Proprioceptors and somatic dysfunction*

IRVIN M. KORR, PH.D.
Kirksville, Missouri

Functional properties of osteopathic lesions, as clinically described, have been reviewed in relation to the physiology of proprioceptors. It is shown that muscle spindles in which the "gain" has been turned up by intensified activity in their gamma motor innervation may, together with other sensory inputs, account for many of the motion characteristics and palpatory features of the osteopathic lesion. "Turning down" of the gain seems to be a common denominator in a variety of osteopathic manipulative procedures. Possible origin of the high gain is discussed also.

The musculoskeletal system is the most massive system of the body, yet in the performance of its infinite repertoire of motions and postures, it is the most delicately controlled and coordinated. Accordingly, the musculoskeletal system is the recipient of most of the efferent outflow from the central nervous system (CNS), with the largest portion by far going via the ventral roots of the spinal cord to the muscles, which carry out the motor commands of the CNS.

It is less well appreciated, however, that for related reasons the musculoskeletal system is also the source of the preponderant sensory input to the CNS, an input that is also the most widespread, the most continuous, and the most variable. This sensory feedback, from countless thousands of reporting stations in myofascial and articular components, entering the cord via the dorsal roots, is essential to the moment-to-moment control and fine adjustment of posture and locomotion.

In addition to this influence on the motor pathways, the sensory reporting is selectively routed to various other centers throughout the nervous system, including, of course, the cerebral cortex, where it enters into consciousness and the ordering of volitional motor activity. Relevant portions of the reports also reach and are utilized by the autonomic nervous system in the tuning of visceral, circulatory, and metabolic activity to musculoskeletal demand. Indeed, the sensory input from the musculoskeletal system is so extensive, intensive, and unceasing as to be a dominant influence on the CNS and therefore the person as a whole.

It may be expected, therefore, that disturbances in the sensory input from the musculoskeletal system, whether generally or locally, would significantly impair not only motor function, but also other functions — and that of the person himself. For those engaged in the study of the neural and reflex mechanisms, that premise is at the heart of the clinical significance of the osteopathic lesion — now modestly and euphemistically designated as "somatic dysfunction." One of the first products of experimental research into those mechanisms, pioneered by Denslow, was the concept of chronic segmental facilitation. In 1947, the hypothesis was stated as follows:

(An) osteopathic lesion represents a facilitated segment of the spinal cord maintained in that state by impulses of endogenous origin entering the corresponding dorsal root. All structures receiving efferent nerve fibers from that segment are, therefore, potentially exposed to excessive excitation or inhibition.

In speculating further about the site of the "endogenous origin," the author suggested that the proprioceptors, particularly the muscle spindles, were the most likely candidates because: 1) they would be sensitive to musculoskeletal stresses; 2) they are nonadapting receptors, sustaining streams

The spinal cord as organizer of disease processes: III. Hyperactivity of sympathetic innervation as a common factor in disease.

Korr IM.

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The Sympathetic Nerve—An Integrative Interface between Two Supersystems: The Brain and the Immune System

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Abstract

Since 1987, only a few neuroanatomical studies have been conducted to identify the origin of innervation for the immune system. These studies demonstrated that all primary and secondary immune organs receive a substantial sympathetic innervation from sympathetic postganglionic neurons. Neither the thymus nor spleen receive any sensory neural innervation; however, there is evidence that lymph nodes and bone marrow may be innervated by sensory neurons located in dorsal root ganglia. There is no neuroanatomical evidence for a parasympathetic or vagal nerve supply to any immune organ. Thus, the primary pathway for the neural regulation of immune function is provided by the sympathetic nervous system (SNS) and its main neurotransmitter, norepinephrine (NE). Activation of the SNS primarily inhibits the activity of cells associated with the innate immune system, while it either enhances or inhibits the activity of cells associated with the acquired/adaptive immune system. Innate immune cells express both alpha and beta-adrenergic receptor subtypes, while T and B lymphocytes express adrenergic receptors of the beta2 subtype exclusively, except for murine Th2 cells that lack expression of any subtype. Via these adrenergic receptors, NE is able to regulate the level of immune cell activity by initiating a change in the level of cellular activity, which often involves a change in the level of gene expression for cytokines and antibodies.

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All primary and secondary immune organs receive a substantial sympathetic innervation from sympathetic postganglionic neurons. There is no neuroanatomical evidence for a parasympathetic or vagal nerve supply to any immune organ. Input to the brain comes from sensory, e.g., dorsal root ganglia, or immune stimuli, e.g., cytokines. The primary pathway for the neural regulation of immune function is provided by the sympathetic nervous system and its main neurotransmitter, norepinephrine. Activation of the SNS primarily inhibits the activity of cells associated with the innate immune system, while it either enhances or inhibits the activity of cells associated with
“Until recently, most immunologists didn’t pay much attention to the innate system, perhaps because the adaptive system seemed more exciting.

However, studies of the adaptive immune system have led to a new appreciation of the role that the innate system plays, not only as a second line of defense (if we count physical barriers as our first defense), but also as an activator and a controller of the adaptive response.” p. 17
Autonomic Failure
A Textbook of Clinical Disorders of the Autonomic Nervous System

FIFTH EDITION

Edited by

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Cerebral metabolic changes in men after chiropractic spinal manipulation for neck pain.


Abstract

BACKGROUND: Chiropractic spinal manipulation (CSM) is an alternative treatment for back pain. The autonomic nervous system is often involved in spinal dysfunction. Although studies on the effects of CSM have been performed, no chiropractic study has examined regional cerebral metabolism using positron emission tomography (PET).

OBJECTIVE: The aim of the present study was to investigate the effects of CSM on brain responses in terms of cerebral glucose metabolic changes measured by [18F]fluorodeoxyglucose positron emission tomography (FDG-PET).

METHODS: Twelve male volunteers were recruited. Brain PET scanning was performed twice on each participant, at resting and after CSM. Questionnaires were used for subjective evaluations. A visual analogue scale (VAS) was rated by participants before and after chiropractic treatment, and muscle tone and salivary amylase were measured.

