

Autoimmune Pain, Insomnia, Fatigue And Depression Uncovered

An autoimmune disease results from an immune response attacking the body's own cells and tissues, a condition that affects millions of Americans. We know very little about what triggers them or how to prevent them from occurring, however we do know what happens to the body and possible ways to minimize symptoms and improve quality of life.

There are more than 80 illnesses caused by autoimmunity, including Type 1 Diabetes, Lupus, Rheumatoid Arthritis, Lyme's, Crohn's, Chronic Fatigue Syndrome and Fibromyalgia. Though autoimmune diseases affect different organs of the body, they share such symptoms as fatigue, insomnia, depression, pain and headaches.

FATIGUE

Autoimmune diseases are generally categorized by an over-expression of immune markers called cytokines. Cytokines regulate the intensity and duration of the immune response. Tumor Necrosis Factor-alpha (TNF) is an important cytokine in immunity and inflammation. In case of a virus or bacteria invasion, our body responds by activating TNF. TNF helps not only fight the pathogen (virus, bacteria, etc.), but it also makes us feel fatigued¹. The fatigue is a defense mechanism, essentially preventing us from compromising our immune system further. When we have the flu, we just feel like sitting on the couch and watching TV. That feeling is the TNF-alpha working. If we did not feel terrible, then we might go out, run a marathon, and compromise our immune system even further.

Overproduction of TNF has been implicated in chronic fatigue prevalent in those with autoimmune diseases². It is interesting to note that, in spite of their active involvement in immune responses to injury or infection, overproduction of TNF and other cytokines leads to sleepiness, fatigue, poor cognition, and enhanced sensitivity to pain³.

TNF-inhibiting drugs have been popular treatments for autoimmune diseases such as rheumatoid arthritis. However, these drugs carry warnings about increased risk of infection due to the body's decreased TNF immune response⁴.

TNF generates free radicals called superoxide anions⁵, which enable TNF to attack infections. However, as excessive amounts of superoxide anions accumulate in the body and overwhelm our antioxidant system, superoxide eventually leads to inflammation. Evidence suggests that increased production of superoxide anions can break down cartilage and bone⁶.

The Science of Bone/Joint Problems

How Excess TNF-alpha Can Affect Bones And Joints



The damaging free radicals—called Reactive Oxygen Species (ROS)—can cause inflammation all over our bodies, from our joints to our heart. They can also deplete Tryptophan and serotonin levels, which leads to insomnia, depression and headaches.

So, could quenching the superoxide free radical limit inflammation and arthritis? Could it limit Tryptophan and serotonin depletion, insomnia, depression and headaches? Could it function like TNF-inhibiting drugs,

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but without compromising the immune system? We would like help finding the answer to these questions.

INSOMNIA

In addition to Tumor Necrosis Factor-alpha (TNF), an inflammatory cytokine called Interferon-gamma (IFN-gamma) is also commonly over-expressed in autoimmune diseases⁷. Over-expression of either TNF or IFN can eventually lead to insomnia.

TNF and IFN synergistically act to break down Tryptophan⁸. On one hand, this Tryptophan depletion is an immune defense mechanism to help halt the growth of bacteria. On the other hand, it can lead to insomnia because Tryptophan starts the natural sleep cycle.

As night falls, the brain begins converting Tryptophan to serotonin, serotonin to melatonin, and then you fall asleep.

The Science Of Sleep

A Natural Process That Begins With Tryptophan



So many people with autoimmune diseases may not just coincidentally have insomnia. The insomnia may be related to the constant over-expression of TNF and IFN (chronic inflammation), and the degradation of Tryptophan and serotonin—the first two crucial steps in relaxing and restorative sleep.

All this knowledge raises the question: Are people with autoimmune disorders “typical” insomniacs or are they simply “Tryptophan and serotonin deficient?”

DEPRESSION

One of the first keys to understanding depression is that Tryptophan is the precursor to serotonin. Without Tryptophan, there can be no serotonin. This is important because serotonin plays a crucial role in healthy sleep, appetite control, addictions, and generating positive feelings of well-being. In fact, popular antidepressants called Selective Serotonin Reuptake Inhibitors (SSRI) try to prevent the reabsorption (reuptake) of serotonin by nerve cells so that more is available in the brain.

Serotonin is a neurotransmitter. It operates in the Central Nervous System (CNS). Due to the effect of inflammatory cytokines (i.e., TNF and IFN) on serotonin in the CNS, it is easy to see why those with autoimmunity suffer from insomnia and depression^{9,10}. Continued immune signaling to the brain (as in autoimmunity) can lead to the worsening of sickness and the development of symptoms of depression.

Nearly one-third of Americans take antidepressants (such as SSRIs), which help the brain use serotonin more efficiently. However, crucial to maintaining healthy serotonin levels is Tryptophan¹¹. Other ways to maintain healthy serotonin levels are through stress-relieving activities like positive social interaction, meditation and exercise.

It should be noted that women take more antidepressants than men do¹² and that women suffer from chronic pain in greater numbers than men do¹³. We will cover this gender disparity in a future newsletter.

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PAIN

What about pain? How does pain begin?

Pain begins with highly damaging excess free radicals called Reactive Oxygen Species (ROS)¹⁴. They include superoxide anion, hydrogen peroxide, and peroxynitrites. Nitric oxide is also involved with ROS.

These excess free radicals overrun the body's antioxidants and generate inflammation¹⁵. This begins the breakdown of tissues (cartilage, bone) and health problems involving our heart, brain or joints.

