The Red Wine Polyphenol Resveratrol Shows Promising Potential for the Treatment of Nucleus Pulposus–Mediated Pain In Vitro and In Vivo

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Pro-Inflammatory Cytokines
Interleukin-1β (IL-1β)
Interleukin-6 (IL-6)
Interleukin-8 (IL-8)
Toll-like receptor 2 (TLR2)
Matrixmetalloproteinase-1 (MMP1)
Matrixmetalloproteinase-3 (MMP3)
Matrixmetalloproteinase-13 (MMP13)

The most common regulated pathway/receptor in inflammation is the transcription factor nuclear factor κB (NF-κB).

BACKGROUND FROM DAN MURPHY:

Cytokines are proteins produced by immune system cells. Pro-inflammatory cytokines increase pain and accelerate tissue degradation (catabolism, like disc degeneration in this study).

Resveratrol is the polyphenol found in red wine; the most is in Pinot Noir. It is made from grape skins. An optimal dose of resveratrol is much greater than you can get from wine, but it can be taken as a supplement. Resveratrol turns off inflammatory cytokines, especially NF-κB. The most consistent intervention that makes animals live longer and healthier is calorie restriction and adequate nutrition. If you get enough protein and vitamins and eat half of the calories, you'll possibly live to 150 years, but you will be hungry for 150 years. Resveratrol turns on the same genes that control calorie restriction and they are called sirtuin genes, as Sir1 and Sir2. When we take resveratrol supplements, they 'turn on' the genes that protect us from disease even though we are not practicing calorie restriction. Resveratrol has shown that it may reduce the risk of many diseases and extend health and survival rate, even when someone is not on the perfect diet. A good book on Resveratrol is:

The Longevity Factor: How Resveratrol and Red Wine Activate Genes for a Longer and Healthier Life, by Joseph Maroon, MD, 2009; Dr. Maroon is the neurosurgeon for the NFL Pittsburgh Steelers.
Study Design. An investigation of the anti-inflammatory and anticatabolic effect of resveratrol in intervertebral discs (IVDs) in vitro and of the analgetic effect in vivo.

Objective. To determine whether resveratrol may be useful in treating nucleus pulposus (NP)–mediated pain.

Summary of Background data. Pro-inflammatory cytokines seem to be key mediators in the development of NP-mediated pain.

Patients with discogenic or radiculopathic pain may substantially benefit from anti-inflammatory substances that could be used in a minimal-invasive treatment approach.

Resveratrol, a polyphenolic phytoalexin found in red wine exhibits anti-inflammatory effects in various cell types and tissues.

Results. In vitro, resveratrol exhibited an anti-inflammatory and anticatabolic effect on the messenger RNA and protein level for IL-6, IL-8, MMP1, MMP3 and MMP13. In vivo, resveratrol significantly reduced pain behavior triggered by application of nucleus pulposus (NP) tissue on the dorsal root ganglion for up to 14 days.

Conclusion. Resveratrol was able to reduce levels of pro-inflammatory cytokines in vitro and showed analgetic potential in vivo. A decrease in pro-inflammatory cytokines may possibly be the underlying mechanism of pain reduction observed in vivo.

Resveratrol seems to have considerable potential for the treatment of NP-mediated pain and may thus be an alternative to other current treatment options.

KEY POINTS FROM THESE AUTHORS:

1) Nucleus pulposus (NP) tissue is a potent inducer of pain (radiculopathy). This effect is due to pro-inflammatory cytokines present in this tissue.

2) Degenerative disc disease (leading to discogenic back pain) is also coupled with increased levels of pro-inflammatory cytokines.

3) Current treatment options for NP-mediated pain such as radiculopathic pain are not ideal. “This is most likely because of the fact that current therapeutic strategies do not account for the biological mechanisms of pain development.”