RESULTS: Increased glucose metabolism was observed in the inferior prefrontal cortex, anterior cingulated cortex, and middle temporal gyrus, and decreased glucose metabolism was found in the cerebellar vermis and visual association cortex, in the treatment condition (P < .001). Comparisons of questionnaires indicated a lower stress level and better quality of life in the treatment condition. A significantly lower VAS was noted after CSM. Cervical muscle tone and salivary amylase were decreased after CSM. Conclusion The results of this study suggest that CSM affects regional cerebral glucose metabolism related to sympathetic relaxation and pain reduction.


Abstract

Objective. The aim of this study was to investigate changes in brain and muscle glucose metabolism that are not yet known, using positron emission tomography with [18F]fluorodeoxyglucose ([18F]FDG PET). Methods. Twenty-one male volunteers were recruited for the present study. [18F]FDG PET scanning was performed twice on each subject: once after the spinal manipulation therapy (SMT) intervention (treatment condition) and once after resting (control condition). We performed the SMT intervention using an adjustment device. Glucose metabolism of the brain and skeletal muscles was measured and compared between the two conditions. In addition, we measured salivary amylase level as an index of autonomic nervous system (ANS) activity, as well as muscle tension and subjective pain intensity in each subject. Results. Changes in brain activity after SMT included activation of the dorsal anterior cingulate cortex, cerebellar vermis, and somatosensory association cortex and deactivation of the prefrontal cortex and temporal sites. Glucose uptake in skeletal muscles showed a trend toward decreased metabolism after SMT, although the difference was not significant. Other measurements indicated relaxation of cervical muscle tension, decrease in salivary amylase level (suppression of sympathetic nerve activity), and pain relief after SMT. Conclusion. Brain processing after SMT may lead to physiological relaxation via a decrease in sympathetic nerve activity.

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The Neurochemically Diverse Intermedius Nucleus of the Medulla as a Source of Excitatory and Inhibitory Synaptic Input to the Nucleus Tractus Solitarii

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Sensory afferent signals from neck muscles have been postulated to influence central cardiorespiratory control as components of postural reflexes, but neuronal pathways for this action have not been identified. The intermedius nucleus of the medulla (InM) is a target of neck muscle spindle afferents and is ideally located to influence such reflexes but is poorly investigated. To aid identification of the nucleus, we initially produced three-dimensional reconstructions of the InM in both mouse and rat. Neurochemical analysis including transgenic reporter mice expressing green fluorescent protein in GABA-synthesizing neurons, immunohistochemistry, and in situ hybridization revealed that the InM is neurochemically diverse, containing GABAergic and glutamatergic neurons with some degree of colocalization with parvalbumin, neuronal nitric oxide synthase, and calretinin. Projections from the InM to the nucleus tractus solitarius (NTS) were studied electrophysiologically in rat brainstem slices. Electrical stimulation of the NTS resulted in antidromically activated action potentials within InM neurons. In addition, electrical stimulation of the InM resulted in EPSPs that were mediated by excitatory amino acids and IPSPs mediated solely by GABA_A receptors or by GABA_A and glycine receptors. Chemical stimulation of the InM resulted in (1) a depolarization of NTS neurons that were blocked by NBQX (2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide) or kynurenic acid and (2) a hyperpolarization of NTS neurons that were blocked by bicuculline. Thus, the InM contains neurochemically diverse neurons and sends both excitatory and inhibitory projections to the NTS. These data provide a novel pathway that may underlie possible reflex changes in autonomic variables after neck muscle spindle afferent activation.

Key words: posture; neck; cardiovascular; respiration; medulla oblongata; autonomic

Introduction

Reflex changes in cardiorespiratory variables during body movements rely on interactions between the somatic and autonomic nervous systems. A prime example of such interaction is the somatosympathetic reflex, in which stimulation of thinly myelinated group III (Aδ) and unmyelinated group IV (C-fiber) limb muscle afferent fibers can reflexly increase cardiorespiratory output (Potts et al., 2000, 2003; Wilson, 2000). These reflexes are mediated via sensory afferent input to the spinal cord, which is then relayed to the nucleus tractus solitarius (NTS), a brainstem site for cardiorespiratory integration (Potts et al., 2003). Cardiorespiratory changes can also be evoked by stimulation of neck muscle afferents (Bolton et al., 1998; Bolton and Ray, 2000), proposed to contribute to alterations in cardiorespiratory outflow in preparation for a change in posture (Bolton and Ray, 2000). In contrast to limb afferents, the sensory signals from these muscles appear to be mediated by group IA muscle spindle afferents (Bolton et al., 1998). However, the neural pathways that link these afferent signals to cardiorespiratory control are completely unknown.

One target for sensory information from neck muscles is the cervical spinal cord where terminations can be found in the dorsal horn (although sparse) and the central cervical nucleus (CCN) (Bakker et al., 1984; Pfäffler and Arvidsson, 1988; Prihoda et al., 1991). The CCN projection is generally considered to underlie spinal somatic reflex circuits, such as those for the tonic neck reflex involved in postural control (Wilson et al., 1984; Brink et al., 1985; Hongo et al., 1988; Popova et al., 1995). There is also a strong direct neck muscle afferent projection to the medulla oblongata where fibers terminate in the external cuneate nucleus and a nucleus located at the lateral edges of the dorsal aspect of the hypoglossal motor nucleus (XII), referred to either as the
The Neurochemically Diverse Intermedius Nucleus of the Medulla as a Source of Excitatory and Inhibitory Synaptic Input to the Nucleus Tractus Solitarii

The Journal of Neuroscience
August 1, 2007

Dorsal Motor Nucleus of the Vagus

Parasympathetic Efferents

Heart
Lungs
Stomach
Intestines
Etc.

Nucleus Tractus Solitarius

Integrated Autonomic And Cardiorespiratory Circuits

Parasympathetic Afferents From Thoracic And Abdominal Viscera

Nucleus Intermedius

External Cuneate Nucleus

Central Cervical Nucleus

Cerebellum

Upper Cervical Mechanoreceptors From Chiropractic Upper Cervical Adjustments

Tonic Postural Reflexes
Review

The intermedius nucleus of the medulla: A potential site for the integration of cervical information and the generation of autonomic responses

Ian J. Edwards, Susan A. Deuchars, Jim Deuchars*

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ABSTRACT

The intermedius nucleus of the medulla (InM) is a small perihypoglossal brainstem nucleus, which receives afferent information from the neck musculature and also descending inputs from the vestibular nuclei, the gustatory portion of the nucleus of the solitary tract (NTS) and cortical areas involved in movements of the tongue. The InM sends monosynaptic projections to both the NTS and the hypoglossal nucleus. It is likely that the InM acts to integrate information from the head and neck and relays this information on to the NTS where suitable autonomic responses can be generated, and also to the hypoglossal nucleus to influence movements of the tongue and upper airways.

