and histone deacetylase (HDAC) activity [63]. These findings point towards a neuroprotective mechanism involving the modulation of histone acetylation pathways.

Another epigenetic layer involves non-coding RNAs. H_2S has been linked to the regulation of several microRNAs (miRNAs) that, in turn, affect H_2S production or action [64,65]. Conversely, some miRNAs respond to alterations in H_2S levels [66,67]. A notable example is miR-125b-5p, a microRNA that directly targets CBS mRNA. In models of hypoxic neuronal injury, overexpression of miR-125b-5p leads to downregulation of CBS, reducing H_2S synthesis and worsening cell damage [67]. Inhibition of miR-125b-5p, on the other hand, prevents the loss of CBS and helps maintain H_2S production, thereby protecting neurons under stress. In other contexts, H_2S has been shown to modulate the levels of long non-coding RNAs such as MALAT1, as well as miRNAs like miR-30c and miR-485-5p, which have been implicated in H_2S-driven protective effects during spinal cord ischemia and in models of neuronal apoptosis [68–70]. Collectively, these findings suggest that H_2S is woven into a complex epigenetic network, influencing epigenetic regulators and is, itself subject to regulation by non-coding RNAs, ultimately impacting gene expression programs that determine neuronal fate.

Developmental roles of H_2S

H_2S is not only important for maintaining adult brain function but also plays significant roles during neurodevelopment. The expression of CBS (the dominant H_2S-producing enzyme in the brain) is highest in the early postnatal period, corresponding with phases of intense neurodevelopmental remodelling [12]. Studies indicate that H_2S promotes neurite outgrowth and axonal elongation, suggesting a guidance role for growing neurons [71]. It also appears to facilitate synaptogenesis i.e. the formation of new synapses, possibly through interactions with calcium signalling pathways and the activation of growth-related kinases like MAPK/ERK [72,73]. These developmental effects of H_2S are consistent with observations in cell culture: adding an H_2S donor to cultured neurons enhances the formation of dendritic spines and synaptic connections [71].

H_2S may additionally protect immature neurons at a life stage when oxidative stress can be particularly harmful. Around the time of birth and in early brain development, neurons experience high metabolic demands and generate significant levels of reactive oxygen species. H_2S helps counteract this oxidative stress, thereby safeguarding developing neural circuits [12]. In animal models, inhibiting H_2S production during development (for example, using a CBS inhibitor) has led to neurodevelopmental deficits, including impaired hippocampal neurogenesis and cognitive dysfunction later in life [74]. Conversely, mice genetically deficient in certain H_2S-producing enzymes show altered brain morphology and behaviour. While research in humans is still nascent, some studies have speculated that aberrant H_2S metabolism might be a contributing factor in developmental disorders such as autism spectrum disorder [75,76]. Although direct evidence for this in patients is limited, the developmental necessity for balanced H_2S signalling is clear from animal studies.

Dysregulation of H_2S in neurological disease

Alzheimer's disease (AD)

Growing evidence suggests that endogenous H_2S is deficient in Alzheimer's disease. Post-mortem analyses of AD brains often show reduced expression of CBS (the primary H_2S-generating enzyme in the brain) and correspondingly lower H_2S levels compared to age-matched healthy brains [77]. This deficit in H_2S correlates with hallmarks of Alzheimer's pathology: increased oxidative damage, accumulation of amyloid-β plaques, and hyperphosphorylation of tau protein. Insufficient H_2S deprives neurons of critical redox buffering and signalling support, potentially accelerating synaptic dysfunction [77]. Supporting this view, experiments in AD animal models have demonstrated that replenishing H_2S can ameliorate disease features. Treatment of APP-transgenic mice with H_2S donors (such as NaHS or the slow-releasing GYY4137) led to improvements in memory tasks and a reduction in soluble Aβ levels and plaque deposition [77,78]. These benefits are attributed to H_2S restoring glutathione content, reducing neuroinflammation, and re-activating pro-survival pathways that are otherwise impaired in the Alzheimer's brain.

Recent work by further clarified the role of endogenous H_2S in Alzheimer's disease by demonstrating that CSE-dependent sulfide production leads to the persulfidation of glycogen synthase kinase 3β (GSK3β), a key regulator of tau phosphorylation [79]. This redox modification suppresses GSK3β activity, thereby limiting tau aggregation, a hallmark of AD pathology. Moreover, *in vivo* administration of H_2S donors improved cognitive function and reduced tau-related neuropathology in transgenic AD mouse models, reinforcing the therapeutic promise of targeting H_2S signalling in tauopathies and neurodegeneration.

Parkinson's disease (PD)

In Parkinson's disease, a loss of H_2S signalling has been linked to the degeneration of dopaminergic neurons. One crucial H_2S-sensitive target in these neurons is the ubiquitin E3 ligase parkin, which helps clear misfolded proteins. Under normal conditions, parkin is persulfidated by H_2S at specific cysteine residues (Cys59, Cys95, and Cys182) [80]. This persulfidation enhances parkin's enzymatic activity, promoting the removal of potentially toxic proteins such as oxidised or misfolded α-synuclein. In PD patients, studies have found that parkin in the substantia nigra and striatum is under-persulfidated, which coincides with a buildup of protein aggregates that parkin would normally help degrade [80]. A deficiency in H_2S whether due to lower CSE/CBS expression or increased consumption of H_2S by oxidative stress could thus impair this protective protein quality-control mechanism. Consistent with this, H_2S donors have shown neuroprotective effects in Parkinson's models: administration of H_2S-releasing compounds in MPTP-treated rats preserves nigral neuron counts and improves motor performance [81]. These outcomes involve H_2S maintaining mitochondrial function (preventing the loss of complex IV activity and ATP depletion that occur in PD models) and limiting neuroinflammatory responses (such as microglial activation). The PD case exemplifies how a drop in H_2S bioavailability can contribute to neurodegenerative processes, and conversely, how boosting H_2S can intervene in those processes.

Huntington's disease (HD)

Huntington's disease is another neurodegenerative disorder where H_2S dysregulation has been observed, albeit *via* a different mechanism. In models of HD, the mutant huntingtin protein (mHTT) aberrantly sequesters various transcription factors, including Specificity Protein 1 (Sp1) [82]. Sp1 is known to regulate the expression of CSE. When Sp1 is trapped by mHTT, CSE expression in affected neurons (especially in the striatum) is markedly reduced. The downstream effect is a decrease in H_2S production in those cells. This loss of H_2S is believed to exacerbate the oxidative stress and metabolic impairment characteristic of Huntington's disease. Normally, H_2S would support mitochondrial function and antioxidant defences, but in its absence, neurons become more susceptible to damage from reactive oxygen species and impaired energy metabolism [82]. While direct supplementation of H_2S in HD models has been less studied than in AD or PD, the mechanistic link between mHTT, Sp1, and CSE provides a rationale for exploring H_2S-elevating therapies in Huntington's disease as well.

Down syndrome (DS)

Down syndrome (trisomy 21) presents a unique scenario in which H_2S is in excess rather than deficient [83]. People with Down syndrome have an extra copy of the CBS gene, leading to overproduction of H_2S [84]. Studies have found that individuals with Down syndrome (DS) tend to have elevated levels of H_2S metabolites; for example, they excrete higher amounts of thiosulfate in urine, reflecting increased H_2S turnover [84]. In the brain, overactive CBS could result in supra-physiological H_2S levels in certain regions. While physiological levels of H_2S are protective, excessive concentrations have been shown to impair ATP production by inhibiting mitochondrial respiration, particularly through inhibition of Complex IV [85], as well as potentially disrupting other metabolic processes in cultured primary fibroblast from DS patients. Some researchers hypothesize that chronically elevated H_2S in Down syndrome could contribute to the developmental and cognitive abnormalities observed in this condition [84]. Indeed, in a novel rat model of DS induced by duplication of a selected region of chromosome

20 (parts of the region from Umodl1 to Prmt2) containing the CBS gene, corresponding elevated H_2S levels were shown to disrupt gamma-frequency brain electrical activity and suppress the expression of key synaptic proteins, including postsynaptic density protein 95 (PSD-95) and synaptophysin [86]. The same research group recently extended these findings in a mouse model employing a similar "minimalistic" duplication of a chromosome region containing the CBS gene, demonstrating that elevated brain H_2S levels impair ER stress responses and reduce autophagy capacity [87]. Notably, this study also reported sex-specific effects, with female animals more affected, and revealed that excess H_2S exerts complex dysregulatory effects on multiple metabolic pathways including amino acid, nucleotide, endocannabinoid, and carbohydrate metabolism ultimately leading to deficits in cognitive functions such as spatial learning and recognition memory. Notably, in both studies from this research group, administration of aminooxyacetic acid (AOAA), an inhibitor of CBS, reversed the observed pathological phenotype, further supporting the specificity of a CBS–H_2S axis in driving neuropathological changes [86,87]. Collectively, these findings underscore that H_2S homeostasis requires careful balance, as both deficiency and excess of H_2S can have detrimental effects on the brain.

Stroke and traumatic brain injury

Acute injuries to the brain, such as ischemic stroke and traumatic brain injury (TBI), are accompanied by disruptions in H_2S signalling. In the case of stroke (especially during the reperfusion phase after ischemia), endogenous H_2S levels in the brain can drop [88–90]. This decline is thought to worsen outcomes because H_2S is needed to induce vasodilation in reperfusing vessels and to neutralise the burst of reactive oxygen species and subsequent oxidative damage that accompanies reperfusion [91–93]. Experiments in rodent stroke models have shown that administering an H_2S donor either just before or during reperfusion significantly reduces brain damage, infarct volumes are smaller with less neuronal death. H_2S helps maintain blood-brain barrier integrity and cerebral blood flow in these settings, likely due to its combined vasodilatory and antioxidant effects [94,95].

In TBI, a somewhat similar pattern emerges: trauma can impair the activity of H_2S-producing enzymes, leading to a transient sulfide deficit when the tissue is under severe oxidative and inflammatory stress [96]. Animal studies of TBI have demonstrated that H_2S-based treatments (such as infusing Na_2S or an H_2S-releasing compound) result in reduced brain edema, decreased release of pro-inflammatory cytokines, and improved neurological recovery [97]. H_2S appears to preserve mitochondrial function in traumatized neurons and may inhibit the activation of apoptosis cascades post-injury. These findings suggest that timely restoration of H_2S following acute brain insults can mitigate secondary damage and improve healing.

Other neurological conditions

Beyond the major disorders above, altered H_2S metabolism has been noted in several other neurological conditions. Patients with amyotrophic lateral sclerosis (ALS), for instance, have shown abnormal levels of sulphur compounds in blood and cerebrospinal fluid in some studies, hinting at a possible involvement of H_2S signalling in motor neuron disease [98–100]. Similarly, in certain forms of epilepsy, researchers have observed changes in the expression of H_2S-synthesizing enzymes in the hippocampus, suggesting H_2S might modulate seizure susceptibility (perhaps through its effects on ion channels and neurotransmitter release [101]. While these connections are still being explored, it is clear that H_2S's influence extends broadly. In conditions like ALS, H_2S could be affecting pathways of excitotoxicity or mitochondrial health in motor neurons. In epilepsy, H_2S might be regulating neuronal excitability and inflammation in the epileptic focus. Overall, whether it is chronic diseases or acute injuries, the common theme is that a deviation from normal H_2S homeostasis either a shortfall or an excess can contribute to neural dysfunction, whereas correcting that imbalance has potential therapeutic value.

Therapeutic potential of H_2S modulation

The recognition of H_2S's neuroprotective effects has spurred interest in therapeutic strategies to modulate H_2S levels in the brain. Broadly, the goal is to restore optimal H_2S signalling in disease states, either by supplementing H_2S using donor compounds or by enhancing the activity of endogenous H_2S-producing enzymes. A wide array of preclinical studies lends support to this approach. Even in models of chronic neurodegeneration like Huntington's disease, preliminary studies suggest that boosting H_2S can ameliorate mitochondrial abnormalities and cell death [82]. Likewise, in rodent models of ischemic stroke, infusion of an H_2S donor during the reperfusion phase reduced the size of the brain infarct and improved functional recovery, presumably by limiting oxidative damage and preserving blood flow [102,103].

Mechanistically, H_2S exerts its beneficial effects through several converging pathways. As discussed earlier, H_2S enhances antioxidant defences (*via* glutathione and Nrf2-dependent enzymes) and curtails harmful ROS accumulation. It also modulates inflammatory signalling, for instance, H_2S can suppress the activation of microglia and astrocytes, resulting in lower production of pro-inflammatory cytokines in the brain milieu [104]. Concurrently, H_2S activates pro-survival signalling cascades. It has been shown to upregulate factors like brain-derived neurotrophic factor (BDNF) and to activate kinases such as Akt, which promote cell survival and neuroplasticity [105,106]. In some contexts, H_2S persulfidation of key metabolic enzymes helps maintain energy production, giving stressed neurons a better chance to survive. Interestingly, All these actions position H_2S as a broad-spectrum protective agent in the CNS.

It is also informative to consider what happens when H_2S production is inhibited in otherwise healthy systems. Pharmacological blockers of H_2S synthesis (such as propargylglycine, which inhibits CSE, or aminooxyacetic acid, an inhibitor of CBS) tend to worsen outcomes in models of disease and can even produce deleterious effects by themselves [107,108]. Genetic knockout studies align with this, where mice lacking CSE or CBS have heightened susceptibility to oxidative damage, inflammation, and hypertension [108,109]. Conversely, cardiac-specific CSE overexpression in rats was associated with an increase in the rate of H_2S production, and had smaller infarct size following myocardial infarction when compared to their wildtype controls [110]. The protective effects of H_2S was later demonstrated to be mediated through Nrf2 signalling [55]. These findings underscore that basal H_2S production is a part of the body's natural defence repertoire. Therefore, a therapeutic strategy aiming to increase H_2S is essentially augmenting an endogenous protective system.

Given H_2S's interactions with other gasotransmitters, there are intriguing possibilities for combination therapies. H_2S and NO, for example, both promote vasodilation but *via* partly distinct mechanisms. H_2S opens K_ATP channels while NO stimulates cGMP production. Studies have found that H_2S can enhance NO signalling by inhibiting phosphodiesterases [111] (which break down cGMP), suggesting a synergistic effect on blood vessels and possibly neurons. This synergistic interplay between endogenously produced and colocalized H_2S and NO has been demonstrated in studies showing that their reaction product, nitroxyl (HNO), activates TRPA1 channels in a redox-sensitive manner (*via* formation of intramolecular disulfide bond). Subsequently, this triggers the release of calcitonin gene-related peptide (CGRP), a potent vasodilator, thereby modulating the neurovascular and endocrine signalling axis [112]. Additionally, H_2S can help mitigate some toxic aspects of NO and *vice-versa*; their reaction product, a nitrosothiol-based specie thionitrous acid (HSNO), perthionitrous acid ($SSNO^-$) or nitroxyl (HNO), may carry its own signalling functions [27,112–114]. In theory, a therapy that provides both NO and H_2S (either *via* two separate donors or a single hybrid donor molecule) could yield additive benefits, such as

improved cerebral blood flow coupled with robust antioxidant protection. While such combination approaches are still largely experimental, they represent a frontier of neurotherapeutic research spurred by the growing understanding of gasotransmitter biology.

Bolstering H_2S signalling is emerging as a promising avenue to combat neurodegenerative diseases and acute neural injuries. By counteracting oxidative stress, modulating inflammation, preserving mitochondrial function, and engaging cell survival programs, H_2S can intervene in multiple steps of neuronal injury cascades. The challenge moving forward is translating these multifaceted benefits into safe and controlled therapies for humans.

H_2S based neurotherapeutics: Chemical classes & delivery strategy

Chemical classes and delivery strategies

Given H_2S's broad neuroprotective roles, therapeutic strategies increasingly aim to restore or enhance H_2S signalling in disease contexts. In animal models, administration of synthetic H_2S donors or upregulation of endogenous biosynthetic enzymes (e.g., CSE, CBS or 3-MST) has been shown to mitigate neuropathology. A variety of chemical H_2S donors have been developed to control H_2S release kinetics and targeting [115–118]. Rapid-release donors include sulfide salts (Fig. 2) such as sodium hydrosulfide (NaHS) and disodium sulfide (Na_2S) which dissociate in solution to yield H_2S but cause a transient high spike. Slow-releasing donors are designed to provide a sustained and stable release of H_2S over several hours, avoiding toxic peaks and allowing H_2S levels to rise gradually and persist longer *in vivo*. NaHS solutions typically contain significant impurity levels (up to 40 %) and rapidly degrade in aqueous systems, which underscores the importance of careful experimental design and the inclusion of appropriate controls to accurately attribute observed effects to H_2S. It is also important to note that GYY4137 (Section 4. 3) is not a pure H_2S source; it contains equimolar morpholine and is commonly synthesized in dichloromethane, a solvent that may yield carbon monoxide production *in vivo*. These elements may contribute to observed biological effects, making it essential to consider the full chemical profile of the donor.

Therefore, to obtain clarity throughout this review, we refer to the biological effects attributed to H_2S donors with the understanding that these effects may derive not solely from H_2S itself, but also from donor-specific pharmacological properties, their parent molecules, by-products, or metabolites. We use the term "H_2S" as a functional shorthand, while recognizing this complexity.

Inorganic salts (NaHS & Na_2S)

In Alzheimer's disease models, chronic administration of H_2S donors, such as the fast-releasing sodium hydrosulfide (NaHS) salt or Tabiano's spa-water, a mineral water with the highest concentration of H_2S among all natural springs in Europe, has been shown to improve cognitive function and slow the progression of pathology [77]. In rat models of AD induced either by β-amyloid peptide injection or streptozotocin exposure, both short- and long-term treatments significantly delayed symptom onset and mitigated cognitive impairments, including deficits in memory and learning. Similar benefits were observed in transgenic 3xTg-AD mice, where these treatments reduced expression of pro-apoptotic and pro-inflammatory proteins, lowered levels of phosphorylated tau, and decreased amyloid-β plaque burden.

In experimental models of Parkinson's disease, H_2S supplementation using NaHS protected dopaminergic neurons in rats with 6-hydroxydopamine (6-OHDA)-induced pathology [81]. In these studies, NaHS-treated animals exhibited reduced markers of neurotoxicity, including preservation of tyrosine hydroxylase-positive cells and decreased levels of malondialdehyde, nitric oxide, and TNF-α. Interestingly, NaHS also prevented the onset of motor dysfunction in the rotenone-induced model of Parkinson's disease, further supporting its neuroprotective potential.

A recent study has further highlighted the neuroprotective potential of gaseous H_2S in experimental Parkinson's disease [119]. In this model, Parkinsonian pathology was induced by administration of the neurotoxin MPTP, after which animals were treated *via* inhalation of 40 ppm H_2S gas for 8 h daily over a one-week period. This exposure prevented the loss of tyrosine hydroxylase-positive neurons and ameliorated locomotor deficits. In addition, animals treated with gaseous H_2S displayed enhanced expression of antioxidant response elements such as glutamate–cysteine ligase (GCL) and haeme oxygenase-1 (HO-1), alongside reductions in pro-inflammatory and pro-apoptotic markers.

Administration of NaHS has also shown protective effects in models of traumatic brain injury (TBI). In a mouse model where TBI was induced *via* craniotomy and mechanical trephine-induced stress, pre-treatment with NaHS resulted in reduced brain edema, improved locomotor performance, and enhanced cognitive outcomes as assessed by the Morris water maze test [120]. Mechanistically, NaHS pre-treatment attenuated the expression of pro-apoptotic markers, including cleaved caspase-3 and Bcl-2, while preserving autophagy flux in the injured brain.

These examples highlight a general trend: when H_2S is restored towards normal physiological levels in a damaged or diseased brain, multiple aspects of pathology (oxidative stress, inflammation, metabolic failure) tend to improve.

Synthetic organic molecules

Synthetic organic H_2S donors have been developed to achieve more controlled release profiles. Among the various H_2S donors developed to date, GYY4137 (morpholine (4-methoxyphenyl)(morpholino)phosphinodithioate) (Fig. 3) designed and introduced by the Whiteman group remains the most extensively studied slow-releasing donor. This compound undergoes spontaneous hydrolysis under physiological conditions, gradually liberating hydrosulfide (HS^-) ions along with its hydrolytic inactive byproducts [121–123]. GYY4137 exhibits neuroprotective effects in Alzheimer's disease models by promoting the sulfhydration of glycogen synthase kinase 3β (GSK3β), thereby inhibiting tau hyperphosphorylation, a critical step in neurofibrillary tangle formation. In the context of Alzheimer's disease, an H_2S-releasing memantine prodrug has been proposed as a next-generation therapeutic agent, potentially combining NMDAR antagonism with redox

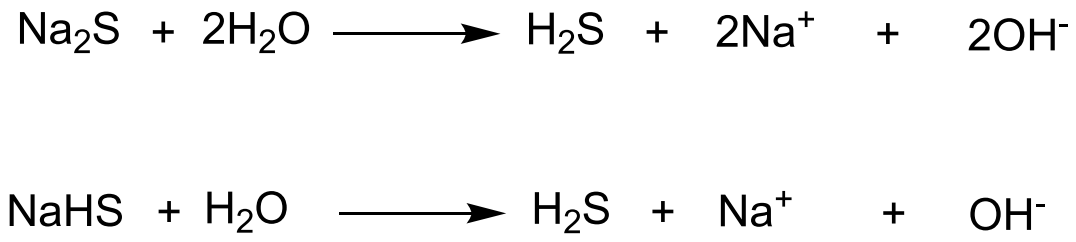

Fig. 2. Chemical structures and hydrolysis-based release mechanism of hydrogen sulfide (H_2S) from disodium sulfide (Na_2S) and sodium hydrogen sulfide (NaHS). Both salts liberate H_2S upon dissolution in aqueous solution through simple hydrolysis.

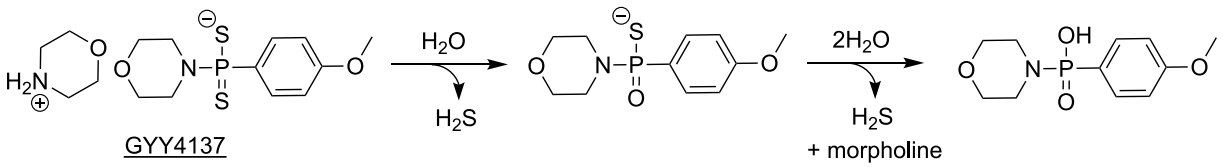

Fig. 3. Chemical structure and proposed H_2S release mechanism of GYY4137 (morpholine (4-methoxyphenyl)(morpholino)phosphinodithioate). GYY4137 is a slow-releasing hydrogen sulfide donor that undergoes stepwise hydrolysis under aqueous conditions, liberating H_2S and morpholine as by-products.

modulation [124]. Similarly, the L-Dopa derivative ACS84, engineered to release H_2S, exerts therapeutic effects in a rat model of 6-hydroxydopamine-induced Parkinson's disease, preserving dopaminergic neurons and improving motor performance [125].

Other classes of H_2S-releasing compounds, although primarily investigated outside of neurological contexts, include hybrid drugs in which conventional therapeutics have been chemically conjugated to H_2S-donating moieties. Examples include NSAIDs such as H_2S–diclofenac (ACS-15) and nitrate-based hybrids, designed to integrate anti-inflammatory effects with controlled H_2S delivery.

Targeted H_2S delivery

The development of organelle-targeted therapeutics has opened new avenues for spatially precise drug delivery, with mitochondria emerging as a particularly compelling target for H_2S-based interventions due to their pivotal role in cellular redox regulation and vulnerability in disease contexts.

Mitochondrial injury is a central event in both acute ischemic episodes (e.g. stroke) and chronic neurodegenerative conditions [126]. In ischemia-reperfusion (I/R) injuries, the abrupt restoration of blood flow to oxygen-deprived tissue sets off a surge of redox-active species (e.g., superoxide ($O_2^{\cdot-}$) and peroxynitrite ($ONOO^{\cdot-}$) anion radicals, hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\cdot}OH$), epoxyallylic peroxyl radicals ($OLOO^{\cdot}$)) that compromise mitochondrial integrity, leading to the initiation of cell death programs [3]. This cascade resembles the degenerative processes seen in disorders such as Parkinson's and Huntington's disease, where proteostasis collapse and mitochondrial distress accelerate neuronal loss. In both contexts, damaged mitochondria act as amplifiers of cellular stress, contributing to secondary injury and long-term functional decline [126]. Among the signalling molecules involved, hydrogen sulfide (H_2S) presents a paradox: while protective at low levels, it becomes detrimental when dysregulated, particularly within mitochondria [127]. These mechanistic overlaps underscore the mitochondria as a key therapeutic target in both acute and chronic neuropathology [128–130]. Insights from ischemia/reperfusion models where modulating H_2S levels can mitigate mitochondrial damage have prompted the development of strategies that precisely deliver H_2S to subcellular compartments [131]. Such targeting is achieved by conjugating H_2S-releasing chemotypes ("warheads") to carrier groups (e.g., lipophilic cation) that accumulate selectively in the organelle. This strategy enables precise dosing, enhances therapeutic potency, and limits off-target effects.

The most widely explored strategy for delivering therapeutic cargo to mitochondria involves the use of lipophilic organic molecules bearing a positively charged moiety that enables selective, membrane potential ($\Delta\Psi m$)-dependent accumulation within the mitochondrial matrix. Among these, the triphenylphosphonium (TPP^+) cation has become the most frequently used mitochondrial targeting scaffold, due to its strong cationic-based uptake into mitochondria driven by the negative membrane potential across the inner mitochondrial membrane [132].

The first mitochondria-targeted H_2S donor employing this strategy AP39 [(10-oxo-10-(4-(3-thioxo-3H-1,2-dithiol-5yl)phenoxy)decyl) triphenylphosphonium bromide] (Fig. 4), was developed by the Whiteman group [133] and it consists of a TPP^+ moiety linked *via* a ten-carbon aliphatic chain to ADT-OH (5-(4-hydroxyphenyl)-3H-1,2-dithiole-3--thione), a natural garlic-derived H_2S-releasing chemotype. This design enables spatially restricted H_2S release within mitochondria, enhancing cytoprotective efficacy while limiting systemic toxicity [134].

In the context of neurotherapeutics, AP39 remains the most extensively studied mitochondria-targeted H_2S donor. In a seminal study using a murine model of cardiac arrest followed by cardiopulmonary resuscitation (CPR), AP39 administered 2 min prior to reperfusion significantly improved neurological outcomes, preserved mitochondrial function, and enhanced post-intervention survival [135]. Recent independent studies further support the neuroprotective potential of AP39 in models of brain ischemia and hypoxia-reperfusion injury. In a rat model of middle cerebral artery occlusion (MCAO), a seven-day pretreatment with AP39 conferred significant ischemic tolerance, reducing infarct size and improving outcomes [136]. Separately, in a neonatal mouse model of hypoxia-reperfusion injury, AP39 administered intranasally in a liposomal formulation 24 h post-injury attenuated neuronal damage and improved histological parameters [137]. A recent study investigating glutamate-induced excitotoxicity following cerebral ischemia in rats (MCAO model) demonstrated that administration of AP39, given 10 min after reperfusion, resulted in a dose-dependent reduction of infarct

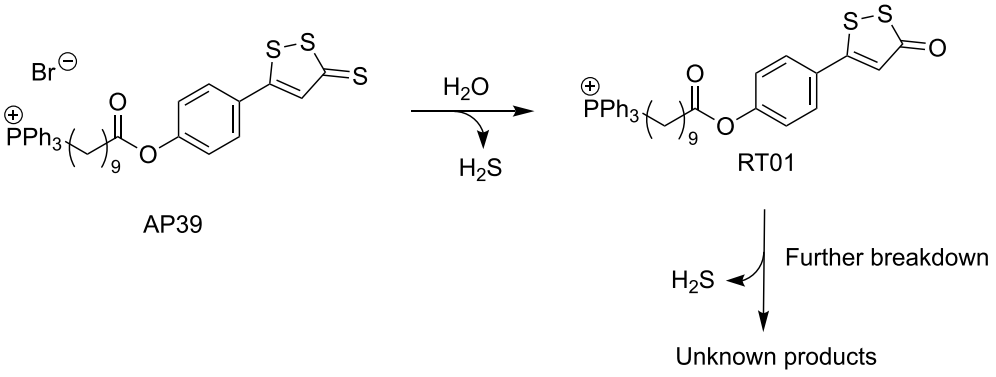

Fig. 4. Chemical structure of the mitochondria-targeted H_2S donor AP39 ([(10-oxo-10-(4-(3-thioxo-3H-1,2-dithiol-5-yl)phenoxy)decyl)triphenylphosphonium bromide]) and its proposed mechanism of hydrogen sulfide release under aqueous conditions. Hydrolysis of the dithiolthione moiety generates H_2S, yielding the intermediate RT01, which undergoes further decomposition to release additional H_2S and form unidentified breakdown products.

volume and neurological impairment [138]. The study further reported that AP39 modulated key components of glutamate homeostasis by upregulating the expression of the excitatory amino acid transporter GLT-1 and downregulating the vesicular glutamate transporter VGLUT1. These effects contributed to decreased glutamate accumulation in the motor cortex and mitigated excitotoxic neuronal damage during post-ischemic recovery.

AP39 has also been investigated in the context of neurodegenerative diseases, particularly Alzheimer's disease (AD) and Parkinson's disease (PD). In primary neuronal cultures derived from APP/PS1 transgenic mice, low concentrations of AP39 were shown to enhance mitochondrial bioenergetics and improve cell viability [139]. Notably, in the same study, six weeks of AP39 administration led to a significant improvement in spatial memory and a marked reduction in cerebral amyloid-β (Aβ) plaque deposition in APP/PS1 mice. A consistent finding across these studies is that AP39 dampens oxidative stress, suppresses reactive oxygen species (ROS) accumulation, and inhibits caspase-1 and caspase-3 activation, mechanistic hallmarks linked to its observed neuroprotective effects.

A recently developed mitochondria-targeted nanomotor H_2S donor (PCM), composed of L-cysteine as the H_2S-releasing moiety, polyethylene glycol (PEG), and a positively charged methacryloyloxyethyl phosphorylcholine component, was reported to achieve efficient blood brain barrier penetration, CBS-dependent H_2S release, and selective mitochondrial localisation in neuronal cells [140]. In the MPTP-induced mouse model of Parkinson's disease, PCM treatment led to behavioural improvements, supporting its potential as a neuroprotective agent [140].

An alternative approach for mitochondrial H_2S delivery involves the use of synthetic peptides that direct the attached donor compound specifically to mitochondria [141–143]. A recent study reported the design of a hybrid molecule, JC112, which combines a naturally occurring tripeptide, L-alanyl-L-cystinyl-L-glutamine (ACQ), with a dithiolethione-based H_2S-releasing moiety ACS48 [144]. In cultured HT22 hippocampal neurons subjected to glutamate-induced excitotoxic stress, JC112 significantly reduced calcium-dependent ROS production, limited the recruitment of apoptosis-inducing factors, and mitigated overall cellular injury, suggesting protective effects in models of neuronal oxidative damage.

Together, these advancements highlight the growing sophistication of mitochondria-targeted H_2S delivery strategies and their therapeutic relevance across a spectrum of acute and chronic neuropathologies, setting the stage for broader discussions on emerging delivery platforms, systemic modulation, and translational potential in neurodegenerative disease.

Natural product (Nation donors diallyl disulfide garlic)

Among natural products with emerging neuroprotective potential such as garlic-derived organosulfur compounds diallyl disulfide (DADS) and allicin [145] (Fig. 5), ergothioneine (Fig. 6) has attracted growing attention for its unique antioxidant properties and possible role in mitigating neurodegenerative disease [146]. Ergothioneine ((2S)-3-(2-thioxo-2,3-dihydro-1H-imidazole-4-yl)-2-(trimethylammonio)propanoate; ERG) is a naturally occurring thiol containing amino acid derived from histidine, first isolated in early 19th century from *Claviceps purpurea*, a strain of ergot fungi [147]. Though mammals cannot synthesize it, ergothioneine accumulates in tissues *via* the organic cation transporter OCTN1 highly expressed in animal tissue, suggesting a conserved physiological role. Historically regarded as a dietary antioxidant sourced primarily from mushrooms, fermented beans and red meat, its redox-active properties have attracted growing attention in the context of cellular stress adaptation [148,149]. Recent research has identified ergothioneine as a potent cytoprotective molecule, capable of scavenging reactive oxygen species and mitigating oxidative stress, key processes implicated in neurodegeneration. Its molecular structure containing sulphur atom that exists in the tautomeric equilibrium between thione and thiolate form allows interaction with sulfur-based redox pathways, including potential crosstalk with endogenous hydrogen sulfide (H_2S) signalling [149]. Two recent parallel studies have provided mechanistic insights demonstrating that H_2S-synthesizing enzymes (CSE and 3-MST) are key targets mediating the beneficial effects of ergothioneine-derived H_2S on cellular bioenergetic status *in vivo* [150,151]. Both studies point to ergothioneine acting as a H_2S-related modulator of mitochondrial enzymes, improving bioenergetic capacity, exercise performance and contributing to lifespan. Emerging evidence suggests that decreased ergothioneine levels correlate with cognitive and functional memory decline and neurodegenerative pathologies such as Alzheimer's and Parkinson's disease [152–154].

A recent investigation demonstrated that ergothioneine (ERG), when administered intranasally, enhanced short-term memory performance in a mouse model of multiple system atrophy (MSA) [155]. In this study, ERG treatment was shown to promote an increase in monomeric α-synuclein expression while concurrently decreasing dimeric α-synuclein levels, ultimately leading to an overall reduction in α-synuclein oligomerisation. These findings indicate that ERG may facilitate the clearance of pathogenic α-synuclein aggregates, supporting its potential as a therapeutic candidate for individuals with MSA. These findings have fuelled interest in its therapeutic potential as a dietary supplement or adjunctive agent aimed at restoring redox balance and protecting mitochondrial function in vulnerable neuronal populations.