4) There is a need to develop therapeutic procedures that can interfere with the biological mechanisms of nucleus pulposus-mediated pain by inhibiting the production of “pain-mediating pro-inflammatory cytokines.”
5) Natural anti-inflammatory substances may reduce pro-inflammatory cytokines. Natural bioactive compounds have a pronounced anti-inflammatory effect and “could thus possibly replace corticosteroids.”

6) “Resveratrol (3,5,4-trihydroxy-trans-stilbene) is a polyphenolic phytoalexin found in red wine that has previously been shown to demonstrate anti-inflammatory, anticancer, immunomodulatory, cardioprotective, antioxidative, and chemopreventive capabilities in various cell and tissue types.”

7) Resveratrol was able to reduce expression of pro-inflammatory cytokines:

<table>
<thead>
<tr>
<th>Pro-Inflammatory Cytokine</th>
<th>Percentage Reduced</th>
</tr>
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<tbody>
<tr>
<td>IL-6</td>
<td>76%</td>
</tr>
<tr>
<td>IL-8</td>
<td>55%</td>
</tr>
<tr>
<td>MMP1</td>
<td>51%</td>
</tr>
<tr>
<td>MMP3</td>
<td>48%</td>
</tr>
<tr>
<td>MMP13</td>
<td>45%</td>
</tr>
<tr>
<td>TLR2</td>
<td>18%</td>
</tr>
</tbody>
</table>

8) The anti-inflammatory and anticatabolic effect of resveratrol was on the protein level for IL-6, IL-8, MMP1, MMP3, and MMP13.

9) “Results from our cell culture experiments provide clear evidence that resveratrol can effectively reduce mRNA levels of major pro-inflammatory cytokines (IL-6, IL-8), TLR2, and matrix degrading enzymes (MMP1, MMP3, MMP13), which have previously been shown to be involved in disc degeneration and pain induction.”

10) “Resveratrol has been shown to increase proteoglycan synthesis, and therefore providing further evidence that resveratrol may be an innovative treatment of NP-mediated back and leg pain.”

11) Activation of the transcription factor NF-κB leads to an upregulation of pro-inflammatory cytokines and matrix degrading enzymes. “Resveratrol treatment was able to prevent this threshold reduction and thus the pain-related behavior to a certain degree for 14 days.”

12) Resveratrol reduces pain behavior in vivo. “Resveratrol may possibly reduce pain behavior in vivo by reducing or inhibiting cytokines that are released from the nucleus pulposus tissue.”

13) Production and release of pro-inflammatory cytokines play a pivotal role in nucleus pulposus (NP)–mediated pain (discogenic pain, radiculopathy).

14) “Resveratrol, a polyphenol found in red wine, was able to reduce expression of relevant pro-inflammatory cytokines and matrix degrading enzymes on the gene and protein expression level in human intervertebral disc cells in vitro.”
15) Literature shows that resveratrol inhibits toll-like receptor 2 (TLR2) and hence downstream reduction of NF-κB and activates SIRT1.

16) The analgetic potential of resveratrol to reduce nucleus pulposus mediated pain was demonstrated in an in vivo animal model of painful radiculopathy.

COMMENTS FROM DAN MURPHY

This study used human disc cultures and live animals but I believe that these principles apply to live humans. I supplement with 100mg of resveratrol (with Curcumin) for chronic discogenic back pain and I perceive great improvement in symptoms [Nutri-West: Complete Neuro; (800) 443-3333]. My Key Points from this study include:

1) Resveratrol is a natural substance that is made by grapes and is found in red wine. Optimal resveratrol ingestion from red wine consumption would require one to become drunk; supplementation can assure optimal levels without being intoxicated.

2) The degenerating disc, especially the nucleus, produces pro-inflammatory cytokines. This inflammation increases chronic discogenic pain.

3) Resveratrol inhibits the production of pro-inflammatory cytokines, reducing discogenic and radiculopathic pain.

4) Resveratrol inhibits the degeneration of the disc (disc catabolism).

5) Resveratrol increases proteoglycan synthesis, potentially helping the disc to regenerate.