Central to the integratory role of the InM is its neurochemical diversity. Neurones within the InM utilise the amino acid transmitters glutamate, GABA and glycine. A proportion of these excitatory and inhibitory neurones also use nitric oxide as a neurotransmitter. Peptidergic transmitters have also been found within InM neurones, although as yet the extent of the pattern of co-localisation between peptidergic and amino acid transmitters in neurones has not been established.

The calcium binding proteins calretinin and parvalbumin are found within the InM, with parvalbumin being predominantly found within GABAergic neurones and calretinin being predominantly found within glutamatergic neurones.

Neurones in the InM receive inputs from glutamatergic sensory afferents. This glutamatergic transmission is conducted through both NMDA and AMPA ionotropic glutamate receptors.

In summary the InM contains a mixed pool of neurones including glutamatergic and GABAergic in addition to peptidergic neurones. Neurones within the InM receive inputs from the upper cervical region, descending inputs from brain regions involved in tongue movements and those involved in the co-ordination of the autonomic nervous system. Outputs from the InM to the NTS and hypoglossal nucleus suggest a possible role in the co-ordination of tongue movements and autonomic responses to changes in posture.

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Neck muscle afferents influence oromotor and cardiorespiratory brainstem neural circuits.

Edwards IJ, Lall VK, Paton JF, Yanagawa Y, Szabo G, Deuchars SA, Deuchars J.

Abstract

Sensory information arising from the upper neck is important in the reflex control of posture and eye position. It has also been linked to the autonomic control of the cardiovascular and respiratory systems. Whiplash associated disorders (WAD) and cervical dystonia, which involve disturbance to the neck region, can often present with abnormalities to the oromotor, respiratory and cardiovascular systems. We investigated the potential neural pathways underlying such symptoms. Simulating neck afferent activity by electrical stimulation of the second cervical nerve in a working heart brainstem preparation (WHBP) altered the pattern of central respiratory drive and increased perfusion pressure. Tracing central targets of these sensory afferents revealed projections to the intermedius nucleus of the medulla (InM). These anterogradely labelled afferents co-localised with parvalbumin and vesicular glutamate transporter 1 indicating that they are proprioceptive. Anterograde tracing from the InM identified projections to brain regions involved in respiratory, cardiovascular, postural and oro-facial behaviours—the neighbouring hypoglossal nucleus, facial and motor trigeminal nuclei, parabrachial nuclei, rostral and caudal ventrolateral medulla and nucleus ambiguus. In brain slices, electrical stimulation of afferent fibre tracts lateral to the cuneate nucleus monosynaptically excited InM neurones. Direct stimulation of the InM in the WHBP mimicked the response of second cervical nerve stimulation. These results provide evidence of pathways linking upper cervical sensory afferents with CNS areas involved in autonomic and oromotor control, via the InM. Disruption of these neuronal pathways could, therefore, explain the dysphagic and cardiorespiratory abnormalities which may accompany cervical dystonia and WAD.

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The Curse of Louis Pasteur

NANCY APPLETON, Ph.D.
World War I began 100 years ago this month, and in many ways, writes historian Margaret MacMillan, it remains the defining conflict of the modern era.

The cold numbers capture much of the war's horror: more than 9 million men dead and twice as many again wounded—a loss of sons, husbands and fathers but also of skills and talents. Graves in the north of France and Belgium and war memorials across the U.S. bear witness to the 53,000 American soldiers who died. Thousands of civilians died, too, during the war itself, whether of hunger, disease or violence. And then, as the guns were falling silent, a new pestilence struck humanity in the shape of a virulent influenza. As troops returned home, they unwittingly helped carry the disease around the world. It has been estimated that 50 million died.
The Flu as a World-Changer

GETTING

A flu vaccine is a dreary annual chore, made worse by the fact that the serum often doesn’t work against the current strain of the virus. But good news seems to be on the horizon. Scientists now report that they have successfully adjusted a viral protein to teach immune systems to fight groups of viruses—an important step toward creating a universal vaccine.

The breakthrough is long overdue. The flu is an ancient disease—at least 2,000 years old—and one of the deadliest, with 10 pandemics in just the past three centuries.

Such is the flu’s power that it should be added to the list of history-altering diseases like typhoid, malaria and smallpox. The first wiped out almost a third of the Athenian population in 430 B.C., a year into the Peloponnesian War against the Spartans. Sixteen hundred years later, in 1167, a malaria-like epidemic forced the Holy Roman Emperor Frederick I to abandon Rome and retreat with his army to Germany.

Finally, during the Franco-Prussian war of 1871, smallpox had a starring role in its own morality tale. The French authorities failed to inoculate their soldiers. As a consequence, 125,000 of them contracted the disease, while the victorious (and vaccinated) Prussians suffered only 8,463 cases.

Yet the flu is rarely taken seriously. The problem, according to Virginia Woolf in her essay “On Being Ill,” is that the flu is far too prosaic an illness to be taken seriously, in real life or in literature: “Novels, one would have thought, would have been devoted to influenza...but no.” Heroines never succumb to the flu: Mimi in “La Bohème” dies of tuberculosis, Emily Brontë’s Cathy in “Wuthering Heights” in childbirth, Émile Zola’s Nana of smallpox.

As for inspiring great poetry, it is hard to say which is the more annoying: “Ring Around the Rosie,” a ditty thought to be about the Great Plague of 1665, or “I had a little bird / its name was Enza. / I opened up the window / and in flew-Enza,” which became popular during the 1918-19 Spanish Flu pandemic.

That year alone, influenza is estimated to have taken more than 50 million lives—more than during the Black Death in Europe (1347-51), whose toll is generally put at 25 million. The effects of Spanish Flu were so crushing that American life expectancy in 1918 dropped by 12 years.