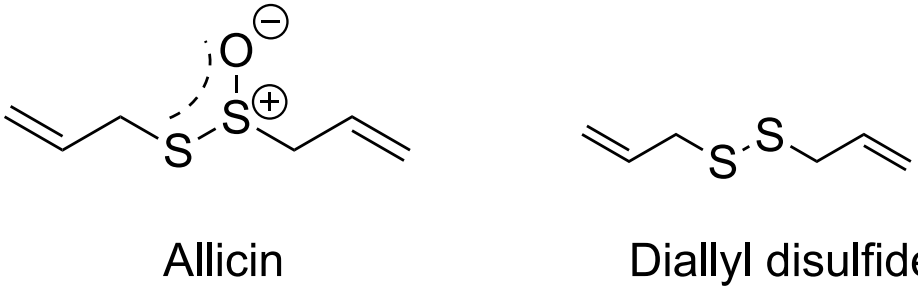

Fig. 5. Chemical structures of naturally occurring organosulfur compounds with hydrogen sulfide (H_2S)-releasing properties. Shown are allicin (S-(prop-2-en-1-yl) prop-2-ene-1-sulfinothioate) and diallyl disulfide (3-[(prop-2-en-1-yl)disulfanyl]prop-1-ene), both derived from Allium species (e.g., garlic) and known to liberate H_2S through thiol-dependent reactions in biological systems.

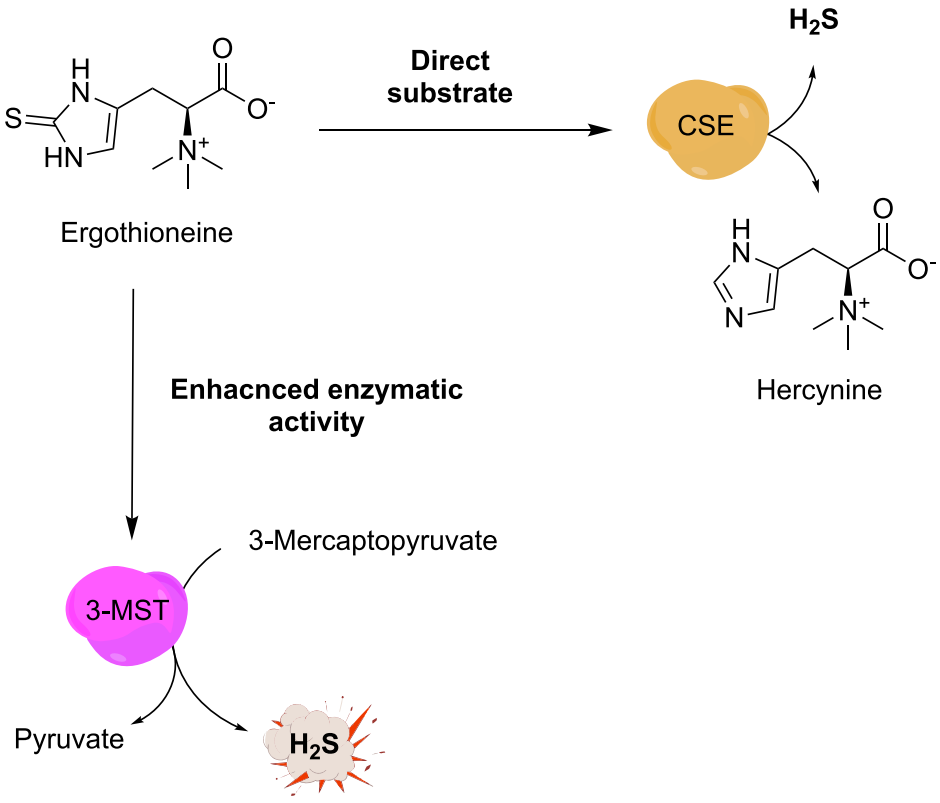

Fig. 6. Mechanism of ergothioneine-mediated H_2S production *via* CSE and 3-MST pathways. Ergothioneine serves as an alternative substrate for cystathionine γ-lyase (CSE), enhancing hydrogen sulfide (H_2S) generation and promoting widespread protein persulfidation, including activation of cytosolic glycerol-3-phosphate dehydrogenase (cGPDH), which elevates NAD^+ levels. Additionally, ergothioneine directly activates mitochondrial 3-mercaptopyruvate sulfurtransferase (3-MST), augmenting mitochondrial respiration and improving exercise performance.

Although ergothioneine has been suggested to act, in part, as a sulphur carrier and antioxidant, its pharmacological effects likely involve broader mechanisms. Its clinical translation remains challenging due to its dietary ubiquity and the associated difficulty in controlling background levels in clinical trials, despite its excellent bioavailability *via* the OCTN1 transporter.

Alternative strategies

In addition to classical H_2S donors, emerging alternative delivery strategies are being explored to improve the precision, kinetics, and targeting of sulfide-based therapeutics. Among these, metal–organic frameworks (MOFs) have attracted significant attention due to their structural tunability, high loading capacity, and ability to provide controlled, sustained release. MOFs are versatile porous coordination polymers with high surface area, tuneable pore environments, and modular structures, making them promising platforms for gasotransmitter storage and delivery, including H_2S [156]. Within MOFs, H_2S coordinates to open-metal sites and is released upon moisture exposure as water molecules displace bound H_2S, enabling controlled, sustained delivery, particularly suited for transdermal applications [157]. For central nervous system (CNS) targeting, functionalising MOFs with blood–brain barrier (BBB)-penetrating ligands (e.g., transferrin, RVG peptides) or embedding them into liposomal or polymeric hybrid carriers can further enhance delivery efficiency [158,159]. MOF-based H_2S systems thus offer a rational, tuneable approach for overcoming pharmacokinetic limitations of conventional donors, with potential applications ranging from wound healing to targeted therapies for neurodegenerative diseases.

Preclinical and clinical evidence in neurological models

As discussed in previous sections, a robust body of animal and cell-based evidence further highlights H_2S's neuroprotective effects. In Alzheimer's models, chronic administration of NaHS or GYY4137 improved cognition and reduced amyloid pathology. In models of ischemic stroke or traumatic brain injury, H_2S donors decreased infarct size, edema and neuronal apoptosis. Neuropathic pain models (e.g. chemotherapy-induced pain) have shown amelioration by H_2S donors. Parkinsonian models (MPTP or 6-OHDA-lesioned rodents) exhibit less dopaminergic degeneration and improved motor function when treated with H_2S-releasing compounds. Mechanistic studies in these models consistently report reduced oxidative markers, suppressed inflammation (NF-κB, cytokines) and upregulated survival signals (BDNF, PI3K/Akt) under H_2S treatment. At the cellular level, neurons exposed to oxygen-glucose deprivation or amyloid-β show greater survival with H_2S supplementation, *via* restored mitochondrial function and antioxidant enzyme activity. Microglial and astrocyte responses are also modulated towards a less inflammatory phenotype by H_2S.

Clinical observations. Direct clinical data on H_2S modulation in neurological disease are limited. No H_2S-specific therapies have yet reached advanced clinical trials for brain disorders. However, associative evidence hints at clinical relevance. For example, Down syndrome patients (trisomy 21) excrete unusually high thiosulfate levels, reflecting elevated CBS activity and H_2S production. Importantly, many preclinical successes in H_2S-based neuroprotection have yet to be tested in humans. While earlier H_2S-releasing NSAIDs such as ATB-346 advanced to clinical trials, subsequent reports of hepatotoxicity have halted further development [160]. Nevertheless, interest in H_2S-based therapeutics

continues, with several companies (e.g., MitoRx Therapeutics, Oxford) exploring novel H_2S modulators for clinical use. An ongoing study with a strong bioanalytical focus is examining the quantification of H_2S in human biological samples, investigating whether alterations in circulating H_2S levels could serve as a biomarker for Alzheimer's disease and age-related cognitive decline (ClinicalTrials.gov ID: NCT05060848). Thus, while translational evidence is still emerging, the preclinical literature strongly supports further clinical exploration of H_2S and H_2S-based therapeutics for neurological therapeutics.

Pharmacokinetics, safety and dosing considerations

The therapeutic application of H_2S demands careful attention to its unique pharmacological profile. Under physiological conditions, endogenous H_2S is maintained at very low (nanomolar to low micromolar) concentrations and undergoes rapid metabolism to thiosulfate and sulphate. By contrast, exogenous administration *via* gaseous H_2S or fast-releasing donor compounds can lead to sharp transient peaks, posing toxicity risks. At high doses, H_2S can acutely inhibit cytochrome *c* oxidase (Complex IV), an effect that may be condition-dependent and even beneficial, for example, during cardiac ischemia-reperfusion and potentially in stroke, where rapid H_2S release from MitoPerSulf, a novel mitochondria-targeted donor [161], transiently inhibits Complex IV, which disrupts reverse electron transport (RET)-driven ROS production to mitigate IR-related damage. Conversely, uncontrolled surges of H_2S can cause respiratory collapse, highlighting the importance of slow-releasing donors for safe *in vivo* application [162]. For instance, it was demonstrated that GYY4137 releases H_2S in a pH-dependent manner, with peak levels observed in phosphate buffer (pH 7.4) at around 15 min, followed by a plateau lasting approximately 75 min [162]. However, despite its widespread use in a variety of experimental setups to date, the actual concentration of GYY4137 administered as well as its pharmacokinetic profile, particularly tissue distribution has not been adequately assessed in biological contexts, especially when delivered *via* ad libitum drinking water or intraperitoneal (i.p.) injection. A significant limitation in the field remains the lack of comprehensive studies that addresses drug's absorption, distribution, metabolism, excretion, and pharmacokinetics (ADME/PK studies) for most H_2S donors. It is unclear whether commonly used compounds such as NaHS or GYY4137 reach pharmacologically relevant concentrations in target tissues such as the brain. The absence of such data complicates the interpretation of therapeutic potential, especially in the context of neurodegeneration where blood–brain barrier permeability is critical. Bioavailability is influenced not only by pharmacokinetics but also by factors such as tissue perfusion and endogenous enzymatic turnover. Interactions with other gasotransmitters further complicate the picture: H_2S can inhibit phosphodiesterases to elevate cGMP [111] or react with nitric oxide and its precursors or metabolites (e.g., nitrite and *S*-nitrosothiol) to form reactive intermediates such as HSNO and nitroxyl (HNO) [114,163,164]. Future studies must place greater emphasis on rigorous chemical validation, donor specificity, and translational pharmacology to accurately determine the role of H_2S-based therapeutics.

Safety data in humans remain limited and derive mostly from non-neurological contexts, where low micromolar blood concentrations appear to be well tolerated, though long-term effects remain unclear. Animal studies show wide variation in dosing regimens; for example, mouse models of Alzheimer's disease typically used GYY4137 at 100–200 μmol/kg intraperitoneally, yielding cognitive improvements [165,166]. Clinical translation will require optimization of dosing schedules. It is important to acknowledge that many widely used H_2S donors, including GYY4137 and NaHS, are often applied at supra-physiological concentrations, frequently in the high micromolar to millimolar range raising questions about the translational relevance of observed effects [167,168]. The actual intracellular or tissue concentrations of H_2S generated under such conditions remain largely undefined due to the lack of rigorous pharmacokinetic (PK) and biodistribution data. As such, interpretations of their bioactivity require careful contextualization, and further studies with precise dosing and quantitative tracking are warranted. In contrast, mitochondria-targeted donors such as AP39 and MitoPerSulf demonstrate biological efficacy at nanomolar concentrations in multiple *in vitro* and *in vivo* models (e.g., worms, fish, mammalian cells), suggesting a more physiologically relevant and potentially translatable approach. These tools exemplify a new generation of H_2S donors with improved targeting and dosing profiles, aligning better with therapeutic feasibility. Moreover, pharmacological inhibitors of endogenous H_2S synthesis (e.g., PAG, AOAA) are non-specific and can induce homocysteine accumulation, which is why current therapeutic efforts focus on donor compounds. In summary, although H_2S diffuses rapidly and has a short biological half-life, advances in donor chemistry and careful dosing strategies offer the potential to achieve neuroprotective concentrations without systemic toxicity.

Future directions and emerging technologies

Future research is poised to advance H_2S-based neurotherapeutics on multiple fronts. Chemical innovation will produce donors with tuneable kinetics and targeting: for example, enzyme-triggered donors that release H_2S only in diseased tissue, or light-activated donors for precise spatiotemporal control. Nanotechnology and biomaterials could enable safe H_2S delivery to the brain (e.g. H_2S-loaded nanoparticles or hydrogels that cross the blood–brain barrier). Beyond direct H_2S storage, metal–organic frameworks (MOFs) can also be designed to encapsulate H_2S-releasing compounds such as thiol-based donors, dithiolone derivatives, or metal-bound persulfides within their porous architecture, allowing controlled, sustained release profiles responsive to local physiological cues such as acidic pH, elevated glutathione concentrations, or reactive oxygen species. Imaging advances will allow tracking of H_2S *in vivo*: new fluorescent probes and PET tracers are being developed to measure endogenous and donor-derived sulfide dynamics in real time. On the biological side, genetic tools (CRISPR/Cas9) can create refined models with neuron-specific CBS/CSE knockouts or mutants, clarifying H_2S's roles. The interplay between microbiome-derived H_2S and the brain (*via* gut–brain axis) is another intriguing area. Mechanistically, much remains to be learned about H_2S's epigenetic effects and interaction with other cellular pathways. For instance, how does H_2S influence histone acetylation or DNA methylation beyond neurons? Can we exploit H_2S-mediated miRNA circuits (e.g. deliver miR-125b inhibitors) to adjust H_2S levels? Systems biology and network analyses may elucidate how H_2S integrates with NO or with recently discovered endogenous pathway responsible for cyanide (CN^-) production [169,170] in neural signalling. Clinically, early-phase trials might explore repurposing H_2S-donating drugs for neuroprotection or as adjuvants in stroke/neurodegeneration. In sum, the convergence of novel chemistries, molecular biology and bioengineering will expand our ability to modulate H_2S safely and effectively in the brain.

Conclusion

Hydrogen sulfide has emerged from its evolutionary legacy as a primordial gas to a versatile neuromodulator with far-reaching therapeutic potential. As reviewed here, H_2S participates in the regulation of redox balance, mitochondrial function, synaptic plasticity, and neuroinflammation, all processes central to neurodegenerative disorders and acute neural injuries. Preclinical evidence strongly supports the idea that carefully restoring H_2S homeostasis can confer neuroprotection, and new delivery technologies, including organelle-targeted donors and natural compounds like ergothioneine, are expanding the therapeutic toolkit. Although clinical translation remains in its infancy, advances in donor chemistry, delivery platforms, and mechanistic understanding

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Is ergothioneine the longevity vitamin?

(Longevity Nutrients part I)

What is ergothioneine and why is it called "the longevity vitamin" by top scientists? Ergothioneine is an amino acid found mainly in mushrooms as a dietary source, but not many other sources contain substantial amounts. It is called the longevity vitamin by reputable researchers, including RB Beelman et al., who noted in the Journal of Nutritional Sciences (Cambridge) "***we believe that ergothioneine is a 'longevity vitamin' that is limited in the American diet"***[1] These researchers posit that "limited intake of ergothioneine in the diet may compromise long-term health and life expectancy", and therefore should be considered a conditionally essential amino acid/vitamin.

When it comes to support for longevity, there are several things that we know. Anything that **combats cellular damage** is helpful because the preservation of cell integrity keeps all biological processes in homeostasis and functioning as they should. Anything that **aids in the process of cellular repair, function or replication** (such as the basic stem cells that allow tissue regeneration) should be considered as part of a longevity protocol. There are many nutrients that support healthy aging cellular function, repair and regeneration. There are a lot of environmental influences that prematurely age cells and cause dysfunction. Avoiding damage to the **telomeres** that have limited reproductive powers and that are associated with an optimal aging process is critical for any longevity protocol. **Antioxidants** that counteract damaging free radicals (oxidation) enhance the defenses of all cells (such as the mitochondria) and are major players for any longevity protocol.

Shortened telomeres are associated with aging, and researchers call **ergothioneine** a "novel antioxidant", associated with **specifically targeting** the free radicals that damage the energy producing mitochondria and **telomeres.** Telomere length had been tested under oxidative stress conditions, and ergothioneine was correlated with longer telomeres[2]

Shiitake, maitake and oyster mushroom are particularly high in ergothioneine and are considered a good food and supplement source for this aging support nutrient. A cross-sectional study involving over 600 participants reported on the potential role of mushrooms and their bioactive compounds to contribute to neuronal and cognitive health. Participants who consumed more than two portions of mushrooms a week had the best association with cognitive/neuronal support and lack of dysfunction[3]

Dan Murphy DC lectures extensively on important keys to longevity. Dr. Murphy specifically notes longevity expert Bruce Ames PhD, the famous biochemist who developed the Triage Theory on Longevity. Dr. Ames explains that that there are proteins needed for immediate survival and reproduction (survival proteins) and proteins that function in long-term health (longevity proteins) and proposes that any modest deficiency in any of the nutrients or co-factors needed for survival proteins will sacrifice nutrients or co-factors that are needed for optimal function of the longevity proteins needed for long term healthy aging. And so, many nutrients play a double role in survival and longevity and **draining valuable resource nutrients for survival can result in sub-optimal unhealthy aging processes.**

Dr. Ames lists several of these nutrients at the top of his list, such as **ergothioneine.** Other evidence led Dr. Ames to classify **taurine** as a conditional vitamin, stating that other conditional vitamins should include **lipoic acid, co-q-10, and carnitine**. Dr. Ames explains that aside from essential vitamins and minerals needed for survival, there are dietary biochemicals that are putative longevity nutrients, and that list includes: **pyrroloquinoline quinone (PQQ) lutein, zeaxanthin, lycopene** and **astaxanthin.**[4] While ergothioneine appears to be a powerhouse longevity nutrient, it is not the only one, and synergy with other longevity nutrients is recommended for optimal healthy aging. In the next issue, we'll look closer at some of these other longevity nutrients and their role in keeping us at our best!

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Ergothioneine:
A Stress Vitamin with Antiaging, Vascular, and Neuroprotective Roles?

Antioxidants and Redox Signaling
June 2022; Vol. 36; No. 16–18; pp. 1306-1317

Bindu D. Paul, from Johns Hopkins University School of Medicine. This study cites 138 references.

Ergothioneine (ET) is an unusual sulfur-containing amino acid acquired predominantly from food.

Its depletion is associated with deleterious consequences in response to stress stimuli in cell culture models, prompting us to classify it as a vitamin in 2010.

ET possesses antioxidant and anti-inflammatory properties that confer cyto-protection.

ET crosses the blood–brain barrier and has been reported to have beneficial effects in the brain.

This study discusses the cytoprotective and neuroprotective properties of ET, which may be harnessed for combating neurodegeneration and decline during aging.

ET is essential for optimal physiological functioning and maintenance of health span.

"As ET is a stable antioxidant with anti-inflammatory properties, whose levels decline during aging, supplementing ET in the diet or consuming an ET-rich diet may prove beneficial."

Mammals cannot synthesize ET and acquire it predominantly from food.

"Its depletion is linked to impaired stress responses and toxicity, prompting us to designate it as a vitamin."

ET is a colorless, and odorless compound that is readily soluble in water.

"An important feature of ET is its thermostability (it does not decompose upon cooking), a feature desirable for its use in culinary preparations."

"Another characteristic of ET, that contributes to its cytoprotective properties, is its capacity to absorb ultraviolet (UV) light."

ET prevents DNA damage induced by UV irradiation in a dose-dependent manner.

"Mammalian skin is particularly vulnerable to UV damage, which may induce sunburn, immunosuppression, skin aging, and carcinogenesis, in addition to other damage. ET accumulates in skin cells and not only prevents oxidative damage but also facilitates DNA repair in UV-irradiated cells."

"The biosynthetic pathway of ET involves a series of reactions involving histidine and cysteine." **[Really Important]**

"ET is concentrated in cells and tissues that are frequently exposed to oxidative stress, such as blood, liver, eye lens, and seminal fluid, and its concentration approaches high micromolar or millimolar levels in some of these tissues."

"It appears that ET is a stress vitamin that comes into play during adverse conditions or under duress."

"Foods such as mushrooms are a rich source of ET, with certain species, including king oyster, enoki, and shiitake mushrooms, having higher levels."

"Plants obtain ET from the soil, presumably through fungi present in their vicinity." **[Important]**

Differences in abundance of fungi in soil may also give rise to variations in the ET content of crops. It has been reported that excessive tillage of the soil can deplete ET levels in crops.

Levels of ET decrease as a function of aging in blood.

ET content was positively correlated with gait speed in middle-aged adults

In a study analyzing mortality and coronary artery disease, ET was identified as the metabolite most significantly associated with lower morbidity and mortality, being associated with a lower risk of CAD.
[Smith E, Ottosson F, Hellstrand S, Ericson U, Orho-Melander M, Fernandez C, and Melander O. Ergothioneine is associated with reduced mortality and decrease risk of cardiovascular disease. Heart 106: 691–697, 2020.]

- "This study also proposed ET as a biomarker for a healthy diet and low cardiometabolic risk."

"Consumption of an ET-based nutritional supplement has also been reported to improve joint range of motion and reduction of chronic pain."
[Benson KF, Ager DM, Landes B, Aruoma OI, and Jensen GS. Improvement of joint range of motion (ROM) and reduction of chronic pain after consumption of an ergothioneine-containing nutritional supplement. Prev Med 54(Suppl): S83–S89, 2012.

"Decrease in ET in the whole blood of human subjects has identified it as a potential marker of frailty."
[Kameda M, Teruya T, Yanagida M, and Kondoh H. Frailty markers comprise blood metabolites involved in antioxidation, cognition, and mobility. Proc Natl Acad Sci USA 117: 9483–9489, 2020.]

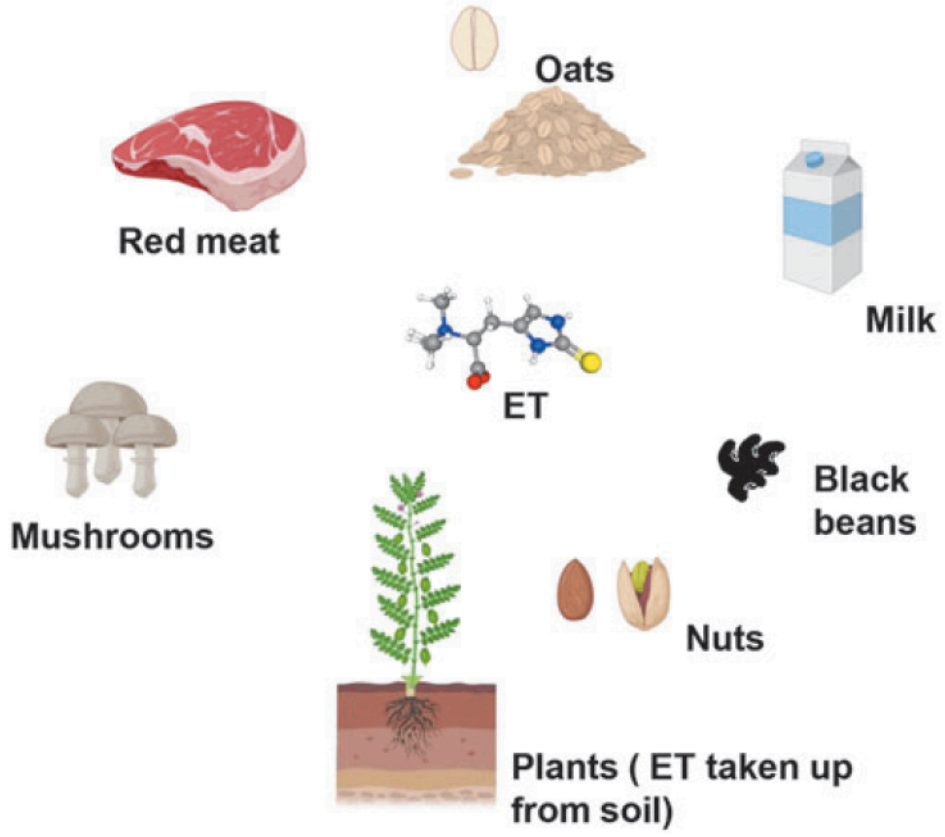


FIG. 3. Dietary sources of ET. ET (depicted as a ball and stick model) is present in a variety of foodstuffs. It is enriched in mushrooms and fungi in the soil, which is taken up by plants. ET is also enriched in red meat, black beans, nuts, milk, and oats.

High levels of ET are present in red blood cells.

ET is present in the mitochondria, which produce reactive oxygen species during respiration.

"ET mitigates deleterious effects of several free radicals, including reactive oxygen and reactive nitrogen species."

"ET protects against the deleterious effects of hydroxyl radicals, peroxynitrite, hypochlorous acid, and singlet oxygen."

ET is a better scavenger of oxygen ROS than GSH.

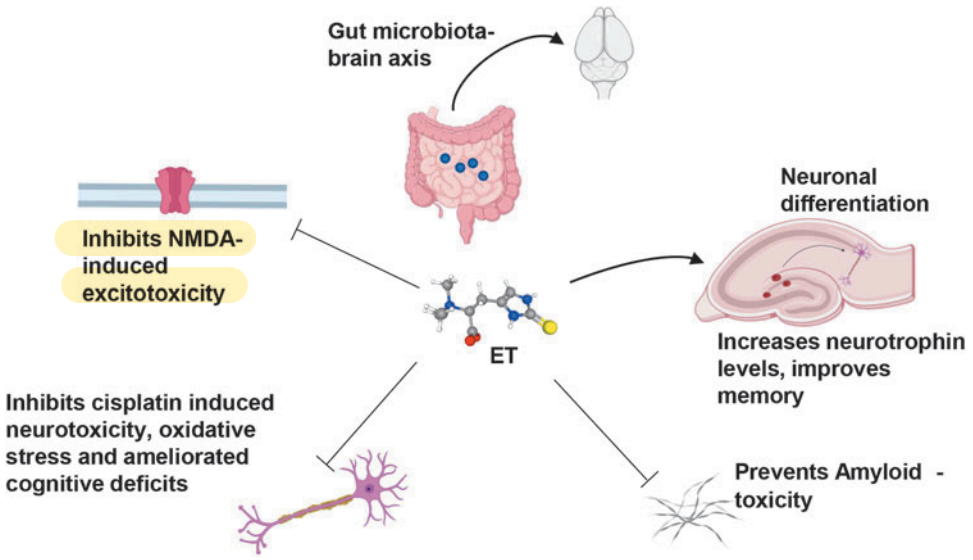
ET can chelate Cu2+, accounting for its ability to counteract Cu2+-mediated DNA damage.

ET reduces proinflammatory cytokines.

ET is enriched in the cerebellum as its transporter is abundant in other brain regions.

"Exogenous administration of ET revealed that ET is widely distributed in the brain in regions such as the cerebellum, striatum, medulla and pons, midbrain, hippocampus, hypothalamus, and cortex and the concentration correlates with the expression of its transporter, indicating its ability to cross the blood–brain barrier." **[Key Point]**

"ET exerts potent neuroprotective effects in the brain."



ET enhances cognition through inhibition of oxidative stress and restoration of acetylcholinesterase (AChE) activity in neuronal cells.

"Metabolomic analysis of Parkinson's disease (PD), the second most common neurodegenerative disease after Alzheimer's disease (AD), revealed a significant decline in ET levels, suggesting a decreased ability in antioxidant defenses."

Decrease in ET levels has been observed in vascular dementia and dementia.

Oral delivery of ET significantly prevented major depressive disorder (MDD)-like social avoidance and sleep abnormalities.

ET participates in the gut–brain axis via the microbiota that produce it.

"Blood ET levels have been found to decrease significantly beyond 60 years of age."

"The population exhibiting mild cognitive impairment had significantly lower plasma ET levels compared with age-matched controls, indicating that ET deficiency could contribute to aging."
[Cheah IK, Feng L, Tang RMY, Lim KHC, and Halliwell B. Ergothioneine levels in an elderly population decrease with age and incidence of cognitive decline; a risk factor for neurodegeneration? Biochem Biophys Res Commun 478: 162–167, 2016.]

"Due to its cytoprotective properties and UV filtering capability, ET is one of the top ingredients used in antiaging creams."

"ET is also protective in the eye, and formation of cataract is associated with a decline in ET levels."

"Endothelial dysfunction is a major cause of cardiovascular disease with links to oxidative and nitrosative stress. ET, with its proven in vitro antioxidant functions, has also been reported to be imported by endothelial cells and reduce markers of oxidative damage."

"ET is an unusual antioxidant, in that it is exceptionally stable and does not auto-oxidize at physiological pH and is not destroyed upon heating."

"ET is water soluble and neutralizes several reactive oxygen and nitrogen species."

"Accumulating evidence suggests that ET is endowed with cytoprotective signaling functions in addition to its antioxidant and anti-inflammatory role in cells. It has also been posited that ET is an adaptive antioxidant, with cells deliberately accumulating ET in times of stress."

"ET has not been associated with any toxic or adverse effects, support its use in therapies against a wide range of diseases and conditions, ranging from cardiovascular diseases to aging and neurodegeneration."

"ET is a rare antioxidant–cytoprotectant capable of crossing the blood–brain barrier, a feature that is necessary to treat neurodegenerative disorders where oxidative stress plays a central role in disease progression."

"It is present in mitochondria, which is a feature that can be harnessed in therapies for disorders involving mitochondrial dysfunction such as PD, where this molecule is significantly depleted."

"Because of its antioxidant and anti-inflammatory properties, the use of ET as a therapeutic in the treatment of COVID-19 patients has been proposed."
[Cheah IK and Halliwell B. Could ergothioneine aid in the treatment of coronavirus patients? Antioxidants (Basel) 9: 595, 2020.]

- "A feature of COVID-19 is dysregulated redox balance, which is also observed in patients exhibiting chronic fatigue (COVID-19 long haulers) long after the infection was cleared."

"ET fits the definition of a vitamin." **[Key Point]**

Diet-Derived Antioxidants:
The Special Case of Ergothioneine [ET]

Annual Reviews of Food and Science Technology
March 27, 2023; Vol. 14; pp. 323-345

DEFINITIONS OF TERMS RELATING TO REDOX BIOLOGY

Reactive oxygen species (ROS) is a collective term for species that are derived from O2 and that are more reactive than O2.

The term includes not only the superoxide radical anion (O2•−), hydroxyl radical (•OH), and some other oxygen radicals but also some nonradical derivatives of O2, such as hydrogen peroxide (H2O2), hypochlorous acid (HOCl), and peroxynitrite/peroxynitrous acid (ONOO−/ONOOH).

Hence, all oxygen radicals are ROS, but not all ROS are radical species (the latter being defined as a species with one or more unpaired electrons).

Reactive is a relative term; O2•− and H2O2 are selective in their reactions with biological molecules, leaving most of them unscathed, whereas •OH attacks everything.

An antioxidant is often defined as a scavenger of ROS, whereas food chemists often define it as an inhibitor of lipid peroxidation.

In a broader definition, an antioxidant is any substance that delays, prevents, or removes oxidative damage to a target molecule: "a substance that reacts with an oxidant to regulate its reactions with other targets, thus influencing redox-dependent biological signaling pathways and/or oxidative damage."

Oxidative damage is the biomolecular damage caused by the attack of ROS upon the constituents of living organisms (lipids, protein, DNA, RNA, carbohydrates).

Increased levels of oxidative damage can result from not only increased ROS production but also decreased repair or removal processes, e.g., failure to clear oxidized proteins and repair oxidized DNA sufficiently rapidly; both of these failures can occur in certain diseases.

Ergothioneine (ET) "has been declared safe for human consumption as a dietary supplement, even in pregnant women and children [2017], by the European Commission EFSA panel, and the US Food and Drug Administration in 2018 designated it as GRAS (generally recognized as safe) [2021]."

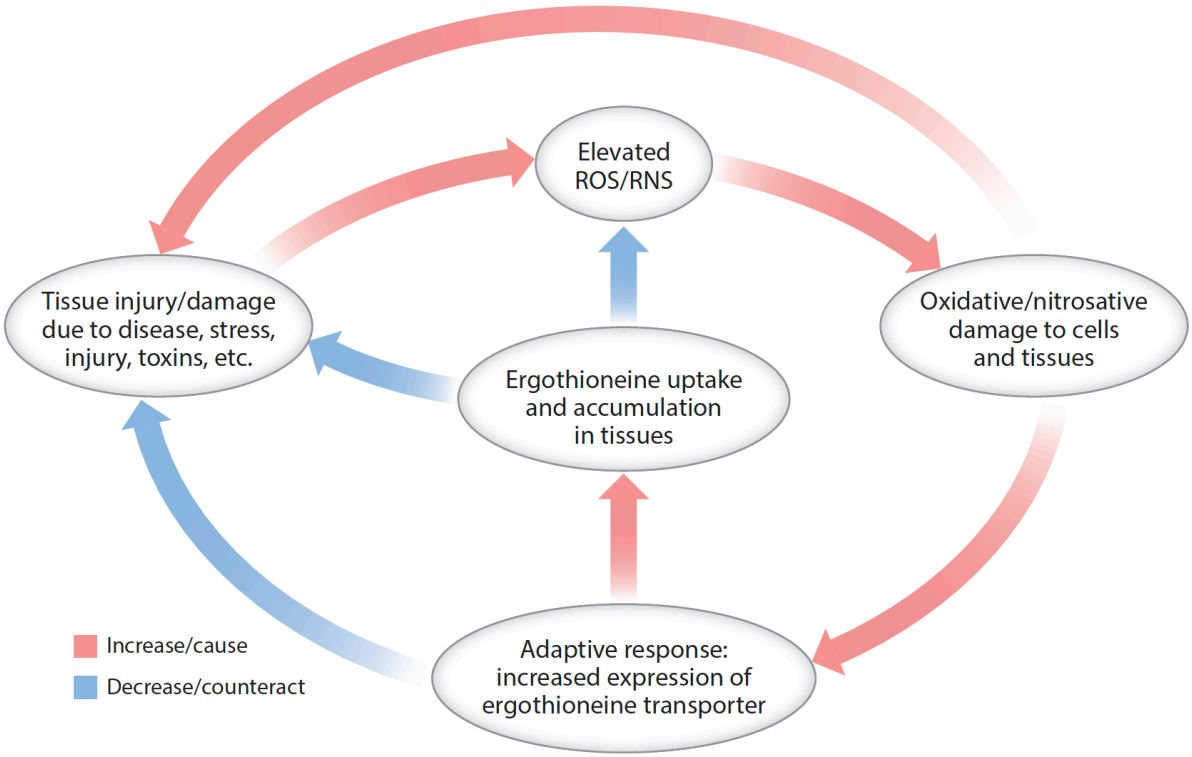
"ET is colorless, odorless, tasteless, and highly soluble in water."