If the flu had attacked the U.S. at the beginning of World War I instead of at the end, the course of the war might have been very different. As it was, 40% of the U.S. Navy and 26% of the Army were incapacitated by the disease in 1918.

It even played an extended role in the negotiations of the Treaty of Versailles in 1919. President Woodrow Wilson, struck down by flu in the middle of talks, became too ill to defend his Fourteen Points blueprint for world peace. His absence allowed more vengeful arguments to prevail, which helped to pave the way for World War II.

The flu may not be exciting, as Virginia Woolf complained. But it can still be devastating. Be prudent. Get vaccinated.
Osteopathic methods and the great flu pandemic of 1917–1918

MM Patterson

THE "FLU" AND YOU!

Medical Doctors
Osteopaths
Chiropractors

1919

A Few Facts and Figures Done Up in Statistics
CHAPTER VI:
THE THREE GREAT SURVIVAL FACTORS
[Excerpts by Dan Murphy, DC]

“The 1917 - 1918 influenza epidemic swept silently across the world bringing death and fear to homes in every land. Disease and pestilence, especially the epidemics, are little understood even now and many of the factors that spread them are still mysterious shadows, but in 1917-1918 almost nothing was known about prevention, protection, treatment or cure of influenza. The whole world stood at its mercy, or lack of it."

“But out of that particular epidemic, the young science of chiropractic grew into a new measure of safety. While many struggles would lie ahead this successful passage of the profession into early maturity assured its immediate survival and made the eventual outcome of chiropractic a matter for optimism. If there had been any lack of enthusiasm among the doctors of chiropractic, or a depleting of the sources of students then the epidemic took care of them too. These chiropractic survivors of the flu epidemic were sure, assured, determined, and ready to fight any battle that came up. The effect of the epidemic becomes evident in interviews made with old-timers practicing in those years. The refrain comes repeatedly,”

‘I was about to go out of business when the flu epidemic came - but when it was over, I was firmly established in practice.’

“Why?
The answer is reasonably simple. Chiropractors got fantastic results from influenza patients while those under medical care died like flies all around.”

“Statistics reflect a most amazing, almost miraculous state of affairs. The medical profession was practically helpless with the flu victims but chiropractors seemed able to do no wrong.”

“In Davenport, Iowa, 50 medical doctors treated 4,953 cases, with 274 deaths. In the same city, 150 chiropractors including students and faculty of the Palmer School of Chiropractic, treated 1,635 cases with only one death.”

“In the state of Iowa, medical doctors treated 93,590 patients, with 6,116 deaths - a loss of one patient out of every 15. In the same state, excluding Davenport, 4,735 patients were treated by chiropractors with a loss of only 6 cases - a loss of one patient out of every 789.”
Psychological stress and susceptibility to the common cold.


Cohen S, Tyrrell DA, Smith AP.

Department of Psychology, Carnegie Mellon University, Pittsburgh

These authors prospectively studied the relation between psychological stress and the frequency of documented clinical colds among subjects intentionally exposed to respiratory viruses.

After completing questionnaires assessing degrees of psychological stress, 394 healthy subjects were given nasal drops containing one of five respiratory viruses.

The subjects were then quarantined and monitored for the development of evidence of infection and symptoms.

The rates of both respiratory infection and clinical colds increased in a dose-response manner with increases in the degree of psychological stress.

Infection rates ranged from approximately 74 percent to approximately 90 percent, according to levels of psychological stress, and the incidence of clinical colds ranged from approximately 27 percent to 47 percent.

CONCLUSIONS:
Psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness.

ALSO NOTED IN ARTICLE AND ITS FOLLOW-UP:

“Psychological stress is thought to influence immune function through autonomic nerves innervating lymphoid tissue, or hormone-mediated alteration of immune cells.”

“In biomedical terms, ‘stress’ refers to any adverse physical, mental, or emotional stimulus (stressor) that upsets the organism’s homeostasis.”

“At the physiological level, stress has been the subject of study going back to Walter B. Cannon’s description of the ‘fight or flight’ response involving actions of the sympathetic nervous system and the adrenal medulla.”
Nonsynaptic noradrenaline release in neuro-immune responses.


Vizi ES, Elenkov IJ.

Evidence has recently been obtained that the branches of the autonomic nervous system, mainly, the sympathetic, regulate cytokine production.

Not only the primary (thymus, bone marrow) and secondary (spleen, tonsils, and lymph nodes) lymphoid organs, but also many other tissues are involved in immune responses and are heavily influenced by noradrenaline (NA) derived from varicose axon terminals of the sympathetic nervous system.

Besides NA released from nonsynaptic varicosities of noradrenergic terminals, circulating catecholamines (adrenaline, dopamine, NA) are also able to influence immune responses, the production of pro- and anti-inflammatory cytokines by different immune cells.

The sympathetic nervous system (catecholamines) and the hypothalamic-pituitary-adrenal (HPA) axis (cortisol) are the major integrative and regulatory components of different immune responses.

NA released non-synaptically from sympathetic axon terminals is able to inhibit production of pro-inflammatory (TNF-alpha, IFN-gamma, IL-12, IL-1) and increase anti-inflammatory cytokines (IL-10) in response.

The effects are mediated via beta2-adrenoceptors expressed on immune cells and coupled to cAMP levels.
noradrenaline alert the CNS that there are microbial threats or cytokine excess and thereby stimulate an anti-inflammatory counter-response to prevent systemic inflammation.

The transmitter between the vagus nerve and the innate immune system is acetylcholine [11–12]. Macrophages express cholinergic receptor activity; acetylcholine significantly inhibits LPS-induced TNF protein release through a post-transcriptional mechanism [11]. Acetylcholine significantly inhibits the release of other pro-inflammatory cytokines, including IL-1β, IL-6, and IL-18, but not IL-10, an anti-inflammatory cytokine. Other cholinergic agonists (nicotine and muscarine) also inhibit LPS-induced TNF release; macrophage cholinergic receptor activity is exquisitely sensitive to α-conotoxin, implicating nicotinic-type receptor activity in the transduction of the cytokine-inhibiting signal. Collectively, these observations
"These experiments demonstrate that the SNS [sympathetic nervous system] regulates all aspects of immune function in vivo, including proliferation, cytokine production, antibody production, and lymphocyte migration."

**INNATE IMMUNITY**

"Innate immunity is present from birth."

"It operates against almost any substance that threatens the body."

"Its principle role is to provide an early, nonspecific, first line of defense against pathogens."

"Most microorganisms encountered daily in the life of a healthy individual are detected and destroyed within minutes to hours by innate defense mechanisms." p.11

"Innate immunity is an attribute of every living organism." P. 18

**PRIMARY PLAYERS:**
Macrophages (monocytes), Neutrophils, Natural-Killer cells

**ADAPTIVE or ACQUIRED IMMUNITY**

"Under the circumstances in which an infectious organism is not eliminated by nonspecific innate immune mechanisms, adaptive immune responses ensue." p. 18

**PRIMARY PLAYERS:**
T cells (mature in the thymus), B cells (mature in the bone marrow)

| T cells (mature in the thymus), Synthesize and release cytokines (proteins) | B cells (mature in the bone marrow), Synthesize and release to serum antibodies (proteins) |
| Called cellular or cell mediated immunity | This is called HUMORAL immunity |
| Cytokines affect other cells |  |
| Th (helper) Express CD4 molecules on cell surface |  |
| Th1 (IgG); Th2 (IgE) |  |
| Tc (cytotoxic) Express CD8 molecules on the cell surface |  |
“In a healthy person, the response to infectious agents or tissue injury is rapid and efficient and will frequently lead to resolution [innate response] (resolution means that the eliciting agent is removed) before the [adaptive] immune system is activated (this is called ‘acute inflammation’).”

In an individual with overwhelming infection or who is chronically ill with an impaired acute inflammatory response, [adaptive / acquired] the immune system becomes activated and participates in the inflammatory response (this is called chronic ‘inflammation’”). p. 70

[This author is suggesting that in a healthy person, the innate immune system handles problems without inflammation, and with no symptoms].

[When the innate system does not handle the problem and the adaptive system is called to help, there is inflammation and symptoms].

Th2 response increases the production of IgE, which attaches to mast cells, which causes mast cell membrane degranulation, which increases the production of PGE2. p. 88

When the sympathetic nervous system increases, “the activity of the immune system decreases with a resultant increased susceptibility to infection.” p. 114

Activation of the hypothalamus activates the sympathetic nervous system, activating “catecholamine release in lymphoid tissues with a subsequent alteration of immune cell function and trafficking.” p. 129
"The sympathetic efferent fibers innervate every organ in the body and control diverse involuntary function." p. 89

"Stimulation of sympathetic post-ganglionic neurons promotes neurogenic inflammation." p. 126 This alters the function of the immune system [primarily the Th1/Th2 balance].

"The sympathetic nervous system is an important modulator of the immune system." p. 92

Chronic release of "catecholamines decrease the number of lymphocytes, and particularly of natural killer cells in the peripheral blood." "Catecholamines inhibit T-cell proliferation." p. 73

"Catecholamines are in general, immunosuppressive." p. 74

"Catecholamines affect the Th1/Th2 balance." p. 75

"Catecholamines induce a switch to IgE." p. 78

"Activity of the sympathetic nervous system may play a role in the pathogenesis of infections, autoimmune and atopic / allergic reactions, and atherosclerosis and tumor growth." p. 80

PGE2 activates the sympathetic nervous system release of catecholamines. p. 21
Sympathetic Segmental Disturbances

The Evidences of the Association, in Dissected Cadavers, of Visceral Disease with Vertebral Deformities of the Same Sympathetic Segments

Medical Times, November 1921, pp. 1-7

Henry Winsor, MD

THIS AUTHOR NOTES:

“The object of these necropsies was to determine whether any connection existed between minor curvatures of the spine, on the one hand, and diseased organs on the other.”

This author used 50 cadavers from the University of Pennsylvania.

49 of the 50 cadavers displayed minor curvatures of the spine, and 1 cadaver displayed the normal “slight smooth lateral curve in the thoracic spine.”

This 1 cadaver still showed “very minor visceral pathology in the segments immediately above and below the reported curve,” at “segments which should form compensatory curves.”

“All [other] curves and deformities of the spine were rigid, apparently of long duration; irreducible by ordinary manual force: extension, counter-extension, rotation, even strong lateral movements failed to remove them or even cause them to change their relative positions.”

Importantly, minor spinal curvatures “their association with disease of organs belonging to the same sympathetic segment is more frequent than with gross curves.”

Also importantly, in the 4 spines with gross curvatures “diseased organs were not found to belong to the same sympathetic segments as the gross curves, but were [found at] the same sympathetic segments as the minor compensatory curvatures above and below the greater curves.”
5) “The organs were in many instances affected by acute disease, while the deformed vertebrae proved that the curvatures preceded the organic diseases…” [EXTREMELY IMPORTANT]

6) “…though theoretically, reflexes through muscle spasm may reverse the order of precedence.” [WOW!]

The author notes that spondylosis is a process, “the last stage being fixation of segments, immobilization of painful joints being one of nature’s later efforts to check disease.”

“The disease [process then] going to the point of least resistance, in this instance to the minor curvatures of the spine.”

The author describe the spondylosis process as follows:
A "sacro-iliac subluxation, an apparent shortening of the leg, comparative elevation of the posterior superior iliac spine of the ilium, combined with lateral curve in the lumbar region, lumbar curve and sacro-iliac subluxation (rotation of the innominate) appear to be interdependent.”

[He even uses subluxation in the same context as a chiropractor].

“The stages of the process appears to be:
1) Minor curves, or so-called sacroiliac subluxations;
2) The muscles are converted into ligaments, ligaments to bone.
3) Finally true bony ankylosis occurs.”

[This perfectly describes the phases of subluxation degeneration from Renaissance from the 1970s by Feleesia and Riekeman].

“The disease appears to precede old age and to cause it. The spine becomes stiff first and old age follows. Therefore, we may say a man is as old as his spine, the arteries becoming hardened later from constant vaso-motor spasm, following sympathetic irritation.” [Wow, can you believe this?]