"ET was studied intensively in the 1950s, with considerable emphasis placed on its antioxidant activities." There has been an upsurge in attention in recent years.

"One feature of ET that may contribute to its use in cosmetics is its ability to absorb UV light in the wavelength range similar to DNA, thus protecting DNA in skin cells against damage (Paul 2022)."

"ET is a fascinating compound: It is taken up into the human body by a specific transporter."

"Many animal and epidemiological studies suggest that ET can protect against the development of several human age-related diseases and that ET may even have therapeutic uses against several such diseases."



Synergistic Longevity Nutrients

By Lynn Toohey

(Longevity Nutrients part II)

Dr. Bruce Ames proposes that many nutrients play a double role in survival and longevity and that draining valuable resource nutrients for survival can result in sub-optimal unhealthy aging processes.

Ergothioneine was listed at the top of Dr. Ames's list, but it is certainly not the only longevity nutrient. There are several other synergistic nutrients heading that list:

Convincing evidence led Dr. Ames to classify taurine as a conditionally essential vitamin, stating that other conditionally essential vitamins should include *lipoic acid*, *CoQ-10*, and *carnitine*. There are other dietary biochemicals that are putative longevity nutrients on Dr. Ames's list, and they include *pyrroloquinoline quinone (PQQ), lutein, zeaxanthin, lycopene and astaxanthin*.1

Taurine: There is a wealth of information in academic literature databases linking taurine to longevity support, most notably two articles published in the highly regarded Science magazine June of 2023, linking taurine to healthy aging, and a lack of taurine to an accelerated aging process.2,3 Additionally, a researcher noted in July of the same year that taurine levels modulate aging.4

Dr. Bruce Ames's nutrients recommended to be "conditionally essential" – *Alpha Lipoic Acid (ALA), Co-Q-10 & L-carnitine*:

Alpha Lipoic Acid (ALA): ALA is synthesized by the mitochondria, the "powerhouses" of the cell. What is seen in many dysfunctional mitochondriopathies is lowered lipoic acid, and therefore lowered antioxidant status. Healthy mitochondria are essential to the theme of longevity and consistently produced energy in the cells for all biochemical reactions. Researchers published in Biomedical Research International maintain that alpha lipoic acid is one of the main longevity antioxidants involved in the antioxidant theory of aging.5 Lipoic acid reduces NAD to NADH at the very beginning of the Kreb's cycle; NADH is a powerful reducing agent that regulates cellular and metabolic signaling pathways, thereby having a tremendous influence on the aging process.6

Co-Q-10: Coenzyme Q 10 is an antioxidant, in addition to being a critical component of the energy-producing Kreb's Cycle in the mitochondria. It is best absorbed in the reduced form (ubiquinol). Our endogenous levels of Co-Q-10 in the body decrease with age. The support that Co-Q-10 offers the mitochondria alone puts it in a category of its own as a longevity nutrient.

L-Carnitine: Scientists report that L-carnitine activates what is known as "vitagenes". Vitagenes consist of a group of genes involved in preserving cellular homeostasis during stressful conditions. "Maintenance of optimal long-term health conditions is

accomplished by a complex network of longevity assurance processes that are controlled by vitagenes".7

Other putative longevity nutrients:

Pyrroloquinoline quinone (PQQ): PQQ, referred to as a "potent antioxidant" boosts the energy function of Co-Q-10, and has actually been shown to increase mitochondrial biogenesis!8

Some researchers believe that this potent antioxidant activity is involved in enhancing longevity support and positively supporting a healthy life span. The induction and development of cellular senescence is believed to be closely connected with inflammatory reactions, and PQQ is thought to create a cellular environment that does not contribute to cellular senescence. In fact, article authors declared that they "provided evidence that PQQ delays TNF-α -induced cellular senescence and has anti-inflammaging properties. 9

Lutein, zeaxanthin, lycopene and astaxanthin: These powerhouse antioxidants have individually and collectively been associated throughout scientific literature as being integral to any longevity protocol; there is a reason that they make the top of Dr. Bruce Ames's list of longevity nutrients. *Lutein* is one of the major carotenoids in most fruits and vegetables. It upregulates the endogenous antioxidant enzymes catalase and superoxide dismutase, and it is thought that this is the mechanism by which it is associated with support of lifespan activity. 10

Zeaxanthin is one of the powerful antioxidants that has been linked to helping microbial dysbiosis. Microbial dysbiosis is an imbalance of microbial species and a reduction in microbial diversity within certain microbiomes. This is correlated with changes in blood bacterial DNA concentration (BB-DNA). BB-DNA has surfaced as one of the potential theories of aging, since microbial dysbiosis can result in inflammation and dysfunction. The scientific conclusion in one study was that zeaxanthin supports an absence of dysfunctional BB-DNA. 11

"The role of the microbiome in human aging is important: the microbiome directly impacts aging through the gastrointestinal system", and stresses the importance of supplementing with a good variety of pre- and pro-biotics - it has been suggested that *"Probiotics and prebiotics* may be effective alternatives, considering the relationship between the microbiome and healthy aging".12 Additionally, Lactobacillus varieties of probiotics appear able to absorb and accumulate ergothioneine from their surroundings.13

Astaxanthin is not only a powerful antioxidant, it has a property that allows it to bind to DNA, thereby putting it in close proximity to the DNA in order to provide antioxidant support. This ability is closely related to the associations that have been made with astaxanthin and longevity.14

There are many nutrients that can help us live long, healthy lives. Many of them have synergistic action, and work on varied biological pathways that influence our life span. To take advantage of all of these synergistic actions is an effort to maximize the input we have to environmental influences on longevity.

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Longevity Lifestyle

Impact of 8 Lifestyle Factors on Mortality and Life Expectancy Among United States Veterans: The Million Veteran Program

The American Journal of Clinical Nutrition
January 2024; Vol. 119; No. 1; pp. 127-135

Xuan-Mai T Nguyen, Yanping Li, Dong D Wang, Stacey B Whitbourne, Serena C Houghton, Frank B Hu, Walter C Willett, Yan V Sun, Luc Djousse, John Michael Gaziano, Kelly Cho, Peter WF Wilson; from the Illinois College of Medicine, Harvard Medical School, and Emory University. This study cites 43 references.

The objective of this study was to estimate mortality risk and longevity associated with individual lifestyle factors. The study assessed 276,132 military veterans (256,816 male; 19,316 female), aged 40–99 years.

This study is the first time that the concept of prevention is being used to estimate life expectancy. **[Important]**

The authors used comprehensive information on 3 risky substances, including *smoking*, *opioid use*, and *alcohol* use.

Information on covariates, including age, sex, BMI, race, ethnicity, socioeconomic status, current marriage status, and education level, was collected. Sensitivity analysis adjusted for hypertension, hypercholesterolemia, diabetes, cancer, and cardiovascular disease at baseline.

KEY POINTS FROM THIS ARTICLE:

1) "Lifestyle medicine has been proposed as a way to address the root causes of chronic disease and their associated health care costs." **[Important]**

2) "The concept of lifestyle medicine uses evidence-based lifestyle interventions such as adopting a whole-food, plant-predominant eating pattern, regular physical activity, restorative sleep, stress management, avoidance of risky substances, and positive social connections as a low-risk approach for the treatment and potential reversal of chronic diseases."

3) "As lifestyle medicine treats the underlying causes of disease rather than its symptoms, it provides a potential avenue for altering the course of spiraling health care costs incurred in part as a result of prescription medications and surgical procedures." **[Key Point]**

4) "Noncommunicable chronic diseases are associated with >80% of all health care dollars and are the leading cause of morbidity and mortality in the United States." **[Important]**

20) "The continuous and graded prolonged life expectancy associated with increasing number of low-risk lifestyle factors suggests that any improvement in lifestyle toward adopting low-risk factors would result in certain benefit, and the more intensive, the better." **[Key Point]**

21) "Our estimation of graded prolonged lifestyle expectancy associated with increasing intensive low-risk lifestyle changes provides scientific support to promote lifestyle medicine as a means for individuals to directly influence their own health." **[Key Point]**

COMMENT FROM DAN MURPHY: This study was reviewed by New Scientist. Their review noted that lifestyle decisions were much more important to longevity than access to medicines and to medical doctors. The review is included below:

Health
Eight Healthy Habits Linked to Living Decades Longer

Annual Meeting of the American Society for Nutrition
Boston
July 24, 2023

Grace Wade

Xuan-Mai Nguyen
VA Boston Healthcare System

700,000 US military veterans between 40 and 99 years old

"People who adopt eight healthy habits by the age of 40 may live about two decades longer than those who don't."

"The effect is lower, but still significant, for people who have these eight habits by the time they are 60."

- Healthy Diet [undefined in review, "mostly whole foods"]
- Physical Activity Regular Moderate Exercise
- Sleep Sleeping Well "7 to 9 hours a night"
- Mental Health Managing Stress

- Relationships — Maintaining Positive Social Relationships
- Alcohol Use — Minimal
- Smoking — Never Smoking
- Opioid Use — Not Having Opioid Use Disorder

These eight habits were correlated with a lower risk of dying from any cause.

"Physical activity influenced longevity the most."

- "Moderate exercise—equivalent to at least briskly walking a few blocks each day—was associated with a 46% lower risk of dying ... than being sedentary."
- "Those who never smoked had a 29% lower risk [of dying] versus current or former smokers."

Men who adopted all eight habits by the age of 40 would live 24 years longer.

Women who adopted all eight habits by the age of 40 would live 23 years longer.

"If people implemented the habits by the age of 60, they could extend their lives by up to 18 years."

"These eight lifestyle factors don't involve medications."

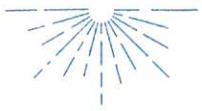
"Doctors don't necessarily need to be involved."

"This is very powerful because it shows that individuals really can have a say over their future health."

"A MONUMENTAL WORK."
—DAVID PERLMUTTER, MD,
author of the #1 *New York Times* bestsellers *Grain Brain* and *Brain Maker*

The End *of* Alzheimer's

The First Program to Prevent and Reverse Cognitive Decline



2017

DALE E. BREDESEN, MD

Professor and Founding President, Buck Institute; Professor, UCLA

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7 Overlooked Triggers of Alzheimer's Disease

You can prevent, slow, or reverse cognitive decline if you address the many causes behind it.

Dale E. Bredesen, MD
Pacific Neuroscience Institute

There are simple illnesses and there are complex illnesses. Pneumonia is an example of a simple illness. It usually has one dominant contributor, like the bacteria *streptococcus pneumoniae,* and therefore a single treatment like penicillin can kill the bacteria and cure the problem.

But complex illnesses have many contributors, and none of them are dominant. To deal effectively with a complex illness—to prevent, slow or reverse it—you have to identify and address multiple factors. Alzheimer's disease (AD) is a complex illness.

There are many factors that can trigger the amyloid plaques and tau tangles that damage neurons and produce the memory loss, language problems, confusion, mood swings, and other symptoms of AD. But conventional care for AD usually overlooks these multiple factors, with doctors telling patients, "There is not much we can do."

This hopelessness is false. In the majority of cases of cognitive decline and AD, triggers can be detected and treated. This approach is called precision or personalized medicine. It identifies and corrects the triggers of a particular individual. And science is proving that it works.

In a paper published in the August 6, 2024, issue of *Biomedicines,* a team of scientists reported "sustained cognitive improvement" for more than a decade in AD patients treated with a personalized protocol.

In a study of 255 people, also published in *Biomedicines,* enrolling in a precision medicine protocol for cognitive decline significantly improved or stabilized cognitive scores after a few months of treatment. In research published in the *Journal of Alzheimer's Disease,* 25 people with mild cognitive impairment or dementia were evaluated and treated for several triggers of cognitive decline. After nine months of treatment with a personalized, precision medical protocol, the study participants had significant improvements in cognitive ability, as rated by three tests.

The most common triggers

Almost everyone with any degree of cognitive decline—from age-related memory loss to AD—has at least one of the most common triggers. The key is getting tests to detect *your* triggers, and getting treatments for them. Here are some of the most important (and often overlooked) triggers in AD:

Trigger #1: Nutritional deficiencies. The most important nutrients for brain health aid in the formation and maintenance of synapses, which help send messages from neuron to neuron. They include omega-3 fats, choline, vitamin B_{12}, vitamin D, vitamin A (retinol), and zinc.

People with vitamin D deficiency are twice as likely to develop dementia. The most protective blood level of vitamin D is between 50 and 80 ng/mL. To reach your optimal level, use the "hundreds rule": Subtract your current level (25 is fairly typical), from your target (let's say, 60), which equals 35—which means you would take 3,500 IU daily of vitamin D.

Vitamin D boosts the absorption of calcium, so include at least 100 micrograms of vitamin K_2 to prevent the deposition of calcium in arterial walls. And to prevent toxicity, don't exceed a daily dosage of 10,000 IU.

Trigger #2: Insulin resistance. The hormone insulin helps move blood sugar (glucose) out of the bloodstream and into cells, including brain cells. Adequate glucose is a must for brain health and cognitive health. The brain is 2 percent of body weight, but it uses 20 percent of the body's total glucose supply. Half of all American adults have insulin resistance, which stops needed glucose from reaching cells and increases the risk of AD by 30 to 100 percent.

A fasting insulin test can detect insulin resistance, with a target range of 3 to 5 µIU/mL (micro-international units per milliliter). You're very likely to be insulin resistant if you're a man with a waist circumference of 40 inches or over, or a woman with a waist circumference of 35 inches or over.

There are several key ways to correct insulin resistance:

- **Eat a plant-rich, fiber-rich diet,** high in healthy fats and low in refined carbohydrates. Fast overnight for at least 12 hours.
- **Take zinc** (20 to 50 milligrams [mg] daily), which helps regulate insulin and its use.
- **Reduce stress**—for example, by not overscheduling or multitasking. Or for immediate relief, try a few minutes of "square breathing," exhaling slowly through your mouth to the count of four, holding to the count of four, inhaling slowly through your nose to the count of four, and holding to the count of four.
- **Take a glucose-regulating supplement,** like berberine (500 mg, three times daily) or cinnamon (½ teaspoon daily).

Trigger #3: Reduced oxygen while sleeping. To function well, the brain needs oxygen. If you want to prevent, slow, or reverse cognitive decline, you must be checked for your nighttime oxygen levels. It's easy to do on your own. Just purchase an oximeter, which you wear on your finger overnight, checking it whenever you wake up. Optimally, your "oxygen saturation" level should stay in the 96 to 98 percent range. If you're down in the 80s or 70s, you're doing your brain a disservice. The usual cause of reduced oxygen during sleep is sleep apnea, repeated interruptions in breathing during sleep. If oxygen levels are low, talk to your doctor about trying a dental device to improve breathing. Or use a CPAP (continuous positive airway pressure) device, which works by maintaining a continuous airflow, preventing airway collapse.

Trigger #4: Circulatory disease. Any reduction in blood flow to the brain can trigger cognitive decline. There are many ways to improve circulation, including regular aerobic exercise and strength training. Increase your movement throughout the day by getting up regularly whenever you're sitting for hours at a time and walk around for a minute or two. For supplementation, consider beet root extract, which increases nitric oxide, a biochemical that dilates blood vessels. (Follow the dosage recommendation on the label.)

Trigger #5: Toxins. You are exposed to hundreds of toxins—from the mercury in seafood to air pollution to the benzene in paraffin candles to poisons from the black mold growing in water-damaged homes. All of these toxins affect neurons, compromising cognition.

The key is to minimize exposure, identify any toxins to which you are exposed (using a range of tests that you can discuss with your doctor, such as a urine test for chemical toxins like benzene and toluene, and the urinary test for mycotoxins), and increase the metabolism and excretion of toxins.

To increase excretion, increase glutathione, a compound the liver uses to detoxify. To do that, eat more cruciferous vegetables like broccoli and Brussel sprouts, and more onion and garlic, mushrooms, spinach, asparagus, avocados, okra, and liver.

Supplements that aid in detoxification include curcumin, N-acetylcysteine, alpha-lipoic acid, selenium, zinc, and milk thistle. (Follow the dosage recommendations on the label.)

Also, stay well hydrated, eat plentiful amounts of plant fiber, and induce sweating with exercise or by taking regular saunas.

Trigger #6: Leaky gut. The lining of the gut is a one-cell thick barrier—a barrier that's constantly battered by toxins and stress. If the junction between cells loosens, you have what is called leaky gut, or increased intestinal permeability. The compounds that sneak through the barrier cause inflammation, which, in turn, causes neuroinflammation.

You can help protect and heal your gut lining—tightening the junction between cells—with bone broth, which is rich in glutamine, the preferred fuel of enterocytes, the cells that line the gut. Enjoy three or four servings per week. (More is not helpful.)

Trigger #7: Poor oral health. The bacteria generated by gum disease (periodontitis)—like *P. gingivalis, T. denticola, and F. nucleatum*—have been found in the brains of people with AD, and are linked to AD. A study published in *Alzheimer's Research & Therapy* looked at 25,000 people ages 50 and older and found that people who had gum disease for 10 years or more were 70 percent more likely to develop AD.

To counter poor oral health, brush and floss regularly, and have routine dental checkups, including cleaning. You can also take an oral probiotic, a supplement of friendly bacteria that crowd out and replace the disease-causing bacteria of periodontitis.

3 Breakthrough Tests for Alzheimer's Disease

In the last few years, several accurate blood tests for Alzheimer's disease (AD) have become available. If you take these three tests starting at age 35, and every five years thereafter, you will know if you're headed for Alzheimer's. You can then work with a physician to develop a protocol to prevent the disease, based on discovering and addressing triggering factors. Even taking these tests later in life is helpful in understanding whether or not you're at higher risk for AD—and doing something about it. The three tests are:

- **P-Tau 127 (Phosphorylated Tau at Threonine 127).** This protein is a specific marker for tau, the so-called "tangles" inside neurons that are a hallmark of AD.
- **GFAP (Glial Fibrillary Acidic Protein).** Found in the astroglial cells of the brain and spine, higher levels of this protein are a marker for neuroinflammation, which is one of the factors leading to AD (and other neurological diseases).
- **NFL (Neurofilament Light Chain).** When neurons are damaged, this protein leaks into the bloodstream. It's an indicator of neurodegeneration, including AD.

Bottom Line Health interviewed Dale E. Bredesen, MD, the senior director of the Precision Brain Health Program at Pacific Neuroscience Institute in Santa Monica, Calif., the founding president and professor emeritus of the Buck Institute for Research on Aging, and the author of the New York Times bestseller, *The End of Alzheimer's.*

Bioaccumulation of Microplastics in Decedent Human Brains

Nature Medicine
April 2025; Vol. 31; No. 4; pp. 1114-1119

Alexander J. Nihart, Marcus A. Garcia, Eliane El Hayek, Rui Liu, and 17 more; from the University of New Mexico, Oklahoma State University, Universidad del Valle (Cali, Colombia), and Duke University. This study cites 21 references.

The authors obtained postmortem human liver, kidney, and brain samples and assessed quantities of environmental microplastics and nanoplastics (MNPs).

KEY POINTS FROM THIS ARTICLE:

1) "The mantra of the field of toxicology—'dose makes the poison' (Paracelsus)."

2) "Rising global concentrations of environmental microplastics and nanoplastics (MNPs) drive concerns for human exposure and health outcomes."

3) "In controlled cell culture and animal exposure studies, MNPs exacerbate disease or drive toxic outcomes."

4) "Visual microscopic spectroscopy methods have identified particulates in organs, such as the lungs, intestine and placenta."

- "These methods are often limited to larger (>5 μm) particulates; thus, smaller nanoplastics are unintentionally excluded."

5) Studies using various technologies "confirm the presence of MNPs in human kidney, liver and brain."

- "MNPs in these organs primarily consist of polyethylene (PE), with lesser but significant concentrations of other polymers."

  •• PE had the highest abundance and concentrations in all organs.

- "Brain tissues harbor higher proportions of polyethylene compared to the composition of the plastics in liver or kidney, and electron microscopy verified the nature of the isolated brain MNPs, which present largely as nanoscale shard-like fragments."

- Plastic concentrations in these tissues increase over time.

- "Even greater accumulation of MNPs was observed in a cohort of decedent brains with documented dementia diagnosis, with notable deposition in cerebrovascular walls and immune cells." **[Very Important]**

- "Recent studies associated MNP presence in carotid atheromas with increased inflammation and risk of future adverse cardiovascular events."

- "Brain MNP concentrations were significantly higher than liver and kidney."

- "Brain samples, all derived from the frontal cortex, exhibited substantially higher concentrations of MNPs than liver or kidney."

6) "Environmental concentrations of anthropogenic microplastic and nanoplastic (MNP), polymer-based particulates ranging from 500 μm in diameter down to 1 nm, have increased exponentially over the past half century." **[Very Important]**

7) "Liver and brain samples from 2024 had significantly higher concentrations of MNPs than 2016 samples." **[Important]**

8) Total plastics concentrations in dementia samples were higher than in any normal frontal cortex cohort. **[Important]**

- "Atrophy of brain tissue, impaired blood–brain barrier integrity and poor clearance mechanisms are hallmarks of dementia and would be anticipated to increase MNP concentrations; thus, no causality is assumed from these findings."

9) "We suspected that much of the MNPs may be present in the nanoscale range, too small for visualization by light microscopy." **[Very Important]**

- "Given the observed small size of nanoscale particles isolated from the human specimens (typically <200 nm in length), it is likely that ultracentrifugation incompletely collected nanoplastics in the analytical samples, also contributing to potential underestimation." **[Important]**

10) In brain tissues:

- Light microscopy of the brain showed 100–200 nm long shards or flakes.

- "In dementia samples, many refractile inclusions were prominent in regions with inflammatory cells and along the vascular wall."

- "Total mass concentration of plastics in the brains analyzed in this study increased by approximately 50% in the past 8 years."

11) "We postulate that the exponentially increasing environmental concentrations of MNPs may analogously increase internal maximal concentrations." **[Important]**

12) "The shape and size of observed nanoparticles in the isolated material from human specimens taxes the limits of modern analytical instrumentation but may

reflect an end-stage product of plastic degradation that is uniquely suited for human uptake and accumulation."

13) Conclusions

- "The present data suggest a trend of increasing MNP concentrations in the brain and liver."

- "The majority of MNPs found in tissues consist of PE and appear to be nanoplastic shards or flakes."

- "MNP concentrations in normal decedent brain samples were 7–30 times greater than the concentrations seen in livers or kidneys, and brain samples from dementia cases exhibited even greater MNP presence." **[Very Important]**

14) "Given the exponentially rising environmental presence of MNPs, these data compel a much larger effort to understand whether MNPs have a role in neurological disorders or other human health effects."

COMMENT FROM DAN MURPHY:

This article was reviewed in *Science News*: April 2025; Vol. 207; No. 4:
Plastic Shards Permeate Human Brains, stating, in part:

"Minuscule shards and flakes of polymers are surprisingly abundant in brain tissue, a study of postmortem brains shows."

People with MNPs in "blood vessels plaques were at higher risk of heart attacks, strokes and death."

"From 2016 to 2024, the median concentration of MNPs increased by about 50%, from 3,345 micrograms per gram to 4,917 micrograms per gram—roughly 3 bottle caps worth of plastic."

"The levels of plastic being detected in the brain are almost unbelievable says study coauthor Andrew West, a neuroscientist at Duke University."

"Microplastics are in the food we eat, the water we drink and even the air we breathe."

"Previous studies have found them in lungs, intestines, blood, livers and placentas."

"Thin, sharp particles—not solid grains—were present in the brain tissue."

Also, see *Article Review 20-24*:
Rapid Single-particle Chemical Imaging of Nanoplastics by SRS Microscopy

Nat Aging. 2025 Feb 3. doi: 10.1038/s43587-024-00793-y. Online ahead of print.

Individual and additive effects of vitamin D, omega-3 and exercise on DNA methylation clocks of biological aging in older adults from the DO-HEALTH trial

Heike A Bischoff-Ferrari [1 2 3], Stephanie Gängler [4 5 6], Maud Wieczorek [4 5 6], Daniel W Belsky [7], Joanne Ryan [8], Reto W Kressig [9], Hannes B Stähelin [10], Robert Theiler [4 5], Bess Dawson-Hughes [11], René Rizzoli [12], Bruno Vellas [13 14 15], Laure Rouch [15 16 17], Sophie Guyonnet [13 14 15], Andreas Egli [4 5], E John Orav [18 19 20], Walter Willett [21], Steve Horvath [22]

Affiliations

PMID: 39900648 DOI: 10.1038/s43587-024-00793-y

Abstract

While observational studies and small pilot trials suggest that vitamin D, omega-3 and exercise may slow biological aging, larger clinical trials testing these treatments individually or in combination are lacking. Here, we report the results of a post hoc analysis among 777 participants of the DO-HEALTH trial on the effect of vitamin D (2,000 IU per day) and/or omega-3 (1 g per day) and/or a home exercise program on four next-generation DNA methylation (DNAm) measures of biological aging (PhenoAge, GrimAge, GrimAge2 and DunedinPACE) over 3 years. Omega-3 alone slowed the DNAm clocks PhenoAge, GrimAge2 and DunedinPACE, and all three treatments had additive benefits on PhenoAge. Overall, from baseline to year 3, standardized effects ranged from 0.16 to 0.32 units (2.9-3.8 months). In summary, our trial indicates a small protective effect of omega-3 treatment on slowing biological aging over 3 years across several clocks, with an additive protective effect of omega-3, vitamin D and exercise based on PhenoAge.

Related information

MedGen

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Full Text Sources

Nature Publishing Group

Nat Med. 2025 Mar 24. doi: 10.1038/s41591-025-03570-5. Online ahead of print.

Optimal dietary patterns for healthy aging

Anne-Julie Tessier [1 2 3 4], Fenglei Wang [5], Andres Ardisson Korat [6 7], A Heather Eliassen [5 8 9], Jorge Chavarro [5 8 9], Francine Grodstein [10], Jun Li [5 11], Liming Liang [8 12], Walter C Willett [5 8 9], Qi Sun [5 8 9], Meir J Stampfer [5 8 9], Frank B Hu [13 14 15], Marta Guasch-Ferré [16 17 18]

Affiliations

PMID: 40128348 DOI: 10.1038/s41591-025-03570-5

Abstract

As the global population ages, it is critical to identify diets that, beyond preventing noncommunicable diseases, optimally promote healthy aging. Here, using longitudinal questionnaire data from the Nurses' Health Study (1986-2016) and the Health Professionals Follow-Up Study (1986-2016), we examined the association of long-term adherence to eight dietary patterns and ultraprocessed food consumption with healthy aging, as assessed according to measures of cognitive, physical and mental health, as well as living to 70 years of age free of chronic diseases. After up to 30 years of follow-up, 9,771 (9.3%) of 105,015 participants (66% women, mean age = 53 years (s.d. = 8)) achieved healthy aging. For each dietary pattern, higher adherence was associated with greater odds of healthy aging and its domains. The odds ratios for the highest quintile versus the lowest ranged from 1.45 (95% confidence interval (CI) = 1.35-1.57; healthful plant-based diet) to 1.86 (95% CI = 1.71-2.01; Alternative Healthy Eating Index). When the age threshold for healthy aging was shifted to 75 years, the Alternative Healthy Eating Index diet showed the strongest association with healthy aging, with an odds ratio of 2.24 (95% CI = 2.01-2.50). Higher intakes of fruits, vegetables, whole grains, unsaturated fats, nuts, legumes and low-fat dairy products were linked to greater odds of healthy aging, whereas higher intakes of trans fats, sodium, sugary beverages and red or processed meats (or both) were inversely associated. Our findings suggest that dietary patterns rich in plant-based foods, with moderate inclusion of healthy animal-based foods, may enhance overall healthy aging, guiding future dietary guidelines.

Related information

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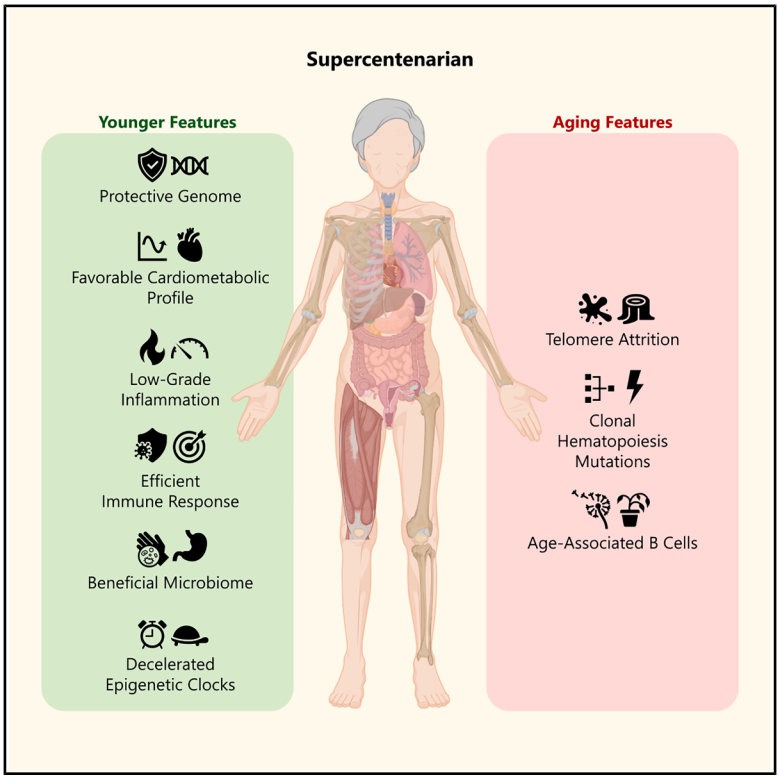
Article

The multiomics blueprint of the individual with the most extreme lifespan

Graphical abstract



Highlights

- (Epi)genome, transcriptome, metabolome, proteome, and microbiome study of the oldest human
- Despite molecular hallmarks of aging, absence of major age-associated diseases
- Resilient genetic variants and low-inflammation metabolic profile reduce aging risks
- Bacteria occurrence and epigenome profile resembling younger individuals

Authors

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Aleix Noguera-Castells,
Marta Casado-Pelaez, ..., Hafid Laayouni,
Arcadi Navarro, Manel Esteller

Correspondence

mesteller@carrerasresearch.org

In brief

In brief, Santos-Pujol and colleagues characterize the multiomics landscape of the human with the most extreme longevity. The study enables the association of advantageous genetic variants, an engaged lipid metabolism, low inflammation levels, a proficient immune system, a rejuvenated microbiome composition, and a younger epigenetic age with the extraordinary lifespan.

Santos-Pujol et al., 2025, Cell Reports Medicine 6, 102368
October 21, 2025
https://doi.org/10.1016/j.xcrm.2025.102368

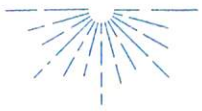
CellPress

Vagus Nerve

"A MONUMENTAL WORK."
—DAVID PERLMUTTER, MD,
author of the #1 *New York Times* bestsellers *Grain Brain* and *Brain Maker*

The End *of* Alzheimer's

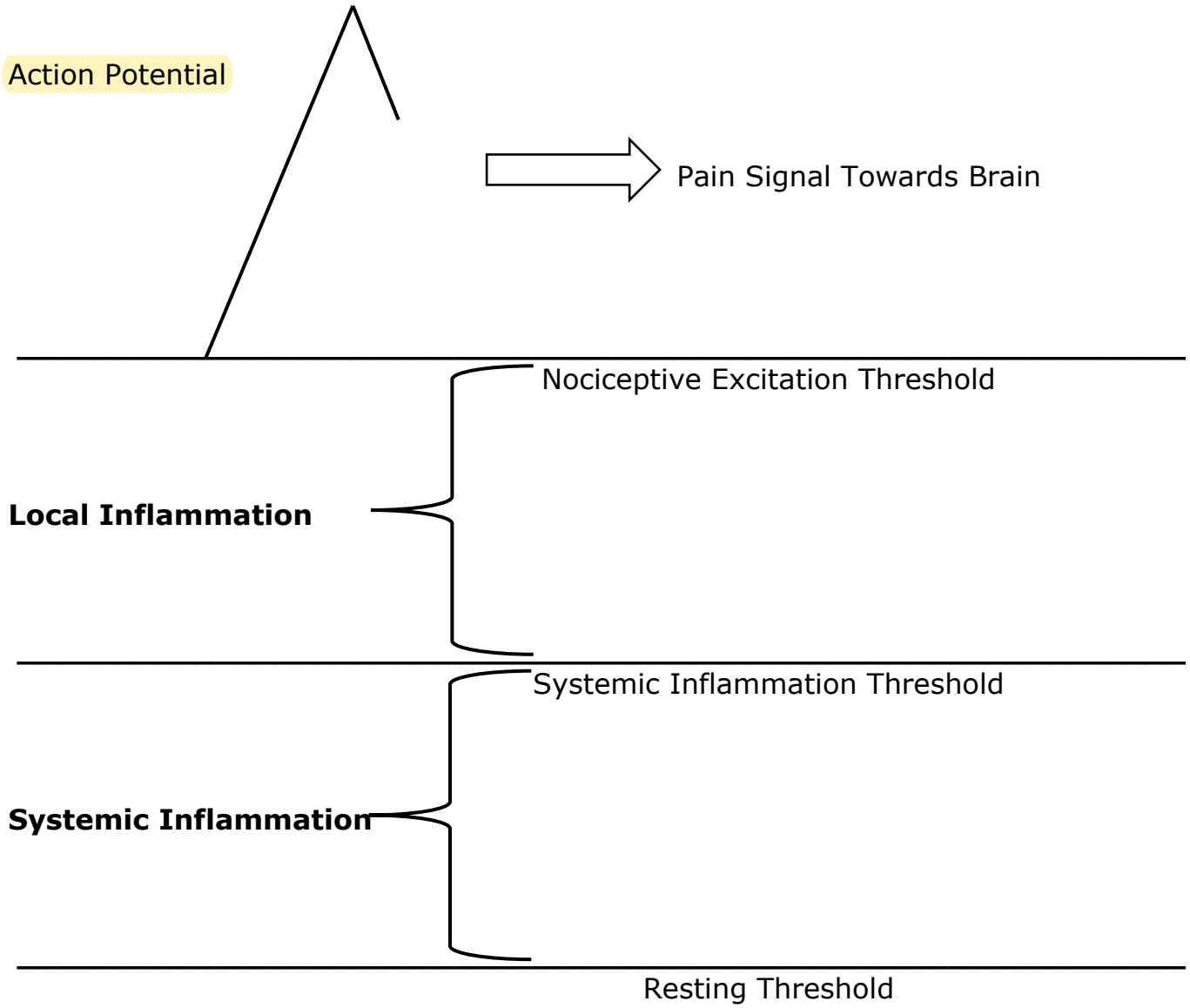
The First Program to Prevent and Reverse Cognitive Decline



2017

DALE E. BREDESEN, MD

Professor and Founding President, Buck Institute; Professor, UCLA



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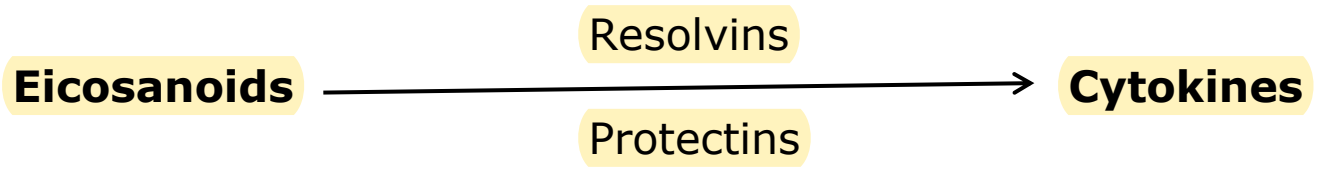
Inflammatory Chemicals
Brief Summary

Eicosanoids	**Cytokines**
Prostaglandin E2 PGE2 Hormone-Like Molecules Derived from Omega-6 Fatty Acid *Arachidonic Acid* Linoleic Acid (Corn/ Soy) Insulin-D5D → Arachidonic Acid COX → PGE2 High Omega-6/Omega-3 ratio >3/1 <u>Ratio Improved By</u> •Limiting omega-6 and grained meat/egg consumption •Increasing omega-3 and wild fish consumption **COX Enzymes are Inhibited by Red LLLT** **Red LLLT Reduces PGE2 Accumulation** Motion Disperses Accumulation Chiropractic, etc. Inflammatory Eicosanoids Increase Inflammatory Cytokines	Interleukin-6 IL-6 Proteins Derived from Immune Cell Activation Infection Excessive Immunological Responses Autoimmune Diseases Leaky Gut Low Vitamin D Altered Vitamin D Receptor Low Levels of IL-10 <u>Improved/Reduced By</u> Immune Enhancing Supplements •Vitamin D •Vitamin C •Magnesium •Zinc •Omega-3s Heal the Leaky Gut Avoid Harmful Wavelengths >850 nm **Violet LLLT Are Antimicrobial** **Violet LLLT Reduce/Inhibit IL-6** **Red LLLT Reduce/Inhibit IL-6** **Red LLLT Increases IL-10** Vigorous Exercise Increases IL-10 Chiropractic Increased IL-10 Chiropractic May Be Immunoenhancing Motion Disperses Accumulation Chiropractic, etc. Inflammatory Eicosanoids Increase Inflammatory Cytokines

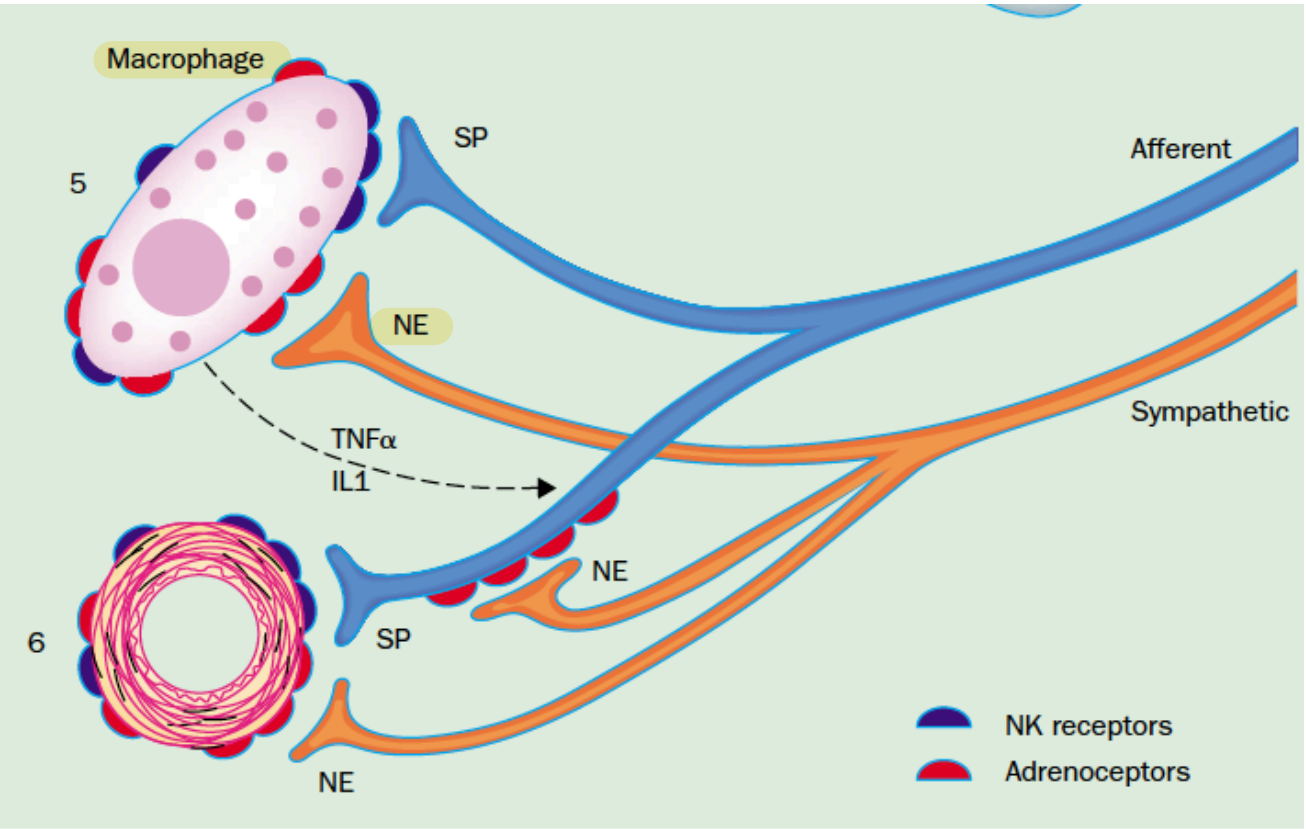
Macrophage



Complex Regional Pain Syndrome: Mystery Explained?

THE LANCET, Neurology
November 2003; Vol. 2; No. 11; p. 691

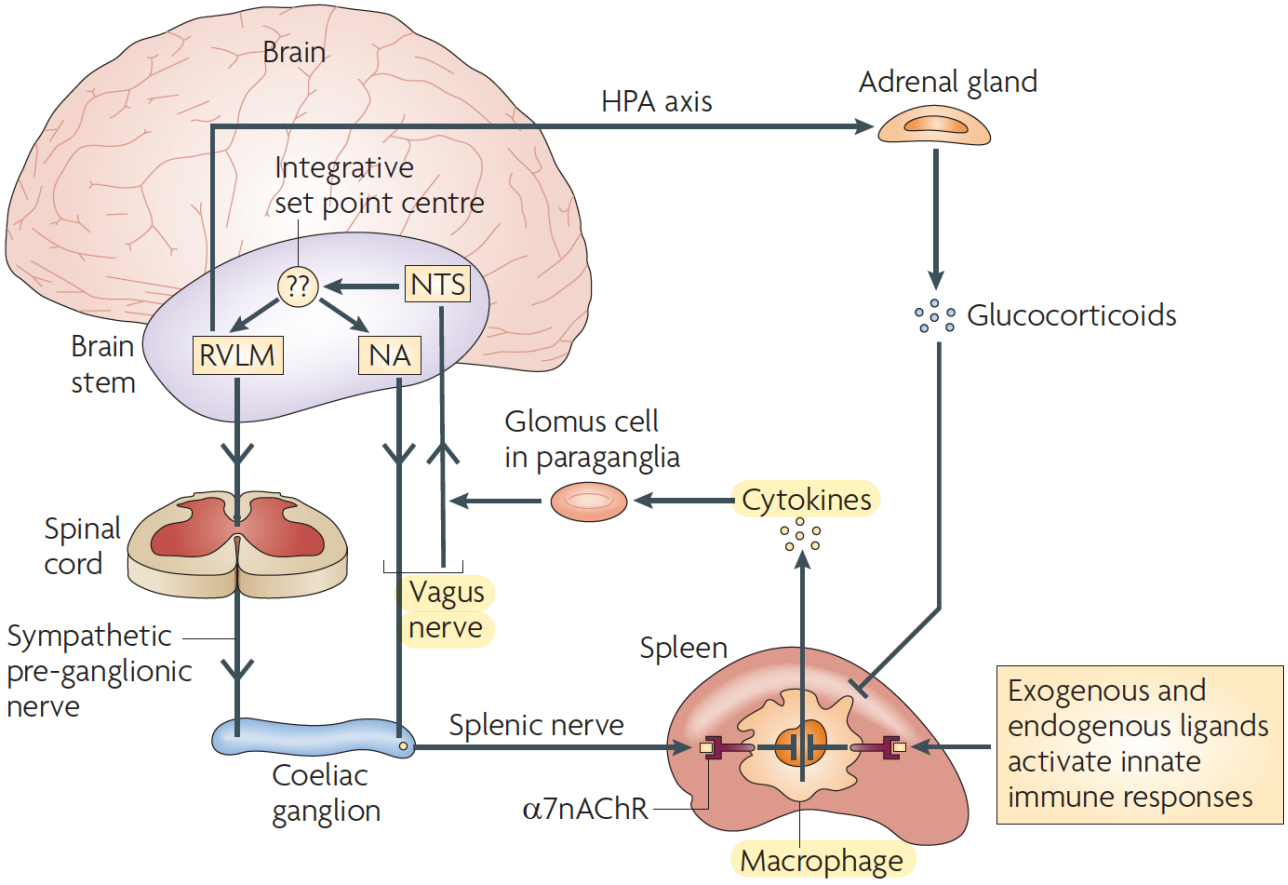
Wilfrid Jänig and Ralf Baron:
Department of Physiology, Christian-Albrechts University of Kiell, Germany



Reflex Control of Immunity

Nature Immunology
June 2009

Kevin Tracey



By Bernadine Healy, M.D.

The Dangerous Art of the Tattoo

TATTOOS ARE FAST BECOMING A MARK of the 21st century, with one quarter or more of those under the age of 30 adorning their skin with at least one. Whether driven by the urge for personal expression or just plain youthful impulsiveness, most people get tattooed without a clue about the health implications of this invasive skin-puncturing procedure. I'd suggest that all tattooing require a signed consent form outlining risks—the most obvious one being a major case of remorse.

Upwards of 50 percent of those who get tattoos later wish they hadn't. Their regrets become medical when they visit a dermatologist to have the tattoos removed, which is both painful and expensive. In the July issue of the *Archives of Dermatology*, researchers at Texas Tech University Health Sciences Center report on what's behind the change of heart: moving on from the past, problems wearing clothes, embarrassment, and concerns that tattoos could adversely affect job or career.

But tattooing is designed to last forever, delivering permanent ink deep under the epidermis. The skin reacts by protectively encapsulating the alien clumps of pigment in dense fibrous tissue while a few nearby lymph nodes collect what migrates out. For a long time, removal meant surgical excision or deep abrasion of the skin, invariably causing scarring and sometimes the need for skin grafting. In the preferred approach now, the tattoo gradually fades away under many months of laser treatments tailored to the wavelength of the pigments. Sounds easy. But with disruption, the fading tattoo becomes more like a toxic chemical dump.

Chemists from several laboratories, including the government's National Center for Toxicological Research, have identified low levels of carcinogens in tattoo ink. But the laser removal process, which demolishes the pigment by scorching it with heat, triggers chemical reactions that generate carcinogenic and mutation-inducing breakdown products, which are then absorbed by the body. Recently, German scientists reported that concentrations of toxic molecules from red and yellow pigments increased up to 70-fold after laser irradiation. And the bigger the tattoo, the greater the toxic release. This can only make one wonder whether it's better to let the sleeping paint lie, walled off by the body's own protective devices. Only time and a lot more study will tell.

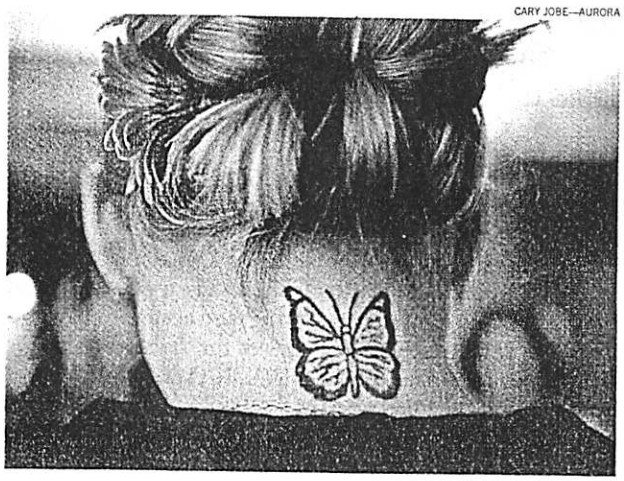
We know so woefully little about tattoos. The Food and Drug Administration, which goes after cosmetics with a vengeance, does not regulate the tattoo industry. In fact, no one really knows exactly what's in the numerous commercial and homemade inks. But they do contain solvents and metals like lead and mercury and a range of impurities acceptable for computer printers or car paint—but not for human injection.

Allergic reactions and skin infections can occur after tattooing. And though they may be coincidental, skin cancers, including melanomas, have been reported within tattoo sites, bearing very close watching. The FDA warns about the risk of tattoo parlors transmitting viruses like HIV and the cancer-causing hepatitis C. Because of this, blood banks typically ban donations from people who have been tattooed in the previous 12 months. The FDA also warns patients that if they have an MRI scan, their tattoos can swell or burn, presumably related to the metal in some inks.

Stigma. Once mainly a guy thing, tattoos now decorate men and women equally, and increasingly they are a women's health issue. It should be obvious that getting or removing tattoos during pregnancy is not a good idea. And some anesthesiologists have expressed concerns about performing epidurals, used during labor, through those symmetrically designed female lower-back tattoos because of the slim possibility that the needle might carry pigment into the spinal canal. Perhaps not surprisingly, most patients seeking removal are women, prompted by a disproportionate level of psychological distress and even tattoo stigma. Witness the tasteless moniker used to describe those lower-back tattoos: "tramp stamp."

Laser removal, which demolishes tattoo pigment, may sound easy. But it opens up a toxic chemical dump.

CARY JOBE—AURORA



I asked a few of my *U.S. News* colleagues about their take on women and tattoos. One said there was something trendy if not sexy about them—but maybe not for his fiancée. Another said he'd date a girl with one if it were not too obvious. A third saw only harmless self-expression. I'm with one young reporter who visited a tattoo parlor for a piece she was writing. She's down on tattoos because of the murky risks—and the idea of looking at the deeds of her youth for 80 years. ●

Immunology

The effect of tattoos on the body is more than skin deep

Christa Lesté-Lasserre

TATTOO ink collects in lymph nodes and interferes with the immune system, causing potentially lifelong changes to the body's disease-fighting mechanisms.

That is the conclusion of a study in mice, in which tattooed animals showed chronic inflammation in their lymph nodes – which were pigmented with the ink – and had altered antibody responses to vaccines. Human lymph nodes from tattooed individuals had similar inflammation and colouring.

"When you're tattooing, you're actually injecting ink into your body," says Santiago González at the University of Lugano in Switzerland. "It's not just a cosmetic effect... there are effects on the immune system as well."

Tattooing has become a global trend. Between 30 and 40 per cent of people in Europe and the US under the age of 40 have at least one tattoo.

González says he and his colleagues were working on an unrelated research project on inflammation in mice when they realised the animals developed "crazy inflammatory reactions" after being given small tattoos for identification.

To find out more, they used standard commercial inks in black, red and green to tattoo a 25-square-millimetre patch of skin on the hind feet of dozens of mice. With specialised imaging equipment, they watched the ink travel along the lymphatic vessels inside the leg up to the nearby lymph nodes almost immediately.

There, the team saw that macrophages – immune cells that clean up debris, pathogens and dead cells – captured the ink, tinting the nodes and provoking acute inflammation. Within about 24 hours, those macrophages died, releasing the ink, which then got captured by other macrophages. Those, too, would die and release ink, which would get taken up by yet other macrophages – creating a cycle of chronic inflammation that lasted well after the tattoo site had healed (*PNAS*, doi.org/qhd9).

EDEN BREITZ/ALAMY

By the end of the experiment, two months after tattooing, the mice's lymph nodes still had levels of inflammatory markers up to five times higher than normal, says González.

"Tattooing is not just cosmetic, there are effects on the immune system as well"

To investigate whether this inflammation affected immune function, they injected vaccines directly into the tattooed skin. The tattooed mice's antibody response to a covid-19 mRNA vaccine was noticeably weaker than in control mice, but their response to an influenza vaccine was stronger.

Tattooing has now become a global trend

Further analyses showed the lymph node macrophages of tattooed mice were so full of ink, they captured less of the covid-19 vaccine – which, as an mRNA vaccine, needs processing by macrophages to be functional. For the protein-based influenza vaccine, however, inflammation boosted the antibody response, perhaps because there were more immune cells recruited to the tattooed site.

Finally, they examined a small set of lymph node biopsies from people who had been tattooed in regions near the nodes. Even two years after tattooing, the nodes still contained visible pigment, packed into the same kinds of macrophages as seen in the mouse study.

Michael Giulbudagian at the German Federal Institute for Risk Assessment in Berlin says "the relevance for human health, in particular after the complete healing of the wound, must be further investigated".

Journal of
Clinical Medicine

MDPI

Concept Paper

The Vagus Nerve Can Predict and Possibly Modulate Non-Communicable Chronic Diseases: Introducing a Neuroimmunological Paradigm to Public Health

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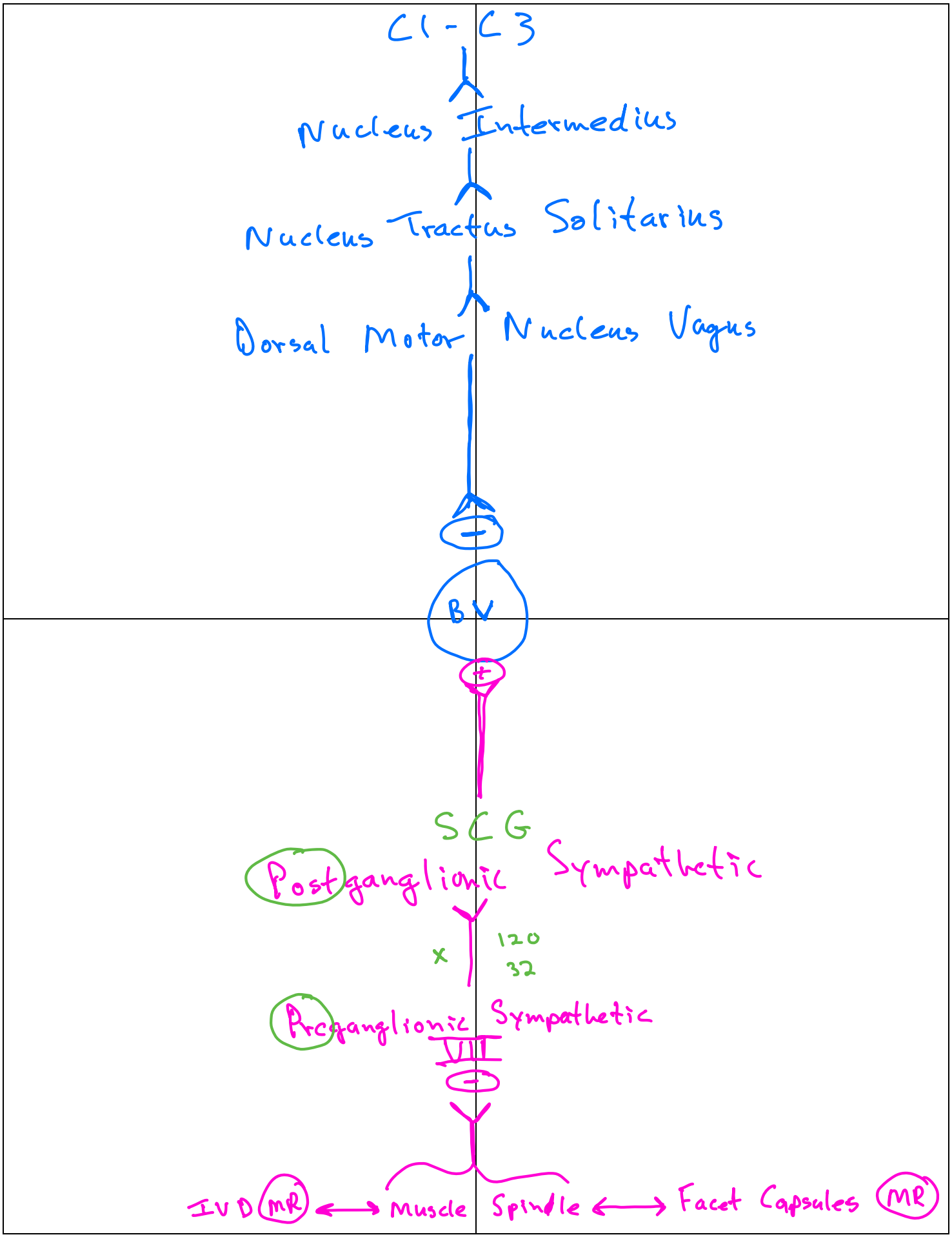
Abstract: Global burden of diseases (GBD) includes non-communicable conditions such as cardiovascular diseases, cancer and chronic obstructive pulmonary disease. These share important behavioral risk factors (e.g., smoking, diet) and pathophysiological contributing factors (oxidative stress, inflammation and excessive sympathetic activity). This article wishes to introduce to medicine and public health a new paradigm to predict, understand, prevent and possibly treat such diseases based on the science of neuro-immunology and specifically by focusing on vagal neuro-modulation. Vagal nerve activity is related to frontal brain activity which regulates unhealthy lifestyle behaviors. Epidemiologically, high vagal activity, indexed by greater heart rate variability (HRV), independently predicts reduced risk of GBD and better prognosis in GBD. Biologically, the vagus nerve inhibits oxidative stress, inflammation and sympathetic activity (and associated hypoxia). Finally, current non-invasive methods exist to activate this nerve for neuro-modulation, and have promising clinical effects. Indeed, preliminary evidence exists for the beneficial effects of vagal nerve activation in diabetes, stroke, myocardial infarction and possibly cancer. Thus, we propose to routinely implement measurement of HRV to predict such GBD in populations, and to test in randomized controlled trials effects of non-invasive vagal nerve activation on prevention and treatment of GBD, reflecting possible neuro-modulation of health.

Keywords: global burden of diseases; neuroimmunology; neuromodulation; vagal nerve; prediction; prevention

1. The Problem

Major non-communicable causes of death and of years of life lost today include coronary heart disease (CHD), stroke, cancer and pulmonary diseases [1]. Many risk factors (pollution, smoking, diet-driven cholesterol, insufficient exercise, etc.) explain a large proportion of major global burden of diseases—GBD (e.g., [2]). Furthermore, many of these diseases have common underlying biological causes, as we shall see below.

While modernization has brought many positive developments (e.g., transportation, huge improvements in disease detection and treatment, immense improvements in access to information via


C1 - C3
Nucleus Intermedius
Nucleus Tractus Solitarius
Dorsal Motor Nucleus Vagus
BV
SCG
Postganglionic Sympathetic
x
120
32
Preganglionic Sympathetic
IVD MR
Muscle Spindle
Facet Capsules MR

Nasal Specific → Sphenoid

Upper Cervical → Occiput/Atlas → Cork CSF

* Calming
* Vasodialation
  - ↓ B.P.
  - ↓ artery disease
* Immune Enhancing
* Longer Telomere

Acetylcholine

HRV

Stress
Fight/Flight
↓
Vasoconstriction
↑ BP
↑ artery disease
Immune Supression
Shorter Telomeres
Shrink Brain

Norepinephrine
↑
SNS
↑
VII
(−)
↑
Mechanoreceptors

The New Science of the *Vagus Nerve* and How to Harness Its *Healing Reflexes*

THE GREAT NERVE

2025

KEVIN J. TRACEY, MD

The Great Nerve
The New Science of the *Vagus Nerve* and How to Harness Its *Healing Reflexes*

Kevin Tracey MD
Avery, 2025

"Your vagus nerve is great because it reaches into so many life and health-giving systems in your body and keeps them all in balance."

"The vagus nerve can regulate your body's vital systems and heal a wide variety of medical conditions."

"The vagus nerve is fundamental to our health and vitality..."

"The previously unknown power of the vagus nerve to reverse inflammation, balance the immune system, treat chronic illness..."

"Inflammation has replaced infection as the greatest threat to healthful human longevity."

"A functioning vagus nerve is truly a life-or-death matter; it is the only nerve we have that when cut on both sides, we die."

"How do you know if your vagus nerve is being stimulated? A simple answer is that you know it is being stimulated when your pulse goes down?

Do inflammatory cytokines cause low back pain?

Google AI Overview
February 14, 2026

Inflammatory cytokines, particularly IL-6, IL-8, and TNF-alpha, play a key role in the development and persistence of low back pain (LBP) by promoting inflammation, disk degeneration, and nerve sensitization. These biomarkers are frequently elevated in patients with chronic LBP, disc herniation, and degenerative disc diseases.

Key Cytokines and Their Roles

Interleukin-6 (IL-6):
Persistently increased levels of IL-6 are associated with chronic lumbar radicular pain and disc herniation.

Interleukin-8 (IL-8)
Identified as a crucial cytokine in disc-related pain, IL-8 levels are higher in patients with chronic LBP and correlate with pain severity.

Tumor Necrosis Factor-alpha) (TNF-alpha):
Higher concentrations are found in patients with restricted lumbar mobility and contribute to the inflammatory process in disc degeneration.

Grok AI Overview
February 14, 2026

Yes, inflammatory cytokines contribute to low back pain (LBP) in many cases.

Research shows that pro-inflammatory cytokines play a significant role in both **disc-related** (e.g., herniation, degeneration) and **non-specific** low back pain by:

- Directly sensitizing nociceptors (pain-sensing nerves)
- Promoting inflammation in disc tissue, muscles, facet joints, or surrounding structures
- Contributing to central and peripheral sensitization
- Amplifying pain signaling pathways

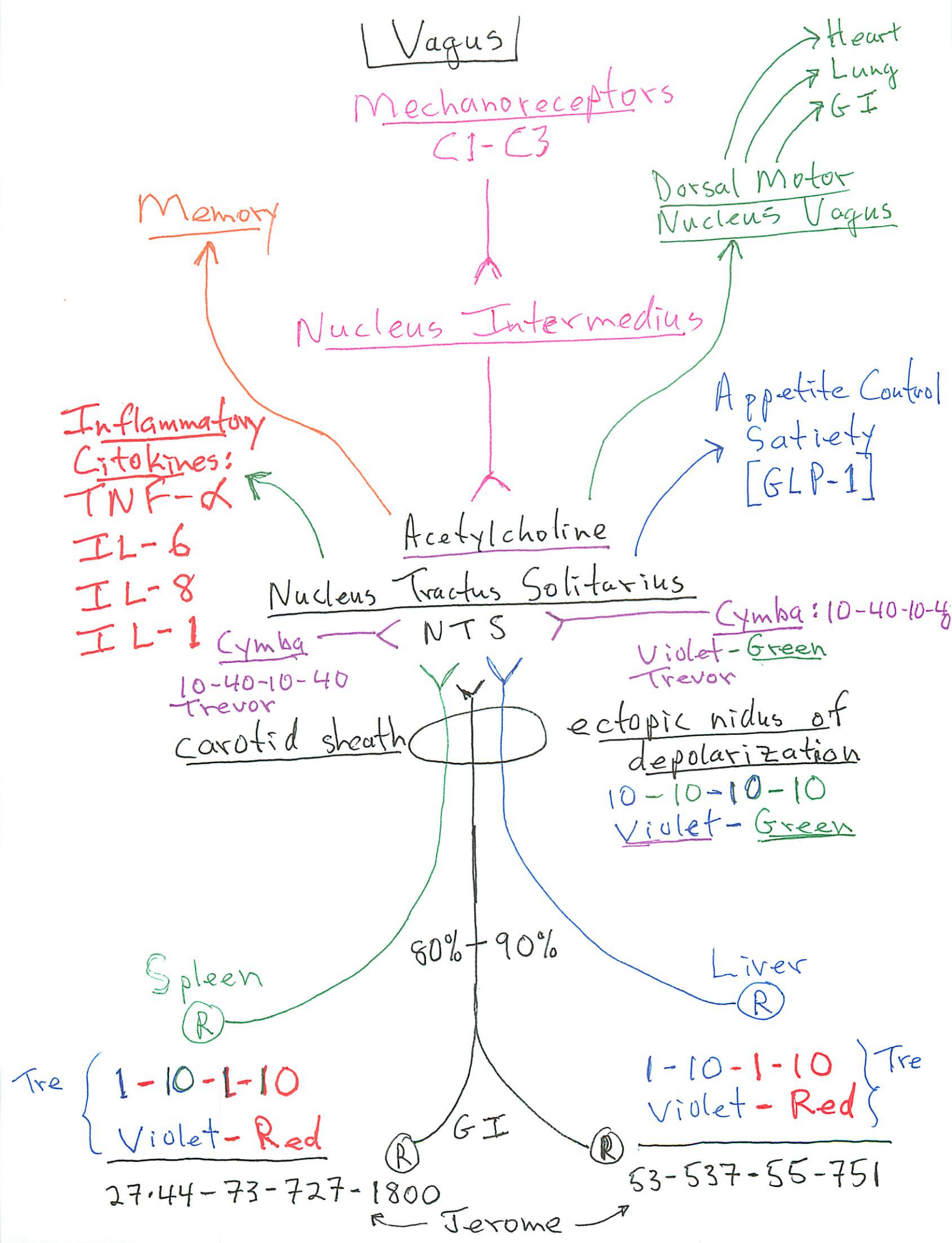
Key Cytokines Involved in Low Back Pain

Cytokine	Type	Main Findings in LBP Patients
TNF-α	Pro-inflammatory	Frequently elevated in chronic LBP and disc herniation; correlates with pain intensity and radicular symptoms
IL-6	Pro-inflammatory	Commonly increased in both acute and chronic LBP; linked to pain severity and systemic inflammation
IL-1β	Pro-inflammatory	Elevated in many studies; promotes disc degeneration and nociceptor sensitization
IL-8	Pro-inflammatory	Often significantly higher in disc-related LBP; correlates with radicular pain and herniation
IL-10	Anti-inflammatory	Often decreased in LBP patients → imbalance favoring inflammation

Evidence Summary by Pain Type

- **Disc herniation / radicular pain / sciatica** Very strong evidence that inflammatory cytokines (especially **TNF-α**, **IL-1β**, **IL-6**, and **IL-8**) are major contributors. These are released from the herniated disc material, nucleus pulposus, and surrounding tissues, directly sensitizing nerves and causing chemical radiculitis even when mechanical compression is reduced.

- **Chronic non-specific low back pain** Most systematic reviews and case-control studies show elevated pro-inflammatory cytokines (**TNF-α**, **IL-6**, **IL-1β**) and reduced anti-inflammatory cytokines (**IL-10**). This imbalance is associated with pain persistence, central sensitization, and higher pain scores. However, findings are more variable than in disc-related pain, and not all patients show the same pattern.


Vagus
Mechanoreceptors
C1-C3
Heart
Lung
GI
Dorsal Motor Nucleus Vagus
Memory
Nucleus Intermedius
Inflammatory Cytokines:
TNF-α
IL-6
IL-8
IL-1
Appetite Control
Satiety
[GLP-1]
Acetylcholine
Nucleus Tractus Solitarius
NTS
Cymba
10-40-10-40
Trevor
Cymba: 10-40-10-40
Violet-Green
Trevor
carotid sheath
ectopic nidus of depolarization
10-10-10-10
Violet-Green
80%-90%
Spleen
R
Liver
R
Tre
1-10-1-10
Violet-Red
1-10-1-10
Violet-Red
Tre
GI
R
R
27.44-73-727-1800
53-537-55-751
Jerome

Exercise

Ultraprocessed Foods

Omegas

LA
Linoleic Acid
18:2 n-6

cottonseed
corn
soy
sun
saff
peanut
canola

D5D
↑
insulin

4

AA
Arachadonic Acid
20:4 n-6

NSAIDs
↓
COX →
↑
LLLT

PGE2
inflammation
PAIN
artery disease
dementia
cancer
auto-immune disease
DJD

ALA
Alpha-linolenic Acid
18:3 n-3

flax
walnut
hemp

Cu / Zn →

1

EPA
eicosopentaenoic
20:5 n-3

→ PGE3
≈ 2000 mg/d

DHA
docosahexaenoic
22:6 n-3 ≈ 1000 mg/d

W-25
6

Omega Books

for the

Doctor

Phospholipid Spectrum Disorders in Psychiatry and Neurology

Second Edition

Edited by

Malcolm Peet, Iain Glen and David F. Horrobin

Marius Press

American Academy of Pain Management
Weiner's Pain Management
A Practical Guide for Clinicians
Seventh Edition, 2006, pp.584-585
Edited by Mark Boswell and B. Eliot Cole

"Changes in the modern diet are largely responsible for the increasing incidence of essential fatty acid (EFA) imbalances and deficiencies."