The author notes that the sympathetic nerves can become entrapped extraspinally, peripherally. “When the lungs were pulled out of the cadavers [of pleurisy patients with pleural adhesions], the adhesions were sufficiently strong to pull the intercostals vessels and nerves” including the sympathetic nerves. This “irritation of the sympathetic nerves causes reflex spasm of the vaso-motors deranging the blood-supply of the organs supplied by the sympathetic segment in curve.” The results are an increase in lung disease, heart disease, and pneumonia [infection].

“Of three cadavers with inguinal disturbances (bilateral hernia, hydrocele, idiopathic bubo or cancer, which had been excised in an old woman), all showed rotation of the twelfth dorsal vertebrae; the connection links being the ilio-inguinal and genito-crural nerves.” [WOW!]

“Skin diseases: two cadavers with warts exhibited minor curvatures in the region from which the affected skin derived its nerve supply.” [WOW!]
Osteopathic Methods and the Great Flu Pandemic of 1917-1918

JAOA - Vol. 100 - No 5 - May 2000 - 309-328

Michael Patterson, PhD, JAOA Associate Editor

Dr. Patterson notes:

The great influenza pandemic of 1917-1918 has been legend in osteopathic lore. It killed almost 1.5 times as many people worldwide (10 million) in 6 months as did the entire World War I in more than 4 years (7.5 million). Some sources put the death toll of the pandemic at closer to 20 million.

“The osteopathic medical community treated patients with influenza and its more potent sequela, pneumonia, with various forms of manipulative treatment, rest, and hydration. After the death sweep had abated, the leaders of the profession surveyed osteopathic practitioners nationwide regarding their experiences with treatment.”

The results showed that patients treated by osteopathic physicians had a death rate of 0.5%, whereas medically treated patients had an average 6% death rate (up to 27% in Boston).

“Patients with pneumonia under osteopathic care had a death rate of less than 10%, as opposed to 33% of medically treated cases.”

“It is apparent that osteopathic methods were highly effective in the epidemic.”

Patterson quotes a 1919 study indicating that “people receiving routine osteopathic care seemed to have contracted that influenza at a much lower rate than did the untreated population.”

He discusses a 1937 article that indicated that drugs used to treat influenza, pneumonia, and other diseases by the medical profession were actually harmful to those receiving them. [It is noteworthy that the same drugs and classes of drugs are being used today.]

Lastly, he notes that “the best defense against disease and infection remains health. Optimal health is the result of the optimization of the function of each individual. Osteopathic care that includes intelligently applied manipulative treatment is an excellent preventative treatment.”

Following this, the JAOA reprinted 4 articles from their archives.

This first is an editorial by Dr. CP McConnell. It was originally printed October 1918.
Avian influenza: an osteopathic component to treatment

Osteopathic Medicine and Primary Care

July 9, 2007

Raymond J Hruby and Keasha N Hoffman
These authors are from the Department of Osteopathic Manipulative Medicine, Western University of Health Sciences, College of Osteopathic Medicine of the Pacific, Pomona, CA.

KEY POINTS FROM DAN MURPHY

1) There is a fear that an Avian influenza pandemic could result in the kind of mortality that was seen with the Spanish influenza pandemic of 1918–1919, where the number of deaths was estimated to be as high as 40 million people.

2) During the 1918–1919 influenza pandemic “osteopathic physicians (DOs), using their distinctive osteopathic manipulative treatment (OMT) methods, observed significantly lower morbidity and mortality among their patients as compared to those treated by allopathic physicians (MDs) with standard medical care available at the time.”

3) “The known data regarding the success of DOs treating influenza were gathered from the 1918 Spanish influenza pandemic and was first presented by R. Kendric Smith, MD, in a paper in which he described the ‘osteopathic conquest of disease in which medicine has failed’.”

4) “Doctor Smith reported that the mortality rate for a total of 110,120 patients with influenza treated by 2,445 DOs was 0.25%. Mortality due to influenza in patients receiving traditional medical care, however, was estimated to be 5% to 6%.”

5) “Patients with pneumonia treated with standard medical care had a mortality rate estimated at 33% overall, and as high as between 68% and 78% in some large cities. Of 6,258 patients cared for by osteopathic physicians the death rate due to pneumonia was 10%.”

6) “Certain OMT procedures can have a positive stimulating effect on the immune system, possibly allowing the patient to avoid the complications of, and eventually recover from, such illnesses as influenza.”

7) “Based on the results (discussed above) of the use of OMT during the 1918 Spanish influenza pandemic, we propose that OMT be included as a part of the overall treatment plan for patients with influenza.”
Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens

*Nature Reviews Immunology*  
6, April 2006, pp 318-328

Esther M. Sternberg  
This article has 140 references

KEY POINTS FROM DAN MURPHY

1) The central nervous system regulates innate immune responses through hormonal and neuronal routes.

2) Our first line of defense from infections locally is by the nervous system release of neuropeptides that cause inflammation, which controls infection. [Key]

3) The innate immune system provides the first line of defense against invading pathogens.

4) The neuroendocrine stress response, and both the sympathetic and parasympathetic nervous systems generally inhibit innate immune responses.

5) The innate immune system’s initial response to pathogens is inflammation that both contains and eliminates the pathogens. The triggers for this inflammatory response are neurological in origin. [Very Important]

6) Cytokines released by the innate immune system “activate neural responses that both amplify local immune responses to clear pathogens and trigger systemic neuroendocrine and regional neural responses that eventually return the system to a resting state.”

7) An increased or prolonged sympathetic nervous system response following infection results in uncontrolled infection. [Very Important]

8) A reduced sympathetic nervous system response following infection results in excess inflammation, allergies (atopic disorders) and autoimmune disorders. [Very Important]

9) The sympathetic (adrenergic) nervous system, and the parasympathetic (cholinergic) nervous system innervate the immune organs, inhibit inflammation, and reduce the initial immunological response against pathogens.

10) Immunological neuroendocrine responses systemically reduce inflammation through the hypothalamic–pituitary–adrenal axis by stimulating the release of anti-inflammatory glucocorticoids from the adrenal cortex.
11) The nervous system also influences immune-cell maturation. [Very important for our pediatric patients]

12) Increased activity of the HPA-axis (from chronic stress, as an example), elevates glucocorticoids levels, which increases susceptibility to viral infections, prolongs wound healing and decreases antibody production. [This means that chronic stress is immunosuppressive]

13) Glucocorticoids are anti-inflammatory, which decreases the innate and adaptive immune responses.