"The ratio of omega-6 to omega-3 fats has changed dramatically due to the widespread use of vegetable oils (mostly n-6 fats) in cooking and to the processing of oils to alter omega-3 fats to improve shelf life and eliminate their stronger taste (just think of the distinctive tastes of cod liver or flax oil)."

"Historical estimates place the ratio of omega-6 to omega-3 oils at nearly 1:1 for prehistoric humans."

By the turn of the century (1900), the ratio had increased to about 4:1.
The current American ratio is about 25:1.

"The sharp rise is due to increased vegetable oil consumption:
from 2 lb. per year in 1909 to 25 lb. per year in 1985!"

"Many of the chronic inflammatory conditions that accompany EFA imbalance are currently treated with symptom-specific pharmaceutical drugs such as steroids, prednisone, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, and colchicine."

"The problem with such drug therapies is that they prevent the formation of 'good' anti-inflammatory eicosanoids, or they shift the production of one type of eicosanoid to another."

"For effective, long-term management, eicosanoid production should be modified through dietary changes (balancing dietary intake of specific fats) and controlling insulin levels in the circulation."

"Maintaining a proper balance between the various families of dietary fats may be one of the most important preventative measures a person can take to reduce the likelihood of developing one of the chronic diseases of modern civilization, such as diabetes, heart disease, obesity, irritable bowel syndrome, and autoimmune disease."

"And for patients who may already have one of these diseases, EFA testing and therapy has been demonstrated to reduce both morbidity and mortality associated with these diseases."

In Defense of Food
Michael Pollan
2008

Omega-3s

"We're eating a lot more seeds and a lot fewer leaves (as do the animals we depend on)." "Leaves provide a host of critical nutrients a body can't get from a diet of refined seeds. There are antioxidants and phytochemicals; there is the fiber; and then there are the essential omega-3 fatty acids found in leaves, which some researchers believe will turn out to be the most crucial missing nutrient of all." pp. 124-125

"Too much omega-6 may be just as much a problem as too little omega-3" p. 126

"For years plant breeders have been unwittingly selecting for plants that produce fewer omega-3s, because such crops don't spoil as quickly." p. 127

"When food makers partially hydrogenate oils to render them more stable, it is the omega-3s that are eliminated." p. 127

"Researchers are convinced that these historically low levels of omega-3 (or, conversely, historically high levels of omega-6) bear responsibility for many of the chronic diseases associated with the Western diet." pp. 127-128

"Could it be that the problem with the Western diet is a gross deficiency in this [omega-3s] essential nutrient? A growing number of researchers have concluded that it is." p. 130

"The billions we spend on anti-inflammatory drugs such as aspirin, ibuprofen, and acetaminophen is money spent to undo the effects of too much omega-6 in the diet." p. 131

"Of all of the changes to our food system that go under the heading "The Western Diet," the shift from a food chain with green plants as its base to one based on seeds may be the most far reaching of all. Nutritional scientists focus on different nutrients—whether the problem with the modern diet is too many refined carbohydrates, not enough good fats, too many bad fats, or a deficiency of any number of micronutrients or too many total calories. But at the root of all these biochemical changes is a single ecological change. For the shift from leaves to seeds affects much more than the levels of omega-3 and omega-6 in the body. It also helps account for the flood of refined carbohydrates in the modern diet and the drought of so many micronutrients and the surfeit of total calories. From *leaves* to *seeds*: It's almost, if not quite, a Theory of Everything." p. 132

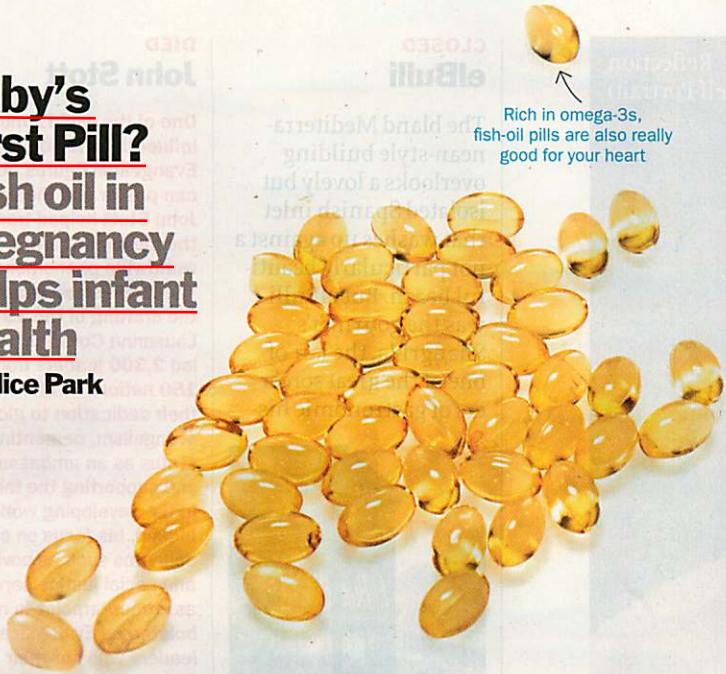
"The rule about eating more leaves and fewer seeds applies not only to us but also to the animals in our food chain." p. 168

Vegetarian Pregnancy References

Health&Science

Baby's First Pill? Fish oil in pregnancy helps infant health

By Alice Park



Rich in omega-3s, fish-oil pills are also really good for your heart

For good or ill, everything mothers do during pregnancy affects the health of their babies. That includes taking daily supplements, according to a new study that found that children born to mothers who take fish-oil pills while pregnant may benefit from an early boost in immunity.

Researchers randomly assigned about 1,000 pregnant women to take daily supplements of docosahexaenoic acid (DHA), a major omega-3 fatty acid in fish oil, or a placebo. The babies' health was evaluated when they were 1 month, 3 months and 6 months old. At every stage, babies whose mothers took fish-oil pills were healthier than those whose mothers didn't. At 1 month, they were 24% less likely to have cold symptoms such as coughing, nasal congestion and runny noses. At 3 months, they were 14% less likely to be sick. By 6 months, infants whose mothers had taken DHA developed cold symptoms as often as babies whose moms took the placebo, but their colds didn't last as long.

How does prenatal fish oil affect a baby's ability to fight off sniffles? A developing fetus's immune system relies on cues from its environment—in this case, the womb—to start building the cellular defense system that recognizes and kills bacteria and viruses. Although the mechanism is unclear, the DHA seems to give the fetus a head start. In the study, expectant mothers got 400 mg of DHA daily, starting at 18 to 22 weeks, which is significantly more than the 200 mg that the average American woman consumes in a day.

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

High-Dose Docosahexaenoic Acid Supplementation of Preterm Infants: Respiratory and Allergy Outcomes

Brett J. Manley, Maria Makrides, Carmel T. Collins, Andrew J. McPhee, Robert A. Gibson, Philip Ryan, Thomas R. Sullivan, Peter G. Davis and for the DINO Steering Committee

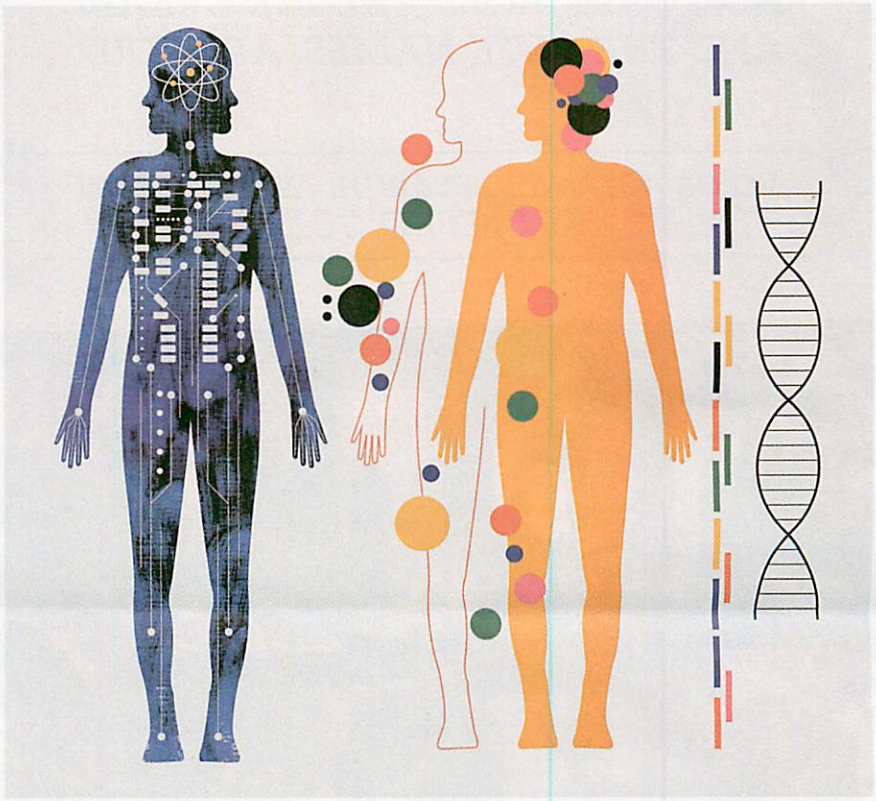
Pediatrics 2011;128;e71; originally published online June 27, 2011;
DOI: 10.1542/peds.2010-2405

1 first

CLOSER LOOK

RETHINKING THE WAR ON CANCER

DR. DAVID AGUS, a noted USC oncologist and one of Steve Jobs' doctors, has written a book that turns much of what we thought we knew about medicine upside down. ***By Brian Dumaine***



AT A MEETING OF the nation's top oncologists in Denver a couple of years back, Dr. David Agus, a prominent cancer researcher, was giving a keynote address. Agus talked about the need to take a new approach to treating cancer. He argued that focusing on killing or slowing the spread of cancerous cells was not enough. After all, despite a half-century of research by some of the best medical minds in the world, the death rate from cancer hasn't changed much since the 1950s. Instead, doctors should try to keep a patient's entire system healthy so the disease is less likely to take root in the first place. He said we should be able to control cancer without fully understanding it. At that, hisses arose from the audience.

A few Bronx cheers aren't enough to discourage a scientist as determined as Agus. He believes he has found a new way to greatly reduce the odds of getting sick and has set out his philosophy in a potentially game-changing new book, *The End of Illness*, which just became a *New York Times* bestseller. In it, he offers his prescription for preventive medicine, and backs it with studies and lively anecdotes.

When I caught up with this slim, casually dressed man, he rattled off ideas as if he couldn't let the world know fast enough about his thinking: "I want doctors to treat toward health and not treat toward disease," he said. Agus had his eureka moment after reading a 2004 *Fortune* article called "Why We're Losing the War on Cancer," by Cliff Leaf. Himself a cancer survivor, Leaf, a *Fortune* editor at the time, wrote that researchers have come to treat the individual features of cancer rather than putting their efforts into directly controlling cancer. "We have forgotten that curing cancer," says Agus, who was on the team of doctors who treated Jobs in the last years of his life, "starts with preventing cancer in the first place."

Today, if we get cancer, we attack the cells. If we get a heart attack, we perform a bypass. That's fine, but why not avoid the disease in the first place? Agus believes that diseases like cancer and heart disease should be thought of as verbs and not nouns. In his lexicon, "cancering" suggests a systemic problem. He points to a study of women who, after treatment for breast cancer, were given either an osteoporosis drug or a placebo. The ones who took the drug had a 40% lower rate of recurrence of the cancer, as their system was changed and the cancer didn't grow back. "Keep the soil healthy," says Agus, "and the bad seed won't grow."

One way to keep your body's soil healthy is to treat inflammation. When something is wrong with your body, it goes into panic mode and

Illustration by MIKE LEMANSKI

Time
6/4/12

Parenting Debate

Your recent cover article on attachment parenting has provoked much discussion about breast-feeding [May 21]. Anthropological surveys across many cultures indicate that the mean age at weaning in our species is 2.5 to 3 years. The evolutionary explanation for this long nursing period is clear. Our unusually large brains require large amounts of omega-3 fats, and breast milk concentrates these fats from mothers' bodily resources. Unfortunately, the omega-6-laden American diet, based on corn and soybean oil and animals fed on these crops, deprives infants and children of the omega-3 fats needed for healthy brain development. Thus early weaning and bad diets are delivering a one-two punch to American kids.

Steven J.C. Gaulin, Professor of Anthropology, University of California at Santa Barbara, and Dr. William D. Lassek, Former Assistant Surgeon General

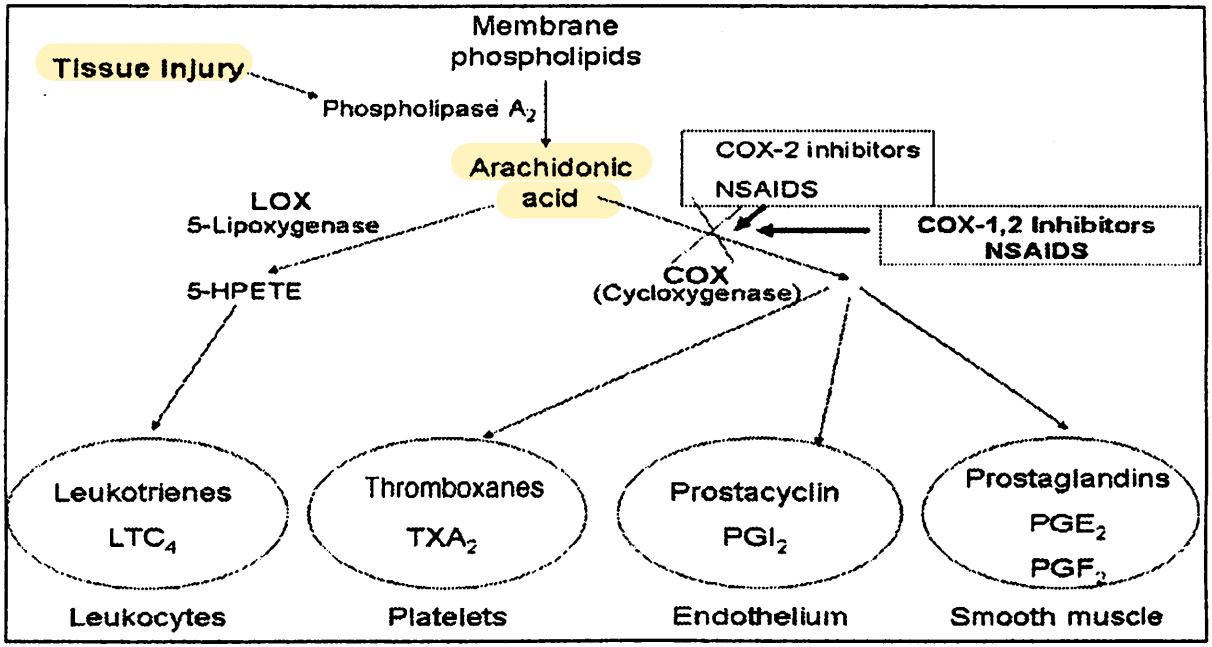
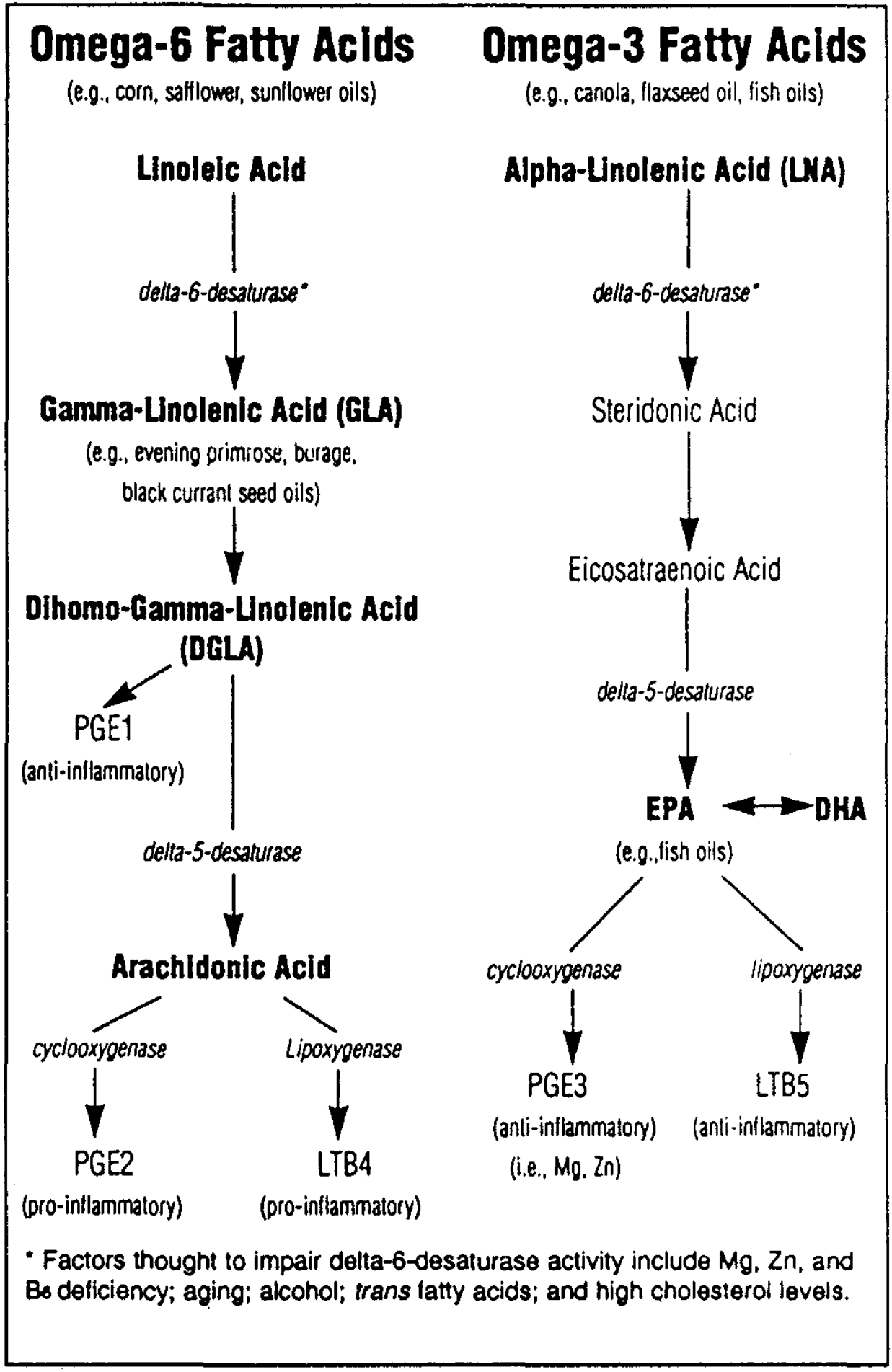
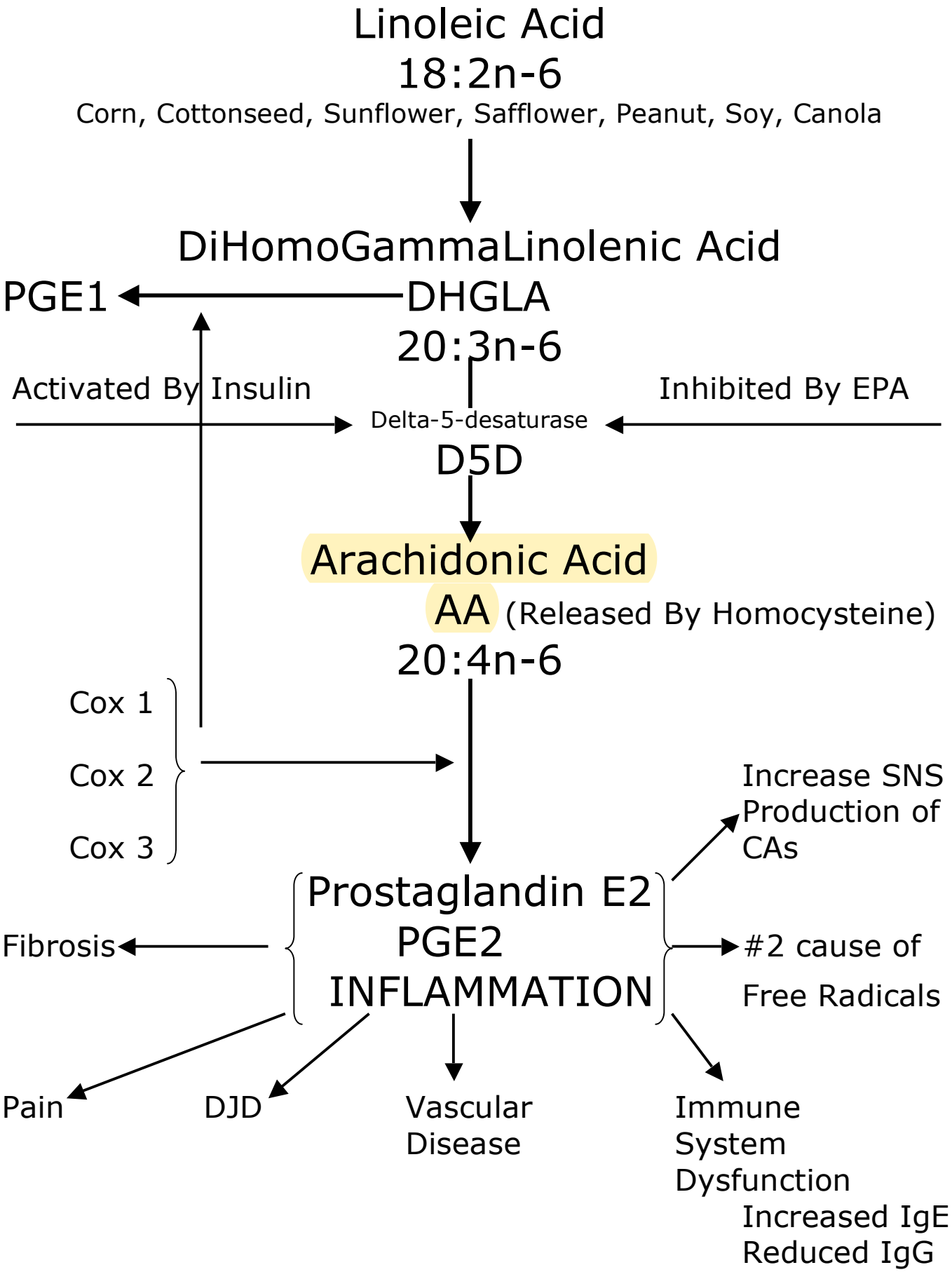
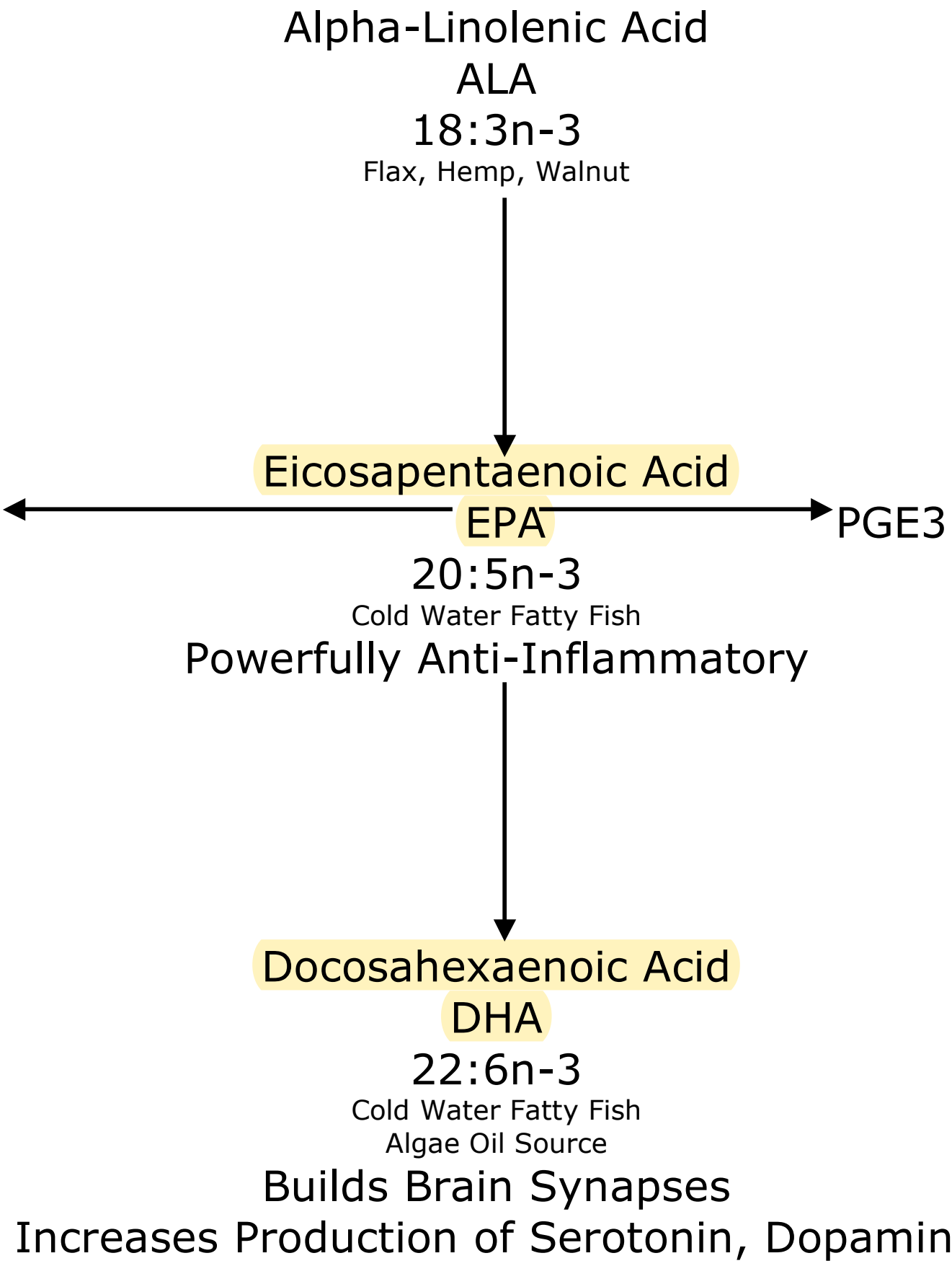


Figure 1: Schematic showing that when a cell membrane is injured the arachidonic acid pathway is activated to initiate the local inflammatory response through the production of prostaglandins, thromboxanes, and leukotrienes. Their activation requires the enzymes COX and LOX. The NSAIDs can block COX action and thereby prevent the formation of the COX-derived inflammatory mediators. 5-HPETE = 5-hydroperoxyeicosatetraenoic acid; LTC4 = leukotriene C4; PGE2 = prostaglandin E2; PGF_2 = prostaglandin F2; PGI_2 = prostacyclin; TXA_2 = thromboxane.

Maroon JC; Surgical Neurology International; December 2010


Omega-6 Fatty Acids
(e.g., corn, safflower, sunflower oils)
Linoleic Acid
delta-6-desaturase*
Gamma-Linolenic Acid (GLA)
(e.g., evening primrose, borage, black currant seed oils)
Dihomo-Gamma-Linolenic Acid (DGLA)
PGE1
(anti-inflammatory)
delta-5-desaturase
Arachidonic Acid
cyclooxygenase
Lipoxygenase
PGE2
(pro-inflammatory)
LTB4
(pro-inflammatory)
Omega-3 Fatty Acids
(e.g., canola, flaxseed oil, fish oils)
Alpha-Linolenic Acid (LNA)
delta-6-desaturase*
Steridonic Acid
Eicosatraenoic Acid
delta-5-desaturase
EPA
DHA
(e.g.,fish oils)
cyclooxygenase
lipoxygenase
PGE3
(anti-inflammatory)
(i.e., Mg, Zn)
LTB5
(anti-inflammatory)
* Factors thought to impair delta-6-desaturase activity include Mg, Zn, and B6 deficiency; aging; alcohol; trans fatty acids; and high cholesterol levels.


Linoleic Acid
18:2n-6
Corn, Cottonseed, Sunflower, Safflower, Peanut, Soy, Canola
DiHomoGammaLinolenic Acid
PGE1
DHGLA
20:3n-6
Activated By Insulin
Inhibited By EPA
Delta-5-desaturase
D5D
Arachidonic Acid
AA
(Released By Homocysteine)
20:4n-6
Cox 1
Cox 2
Cox 3
Increase SNS
Production of
CAs
Prostaglandin E2
PGE2
INFLAMMATION
Fibrosis
#2 cause of
Free Radicals
Pain
DJD
Vascular
Disease
Immune
System
Dysfunction
Increased IgE
Reduced IgG


Alpha-Linolenic Acid
ALA
18:3n-3
Flax, Hemp, Walnut
Eicosapentaenoic Acid
EPA
20:5n-3
Cold Water Fatty Fish
Powerfully Anti-Inflammatory
PGE3
Docosahexaenoic Acid
DHA
22:6n-3
Cold Water Fatty Fish
Algae Oil Source
Builds Brain Synapses
Increases Production of Serotonin, Dopamine

ORIGINAL ARTICLE

Omega 3 Fatty Acids in Bipolar Disorder

A Preliminary Double-blind, Placebo-Controlled Trial

Andrew L. Stoll, MD; W. Emanuel Severus, MD, PhD; Marlene P. Freeman, MD; Stephanie Rueter; Holly A. Zboyan; Eli Diamond; Kimberly K. Cress, MD; Lauren B. Marangell, MD

Background: ω3 Fatty acids may inhibit neuronal signal transduction pathways in a manner similar to that of lithium carbonate and valproate, 2 effective treatments for bipolar disorder. The present study was performed to examine whether ω3 fatty acids also exhibit mood-stabilizing properties in bipolar disorder.

Methods: A 4-month, double-blind, placebo-controlled study, comparing ω3 fatty acids (9.6 g/d) vs placebo (olive oil), in addition to usual treatment, in 30 patients with bipolar disorder.

Results: A Kaplan-Meier survival analysis of the cohort found that the ω3 fatty acid patient group had a significantly longer period of remission than the placebo group ($P = .002$; Mantel-Cox). In addition, for nearly every other outcome measure, the ω3 fatty acid group performed better than the placebo group.

Conclusion: ω3 Fatty acids were well tolerated and improved the short-term course of illness in this preliminary study of patients with bipolar disorder.

Arch Gen Psychiatry. 1999;56:407-412

From the Psychopharmacology Unit, Division of Psychiatry, Brigham and Women's Hospital (Drs Stoll, Severus, and Freeman, Ms Rueter, and Mr Diamond), and Department of Psychiatry, Harvard Medical School (Drs Stoll and Freeman), Boston, Mass; Free University of Berlin, Berlin, Germany (Dr Severus); and Department of Psychiatry, Baylor College of Medicine, Houston, Tex (Ms Zboyan and Drs Cress and Marangell). Dr Stoll is now with the Psychopharmacology Research Laboratory, McLean Hospital, Belmont, Mass, and continues with the Department of Psychiatry, Harvard Medical School.

BIPOLAR DISORDER (manic-depressive illness) is a common neuropsychiatric illness with a high morbidity and mortality.[1] Despite available mood-stabilizing drugs, such as lithium carbonate and valproate, the illness is characterized by high rates of recurrence.[1,2] Recent research suggests that all of the currently available mood-stabilizing drugs have inhibitory effects on neuronal signal transduction systems. These findings have led to the hypothesis that overactive cell-signaling pathways may be involved in the pathophysiological mechanisms underlying bipolar disorder.[3-6] By using this model of mood stabilizer action based on suppression of neuronal signal transduction mechanisms, novel mood-stabilizing agents can be rationally developed. One promising group of compounds is the ω3 fatty acids, obtained from marine or plant sources.[7] Among other effects, the ingestion of large amounts of ω3 fatty acids is associated with a general dampening of signal transduction pathways associated with phosphatidylinositol, arachidonic acid, and other systems.[8,9] Thus, ω3 fatty acids may be useful in conditions such as bipolar disorder, where the pathophysiological process may involve overactivity of cell signal transduction.

We hypothesized that orally administered ω3 fatty acids would exhibit inhibitory effects on signal transduction mechanisms in human neuronal membranes, and that high-dose ω3 fatty acids would be an effective mood stabilizer in bipolar disorder. The goal of this preliminary study was to assess the subacute mood-stabilizing effects of ω3 fatty acids in patients with unstable bipolar disorder.

See also pages 413 and 415

RESULTS

The results for the 30 patients with evaluable data, as defined above, are presented herein. There were no significant differences in the demographic and baseline clinical characteristics of the ω3 fatty acid and placebo groups (Table 1). **Figure 1** depicts a Kaplan-Meier survival analysis of the study cohort. The duration of time remaining in the study was significantly

This article is also available on our Web site: www.ama-assn.org/psych.

PubMed

Format: Abstract

Lipids. 2004 Dec;39(12):1207-13.

Increasing homicide rates and linoleic acid consumption among five Western countries, 1961-2000.

Hibbeln JR[1], Nieminen LR, **Lands** WE.

Author information

[1]Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland 20892, USA. jhibbeln@mail.nih.gov

Abstract

Clinical intervention trials and animal studies indicate that increasing dietary intakes of long chain n-3 FA or reducing linoleic acid intake may reduce aggressive and violent behaviors. Here we examine if economic measures of greater n-6 consumption across time and countries correlate with greater risk of homicide. Linoleic acid available for human consumption was calculated from World Health Organization disappearance data for 12 major seed oils in the food supply for the years 1961 to 2000 in Argentina, Australia, Canada, the United Kingdom, and the United States (US). Homicide mortality rates, adjusted for age, were obtained from the central judicial authority of each country. Apparent linoleic acid intake from seed oil sources ranged from 0.29 en% (percentage of daily food energy) (Australia 1962) to 8.3 en% (US 1990s). Greater apparent consumption of linoleic acid correlated with higher rates of homicide mortality over a 20-fold range (0.51-10.2/100,000) across countries and time in an exponential growth regression model ($r = 0.94$, $F = 567$, $P < 0.00001$). Within each country, correlations between greater linoleic acid disappearance and homicide mortality over time were significant in linear regression models. Randomized controlled trials are needed to determine if reducing high intakes of linoleic acid by seed oils with alternative compositions can reduce the risk of violent behaviors. These dietary interventions merit exploration as relatively cost-effective measures for reducing the pandemic of violence in Western societies, just as dietary interventions are reducing cardiovascular mortality. Low linoleate diets may prevent behavioral maladies that correctional institutions, social service programs, and mental health providers intend to treat.

PMID: 15736917

[PubMed - indexed for MEDLINE]

Evolutionary Aspects of Diet: The Omega-6/Omega-3 Ratio and the Brain

Molecular Neurobiology
October 2011; Vol. 44; No. 2; pp. 203-215

Artemis P. Simopoulos
This article has 116 references
LA = linoleic acid (plant derived omega-6 fatty acid)
ALA = alpha linolenic acid (plant derived omega-3 fatty acid)

FROM ABSTRACT:

Humans evolved on a diet that had a ratio of omega-6 to omega-3 fatty acids (FA) of about 1/1.

Today, Western diets have a ratio of 10/1 to 20–25/1, indicating that Western diets are deficient in omega-3 FA compared with the diet on which humans evolved and their genetic patterns were established.

Omega-6 and omega-3 FA are not interconvertible in the human body and are important components of practically all cell membranes.

DHA accounts for 40% of the membrane phospholipid fatty acids in the brain. Docosahexaenoic acid (DHA) is essential for the normal functional development of the brain and retina, particularly in premature infants.

EPA and DHA could play a role in reduced hostility, violence, substance abuse disorders and alcoholism.

The balance of omega-6 and omega-3 FA is important for homeostasis and normal development throughout the life cycle. **[Important]**

KEY POINTS FROM THIS ARTICLE:

1) Nutrition is an environmental factor that influences gene expression.

2) Major changes have taken place in our diet over the past 10,000 years since the beginning of the Agricultural Revolution, but our genes have not changed.

3) "Our genes today are very similar to the genes of our ancestors during the Paleolithic period 40,000 years ago, at which time our genetic profile was established."

4) "Humans today live in a nutritional environment that differs from that for which our genetic constitution was selected."

5) "The beneficial health effects of omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were described first in the Greenland Eskimos who consumed a high seafood diet and had low rates of coronary heart disease, asthma, type 1 diabetes mellitus, and multiple sclerosis. Since that observation, the beneficial health effects of omega-3 fatty acids have been extended to include benefits related to cancer, inflammatory bowel disease, rheumatoid arthritis, psoriasis, and mental health."

6) The change of omega-6/omega-3 ratio in the food supply of Western societies has occurred over the last 150 years.

7) "During evolution, omega-3 fatty acids were found in all foods consumed: meat, wild plants, eggs, fish, nuts, and berries."

8) Today in Western societies the omega-6/omega-3 ratio is very high due to the high intake of soybean oil, corn oil, sunflower, safflower, and linseed oil.

9) "LA is found in high amounts in grains with the exception of flaxseed, chia, perilla, rapeseed, and walnuts that are rich in ALA."

10) The green leaves of plants are higher in ALA than LA.

11) The conversion of ALA to EPA and DHA "appears to be limited."

- Omega-3 intake from ALA does not provide adequate intakes of EPA and DHA.

12) The omega-6/omega-3 ratio is associated with normal "growth and development, as well as in the outcome of hypertension, cancer, arthritis, mental health, allergies and other autoimmune diseases," as well as the "pathophysiology of atherosclerosis, inflammation, and aging."

13) "DHA is found in high amounts in the membranes of brain and retina and is critical for proper neurogenesis, neurotransmitter metabolism, neuroprotection and vision. The consumption of high amounts of DHA has been associated with multiple health benefits including brain and retinal development, aging, memory formation, synaptic membrane function, photoreceptor biogenesis and function, and neuroprotection. DHA is essential for pre-natal brain development." **[Key Point]**

14) "LA more than any other nutrient is associated with shorter telomeres and shorter telomeres are associated with aging, cancer and coronary heart disease."

15) "Clinical studies show that cognitive performance improves with omega-3's."

16) Omega-3's can affect not only cognitive functions, but also mood and emotional states and may act as a mood stabilizer."

17) Omega-3 deficiency in childhood delays brain development, and produces irreversible effects, while the same deficiency in aging accelerates the deterioration of brain function. **[Important]**

18) Daily administration of 3 g of omega-3's for 3 months significantly decreased feelings of anger, anxiety and aggression.

19) "Western diets are characterized by high omega-6 and low omega-3 fatty acid intake, whereas during the Paleolithic period when human's genetic profile was established, there was a balance between omega-6 and omega-3 fatty acids. Therefore, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected."

20) "The balance of omega-6/omega-3 fatty acids is an important determinant in maintaining homeostasis, normal development, and mental health throughout the life cycle."

21) The balance of omega-3 and omega-6 fatty acids to the "developing brain may be necessary for normal growth and functional development." **[Important]**

22) Omega-3 deficiency in the brain is associated with "decreased learning ability, with a lower synaptic vesicle density in the hippocampus; whereas, chronic administration of omega-3's improves reference memory-related learning probably due to increased neuroplasticity of the neural membranes." **[Important]**

23) "Cognitive performance improves with omega-3's supplementation possibly due to increased hippocampal acetylcholine levels, the anti-inflammatory effects of omega-3's, decreased risk of cardiovascular disease or increased neuroplasticity."

24) Omega-3 fatty acid supplementation could play a role in [reduced] hostility and violence.

25) "In humans, the brain is the most outstanding organ in biological development: it follows that the priority is brain growth and development, and in the brain the balance between omega-6 and omega-3 PUFA metabolites is close to 1:1. This ratio should be the target for human nutrition."

26) "The ratio of omega-6/omega-3 fatty acids in the brain between 1:1 and 2:1 is in agreement with the data from the evolutionary aspects of diet and genetics."

27) "A ratio of 1:1 to 2:1 omega-6/omega-3 fatty acids should be the target ratio for health."

COMMENTS FROM DAN MURPHY
The omega-3 oils I take are from Nutri-West; I believe their ratios of ALA, EPA, DHA, and GLA are optimal: (800) 443-3333. They have a specific formula for children (higher in DHA) and children love the taste.

Resolvins

Resolvins are endogenous pro-resolving and anti-inflammatory mediators that stimulate the resolution of inflammation by increasing macrophage phagocytosis of debris and countering pro-inflammatory molecules.

Role of Resolvins in the Inflammatory Resolution of Neurological Diseases

Frontiers in Pharmacology
May 8, 2020; Vol. 11

"The occurrence of neurological diseases including neurodegenerative disorders, neuroimmune diseases, and cerebrovascular disorders is closely related to neuroinflammation."

"Inflammation is a response against infection or injury."

"Our immune system can cause massive damage when the inflammatory response becomes dysregulated."

"Inflammatory resolution is an effective process that terminates the inflammatory response to maintain health."

"Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-three polyunsaturated fatty acids that play a crucial regulatory role in the development of inflammation."

"Resolvins (Rvs) derived from EPA and DHA constitute the Rvs E and Rvs D series, respectively."

"Numerous studies on the effect of Rvs over inflammation reveal that they have both anti-inflammatory and pro-resolving capabilities."

1,878 results

Did you mean ***resolving*** (312,029 results)?

1 Species-specific optimization of oxylipin ionization in LC-MS: a design of experiments approach to improve sensitivity.
Schmidt L, Garscha U.
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PMID: 39865019 Chinese.

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5 Effect of a Diet Supplemented with Marine Omega-3 Fatty Acids on Inflammatory Markers in Subjects with Obesity: A Randomized Active Placebo-Controlled Trial.
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Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals

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Abstract

Aspirin (ASA) is unique among current therapies because it acetylates cyclooxygenase (COX)-2 enabling the biosynthesis of R-containing precursors of endogenous antiinflammatory mediators. Here, we report that lipidomic analysis of exudates obtained in the resolution phase from mice treated with ASA and docosahexaenoic acid (DHA) (C22:6) produce a novel family of bioactive 17R-hydroxy-containing di- and tri-hydroxy-docosanoids termed resolvins. Murine brain treated with aspirin produced endogenous 17R-hydroxydocosahexaenoic acid as did human microglial cells. Human COX-2 converted DHA to 13-hydroxy-DHA that switched with ASA to 17R-HDHA that also proved a major route in hypoxic endothelial cells. Human neutrophils transformed COX-2-ASA-derived 17R-hydroxy-DHA into two sets of novel di- and trihydroxy products; one initiated via oxygenation at carbon 7 and the other at carbon 4. These compounds inhibited (IC(50) approximately 50 pM) microglial cell cytokine expression and in vivo dermal inflammation and peritonitis at ng doses, reducing 40-80% leukocytic exudates. These results indicate that exudates, vascular, leukocytes and neural cells treated with aspirin convert DHA to novel 17R-hydroxy series of docosanoids that are potent regulators. These biosynthetic pathways utilize omega-3 DHA and EPA during multicellular events in resolution to produce a family of protective compounds, i.e., resolvins, that enhance proresolution status.

Figures

J Biol Chem. 2003 Apr 25;278(17):14677-87. doi: 10.1074/jbc.M300218200. Epub 2003 Feb 17.

Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation

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PMID: 12590139 DOI: 10.1074/jbc.M300218200

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Abstract

Docosahexaenoic acid (DHA, C22:6) is highly enriched in brain, synapses, and retina and is a major omega-3 fatty acid. Deficiencies in this essential fatty acid are reportedly associated with neuronal function, cancer, and inflammation. Here, using new lipidomic analyses employing high performance liquid chromatography coupled with a photodiode-array detector and a tandem mass spectrometer, a novel series of endogenous mediators was identified in blood, leukocytes, brain, and glial cells as 17S-hydroxy-containing docosanoids denoted as docosatrienes (the main bioactive member of the series was 10,17S-docosatriene) and 17S series resolvins. These novel mediators were biosynthesized via epoxide-containing intermediates and proved potent (pico- to nanomolar range) regulators of both leukocytes reducing infiltration in vivo and glial cells blocking their cytokine production. These results indicate that DHA is the precursor to potent protective mediators generated via enzymatic oxygenations to novel docosatrienes and 17S series resolvins that each regulate events of interest in inflammation and resolution.

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Review > Rheum Dis Clin North Am. 2004 Feb;30(1):69-95.
doi: 10.1016/S0889-857X(03)00117-0.

Novel endogenous small molecules as the checkpoint controllers in inflammation and resolution: entrée for resoleomics

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Affiliations

PMID: 15061569 DOI: 10.1016/S0889-857X(03)00117-0

Abstract

Endogenously-generated small chemical mediators or autacoids play key roles in controlling inflammation and its organized resolution. Among them, lipoxins are the trihydroxy-tetraene-containing eicosanoids that are generated primarily by tight cell-cell interactions by way of transcellular biosynthesis and serve as local endogenous anti-inflammatory mediators. These "stop signals" in inflammation and other related processes may be involved in switching the cellular response from additional PMN recruitment toward monocytes (in a nonphlogistic fashion) that could lead to resolution of the inflammatory response or promotion of repair and healing. ASA impinges on this homeostatic system and evokes the endogenous biosynthesis of the carbon 15 epimers of lipoxins, namely ATLs, that mimic the bioactions of native LX in several biologic systems and, thus, can modulate in part, the beneficial actions of ASA in humans. Moreover, the temporal and spatial components in LX formation and actions are important determinants of their impact during an acute inflammatory reaction. Generation of lipid (ie, ATL) versus protein (ie, ANXA1) mediators during the host inflammatory response display different time courses. The temporal difference suggests that ALX could regulate PMN by interacting with each class of ligands within specific phases of the inflammatory response. ALX is the first cloned lipoxygenase-derived eicosanoid receptor. The signaling pathways and bioactions of ALX are cell type-specific. In agreement with in vitro results, ALX agonists, namely LXA4 and 15-epi-LXA4 and their stable analogs, regulate PMN during acute inflammation. In addition, it seems that LXs also display organ-specific actions, in addition to host defense and immune roles in the eye, kidney, lung, and oral and gastrointestinal tract and within bone marrow progenitors, possibly involving stem cells. The development of these few synthetic stable analogs has provided valuable tools to evaluate the biologic roles, significance, and pharmacologic actions of ALX and provided novel therapies for inflammatory diseases. The relationship between LX generation and current NSAID therapies is more intertwined than currently appreciated. ASA inhibits COX-1 and converts COX-2 into an ASA-triggered lipid mediator-generating system that produces an array of novel endogenous local autacoids from dietary omega-3 PUFA. Some of the local autacoids display potent anti-inflammatory or antineutrophil recruitment activity as well as impinge on the role of these compounds in resolution, and, thus, are termed "resolvins." It is not surprising that investigators recently found a protective action for COX-2 in cardiovascular disease. Together with the lipoxins and 15-epi-lipoxins, the identification of the resolvins gives us new avenues of approach in considering therapies for inflammation, cardiovascular diseases and cancer.

Related information

Review > Prostaglandins Other Lipid Mediat. 2004 Apr;73(3-4):155-72.
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Resolvins, docosatrienes, and neuroprotectins, novel omega-3-derived mediators, and their aspirin-triggered endogenous epimers: an overview of their protective roles in catabasis

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Affiliations

PMID: 15290791 DOI: 10.1016/j.prostaglandins.2004.03.005

Abstract

The molecular basis for the beneficial impact of essential omega-3 fatty acids is of considerable interest. Recently, novel mediators generated from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that displayed potent bioactions were first identified in resolving inflammatory exudates [J. Exp. Med. 192 (2000) 1197; J. Exp. Med. 196 (2002) 1025] and in tissues enriched with DHA [J. Exp. Med. 196 (2002) 1025; J. Biol. Chem. 278 (2003) 14677]. The trivial names Resolvin (resolution phase interaction products) and docosatrienes were introduced for the bioactive compounds belonging to these novel series because they demonstrate potent anti-inflammatory and immunoregulatory actions. The compounds derived from eicosapentaenoic acid carrying potent biological actions (i.e., 1-10 nM range) are designated E series, given their EPA precursor, and denoted as Resolvins of the E series (Resolvin E1 or RvE1), and those biosynthesized from the precursor docosahexaenoic acid are Resolvins of the D series (Resolvin D1 or RvD1). Bioactive members from DHA with conjugated triene structures are docosatrienes (DT) that are immunoregulatory [J. Exp. Med. 196 (2002) 1025; J. Biol. Chem. 278 (2003) 14677], and neuroprotective [J. Biol. Chem., 278 (2003) 43807; Proc. Natl. Acad. Sci. U.S.A. [submitted for publication]] and are termed neuroprotectins. The specific receptors for these novel bioactive products from omega-3 EPA and DHA are abbreviated Resolvin D receptors (i.e., ResoDR1), Resolvin E receptor (ResoER1; RER1), and neuroprotectin D receptors (NPDR), respectively, in recognition of their respective cognate ligands. Aspirin treatment impacts biosynthesis of these compounds and a related series by triggering endogenous formation of the 17R-D series Resolvins and docosatrienes. These novel epimers are denoted as aspirin-triggered (AT)-RvDs and -DTs, and possess potent anti-inflammatory actions in vivo essentially equivalent to their 17S series pathway products. Here, we provide a syntomy overview of the formation and actions of these newly uncovered pathways and products as well as highlight their role(s) as endogenous protective mediators generated in anti-inflammation and catabasis.

Related information

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Review > Curr Opin Clin Nutr Metab Care. 2005 Mar;8(2):115-21.
doi: 10.1097/00075197-200503000-00003.

Novel eicosanoid and docosanoid mediators: resolvins, docosatrienes, and neuroprotectins

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Abstract

Purpose of review: It is well known that arachidonic acid is the precursor to potent mediators. Many clinical studies suggest that omega-3 polyunsaturated fatty acids such as eicosapentaenoic acid and docosahexaenoic acid have beneficial actions in human diseases. The molecular basis of these actions remains of interest.

Recent findings: These demonstrate that eicosapentaenoic acid and docosahexaenoic acid are precursors to potent (nM range) bioactive mediators that possess both anti-inflammatory and protective properties. These mediators were coined resolvins, docosatrienes, and protectins as general classes, since each possesses unique chemical structures that are features of the new chemical classes and are biosynthesized by new pathways. Resolvins, discovered first, were identified during the resolution phase of acute inflammation; hence the term resolution interaction products, because they are also biosynthesized by human cells via cell-cell interactions. Docosatrienes contain conjugated triene structures generated from docosahexaenoic acid as a defining feature. The protectins comprise docosatrienes and resolvins of the D series that are both neuroprotective and anti-inflammatory. Aspirin impacts on these new pathways by triggering formation of their epimers (i.e. R isomers).

Summary: In view of the many beneficial actions attributed to omega-3 dietary supplementation, identification of novel potent mediators from omega-3 that are both anti-inflammatory and protective may have wide implications.

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Review > Lipids. 2004 Nov;39(11):1125-32. doi: 10.1007/s11745-004-1339-7.

Resolvins, docosatrienes, and neuroprotectins, novel omega-3-derived mediators, and their endogenous aspirin-triggered epimers

Charles N Serhan [1], Makoto Arita, Song Hong, Katherine Gotlinger

Affiliations

PMID: 15726828 DOI: 10.1007/s11745-004-1339-7

Abstract

The molecular basis for the beneficial impact of essential omega-3 (n-3) FA remains of interest. Recently, we identified novel mediators generated from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that displayed potent bioactions identified first in resolving inflammatory exudates and in tissues enriched with DHA. The trivial names resolvin (resolution phase interaction products) and docosatrienes were introduced for the bioactive compounds from these novel series since they possess potent anti-inflammatory and immunoregulatory actions. Compounds derived from EPA carrying potent biological actions (i.e., 1-10 nM range) are designated E series and denoted resolvins of the E series (resolvin E1 or RvE1), and those biosynthesized from the precursor DHA are denoted resolvins of the D series (resolvin D1 or RvD1). The number 1 designates the bioactive compounds in this family (#1-4). Bioactive members from DHA-containing conjugated triene structures or docosatrienes (DT) that possess immunoregulatory and neuroprotective actions were termed neuroprotectins. Aspirin treatment initiates a related epimeric series by triggering endogenous formation of the 17R-D series resolvins and docosatrienes. These epimers are denoted as aspirin-triggered (AT)-RvD and DT, and possess potent anti-inflammatory actions in vivo essentially equivalent to their 17S series pathway products. These include five distinct series: (i) 18R resolvins from EPA (i.e., RvE1); (ii) 17R series (AT) resolvins from DHA (RvD1 through RvD4); (iii) 17S series resolvins from DHA (RvD1 through RvD4), (iv) DT from DHA; and (v) their AT form 17R series DT. In this article, we provide an overview of the formation and actions of these newly uncovered pathways and products.

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Controlling Inflammation: A Fat Chance?

Journal of Experimental Medicine
March 7, 2005; Vol. 201; No. 5; pp. 671–674

Roderick J. Flower and Mauro Perretti: William Harvey Research Institute, London, UK.

"The inflammatory response protects the body against infection and injury but can itself become deregulated with deleterious consequences to the host."

"It is now clear that several endogenous biochemical pathways activated during defense reactions can counter-regulate inflammation."

"New experimental evidence adds resolvin E1 to this group of endogenous inhibitors and provides further rationale for the beneficial effects of dietary supplementation with fish oils."

The discovery in the 1930s that certain polyunsaturated fatty acids were "essential" to the health of mammals begged the question of why they were so crucial.

"Initially it was thought that their importance lay in their unique viscotropic effect on biological membranes, but the further discovery in the 1960s that all essential fatty acids were also substrates for prostaglandin synthesis by the cyclooxygenase enzymes lead to the realization that, in addition to being important structural components of the cell, these lipids were the precursors of potent hormones with widespread effects on the cardiovascular and immune systems."

"The essential fatty acids, which include arachidonic and eicosapentaenoic acids, cannot be synthesized by mammals de novo but must be supplied in the diet either as the native lipids or as immediate precursors, such as linoleic or –linolenic acids, which are then converted by chain elongation and desaturation reactions into the required end product."

Arachidonic acid is a 20-carbon fatty acid with 4 unsaturated double bonds that belongs to a group of fatty acids known as omega-6 fatty acids.

"Since the main source of essential fatty acids is foodstuffs, it follows that the actual composition of essential fatty acids in the body reflects to a large extent the nature of the diet."

Although arachidonic acid is abundant in the tissues of many land-dwelling animals, fish and marine mammals have a preponderance of the closely related eicosapentaenoic acid, belonging to the omega-3 group.

"It has been suggested that mankind evolved on a diet where the ratio of omega-6: omega-3 fatty acids was 1:1, as opposed to the prevailing ratio (at least in Western societies) of 10–20:1."

"The implication is that the onset and progress of many inflammatory and other diseases may be exacerbated by this shift in dietary habits."

Eicosapentaenoic acid competitively inhibits arachidonic acid.

"It had been deduced from epidemiological and dietary studies of different populations, such as the Greenland Eskimos, that a preponderance of fish in the diet was generally associated with a reduced incidence of inflammatory and cardiovascular disease."

"Over the years, a great number of studies have tested extracts of fish oil (which usually contain a mixture of eicosapentaenoic acid together with other associated fatty acids such as docosahexaenoic acid) as dietary supplements, finding a beneficial effect in a wide range of human inflammatory conditions including rheumatoid arthritis, cystic fibrosis, ulcerative colitis, UV-induced skin damage, septic shock, and asthma."

"Patients fed diets rich in eicosapentaenoic acid have been shown to express fewer inflammatory biomarkers, reduced leukocyte activation and mobility, and diminished production of prostaglandins and platelet-activating factor."

"Eicosapentaenoic acid is, therefore, one of the few 'nutriceuticals' for which there is compelling evidence of efficacy."

"The most widely accepted explanation for the efficacy of eicosapentaenoic acid was that increasing proportions of this fatty acid incorporated into the cellular phospholipid pool reduces the net fraction of arachidonic acid released during cell activation, leading to less arachidonic acid oxidation overall and to the production of a different panel of lipid mediators."

"In [hu]man, a dose-related replacement of membrane fatty acids occurs after ingestion of up to 1.6 g eicosapentaenoic acid/day, an effect more pronounced when the amount of arachidonic acid in the diet was concomitantly restricted."

Consuming "increased amounts of eicosapentaenoic acid reduced the amount of arachidonic acid present in cells, and led to a reduction in the production of prostaglandins such as PGE2."

"Serhan's group has now placed the whole idea of anti-inflammatory lipids on a new and more relevant therapeutic footing."

2022

A SILENT FIRE

THE STORY OF INFLAMMATION, DIET & DISEASE

SHILPA RAVELLA

A Silent Fire
The Story of Inflammation, Diet & Disease

Shilpa Ravella, MD
Transplant Gastroenterologist with Expertise in Nutrition and an Assistant Professor of Medicine at Columbia University Medical Center
2022

"The resolution of inflammation is indeed an active process. Inflamed tissue does not return to its unadulterated state as a matter of course. The movement to clean up the mess and repair systems relies on specific anti-inflammatory cytokines, growth factors, and other molecules. Macrophages and neutrophils, cells that prompt acute inflammation, switch gears when it comes times for inflammation to die out, releasing new chemicals, the invisible mediators [physician Charles] Serhan had been looking for. He named these chemical molecules *resolvins*."

"Macrophages and neutrophils produce most of the specialized pro-resolving mediators identified during the resolution of inflammation."

"Pro-resolving mediators are unique immune-signaling molecules. Most are derived from lipids, not proteins."

"They [resolvins] help turn off inflammation, ridding the body of any residual inflammatory cytokines and debris. They slow the infiltration of immune cells and push macrophages to ingest dead cells—one of the signals that drives macrophages to switch to an anti-inflammatory state."

"These small molecules [resolvins] have been shown to reverse inflammation in disease and amplify the healing response, prompting tissue regeneration and wound repair."

"They [resolvins] are also especially adept at turning off one of the most aggravating symptoms of inflammation: pain."

"Pro-resolving mediators stimulate special white blood cells known as regulatory T cells (Tregs). Tregs are critical for maintaining inflammatory homeostasis and subduing excessive inflammation."

"Tregs produce anti-inflammatory cytokines like IL-10 that are integral to protecting the body against unwanted immune reactions and resolving inflammation. They tell the body to tolerate its own antigens, preventing horrific, lethal autoimmunity."

"Resolving inflammation is not equivalent to just dampening it. When inflammatory pathways are turned off, as with traditional anti-inflammatory drugs, the risk of unwanted casualties looms large. Pro-resolving mediators, which have both anti-inflammatory and pro-resolving properties, aim to solve the underlying problem, not mask its effects. They strengthen rather than impede signaling pathways that have evolved over millennia, commandeering nature's own anti-inflammatory mechanisms, with little to no risk of immune suppression. In fact, they actively assist the body in killing and eliminating germs."

"Most modern drugs do nothing to foster resolution—and some actively disrupt it. NSAIDs, for example, lower the amplitude of inflammation, decreasing redness, heat, swelling, and pain, but they also delay resolution. The quieter inflammation may linger longer in the body, hidden from view."

"A few routine blood tests can also be useful surrogates for revealing inflammation."

"Homocysteine, an amino acid that travels in the blood, is a risk factor for heart disease acid that travels in the blood, is a risk factor for heart disease and can be altered by diet and other lifestyle choices. A surplus of homocysteine is linked to markers of inflammation and to chronic inflammatory disease."

"Individuals with chronic inflammatory diseases tended to have lower levels [of resolvins]. People with diabetes, for example, had not only too many cytokines swimming in their blood but also too few resolvins. Inflammation's off switch probably played as much of a role as its on switch in a wide array of pathologies, including chronic wounds, typical autoimmune diseases like rheumatoid arthritis, and other modern afflictions tied to hidden inflammation—heart disease, cancer, obesity, diabetes, neurodegenerative diseases, and more."

"Effectively combating hidden inflammation begins with delving deeply into its root causes. Human genetics, which have remained relatively constant, or longer life spans cannot alone explain the steep rise in chronic inflammatory diseases over the last decades. Our destinies are largely shaped by lifestyle. Hidden inflammation is one important mechanistic link between many environmental triggers and the ailments they are associated with."

"Most drugs are missing resolvins, and some foods are full of them. A true anti-inflammatory diet is also a pro-resolving and can be a powerful as a drug—even more so. Food and other lifestyle factors, independent of their effects on inflammation, can alter immunity as well. Vital nutrients feed immune cells, enhancing their ability to defend the body, while malnutrition or an unhealthy diet and lifestyle can inhibit immunity."

"In Boston, in the 1990s, physician Charles Serhan found an unexpected link between certain unsaturated fats and resolvins." "To his shock, the raw material used to make resolvins and most other pro-resolving mediators came, from a special type of polyunsaturated fat called omega-3s, the laboratory chow the mice feasted on was fortified with omega-3s."

"Omega-3s are essential fatty acids. They are required by the body, but unlike cholesterol, which the body makes, omega-3s are obtained only from the diet. They are originally made in plants, which produce omega-3s during photosynthesis."

"Omega-3s flourish in algae including seaweed, and weave their way through the aquatic food chain, building up in seafoods such as oysters, sardines, and salmon. A growing body of research emphasizes the importance of omega-3s in an array of chronic inflammatory diseases."

"The human brain, one of the fattiest organs in the body, craves omega-3s. Some scientists hypothesize that a lack of omega-3s may contribute to problems like autism and attention deficit disorder. Omega-3s may thin out the blood, helping to prevent blood clots. In patients with atherosclerosis, they have been shown to prevent heart attacks, strokes, and even death. They shrink atherosclerotic plaques, as revealed by imaging studies, and help to stabilize them, decreasing the risk of plaque

rupture. Population studies indicate that higher omega-3 levels in the diet are correlated with a lower risk of death from any cause."

"Omega-3s have potent effects on the immune system. They inhibit inflammatory gene regulators like NF-kB and instead activate anti-inflammatory gene regulators."

"They [omega-3s] lower inflammatory cytokines and blood levels of biomarkers like CRP, IL-6, and TNF-a. Their by-products both reduce and resolve inflammation. For example, docosahexaenoic acid and eicosapentaenoic acid, two omega-3 fatty acids, are essential for making resolvins and other pro-resolving mediators."

"Over the years, omega-3 fats have been fleeing the food supply. Since they grow rancid more readily than other types of fats, plant breeders often select for crops with fewer omega-3s. Food industries replace omega-3s with a more stable essential polyunsaturated fatty acid known as omega-6. In broad terms, omega-3 fats give rise to the most powerful anti-inflammatory compounds, while omega-6 fats tend to produce inflammatory ones and encourage blood clots."

"The true dilemma relates to the balance of omega-3s and omega-6s in the body. Because they compete for the same enzymes and space in cell membranes, they engage in a zero-sum game: an excess of omega-6s in the diet hampers the body's ability to process omega-3s and yield an abundance of compounds that rein in and resolve inflammation. Unlike olive oil, any—but not all—plant oils are exceedingly high in omega-6s. Methods employed to extract plant oils can concentrate omega-6 fats, which have become central components of processed foods and most restaurant industries; aside from table sugar, they are the cheapest source of calories. Our ancestors consumed around four times as many omega-6s as omega-3s, but modern diets unleash fifteen to twenty times as many omega-6s, leading to a profound dearth of omega-3s."

"A balanced intake of unsaturated fats can favorably affect immune cells. Unsaturated fats, particularly omega-3s, elicit macrophages' latent, genial qualities involved in tissue repair and resolution of inflammation. When omega-3 fats influence macrophages, anti-inflammatory effects ensue, including a decrease in IL-1ß, IL- 6, and TNF-a and a boost in the anti-inflammatory cytokine IL-10."

"Unsaturated fats, especially those from intact plant foods like nuts, seeds, and avocados, act as prebiotics, or foods that promote human health by nourishing gut microbes. These fats fuel anti-inflammatory microbial species and behaviors. Omega-3s, in particular, promote microbial diversity and spur the growth of bacteria that produce short-chain fatty acids, metabolites that benefit human health in many ways. They can even help to counter the harmful effects of saturated fats upon gut germs."

"During the mid-twentieth century, as research on the role of diet in chronic ailments like heart disease, cancer, obesity, and diabetes flourished, scientists started to realize that remaking fat in a laboratory by pumping hydrogen molecules into vegetable oils produces a unique substance called *trans fat*. Hydrogenation also boosts omega-6s while eliminating omega-3s."

"The immune system does not tolerate trans fats, which are not simply stored as fat. Rather, they displace normal fatty acids in the membranes of every cell in our body, inextricably weaving themselves into our physiology. When this happens, the cells do not function as they should. They make an excess of volatile molecules called free radicals which injure healthy cells."

"Excessive free radicals lead to oxidative stress, ramping up the expression of inflammatory genes. They can irreversibly damage proteins, lipids, genetic information, and other substances in our bodies, exciting the immune system and adversely affecting the functions of our cells. Chronic inflammation is both a cause and a consequence of oxidative stress."

"Many studies have shown that trans fats are tied to chronic, low-level inflammation, with an increase in inflammatory blood markers."

"Paleolithic meat contains around 7% fat, much in the form of omega-3s and almost none saturated. In contrast, modern cuts of cattle raised on corn—and often pumped up with hormones and antibiotics—contain around 35% fat, most of which is saturated fat, and few omega-3."

"Even fish now contain fewer omega-3's and more saturated fat than their predecessors. And modern animal foods also accumulate an overload of omega-6s."

Taking NSAIDs to suppress inflammation dampens the healing process.

"Dozens of human clinical trials across age-groups show that regular exercise tones down chronic, low-level inflammation, reducing markers like CRP, IL- 6, and TNF-a- while increasing Tregs and cytokines that counter inflammation, like IL-10."

"Habitual movement of most kinds benefits the body. Even simple stretching may mitigate inflammation."

"Stimulation of the vagus nerve—which is known to boost anti-inflammatory effects in the body— induces the release of resolvins."

"Stress alters the actions of immune cells. Macrophages become angry and maladaptive, pumping out greater numbers of inflammatory cytokines."

"Stress directly affects immunity, weakening the ability of immune cells to effectively engulf or kill germs."

"To be human is to adapt to an evolving environment." "Nutrients like omega-3s and prebiotic fibers—which feed gut germs—stimulate special hormones that facilitate adaptation."

Acute Inflammatory Response Via Neutrophil Activation Protects Against the Development of Chronic Pain

Science Translational Medicine
May 11, 2022; Vol. 14; Article eabj9954

Marc Parisien, Lucas V. Lima, Concetta Dagostino, Nehme El-Hachem, and 16 more: from McGill University, Montreal, Canada; University of Parma, Italy; Queen's University, Ontario, Canada; University of North Carolina, Laval University, Quebec Canada; Duke University. This study cites 67 references.

These authors investigated the pathophysiological mechanisms underlying the transition from acute to chronic low back pain (LBP).

Their study involved an assessment of immune cells (neutrophils) from 98 subjects with acute LBP and a group of 30 subjects with temporomandibular joint dysfunction (TMD).

Clinicians followed a standardized protocol for treating acute LBP with NSAIDs or systemic steroidal drugs to reduce the acute inflammatory response.

All patients were evaluated using the *numerical rating scale* (NRS) that assesses pain from 0 to 10, where 0 is "no pain" and 10 is "worst pain imaginable." All subjects had a pain level of ≥4 on the NRS, with a duration of no more than 6 wks.

KEY POINTS FROM THIS ARTICLE:

1) "Chronic pain inflicts huge societal costs, in terms of management, loss of work productivity, and effects on quality of life."

2) "Chronic low back pain (LBP) is the most frequently reported chronic pain condition." **[Important]**

- "LBP ranks the highest of all chronic conditions in terms of years lived with disability, with its prevalence and burden increasing with age."

- LBP is a major problem worldwide with prevalence rates of:
  - Any time prevalence rate of 18%
  - 1-month prevalence rate of 31%
  - 1-year prevalence rate of 38%

3) "The transition from acute to chronic pain is critically important but not well understood."

4) "Current treatments for LBP often target the immune system and include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and corticosteroids, although all of these drug classes are minimally effective at best."

5) "The pathophysiology of chronic pain involves a complex interplay between the nervous and immune systems."

- "Chronic pain is a neuroinflammatory disorder mediated by neuronal and non-neuronal cells alike."