14) Glucocorticoids, promote death of macrophages, dendritic cells (DCs) and T cells, leading to inhibition of immune responses.

15) “The SNS includes a neuronal component that regulates immunity at a regional level through the innervation of immune organs and the release of noradrenaline, and a hormonal component that regulates immunity systemically through the release of adrenaline from the medulla of the adrenal glands.” [Extremely Important For Chiropractors]

16) Increased activity of the SNS activity is immunosuppressive.

17) Adrenaline (from the adrenal cortex) decreases circulating numbers of monocytes, B and T cells, and NK cells systemically, and therefore inhibits the innate immune response systemically.

18) Most of the systemic effects of the SNS are anti-inflammatory and therefore immunosuppressive.

19) “The parasympathetic nervous system modulates immune responses at a regional level through both the efferent and afferent fibres of the vagus nerve.”

20) The parasympathetic release of acetylcholine from efferent vagus nerve fibers are also anti-inflammatory and therefore immunosuppressive.

21) Glucocorticoids, the SNS, and the parasympathetic systems are activated by cytokines released during activation of the innate immune system, and then the nervous system in turn provides a negative-feedback anti-inflammation control of innate immune responses to restore homeostasis. [This means that the nervous system turns off the immune system response so that we do not get allergies or autoimmune diseases]

22) The central and peripheral nervous systems regulate immunity and have important physiological roles in both health and disease. [Very Important]

23) The CNS is as integral to the physiological responses to pathogens as is the innate immune system.
Impact of Osteopathic Manipulative Treatment on Secretory Immunoglobulin A Levels in a Stressed Population

Journal of the American Osteopathic Association

Gregory Saggio, DO; Salvatore Docimo, DO; Jennifer Pile, DO; Jennifer Norton, DO, RN; and Wolfgang Gilliar, DO

FROM ABSTRACT:

Context: High levels of human secretory immunoglobulin A (sIgA) have been shown to decrease the incidence of acquiring upper respiratory tract infections. Osteopathic manipulative treatment (OMT) has been shown to improve cardiac indices, increase lymph flow rates through the thoracic duct, and decrease sympathetic tone in postoperative patients and those in intensive care. Therefore, we hypothesized that OMT may also increase sIgA levels in people under high levels of emotional and psychological stress, thereby enhancing immunity and potentially preventing subsequent infections.

Objective: To determine if OMT increases sIgA levels in highly stressed individuals.

Methods: Twenty-five second-year osteopathic medical students were randomly assigned to an experimental group (n=12) or a control group (n=13). All participants were scheduled to take their national board examination within 2 to 3 weeks after the experiment. After each participant submitted a saliva sample for a baseline sIgA level assessment, the experimental group received 20 minutes of OMT while the control group sat quietly and relaxed in a separate area for 20 minutes. Participants in both groups rested quietly for 1 hour after the 20-minute session and then submitted a second saliva sample.

Results: A 2 X 2 repeated measures analysis of variance revealed that the experimental group displayed a statistically significant greater increase in post-intervention sIgA levels than the control group [by 139% increase].

Conclusion: This study demonstrates the positive effect of OMT on sIgA levels in persons experiencing high stress.

Results suggest that OMT may then have therapeutic preventive and protective effects on both healthy and hospitalized patients, especially those experiencing high levels of emotional or physiological stress and those at higher risk of acquiring upper respiratory tract infections.

KEY POINTS FROM THIS STUDY:

1) Secretory immunoglobulin A (sIgA) is also referred to as salivary IgA.
2) “Secretory IgA provides protection from pathogenic organisms by preventing attachment, replication, and colonization of such organisms.”

3) Stress (perceived or physical) can cause a decrease in mucosal sIgA levels.

4) Levels of sIgA in humans indicate immune system potency.

5) High levels of sIgA decrease the incidence of upper respiratory tract infections. Low levels of sIgA are associated with increased incidence of infections.

6) Studies have reported a statistically significant enhanced immunologic response in subjects who received osteopathic manipulative therapy as compared to a control group.

7) An increase in sIgA among patients receiving osteopathic manipulation suggests that manipulation “could be used to increase immunity in vulnerable populations.”

8) Both controls and patients submitted a baseline saliva sample and their sIgA were measured. The controls were reassessed 1 hour after sitting quietly. The patients were reassessed 1 hour after osteopathic manipulation.

9) The sIgA level in the manipulation group increased by an average 139%, more than 100% greater than the control group.

10) “Decreases in sIgA levels have shown to have deleterious effects on the immune system, which leads to an increased risk of infection. Such findings demonstrate the importance of discovering osteopathic clinical practices that increase the level of patients’ sIgA.”

11) Osteopathic manipulation increases lymphatic flow, increases peripheral circulation, improves cardiac indices, and decreases sympathetic tone.

12) This study demonstrates that osteopathic manipulative therapy “significantly increases the sIgA level.” “Participants who received osteopathic manipulative therapy experienced an average increase of 139% in their level of sIgA post intervention.”

13) High levels of human sIgA “have been shown to benefit the immune system by decreasing the risk of acquiring upper respiratory tract infections.”

14) Simple osteopathic manipulative techniques may increase immunity and lower the incidence of infections.