6) The key cell involved in the transition of acute pain to chronic pain is the immune system cell, the *neutrophil*.

- "Transient neutrophil-driven up-regulation of inflammatory responses was protective against the transition to chronic pain."

    - This response was inhibited by both NSAIDs and steroids.

- "Early treatment with a steroid or nonsteroidal anti-inflammatory drug (NSAID) led to prolonged pain despite being analgesic in the short term." **[Key Point]**

7) "Despite analgesic efficacy at early time points, the management of acute inflammation may be counterproductive for long-term outcomes of LBP sufferers."

- There is an elevated risk of persistent pain for subjects taking NSAIDs and/or steroids. **[Key Point]**

8) There is a protective effect of the acute inflammatory response against the development of chronic pain. **[Key Point]**

- This finding was replicated in a prospective independent cohort of patients with temporomandibular disorder (TMD).

- In the TMD cohort, "the recovery group displayed a significantly higher inflammatory response at the acute stage, whereas the chronic pain group displayed a significantly lower acute phase inflammatory response."

- Both the LBP and TMD cohort showed a larger number of neutrophil inflammatory genes expressed in subjects who fully recovered.

- There was elevated neutrophil activation and inflammation in the recovered subjects.

CONCLUSIONS:

9) "Results indicate the importance of the up-regulation of the inflammatory response at the acute stage of musculoskeletal pain as a protective mechanism against the development of chronic pain." **[Key Point]**

- "Impaired inflammatory response [with NDAIDs and/or steroids] prolongs resolution of painful behavior."

- "Active inflammatory responses, particularly those regulated by neutrophils, contribute to pain resolution." **[Key Point]**

- Inhibition of this active immune response will lead to the prolongation of pain.

- Steroids given during the acute pain phase delayed the recovery of the overall pain episode by twofold.

- "Drugs that inhibit inflammation might interfere with the natural recovery process, thus increasing the odds for chronic pain." **[Key Point]**

10) "Individuals with acute back pain were at greater risk [76%] of developing chronic back pain if they reported NSAID usage than if they were not taking NSAIDs, adjusting for age, sex, [and] ethnicity."

11) "The beginning of the inflammatory process programs its resolution, and it is thus the failure to initiate an appropriate inflammatory response that may lead to chronic pain." **[Key Point]**

12) The acute treatment of inflammation with either a steroid or a NSAID, "although both effectively reducing pain behavior during their administration—greatly prolonged the resolution of neuropathic, myofascial, and especially inflammatory pain states." **[Key Point]**

13) In human subjects who reported acute back pain, NSAIDs "increased risk to still report back pain 2 to 6 years later." **[Important]**

14) The findings showed that NSAID use increases the risk of subsequent development of chronic back pain.

- "Higher percentages of neutrophils at the acute pain stage protected against chronic pain development." **[Key Point]**

- "Active immune processes confer adaptation at the acute pain stage, and impairment of such inflammatory responses in subjects with acute LBP (or TMD) increases the risk of developing chronic pain."

- These adaptive inflammatory responses are "modified by both genetics and environmental factors, and can be inhibited by steroids and NSAIDs."

15) "Our conclusions may have a substantial impact on medical treatment of the most common presenting complaint to healthcare professionals."

- "The long-term effects of anti-inflammatory drugs should be further investigated in the treatment of acute LBP and likely other pain conditions."

16) "The replication of our findings in the TMD cohort also suggests that our findings are likely to be applicable to other chronic pain conditions."

COMMENTS FROM DAN MURPHY, IRONY:

Inflammation drives pain, hence, the rationale for the use of anti-inflammatory drugs for patients with acute pain syndromes.

This study confirms short-term benefits of NSAIDs and steroids for patients with acute LBP or TMD pain.

However, ironically, these drugs reduce the genetic expression of inflammatory neutrophil (an immune system cell) genes which actually increase the incidence of chronic pain syndromes by 76%.

This study suggests that ***not*** taking NSAIDs or steroids for an acute episode of pain greatly reduces the risk of suffering from a chronic pain syndrome.

THE PLANT PARADOX

THE HIDDEN DANGERS IN "HEALTHY" FOODS THAT CAUSE DISEASE AND WEIGHT GAIN

STEVEN R. GUNDRY, MD

The Plant Paradox
The Hidden Dangers in "Healthy" Foods that Cause Disease and Weight Gain

Steven Gundry, MD

2017

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

About twelve years ago, I ran into the head of pathology in the hall of my hospital.

What do you know about intestinal webs? I told him that I had never heard of them.

He proceeded to tell me about a woman in her fifties who had come in with intestinal obstruction and was immediately rushed into the operating room where a large part of her small intestine, which was swollen and blocked in several areas, had to be removed.

When the pathologist opened the bowel, he discovered 'webs' of tissue, like washers on the fitting of a garden hose, which almost completely blocked the entire interior of the tube.

This is quite common in people who regularly use NSAIDs, such as Advil and Motrin, both brands of ibuprofen, or Aleve, Naprosyn, Mobic, Celebrex, and aspirin.

All were introduced in the early 1970s for pain and fever relief and as an arthritis medication in lieu of aspirin.

Prolonged use of aspirin was clearly associated with damage to the stomach lining, but because other NSAIDs did not damage the stomach, drug companies heralded them as nothing short of miraculous.

NSAIDs do not damage the stomach lining, which we can view with a gastroscope; instead, they damage the lining of the small intestine, which is beyond the reach of a scope.

Because we could not see their ill effects, NSAIDs have done extreme damage to the barrier that keeps not just lectins, but also LPSs, out of you.

Copious research published over the last half century reveals that gulping down apparently harmless NSAIDs is like swallowing a live grenade. These drugs blow gaping holes in the mucus-lined intestinal barrier.

As a result, lectins, LPSs [lipopolysaccharides], and living bacteria are able to deluge the breaks in your levee, flooding your body with foreign invaders.

Inundated by these foreign proteins and other invaders, your immune system does what if does best, producing inflammation and pain. This pain in turn prompts you to down another NSAID, promoting a vicious cycle, which can ultimately result in your seeking out prescription-level pain relievers.

A course of antibiotics, stomach-acid reducers, or even changes in our food supply also allow bad bacteria to move in and take over, just as NSAIDs do.

Increased intestinal permeability from lectins and LPSs, as well as the regular use of NSAIDs and acid-reducing drugs, produces what is commonly called leaky gut syndrome.

I originally thought that leaky gut was an isolated condition affecting a few unfortunate individuals, now I am convinced that leaky gut underlies all our disease issues, just as Hippocrates posited.

Known by the pharmaceutical industry as 'gateway drugs' to more powerful painkillers, ibuprofen (Advil and Motrin), naproxen (Aleve), Celebrex, Mobic, and other non-steroidal anti-inflammatory drugs (NSAIDs) were introduced in the early 1970s as an alternative to aspirin, which was known to damage the stomach lining.

We now know that NSAIDs damage the mucosal barrier in the small intestine and colon, allowing lectins, LPSs [lipopolysaccharides], and other foreign substances to pass through the intestinal wall, initiating a war within your body.

Evidence of the war is increasing inflammation, which you feel as pain. And the more pain you have, the more NSAIDs you take.

How could we not have known this? Actually, the pharmaceutical companies did, but because our gastroscopes didn't reach that far, we doctors initially had no methods of seeing damage in the small intestine. It wasn't until we had camera pills you could swallow that we realized what was really happening, and by then NSAIDs were ubiquitous.

Remember that poor woman with the intestinal webs? NSAIDs had so destroyed the walls of her gut that massive amounts of scar tissue had formed. That whole process opens up pathways to more invaders, while setting up a vicious cycle: the more LPSs that escape, the more pain; the more pain, the more you use NSAIDs—until you graduate to the big boys, the prescription painkillers.

NSAIDs are both the number-one pharmaceutical seller and the number-one health menace.

The precursors of Advil and Aleve, ibuprofen and Naprosyn, were recognized as so dangerous when they were introduced in the 1970s that they were available only as prescription drugs.

Inflammation Resolution:
A Dual-Pronged Approach to Averting Cytokine Storms in COVID-19?

Cancer and Metastasis Reviews
May 2020

Dipak Panigrahy, Molly M. Gilligan, Sui Huang, Allison Gartung, Irene Cortés-Puch, Patricia J. Sime, Richard P. Phipps, Charles N. Serhan, Bruce D. Hammock:
From Harvard Medical School and the University of California, Davis.

BACKGROUND FROM DAN MURPHY:

In his 2008 book How the Immune System Works, Lauren Sompayrac, PhD, notes that the *Innate* Immune system (*phagocytosis* system) "rules" the *Adaptive* Immune System (*antibody producing* system); And that the primary cell of the innate immune response is the ***macrophage*** (there is a great picture on the cover of his book of a macrophage attacking a bacterium).

••••••••••

[*Eicosa*] is the Greek work for 20. *Eicosanoids* are hormone-like molecules that are synthesized from 20-carbon long polyunsaturated fatty acids. These fatty acids are classified as being either omega-6 or omega-3.

In their 1996 book Protein Power, physicians Michael and Mary Eades (MDs) state:

"Eicosanoids, a gang of at least 100 powerful hormone-like substances that control virtually all physiological actions in your body. The most important thing about eicosanoids is to keep them in balance."

Eicosanoids "are the most powerful agents known to [hu]man, yet they are totally controlled by the diet."

"Eicosanoids exert major effects on just about everything that goes on in the body."

They continue to describe how the definition of health is one's balance of inflammatory (bad) and anti-inflammatory (good) eicosanoids.

An important aspect of essential fatty acid biology is that the 20-carbon long omega-6 and omega-3 fatty acids are the precursors to a group of powerful but short-lived hormone-like compounds called "eicosanoids." One category of eicosanoids is referred to as *prostaglandins*. Another group is referred to as *leukotrienes*. Clinical applications of this biochemistry are summarized here:

"Resolvins are specialized pro-resolving mediators (SPMs) derived from omega-3 fatty acids, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)."

"Medical researchers from the Harvard Medical School, University of California-Davis, Virginia Commonwealth University and Institute for Systems Biology, Seattle have discovered that chemical molecules called resolvins ... could help prevent the cytokine storms caused by the COVID-19 disease."

"The research was published in the journal Cancer & Metastasis Reviews and the study was led by Assistant Professor Dr. Dipak Panigrahy and Dr. Molly Gilligan, both from Harvard Medical School."

"The researchers studied the human body's robust inflammatory response to the SARS-CoV-2 virus, which is now recognized as a hallmark symptom and observed that severe COVID-19 illness can result in excessive inflammation throughout the body, including the lungs, heart and brain."

"Rather than blocking cytokines, medical staff could turn off virus-induced inflammation by broadly activating the body's natural inflammation-clearing activities."

"Resolvins and other SPMs stimulate macrophage-mediated clearance of debris and counter pro-inflammatory cytokine production, a process called inflammation resolution. SPMs and their lipid precursors exhibit anti-viral activity at nanogram doses in the setting of influenza without being immunosuppressive. SPMs also promote anti-viral B cell antibodies and lymphocyte activity, highlighting their potential use in the treatment of COVID-19."

Dr. Gilligan notes, "We are now recognizing the importance of controlling this robust inflammatory response in COVID-19 infection in order to reduce associated organ damage and mortality. Finding new ways to dampen the body's inflammatory response to COVID-19 will likely be as important as finding effective antiviral therapies to control COVID-19 infection and reduce life-threatening organ damage. Moreover, these Resolvins have been found to be non-toxic and non-immunosuppressive in ongoing clinical trials for other inflammatory diseases, making them even more promising candidates for rapid clinical translation."

Among significant findings from the study are:

- A major effect of SARS-CoV-2 infection is a cytokine storm, which is a drastic increase in immune cell production of cytokines.

- COVID-19 disease can cause unchecked inflammation that can cause extensive organ damage, such as lung failure.

- Present therapeutic strategies in COVID-19 focus on inhibiting a single pro-inflammatory cytokine [with a drug] rather than broadly inhibiting the body's inflammatory response.

- Resolvins are lipid mediators derived from omega-3 fatty acids and serve as the body's natural "stop" signals to inflammation.

    - "The medical researchers found that increasing levels of these resolvins or lipid mediators in the body could be a new therapeutic approach to preventing life-threatening inflammation caused by SARS-CoV-2."

    - "What is exciting for us is that these lipid mediators that 'turn off,' or resolve, inflammation are already in clinical trials for other inflammation-driven diseases, such as eye disease, periodontal disease and pain. The mediators can quickly be applied to turn off inflammation in COVID-19 patients."

    - "What makes resolvins ideal is that there are basically derived from omega-3 fatty acids that are already proven safe for human consumption, are inexpensive, easily available and consumed."

The article cautions "that if anyone suspects that they have contracted COVID-19 disease, do no attempt to self-treat but instead immediately report to local health authorities or a nearby hospital and also prior to consuming any supplements, always check first with a doctor."

COMMENTS FROM DAN MURPHY:

Over the decades we have reviewed dozens of articles showing the health benefits of omega-3 fatty acids.

This article adds that adequate levels of omega-3s may reduce the adverseness of the COVID-19 "eicosanoid and cytokine storms," reducing symptoms, improving clinical outcomes, and possibly reducing deaths.

The bottom line is that this is another reason to take omega-3s, as eicosanoid balance is an important factor in optimizing host health.

Our family and practice use the Nutri-West brand: **800-443-3333**

See the summary graph below:

Role of Resolvins in Inflammatory and Neuropathic Pain

Pharmaceuticals
October 2023; Vol. 16; No. 10; Article 1366

Jaeik Park, Jueun Roh, Jingying Pan, Yong Ho Kim, Chul-Kyu Park, Youn Yi Jo. This article cites 135 references.

"This review aimed to evaluate the literature surrounding the resolvins [Rvs] in inflammatory and neuropathic pain."

This review summarizes the studies on the anti-inflammatory and analgesic effects of Rvs, one of the specialized pro-resolving mediators (SPMs) synthesized from ω-3 polyunsaturated fatty acids (PUFAs).

BACKGROUND FROM DAN MURPHY:

- **Nociceptive Pain**: stepping on a person's toe causes *nociceptive pain*. There is **no** tissue injury. Recovery is quick and complete when the foot comes off the person's toe.

- **Inflammatory Pain**: hitting a person's toe with a hammer causes *inflammatory pain*. There **is** tissue injury. Recovery requires the resolution of the inflammatory process.

- **Neuropathic Pain**: *neuropathic pain* occurs when the nerve itself is injured.

KEY POINTS FROM THIS ARTICLE:

1) "Chronic pain is an unpleasant experience associated with actual or potential tissue damage."

- "Inflammatory pain alerts the body to inflammation and promotes healing; however, unresolved inflammation can lead to chronic pain."

- "Neuropathic pain, due to somatosensory damage, can be a disease in itself."

    •• "Inflammation plays a considerable role in the progression of both types of pain."

- "Chronic inflammation may occur in cases of unresolved inflammation, resulting in chronic pain."

2) "Unlike nociceptive and inflammatory pain that arises from disease or tissue damage, neuropathic pain can be a disease in itself."

3) "[Neuropathic pain] is generally chronic and is caused by lesions within the somatosensory system, which bidirectionally communicates with the immune system." **[Very Important]**

4) "Resolvins, derived from omega-3 fatty acids, actively suppress proinflammatory mediators and aid in the resolution of inflammation."

- "Resolvins alleviate various inflammatory and neuropathic pain models by reducing hypersensitivity and regulating inflammatory cytokines and glial activation in the spinal cord and dorsal root ganglia."

- "Resolvins are a promising alternative for pain management with the potential to reduce the side effects associated with conventional medications." **[Key]**

5) Marine natural products (MNPs) are derived from marine life that is distributed in the oceans. They include ***omega-3s***.

- "Omega-3 polyunsaturated fatty acids (ω-3 PUFAs), which are precursors of resolvins (Rvs), are representative MNPs from fish oils."

- "ω-3 PUFAs are precursors of several types of specialized pro-resolving mediators (SPMs) that contribute to anti-inflammatory action, such as protectins, maresins, and Rvs."

6) Biosynthesis of Resolvins

- "Omega-3 fatty acids are primarily acquired through dietary sources, encompassing fish, fish oils, seafood, and some plants."

- "Because it cannot be endogenously synthesized within the human body, omega-3 must be acquired through dietary intake."

- "These fatty acids serve as the substrate for synthesizing Rvs, lipid mediators derived from omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)."

- "Rvs are typically biosynthesized from omega-3 fatty acids and commonly extracted from EPA and DHA."

- Resolvin biosynthesis occurs in various immune cells, including macrophages, eosinophils, neutrophils, and endothelial cells; they are involved in this process by releasing specific fatty acids and utilizing enzymes to convert DHA and EPA into precursor molecules for RvD and RvE series.

7) "Resolvins [Rvs] play a critical role in resolving various inflammation-related physiological responses."

- "Rvs have emerged as promising therapeutic agents for pain management by specifically targeting inflammatory processes."

- Circulating levels of Rvs significantly reduce inflammation-related diseases, such as aneurysmal subarachnoid hemorrhage, acute myocardial infarction, bipolar disorder, irritable bowel syndrome, etc.

- Rvs actively suppress the production of inflammatory mediators, such as cytokines and chemokines.

- Resolvins inhibit the expression of proinflammatory factors and promote the expression of anti-inflammatory factors.

- RvDs [from omega-2 DHA] promote the phagocytic function of macrophages.

- RvDs enhance bacterial phagocytosis in human macrophages by approximately 80% more than the controls.

- "Resolvins help to restore tissue homeostasis and contribute to the overall resolution of inflammation by inhibiting immune cell activation and reducing the release of pro-inflammatory mediators."

8) "Traditionally, nonsteroidal anti-inflammatory drugs (NSAIDs), such as cyclooxygenase inhibitors, have been used to manage inflammatory pain."

- "However, the side effects, including gastrointestinal, cardiovascular, hepatic, renal, cerebral, and pulmonary complications, have been reported in multiple placebo-controlled trials and meta-analyses studies."

- Only minor side effects resulting from prolonged systemic intake of ω-3 PUFAs have been reported. **[Important]**

- "No systemic side effects have been reported with the use of Rvs." **[Key]**

9) "Pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α secreted by activated macrophages, are involved in the pain process."

- "Studies have identified reductions in pro-inflammatory cytokines by Rvs in neuropathic and inflammatory pain models."

10) Functions of Resolvins in Neuropathic Pain

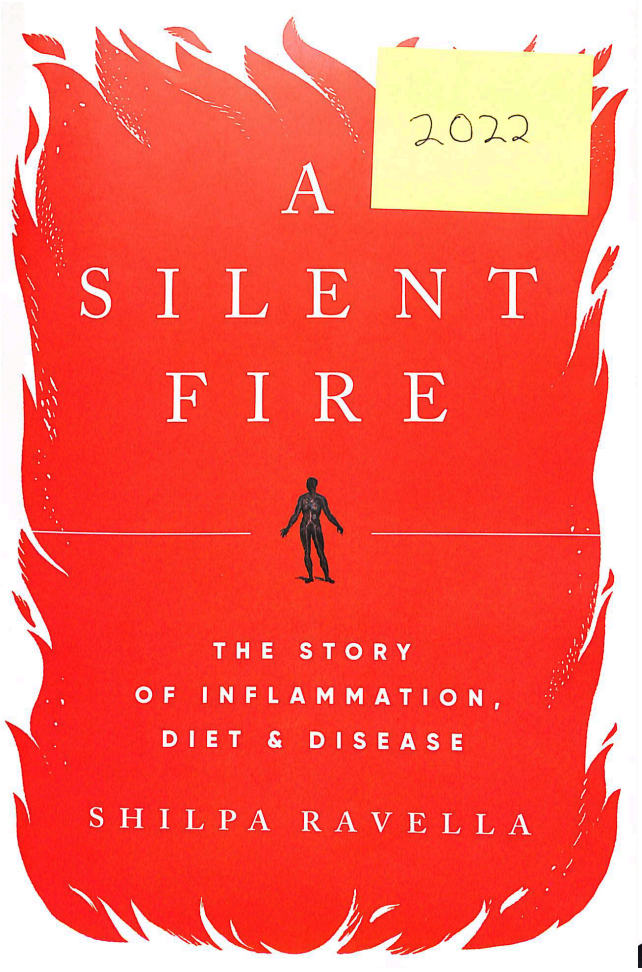
- "Neuropathic pain is caused by damage or disease affecting the somatosensory system." **[injury to the nerve itself]**

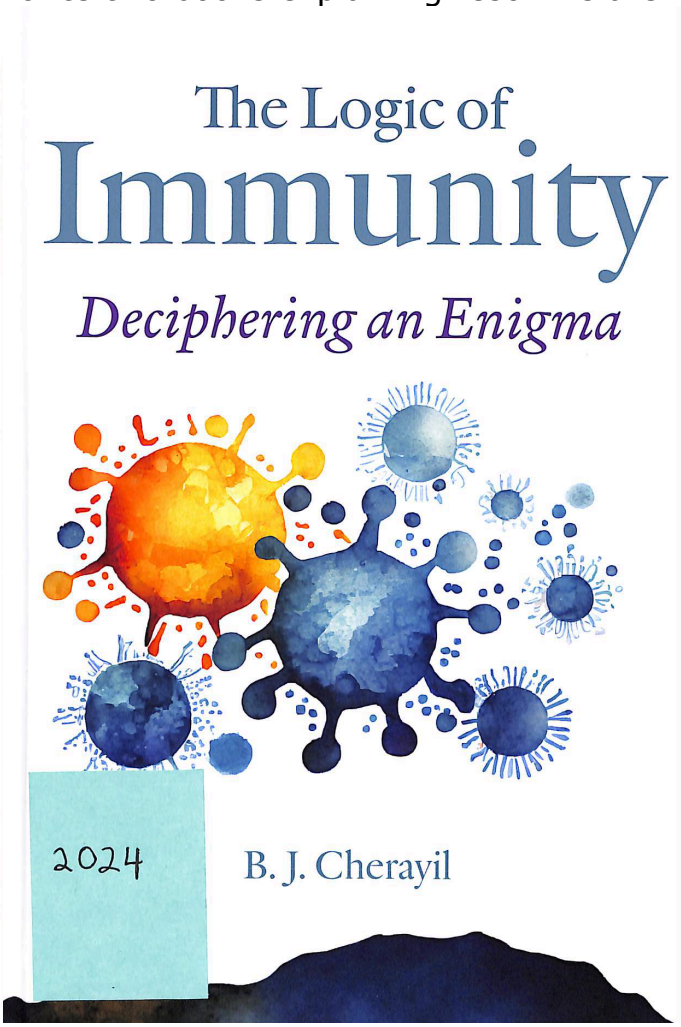
- Resolvins have an analgesic effect in neuropathic nerve injury.

11) "Rvs are endogenous compounds that offer a promising therapeutic potential and an alternative to conventional pain medications, presenting the advantage of reduced side effects commonly associated with current treatments."

12) "Rvs show remarkable efficacy in alleviating both inflammatory and neuropathic pain by regulating immune and glial cells, thereby resolving inflammation in the nervous system." **[Key Point]**

COMMENTS FROM DAN MURPHY: My favorite two books explaining resolvins are:





Both *steroids* and *NSAIDs* can impair the ability to make resolvins from omega-3s; this impairs the ability to fight infection and it also has been linked to causing chronic pain syndrome. See these Article Reviews:

39-13: **Salicylates and Pandemic Influenza Mortality, 1918–1919 Pharmacology, Pathology, and Historic Evidence**

28-20: **Inflammation Resolution: A Dual-Pronged Approach to Averting Cytokine Storms in COVID-19**

***7-23*:** **Acute Inflammatory Response Via Neutrophil Activation Protects Against the Development of Chronic Pain**

Higher Ratio of Plasma Omega-6/Omega-3 Fatty Acids is Associated with Greater Risk of All-cause, Cancer, and Cardiovascular Mortality: A Population-based Cohort Study in UK Biobank

eLife
Epidemiology and Global Health
April 5, 2024; Vol. 12; Article RP90132

Yuchen Zhang, Yitang Sun, Qi Yu, Suhang Song, J Thomas Brenna, Ye Shen, Kaixiong Ye: authors are from the University of Georgia, Cornell University, University of Texas at Austin. This study cites 49 references. Funding of this study was from the National Institute of Health.

These authors investigated plasma omega-3 and omega-6 PUFAs and their ratio in relation to all-cause and cause-specific mortality (all-cause, cancer, and cardiovascular) in a large prospective cohort of 85,425 participants from the UK Biobank.

Strengths of this study include the use of *objective* PUFA biomarkers in plasma instead of the estimated intakes from dietary questionnaires, which increases the accuracy of exposure assessment; the prospective population-based study design; large sample size; the long duration of follow-up (13 years); and detailed information on potential confounding variables, including: age, sex, ethnicity, alcohol consumption, smoking status, body mass index, physical activity, fish-oil supplementation, and comorbidities of hypertension, diabetes, and longstanding illness.

KEY POINTS FROM THIS ARTICLE:

1) "Cancer and cardiovascular disease (CVD) are the two leading causes of non-communicable disease mortality globally."

2) "Fatty acids play an essential role in health."

- "Studies have shown that diets high in omega-3 fatty acids found in foods like fish, fish oil, flaxseed, and walnuts may be beneficial."

- "Some studies have raised concern that too many omega-6 fatty acids in Western diets rich in vegetable oils may be harmful."

- "Scientists have proposed that the balance of omega-3 and omega-6 in diets is vital to health."

3) "A large number of existing observational studies documented the inverse association of circulating levels and intake of omega-3 PUFAs with mortality." **[Important]**

4) "Substantial epidemiologic evidence has linked the dietary or circulating levels of omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) to the risk of all-cause, cancer, and CVD mortality."

5) Circulating omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) have been associated with various chronic diseases and mortality.

- "Few studies examined the role of omega-6/omega-3 ratio in mortality."

6) The omega-3 index is defined as the percentage of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in total fatty acids in red blood cells, and is a validated biomarker of the dietary intake and tissue levels of long-chain omega-3 PUFAs.

- It is used as a risk factor for CVD and related mortality.

- The omega-3 index is also inversely associated with all cause-mortality.

7) "It has been suggested that the high omega-6/omega-3 ratio in Western diets, 20:1 or even higher, as compared to an estimated 1:1, during most of the time of human evolution, contributes to many chronic diseases, including CVD, cancer, and autoimmune disorders." **[Important]**

8) Findings:

- "Omega-3 and omega-6 PUFAs in plasma were all inversely associated with all-cause, cancer, and CVD mortality, with omega-3 showing stronger effects." **[Key Point]**

- "Risk for all three mortality outcomes increased as the ratio of omega-6/omega-3 PUFAs increased."

    - "Comparing the highest to the lowest quintiles, individuals had 26% higher total mortality, 14% higher cancer mortality, and 31% higher CVD mortality." **[Important]**

- Omega-3 and omega-6 PUFAs in plasma were consistently and inversely associated with all-cause, cancer, and CVD mortality, with omega-3 showing stronger effects.

9) Conclusions:

- "The experiments support dietary interventions to raise omega-3 fatty acid levels and maintain a low omega-6 to omega-3 fatty acid ratio to prevent early deaths from cancer, heart disease, or other causes." **[Key Point]**

- "Our findings support the active management of a high circulating level of omega-3 fatty acids and a low omega-6/omega-3 ratio to prevent premature death." **[Key Point]**

The conclusions of this article are supported by these prior *Article Reviews*:

Article Review 3-02:
Blood Levels of Long-Chain n–3 Fatty Acids and the Risk of Sudden Death

Article Review 50-03:
Omega-3 fatty acids and cardiovascular disease

Article Review 32-11:
Fish omega-3 fatty Acid Intakes Decrease Breast Cancer Risk

Article Review 29-12:
Evolutionary Aspects of Diet: The Omega-6/Omega-3 Ratio and the Brain

Article Review 7-18:
Global Survey of the Omega-3 Fatty Acids, Docosahexaenoic Acid and Eicosapentaenoic Acid in the Blood Stream of Healthy Adults

Article Review 15-18:
Promoting Neurovascular Recovery after Ischemic Stroke: Prophylactic Effect of Omega-3 Polyunsaturated Fatty Acids

Article Review 51-18:
Serial Circulating Omega-3 Polyunsaturated Fatty Acids and Healthy Ageing Among Older Adults in the Cardiovascular Health Study

Article Review 28-22:
Effect of Omega-3 Dosage on Cardiovascular Outcomes

Longitudinal Trajectories of Plasma Polyunsaturated Fatty Acids and Associations with Psychosis Spectrum Outcomes in Early Adulthood

Biological Psychiatry
April 15, 2024

David Mongan, Benjamin I. Perry, Colm Healy, Subash Raj Susai, Stan Zammit, Mary Cannon, David R. Cotter

This study cites 71 references.

This is the first assessment of plasma PUFA measures across childhood, adolescence, and early adulthood in a large general population cohort. "Plasma omega-6 to omega-3 ratio and DHA (expressed as percentage of total fatty acids) were measured by nuclear magnetic spectroscopy at 7, 15, 17, and 24 years of age in participants of ALSPAC (Avon Longitudinal Study of Parents and Children)." Outcomes were assessed at 24 years.

Psychotic experiences (PEs), at-risk mental state status, and psychotic disorder were assessed using the Psychosis-Like Symptoms interview (n = 3635; 2247 [61.8%] female).

The authors considered these confounders: sex, ethnicity, body mass, cigarette smoking, alcohol use, and BMI.

"PUFA levels were measured in plasma rather than erythrocyte cell membranes."

- "Plasma has the advantages of being less subject to degradation and greater stability in long-term storage."

- "Erythrocyte membrane levels have slower turnover and thus better reflect PUFA status in the preceding months, whereas plasma levels reflect a shorter time frame of approximately 1 to 2 weeks."

The authors hypothesized that higher n-6/n-3 ratio and lower DHA levels would be associated with increased risk of psychosis spectrum outcomes.

KEY POINTS FROM THIS ARTICLE:

1) "There is growing interest in relationships between nutrition and mental health, including the potential role of polyunsaturated fatty acids (PUFAs)."

2) "PUFAs, which must be obtained from the diet to maintain adequate levels, comprise 2 important subtypes."

- "Omega-6 (n-6) fatty acids, including linoleic acid and arachidonic acid, are found in nuts, eggs, and vegetable oils."

- "Omega-3 (n-3) fatty acids, including a-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid (DHA), are found in oily fish, some green vegetables, and supplements."

3) "Evidence supports associations between [low levels of] polyunsaturated fatty acids such as docosahexaenoic acid (DHA) and psychosis."

4) "Lipid mediators derived from n-6 and n-3 PUFAs have broadly opposing effects."

- "n-6 lipid mediators are generally proinflammatory."

- "n-3 lipid mediators predominantly reduce inflammation."

5) "An n-6:n-3 ratio of 1:1 to 2:1 is considered optimal for normal physiological functioning." **[Very Important]**

- "The average Western diet typically has larger amounts of n-6 relative to n-3 PUFAs."

6) "In the brain, the most abundant n-3 PUFA is DHA, which is postulated to have neuroprotective effects via modulation of neuronal membrane integrity, inflammation, oxidative stress, and synaptogenesis."

- n-3 PUFAs, including DHA, are capable of crossing the blood-brain barrier by passive diffusion or facilitated transport.

7) "Previous studies have provided evidence for associations between PUFAs and psychotic disorders."

- "Meta-analyses have found lower erythrocyte membrane n-3 PUFA levels in people with schizophrenia and lower DHA levels in individuals with first-episode psychosis compared with control participants."

- "A randomized controlled trial found that n-3 supplementation reduced transitions to psychosis among individuals at clinical high risk."

- "In a general population study, higher plasma n-6:n-3 ratio and lower DHA levels were cross-sectionally associated with psychotic disorders in early adulthood."

- "Higher DHA levels in late adolescence were longitudinally associated with reduced odds of incident psychotic disorder in early adulthood."

- "Mendelian randomization analyses support protective effects of long-chain PUFAs on schizophrenia risk."

8) Assessment variables:

- Plasma samples were collected from subjects at 7, 15, 17, and 24 years.
- Fatty acid plasma levels were measured using nuclear magnetic resonance spectroscopy.
- Fatty acid plasma levels require an overnight fasting sample.

9) Findings:

- Persistently high omega-6 to omega-3 ratio was associated with increased odds of PEs and psychotic disorder.
- Persistently low DHA was also associated with increased number of PEs and psychotic disorder.
- "[These authors] found strong evidence for associations of persistently high n-6:n-3 ratio and persistently low DHA with negative symptoms at age 24."

10) "It is possible that early neurodevelopmental periods exist during which PUFA status is especially pertinent in relation to risk of psychotic symptoms, whether in childhood or adolescence." **[Very Important]**

11) Chronic n-3 deficiency is associated with disturbances in synaptic function.

12) "There is evidence for low-grade inflammation during and preceding the onset of psychosis." **[Very Important]**

- "Modulation of inflammation and the innate immune system is one potential mechanism by which PUFAs may influence psychosis outcomes, although effects on oxidative stress and neurotransmission have also been suggested."

13) "n-3 PUFAs such as DHA promote neurite growth and synaptogenesis and thus may limit the dysregulated synaptic pruning during adolescence that is hypothesized to underlie at least part of the pathophysiology of schizophrenia."

14) Deficits in brain hippocampal growth during adolescence has been associated with PEs.

- "Higher hippocampal volume has been associated with higher n-3 levels in cognitively healthy older adults."

15) Average n-3 PUFA intake in the United Kingdom is suboptimal compared with World Health Organization recommendations.

16) "Given several reported health benefits associated with n-3 PUFAs, these findings have implications beyond psychosis." **[Key Point]**

17) Conclusions:

- "The findings of this study are compatible with the idea that optimizing PUFA status during development (whether through supplementation or dietary interventions) may be associated with reduction in psychotic symptoms in early adulthood."

- "Optimization of polyunsaturated fatty acid status during development warrants further investigation in relation to psychotic symptoms in early adulthood." **[Key Point]**

We have reviewed these articles that are related to this topic:

Article Review 15-12:
Dietary Fatty Acids and the Aging Brain

Article Review 29-12:
Evolutionary Aspects of Diet: The Omega-6/Omega-3 Ratio and the Brain

Article Review 46-15:
Longer-term Outcome in the Prevention of Psychotic Disorders by the Vienna Omega-3 Study

Article Review 7-18:
Global Survey of the Omega-3 Fatty Acids, Docosahexaenoic Acid and Eicosapentaenoic Acid in the Blood Stream of Healthy Adults

Article Review 33-19:
Omega-3 Fatty Acid Deficiencies in Neurodevelopment, Aggression and Autonomic Dysregulation

Article Review 46-20:
Effects of Oily Fish Intake on Cognitive and Socioemotional Function in Healthy 8–9-Year-old Children

We have also reviewd articles on omegas as related to arthritis, cardiovascular health, traumatic brain injury, dementia, cancer, and more.

Effect of Omega-3 Polyunsaturated Fatty Acids Supplementation for Patients with Osteoarthritis: A Meta-analysis

Journal of Orthopaedic Surgery and Research
May 24, 2023; Vol. 18; No. 1; Article 381

Deng W, Zhiqian Yi, Enzhi Yin, Rui Lu, Hongbo You, Xuefeng Yuan: This study cites 35 references.

These authors performed a systematic review and meta-analysis to comprehensively evaluate the influence of n-3 PUFAs on symptom and joint function of patients with osteoarthritis (OA).

Nine randomized clinical trials (RCTs) with 2,070 patients with OA contributed to the meta-analysis. The follow-up durations were 1 to 63 months.

KEY POINTS FROM THIS ARTICLE:

1) "Worldwide, osteoarthritis (OA) is the most common degenerative joint disease affecting cartilage and surrounding tissues, which has become a leading cause of disability worldwide, particularly of the older population."

2) "With a growing elderly and obese population, the incidence of OA in recent decades has been increasing, and this has also resulted in a substantial economic burden for the global populations."

3) Due to the adverse events associated with the long-term use of OA drugs, patients have been seeking alternative and complementary agents for relieving the symptoms and improving the function of the affected arthritis.

4) "Omega-3 polyunsaturated fatty acids (n-3 PUFAs) confers anti-inflammatory efficacy."

5) "Omega-3 polyunsaturated fatty acids (n-3 PUFAs), mainly including eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), have been suggested to be effective for patients with OA because of their efficacy for attenuating the systemic inflammatory response and the catabolic environment that accelerates cartilage degradation."

6) Findings:

- "Pooled results showed that n-3 PUFAs supplementation could significantly relieve the arthritis pain as compared to placebo." **[Key Point]**

- "No severe AEs [adverse events] related to the treatment with n-3 PUFA were reported among the included studies."

7) Conclusions:

- "Compared to placebo or no additional treatment, supplementation of n-3 PUFA could significantly relieve arthritis pain and improve joint function in patients with OA."

- No severe treatment related AEs were reported.

- "These results suggest that supplementation of n-3 PUFAs is effective and safe in patients with OA." **[Key Point]**

- "We found that n-3 PUFA is effective in relieving pain and improving joint function in patients with OA."

- "Supplementation of n-3 PUFAs is effective to relieve pain and improve joint function in patients with OA." **[Key Point]**

8) This study has these methodological strengths:

- "An extensive literature search was performed in three commonly used electronic databases, which could provide the up-to-date studies regarding the role of n-3 PUFA supplementation in patients with OA."

- "Only RCTs were included, and all of the included studies were of double-blind design."

- "Besides the symptom of pain, influences of n-3 PUFA supplementation on joint function was also evaluated, as well as the safety outcome."

9) The mechanisms underlying the benefits of n-3 PUFA include:

- "EPA and DHA supplementation could reduce the expression of multiple inflammatory markers involved in the pathogenesis of cartilage degeneration, such as interleukin-1 beta (IL-1β) and inducible nitric oxide synthase."

- Supplementation with EPA and DHA could reduce IL-1β-induced activation of nuclear factor-κB, thereby attenuating leptin-induced cartilage degeneration.

- EPA reduces oxidative stress-induced apoptosis and matrix loss of chondrocytes by inhibiting metalloproteinases and chondrocyte apoptosis.

10) "The optimal dose, components (ratio of EPA to DHA), and treatment duration of n-3 PUFA supplementation for OA remains to be determined."

11) "To sum up, results of the meta-analysis indicate that supplementation of n-3 PUFAs is effective to relieve pain and improve joint function in patients with OA, without increasing the risk of treatment related AEs."

- "These findings support the use of n-3 PUFAs supplementation as an alternative treatment for OA."

COMMENTS FROM DAN MURPHY:

We have reviewed these Articles that also support the use of omega-3s for OA:

Article Review 09-08:
A Meta-analysis of the Analgesic Effects of Omega-3 Polyunsaturated Fatty Acid Supplementation for Inflammatory Joint Pain

Article Review 15-08:
Fish Oil: What the Prescriber Needs to Know

Article Review 35-11:
Effect of Glucosamine Sulfate with or without Omega-3 Fatty Acids in Patients with Osteoarthritis

Article Review 11-13:
Omega-3 Fatty Acids and Synovitis in Osteoarthritic Knees

Article Review 21-06:
Omega-3 Fatty Acids (Fish Oil) as an Anti-inflammatory: An Alternative to Nonsteroidal Anti-inflammatory Drugs for Discogenic Pain

Several of these studies suggest the optimal dose of omega-3s is 3,000 mg/day: EPA 2,000 + DHA 1,000.

Omega-3 Supplementation Reduces Aggressive Behavior: A Meta-analytic Review of Randomized Controlled Trials

Aggression and Violent Behavior
September-October 2024; Vol. 78; Article 101956

Adrian Raine, Lia Brodrick; these authors are from the Departments of Criminology, Psychiatry, Psychology, and the Perelman School of Medicine, University of Pennsylvania. This study cites 44 references.

This meta-analysis summarizes findings from 29 RCTs (randomized controlled trials) on omega-3 supplementation to reduce aggression, yielding 35 independent samples with a total of 3,918 participants.

The maximum dose given so far in trials dealing with aggression is 2.4 g/day.

KEY POINTS FROM THIS ARTICLE:

1) "There is growing interest in the use of nutritional supplements to ameliorate aggressive and antisocial behavior."

2) "There is increasing interest in the use of omega-3 supplements to reduce aggressive behavior."

- "Omega-3 has been hypothesized as one nutritional component that could explain the link between poor nutrition and aggressive/violent behavior."

- "Experimental research in humans based on randomized controlled trials (RCTs) have argued that omega-3 supplementation can reduce aggression in a wide variety of human populations."

- Fish consumption is associated with a reduction in homicides.

3) Findings:

- "Results from these 35 independent samples obtained from RCTs provide substantial evidence that omega-3 supplementation can lead to modest short-term reductions in aggression."

4) "Why would omega-3 supplementation be expected to reduce aggressive behavior?"

- "It is also known that omega-3 is a long-chain fatty acid that plays a critical role in brain structure and function."

- "[Omega-3s] play multiple roles, making up approximately 35% of the cell membrane, enhancing neurite outgrowth, regulating both neurotransmitter

functioning and gene expression, and being involved in neurogenesis and nerve cell signaling."

- "Omega-3 reduces inflammatory processes in the brain and plays a significant role in cerebral blood flow."

- "Structural and functional brain imaging studies on humans have further documented that omega-3 can upregulate a variety of brain regions, with no evidence for any detrimental effect."

- Concentrations of DHA "are at their highest in the prefrontal cortex, an area critical for impulse control and emotion regulation."

    - "Prefrontal upregulation is a viable explanation for why omega-3 reduces impulsive-aggressive behavior."

- "Higher levels of omega-3 are also associated with increased functional connectivity in the frontal pole and anterior cingulate, areas which in part subserve executive functions."

    - "Omega-3 supplementation in turn has also been shown to enhance executive functions."

5) "Omega-3 appears to be effective in reducing aggression in children as well as adults, in females as well as males, in clinical samples as well as community samples, in the general population as well as externalizing populations."
[Key Point]

6) Omega-3 uptake is influenced by many factors.

- "The absorption of DHA and EPA requires digestion of fat, taking omega-3 supplements on an empty stomach or during low-fat meals such as breakfast has been argued to reduce bioavailability."

  "Intestinal microbes influence the absorption and bioavailability of omega-3."

7) Conclusions

- "Results of this study show that omega-3 supplementation significantly reduces aggressive behavior in the short-term."

- This treatment effect applies across a variety of different populations and cuts across age and gender.

    - "Given the enormous economic and psychological cost of aggression and violence in society, even small effects sizes need to be taken seriously."

- "Regarding clinical implications, based on these findings, our considered opinion is that there is now sufficient evidence to begin to implement omega-3 supplementation to reduce aggression in children and adults at a modest level - irrespective of whether the setting is the community, the clinic, or the criminal justice system."

- Caregivers should be informed of the potential benefit of omega-3 supplementation.

8) "Given the additional psychological and physical benefits of omega-3 supplementation and ease of implementation, we believe the time has come both to execute omega-3 supplementation in practice and also to continue to scientifically investigate its longer-term efficacy."

9) The Bottom Line:

- Evidence accumulated over 28 years from 29 RCTs document the efficacy of omega-3s for the management of aggression.

- Omega-3 supplementation reduces psychopathology that is comorbid with aggression, including depression, alcohol use, and more controversially schizophrenia-spectrum disorders.

- "There are well-documented beneficial effects of omega-3 supplementation on other health conditions, including lowering triglyceride levels, coronary heart disease, rheumatoid arthritis, and hypertension, pointing to additional benefits of supplementation over and above aggression reductions."

- "Omega-3 is safe to administer and side effects if any are both mild and minimal."

- "Both the FDA and the European Food Safety Authority concluded that long-term consumption of EPA and DHA supplements at a dosage level of approximately 5 g/day appears to be safe."

- "There are no known disadvantages on health outcomes in taking omega-3 at non-excessive doses."

- Omega-3 intervention is low-cost and very easy-to implement.

- "It is concluded that there is now sufficient evidence to begin to implement omega-3 supplementation to reduce aggression in children and adults - irrespective of whether the setting is the community, the clinic, or the criminal justice system."

HHS Public Access

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Protectins: Their biosynthesis, metabolism and structure-functions

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Abstract

Several lipoxygenase enzymes and cyclooxygenase-2 stereoselectively convert the polyunsaturated fatty acids arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, and n-3 docosapentaenoic acid into numerous oxygenated products. Biosynthetic pathway studies have shown, during the resolution phase of acute inflammation, that distinct families of endogenous products are formed. These products were named specialized pro-resolving mediators, given their specialized functions in the inflammation-resolution circuit, enhancing the return of inflamed and injured tissue to homeostasis. The lipoxins, resolvins, protectins and maresins, together with the sulfido-conjugates of the resolvins, protectins and maresins, constitute the four individual families of these local mediators. When administrated in vivo in a wide range of human disease models, the specialized pro-resolving mediators display potent bioactions. The detailed and individual biosynthetic steps constituting the biochemical pathways, the metabolism, recent reports on structure-function studies and pharmacodynamic data of the protectins, are presented herein. Emphasis are on the structure-function results on the recent members of the sulfido conjugated protectins and further metabolism of protectin D1. Moreover, the members of the individual families of specialized pro-resolving mediators and their biosynthetic precursor is presented. Today 43 specialized pro-resolving mediators possessing pro-resolution and anti-inflammatory bioactions are reported and confirmed, constituting a basis for resolution pharmacology. This emerging biomedical field provides a new approach for drug discovery, that is also discussed.

Keywords

protectins; specialized pro-resolving mediators; lipoxygenases; cyclooxygenase-2; biosynthesis; resolution pharmacology

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Author Contributions

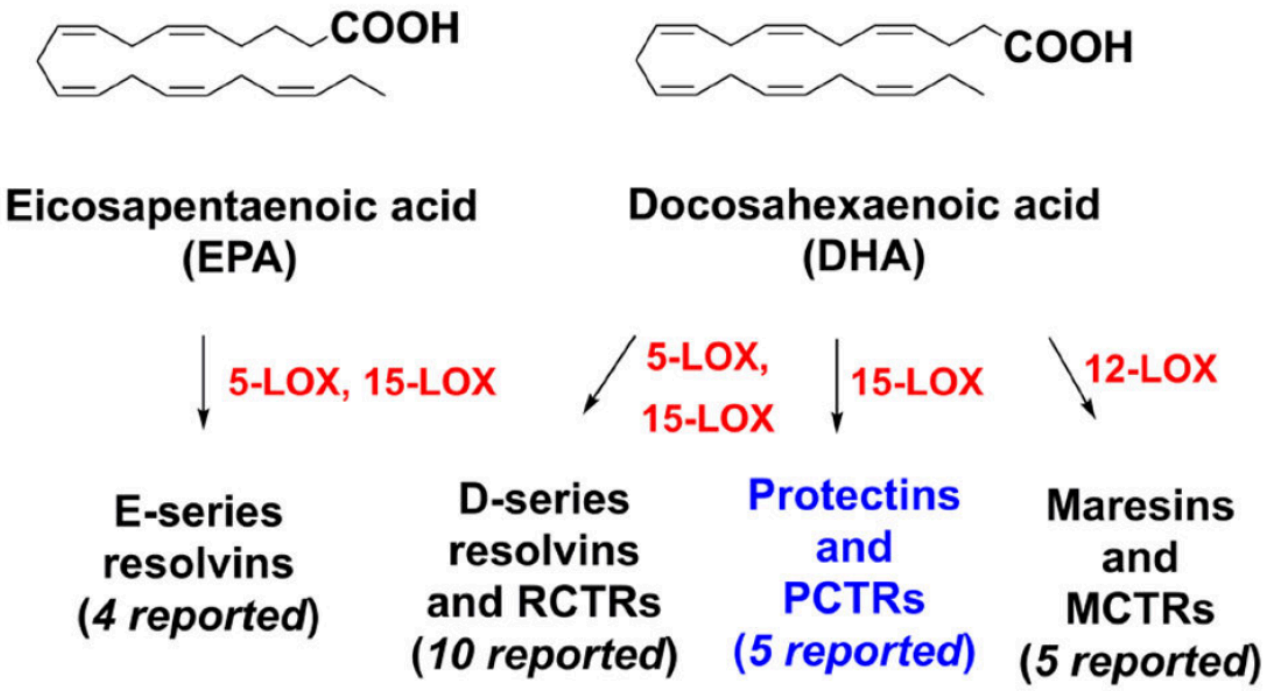
The manuscript was written through contributions of both authors that have approved the final version of the manuscript.

Declaration of interest

C.N.S. has filed patents on protectins and related compounds composition. C.N.S.'s interests are reviewed and are managed by BWH and Partners HealthCare in accordance with their conflict-of-interest policies.

Omega-3

Resolvins, Protectins, Maresins



Omega-3 Levels in Prenatal Supplements

American Journal of Perinatology
December, 2024; Epub

Mary J. Scourboutakos, MD, PhD; Elenee H. Harper; Michael T. Kopec, MD; Lauren Rose, BA, BASc, RD; Milena Forte, MD, CCFP, FCFP: from Eastern Virginia Medical School at Old Dominion University, Virginia; Queen's University, Canada; University of Toronto, Canada.

The objective of this study aimed to systematically document the reported omega-3 levels in commercially available prenatal supplements in the United States and Canada and compare these levels to recommended intakes in pregnancy.

DHA = docosahexaenoic acid EPA = eicosapentaenoic acid

KEY POINTS FROM THIS ARTICLE:

1) "Ninety to ninety-five percent of pregnant and lactating women in North America consume inadequate amounts of omega-3 fatty acids (including docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA])." **[Key Point]**

2) A Cochrane review of 26 randomized controlled trials demonstrated that supplemental intakes of omega-3 fatty acids of about 1,000 mg of EPA plus DHA per day can significantly decrease risk of preterm birth.

- "This is important because worldwide rates of preterm birth are increasing with more than 1 in 10 babies born before 37 weeks."

3) "New guidelines recommend that all women of childbearing age should consume 250 mg/d of DHA+EPA."

- "When intakes are sufficient at baseline, an additional 100 to 200 mg/d of DHA should be consumed during pregnancy."

4) "Pregnant women with low omega-3 intakes should consume 600 to 1,000mg of DHA+EPA, beginning no later than 20 weeks gestation."

5) "While dietary sources provide some omega-3s, only certain varieties of fish (salmon, mackerel, herring, sardines, and anchovies) contain EPA and DHA."

- Many pregnant women avoid fish because of concerns about methylmercury.

- "Prenatal supplements are an important alternative source of omega-3 fatty acids for pregnant women." **[Important]**

- •• "Only 55% of prenatal supplements contain omega-3s, at varying doses." **[Important]**

6) In this study, a total of 50 U.S. products and 18 Canadian products were assessed.

- Only 16% of products in the U.S. and 28% of products in Canada contained the dose of omega-3s recommended for pregnant women with insufficient intakes. **[Important]**

- "Only a minority (16–28%) of products provided the amount of omega-3s recommended for women with inadequate intakes."

- "This is important because most pregnant women (90–95%) have low omega-3 intakes and would benefit from omega-3 supplementation beyond that provided by most prenatal supplements to reduce their risk for preterm birth." **[Key Point]**

7) Key Points from Authors:

- "Omega-3 fatty acids can help prevent preterm birth."
- "New guidelines recommend increased intakes of omega-3 fatty acids during pregnancy."
- "Omega-3 levels in prenatal supplements may or may not be consistent with recommended intake levels."

COMMENTS FROM DAN MURPHY:

In 2011, the magazine Time published this article:

Health & Science
Time
August 15, 2011
Alice Park

Baby's First Pill?
Fish Oil in Pregnancy Helps Infant Health

"For good or ill, everything mothers do during pregnancy affects the health of their babies. That includes taking daily supplements, according to a new study that found that children born to mothers who take fish-oil pills while pregnant may benefit from an early boost in immunity."

"Researchers randomly assigned about 1,000 pregnant women to take daily supplements of docosahexaenoic acid (DHA), a major omega-3 fatty acid in fish oil, or a placebo. The babies' health was evaluated when they were 1 month, 3 months

and 6 months old. At every stage, babies whose mothers took fish-oil pills were healthier than those whose mothers didn't."

"At 1 month, they were 24% less likely to have cold symptoms such as coughing, nasal congestion and runny noses. At 3 months, they were 14% less likely to be sick."

"How does prenatal fish oil affect a baby's ability to fight off sniffles? A developing fetus's immune system relies on cues from its environment— in this case, the womb—to start building the cellular defense system that recognizes and kills bacteria and viruses. Although the mechanism is unclear, the DHA seems to give the fetus a head start."

"In the study, expectant mothers got 400 mg of DHA daily, starting at 18 to 22 weeks, which is significantly more than the 200 mg that the average American woman consumes in a day."

•••••

Docosahexaenoic acid (DHA) is critically important for the formation of synapses in the brain of fetuses, newborns, and children. As such, children still benefit from a supplemental omega-3 formula that has a higher level of DHA. We use the Nutri-West eye-dropper brand ((800) 443-3333): Complete Children's DHA/EPA Liquid:

A serving size is 20 drops, and that contains 40 mg EPA and 85 mg DHA, with 12 mg alpha linolenic acid from flaxseed oil.

We have also reviewed these related articles:

Article Review 37-07:
Dietary Omega-3 Fatty Acids for Women
Biomedicine & Pharmacotherapy

Article Review 42-09:
Dietary Omega 3 Fatty Acids and the Developing Brain
Brain Research

Article Review 24-10:
Omega-3 Fatty Acid Supplementation During Pregnancy
Reviews in Obstetrics & Gynecology

FRONTIERS IN NUTRITIONAL SCIENCE, NO. 1

Nutrition and Immune Function

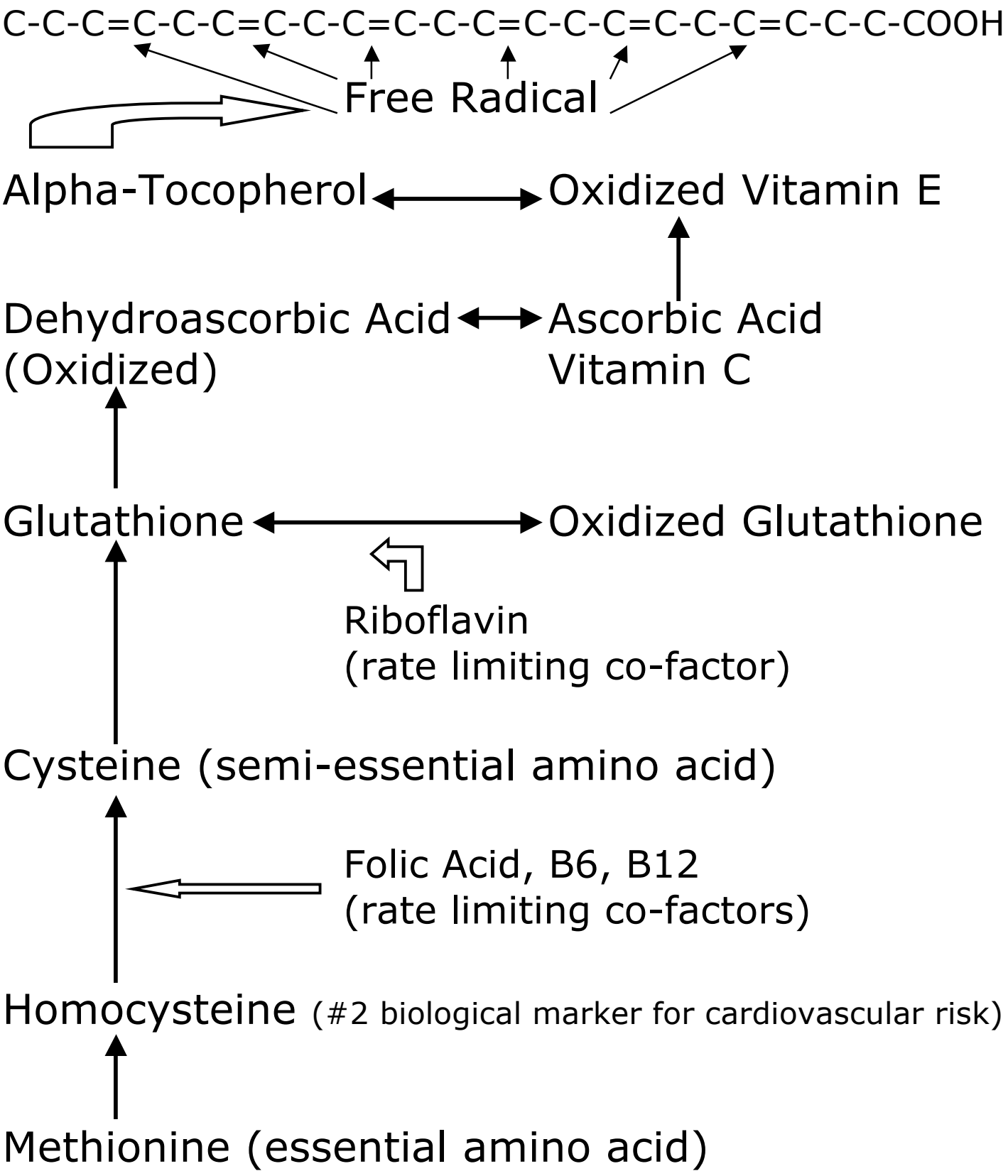
2002

Edited by P.C. Calder, C.J. Field and H.S. Gill

NS

CABI *Publishing*

Docosahexaenoic Acid; DHA; 22:6n-3 (Calder, 2002, p.139)



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Vitamin B-2 (Riboflavin) 50 mg

Vitamin B-6 50 mg

Folic Acid 800 mcg

Magnesium Chelate 150 mg

Selenium 1 mcg

Reduced Glutathione 50 mg

Policosanol 5 mg [this is important because Policosanol, in this dosage, has proven to lower blood lipids better than statin drugs]

CoQ10 5 mg

Alpha Lipoic Acid 5 mg

Dietary omega-3 fatty acids and risk of type-2 diabetes: Lack of antioxidants?

American Journal of Clinical Nutrition
August 2011; Vol. 94; No. 2; pp. 618-619

Bjarne Osterud

This author cites evidence that increased intake of dietary omega-3 fatty acids may increase the risk of type-2 diabetes.

Yet, he also notes that type-2 diabetes "is strongly associated with pro-inflammatory products," and therefore omega-3 fatty acids should prevent type-2 diabetes because they suppress the production of these pro-inflammatory products, noting that it "seems difficult to understand why long-chained omega-3 fatty acids are associated with [increased] risk of type-2 diabetes."

"Intake of omega-3 fatty acids may not always be beneficial because incorporation of these polyunsaturated fatty acids (PUFAs) in the cell membranes makes the cells more susceptible to oxidation if there is a lack of antioxidants where the omega-3 fatty acids are present in the membranes."

"Contrary to an anti-inflammatory effect, PUFAs may cause oxidative stress whereby the production of pro-inflammatory products is enhanced."

"Everywhere where PUFAs are present in live material, there is always an excess of antioxidants, which are removed when the omega-3 fatty acids are refined or when they are isolated. This means that these fatty acids when taken as dietary supplements may cause severe oxidation in their local environment in which support of antioxidants may be quite low. Omega-3 fatty acids may thereby cause oxidative stress and subsequently an increase in pro-inflammatory products known to promote type-2 diabetes."

The lack of type-2 diabetes in native Greenlanders despite their high intakes of omega-3 fatty acids in their diet through seal and whale blubber may be credited to the fact that "their diet is also rich in natural antioxidants associated with omega-3 fatty acids contained in blubber."

Thus, antioxidants may be required for the anti-inflammatory benefit of omega-3 fatty acids in humans.

COMMENTS FROM DAN MURPHY

Over the years a number of other authors have made similar claims as this author: increasing the intake of omega-3 fatty acids increases the requirement for antioxidants. As examples:

Natural Strategies For Cancer Patients
Russell Blaylock, MD
Twin Streams Books, 2003

"The universal problem with polyunsaturated oils, even the good ones, is that they oxidize very easily. When an oil oxidizes, it becomes rancid. Rancid oils can produce harmful substances (lipid peroxides) and free radicals." p. 134

Healthy Fats For Life
Preventing and Treating Common Health Problems with Essential Fatty Acids
Lorna Vanderhaeghe and Karlene Kasrst
Wiley, 2004

"Research has consistently shown that increased intake of essential fatty acids increases the need for antioxidants." p. 184

When taking essential fatty acids, "increasing your antioxidant consumption to prevent free radical damage is very important." p. 185

•••••

I have always advocated that one should take a combination of antioxidants when consuming fish oil. The antioxidant formula I use is a network of exogenous antioxidants that help the cell produce the endogenous antioxidant glutathione, from the book Nutrition and Immune Function, edited by Phillip Calder, CABI Publishing, 2002. It includes a ratio of vitamin E, vitamin C, B2, B6, and B12, plus some necessary minerals. The formula is available from **Nutri-West (800-443-3333)**, and is called **Complete Omega-3 Co-Factors**. I advocate taking 1 **Co-Factor** per gram of fish oil consumed.

"A bold and heroic work [that] will stand shoulder to shoulder with Rachel Carson's *Silent Spring*."

—David Perlmutter, MD, #1 *New York Times* bestselling author of *Grain Brain* and *Brain Wash*

TOXIC LEGACY

HOW THE WEEDKILLER GLYPHOSATE IS DESTROYING OUR HEALTH AND THE ENVIRONMENT

One Scientist's Determined Quest to Reveal the Truth

STEPHANIE SENEFF, PhD

2021

Toxic Legacy
How the Weedkiller GLYPHOSATE is Destroying Our Health and the Environment

Stephanie Seneff, PhD

Protein synthesis is an error prone process.

Amino acid *analogues* are molecules that substitute for an amino acids in protein synthesis.

- This is called a *substitution error*.

Substitution errors during protein synthesis causes protein dysfunction and disease.

Glyphosate substitutes for the amino acid *glycine* (Gly).

Glyphosate has a crippling effect on protein synthesis.

Glutathione

[*Glutathione* (GSH) is an endogenous antioxidant and detoxifier].

[*Glutathione* is your most powerful protector].

Glutathione = glutamate-cysteine-glycine = Glu-Cys-Gly

- 1/3 of the GSH amino acids are Gly

Collagen

"Collagen is the most common protein in the body, making up to 25 percent of the body's proteins."

- "Collagen is considered the body's scaffolding."

[Collagen is about 1,000 amino acids long]

A unique pattern for much of collagen, "every third residual is a glycine."

- This glycine motif "folds into an elegant triple helix."

- "This pattern is essential for collagen to fold properly into its elegant triple-helix structure. It is this structure that gives collagen its unique properties of tensile strength, elasticity, and ability to hold water."

- "Because every third amino acid is a glycine, collagen is tremendously vulnerable to glyphosate substitution, which would disrupt the triple helix formation."

"Mutations in several different glycine residuals in collagen weaken connective tissues, ….. and abnormal scar formation."

"Glyphosate substituting for glycine within collagen is an environmentally induced disruption that may be contributing to the widespread back, shoulder, neck, knee, foot, and hip pain so many of us experience today. This pain often necessitates surgery to repair injured joints."

- "Among people in their 70s, the prevalence of knee surgery among women has increased nearly 11-fold, and the prevalence of hip surgery has increased 9-fold over the past two decades."

- "Among men, the increase has been even more dramatic, with a 26-fold increase in prevalence of hip replacement surgery and a 15-fold increase in knee replacement surgery."

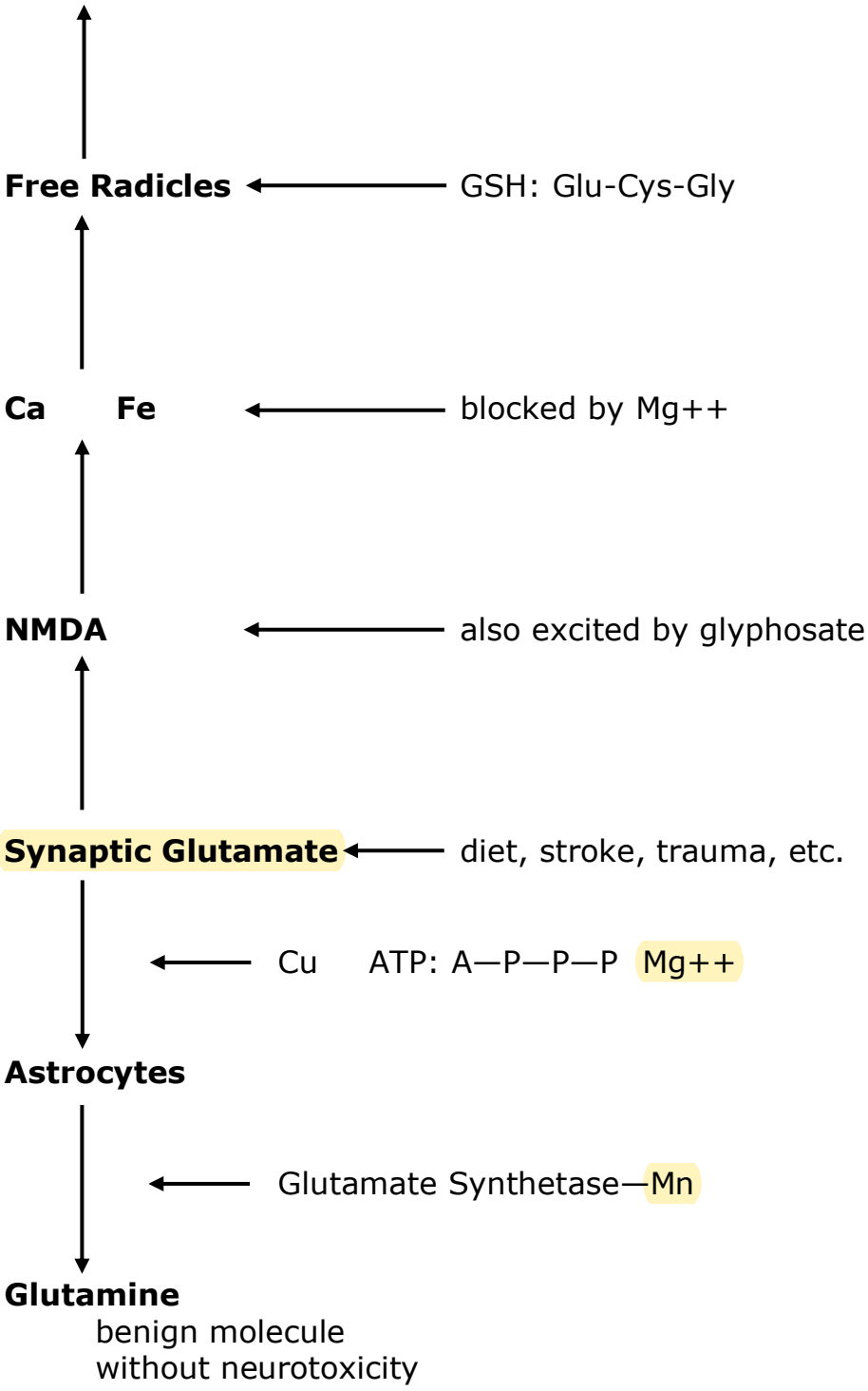
- "Joint replacement is expected to become the most common elective surgical procedure in coming decades."

- It is "likely that glyphosate's disruption of collagen increases the injury, necessitating corrective action."

Glyphosate is a powerful chelator:

Mg++ Mn Zn Co Cu

Neuronal illness and death = Excitotoxicity



"Glutathione is a stored form of sulfur."

Sulphate is essential for life.

Many of our molecules must be sulfated in order to be transported in the blood.

Glyphosate depletes sulphate.

••••••••••

Glyphosate disrupts the shikimate pathway.

- Damages the microbiome.
  - gut-brain: neurodevelopment
    neurodegeneration
  - •• damages immunity: autoimmunity

Glyphosate is patented as an *antibiotic*.

••••••••••

Glyphosate interferes with plant nitrogen uptake.

- Therefore, more synthetic nitrogen is required on crops:
  - •• #1 CO_2 producer……. global warming
  - •• #1 cause of water pollution: dead zones

••••••••••

Glyphosate disrupts the blood brain barrier.

Glyphosate crosses the blood brain barrier.

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KB, San Francisco, March 15, 2023

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