15) “Our findings demonstrate OMTs ability to increase sIgA and to potentially improve immune system function.”
Osteopathic Manipulative Therapy Induces Early Plasma Cytokine Release and Mobilization of a Population of Blood Dendritic Cells

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Abstract

It has been claimed that osteopathic manipulative treatment (OMT) is able to enhance the immune response of individuals. In particular, it has been reported that OMT has the capability to increase antibody titers, enhance the efficacy of vaccination, and upregulate the numbers of circulating leukocytes. Recently, it has been shown in human patients suffering chronic low back pain, that OMT is able to modify the levels of cytokines such as IL-6 and TNF-α in blood upon repeated treatment. Further, experimental animal models show that lymphatic pump techniques can induce a transient increase of cytokines in the lymphatic circulation. Taking into account all these data, we decided to investigate in healthy individuals the capacity of OMT to induce a rapid modification of the levels of cytokines and leukocytes in circulation. Human volunteers were subjected to a mixture of lymphatic and thoracic OMT, and shortly after the levels of several cytokines were evaluated by protein array technology and ELISA multiplex analysis, while the profile and activation status of circulating leukocytes was extensively evaluated by multicolor flow cytometry. In addition, the levels of nitric oxide and C-reactive protein (CRP) in plasma were determined. In this study, our results show that OMT was not able to induce a rapid modification in the levels of plasma nitrates or CRP or in the proportion or activation status of central memory, effector memory or naïve CD4 and CD8 T cells. A significant decrease in the proportion of a subpopulation of blood dendritic cells was detected in OMT patients. Significant differences were also detected in the levels of immune molecules such as IL-8, MCP-1, MIP-1α and most notably, G-CSF. Thus, OMT is able to induce a rapid change in the immunological profile of particular circulating cytokines and leukocytes.

Introduction

Osteopathic medicine is based on the premise that the primary role of the physician is to facilitate the body’s inherent ability to heal itself. Osteopathic physicians view diseases as a disruption of the normal interactions of anatomy, physiology and behavior. One unique aspect of osteopathic medicine is treatment by manually applied procedures, often referred to as manipulative therapies. These therapies have been successfully used by osteopathic physicians for more than a hundred years in order to treat dysfunctions of the neuromusculoskeletal, lymphatic, or vascular tissue. As described in Foundations for osteopathic medicine [1], some of the techniques relevant to osteopathy include: 1) soft-tissue techniques that increase muscle relaxation and circulation of body fluids; and 2) isometric and isotonic techniques that focus on restoring physiological movements and altered joint mechanisms. Manipulative therapies aimed to increase lymphatic flow, such as thoracic or abdominal lymphatic pump, have been extensively used in osteopathic medicine [2,3]. In particular, these techniques are proposed to treat patients with asthma, edema and certain pulmonary infections since an increase in the lymphatic flow may enhance filtering and removal of fluid, inflammatory mediators, and waste products from interstitial spaces [4]. Interestingly, it has been claimed that osteopathic treatment decreased mortality rates associated with the 1918 influenza epidemic in the United States and may be relevant in the case of an avian influenza pandemic [5,6]. Various reports of beneficial clinical responses to lymphatic pump treatments may be related to increased lymph flow [7,8,9,10,11]. In addition, it has been proposed that lymphatic and splenic pump treatments at the time of vaccination were correlated with a faster rise in antibody titers in human subjects receiving the hepatitis B vaccine [7]. In another series of studies, patients receiving thoracic pump treatments showed statistically
Figure 3 | **Functional anatomy of the inflammatory reflex.** Afferent (sensory) neural signals to the brain stem are relayed by the vagus nerve to the nucleus of the solitary tract (nucleus tractus solitarius; NTS). Polysynaptic relays then connect to the outflow centres of the autonomic nervous system, the rostral ventrolateral medullary (RVLM) sympathoexcitatory neurons and the vagal motor neurons in the nucleus ambiguus (NA) and the dorsal vagal motor nucleus. Outflow arrives at the coeliac ganglion from either the vagus nerve or the preganglionic efferent nerves, which originate in the sympathetic
Measureable changes in the neuro-endocrinal mechanism following spinal manipulation.

Kovanur Sampath K¹, Mani R², Cotter JD³, Tumilty S².

Abstract
The autonomic nervous system and the hypothalamic-pituitary-adrenal axis have been shown to be dysfunctional in a number of chronic pain disorders. Spinal manipulation is a therapeutic technique used by manual therapists, which may have widespread neuro-physiological effects. The autonomic nervous system has been implicated to modulate these effects. A theory is proposed that spinal manipulation has the potential to be used as a tool in restoring the autonomic nervous system balance. Further, it is also hypothesised that through its anatomical and physiological connections, the autonomic nervous system activity following a thoracic spinal manipulation may have an effect on the hypothalamic-pituitary-adrenal axis and therefore pain and healing via modulation of endocrine and physiological processes. To substantiate our hypothesis we provide evidence from manual therapy studies, basic science and animal studies. According to the proposed theory, there will be measurable changes in the neuro-endocrinal mechanisms following a thoracic spinal manipulation. This has far-reaching implications for manual therapy practice and research and in the integration of spinal manipulation in the treatment of a wide array of disorders.

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[Indexed for MEDLINE]
Neuroimmunology Loop Overview

C1-C2 Afferents

Rostral Ventral Lateral Region Medulla

Sympathetic Nervous System

Bone Marrow

Macrophage (Innate Immune Response)

Antigen (pathogen, toxin, etc.)

Vestibular Nucleus

Nucleus Intermedius (Medulla)

Nucleus Tractus Solitarius (Medulla)

Spinal Mechanoreceptors

Afferent Vagus Nerve

Cytokines (proteins from the macrophage)
**Neuro-Immunology Summary**

The mechanoreceptors of the spine communicate with the sympathetic nervous system (Jiang, *SPINE*, 1997).


The primary cell of the innate immune response is the MACROPHAGE (Sompayrac, *HOW THE IMMUNE SYSTEM WORKS*, 2008).

The best picture to date of the sympathetic nervous system communicating with the MACROPHAGE: (Mathias, *AUTONOMIC FAILURE*, 2013).

The primary player of the innate immune response, the MACROPHAGE, activates the systemic immune response by using the sensory branches of the vagus nerve; these vagus afferents ascend to the nucleus tractus solitarius of the medulla (Tracey, *Nature Reviews Immunology*, 2009).

The nucleus tractus solitarius is disynaptically post-synaptic from the mechanical afferents of the upper cervical spine: (Edwards: *Journal of Neuroscience*, 2007; *Journal of Chemical Neuroanatomy*, 2009; *Brain Structure & Function*, 2015).

The sympathetic nervous system and the parasympathetic nervous system (nucleus tractus solitarius) interface in the brain stem for a comprehensive immunological response: (Tracey, *Nature Reviews Immunology*, 2009).

This further supports the anecdotes and science of chiropractic neuro-immunity.