The Science Of Health Problems *How Free Radicals Can Affect Your Health*



There is a big correlation between autoimmunity and arthritis, or general joint pain¹⁶. This could be due to the following cascade of events:

The Science of Bone/Joint Problems *How Excess TNF-alpha Can Affect Bones And Joints*



Those over-expressed cytokines in autoimmunity generate ROS free radicals like superoxide anion. Superoxide reacts with nitric oxide to form peroxynitrites, which then breaks down bone and cartilage.

Excess free radicals are caused by poor diet, stress, disease, sickness, injuries, age, pollution, smoking, chemicals, obesity and inadequate exercise. To combat excess free radicals we can stop smoking, start exercising, lose any extra weight and consume many fruits, vegetables and grains loaded with antioxidants. We can also fight excess free radicals with our own body's natural antioxidants. It is these internal antioxidants—superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase—that have shown a novel path to pain reduction, as well as joint protection¹⁷.

GliSODin® is a novel superoxide dismutase (SOD) that boosts all three antioxidant enzymes. GliSODin® is orally absorbable as a dietary supplement.

HEADACHE/MIGRAINE

Women are nearly three times more likely than men to have migraines. Approximately 28 million Americans have migraines. Many migraine treatments target brain serotonin because numerous studies have implicated altered serotonin neurotransmission in incidence of migraines^{18,19}. These pharmaceutical treatments for migraines are triptan drugs (i.e., Treximet, Relpax and Maxalt), which are tryptamines, and related to the amino acid Tryptophan. The most well-known tryptamines are serotonin and melatonin.

Triptan drugs act directly on serotonin receptors in the brain's blood vessels. Triptan drug warnings typically concern use in combination with Selective Serotonin Reuptake Inhibitors (SSRIs). Taking a triptan and SSRI can cause Serotonin Syndrome. The same warning is typically seen with the combination of an SSRI and Tryptophan.

One theory is that inflammation leads to serotonin depletion in autoimmune diseases. And this inflammation and serotonin depletion leads to the fatigue, insomnia, depression, pain and headache associated with autoimmune diseases. As a health supplement, Tryptophan boosts serotonin naturally. The FDA lists Tryptophan as Generally Recognized As Safe (GRAS)²⁰.

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The statements in this document have not been evaluated by the Food and Drug Administration

¹Krueger JM. The role of cytokines in sleep regulation. *Curr Pharm Des.* 2008. 14(32): 3408-16.

²Cavadini G, Petrzilka S, Kohler P, Jud C, Tobler I, Birchler T, Fontana A. TNF-alpha suppresses the expression of clock genes by interfering with E-box-mediated transcription. *Proc Natl Acad Sci U S A.* 2007. 104(31): 12843-8.

³Krueger JM. The role of cytokines in sleep regulation. *Curr Pharm Des.* 2008. 14(32): 3408-16.

⁴<http://enbrel.com/>. Accessed 1/9/09..

⁵Kim YS, Morgan MJ, Choksi S, Liu ZG. TNF-induced activation of the Nox1 NADPH oxidase and its role in the induction of necrotic cell death. *Mol Cell.* 2007. 26(5): 675-87.

⁶Afonso V, Champy R, Mitrovic D, Collin P, Lomri A. Reactive oxygen species and superoxide dismutases: role in joint diseases. *Joint Bone Spine.* 2007. 74(4): 324-9.

⁷Palucka AK, Blanck JP, Bennett L, Pascual V, Banchereau J. Cross-regulation of TNF and IFN-alpha in autoimmune diseases. *Proc Natl Acad Sci U S A.* 2005. 102(9): 3372-7.

⁸Cory M. Robinson, Phillip T. Hale, Joseph M. Carlin. The Role of IFN- γ and TNF- α -Responsive Regulatory Elements in the Synergistic Induction of Indoleamine Dioxygenase. *Journal of Interferon & Cytokine Research.* 2005. 25(1): 20-30. doi:10.1089/jir.2005.25.20.

⁹Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci.* 2008. 9(1): 46-56.

¹⁰Schroeksnadel K, Kaser S, Ledochowski M, Neurauter G, Mur E, Herold M, Fuchs D. Increased degradation of tryptophan in blood of patients with rheumatoid arthritis. *J Rheumatol.* 2003. 30(9): 1935-9.

¹¹Bell C, Abrams J, Nutt D. Tryptophan depletion and its implications for psychiatry. *Br J Psychiatry.* 2001. 178: 399-405.

¹²Geraldine Sealey. What Every Woman Should Know About Antidepressants. *Glamour Magazine.* November 2007. Page 137.

¹³International Association For The Study Of Pain (IASP) Declares The Global Year Against Pain In Women. 10/16/07. <http://www.medicalnewstoday.com/articles/85593.php>. Accessed 1/9/09.

¹⁴Wang ZQ, Porreca F, Cuzzocrea S, Galen K, Lightfoot R, Masini E, Muscoli , Mollace V, Ndengele M, Ischiropoulos H, Salvemini D. A newly identified role for superoxide in inflammatory pain. *J Pharmacol Exp Ther.* 2004. 309(3): 869-78.

¹⁵Cuzzocrea S. Role of nitric oxide and reactive oxygen species in arthritis. *Curr Pharm Des.* 2006. 12(27): 3551-70.

¹⁶Zwerina J, Hayer S, Tohidast-Akrad M, Bergmeister H, Redlich K, Feige U, Dunstan C, Kollias G, Steiner G, Smolen J and Schett G. Single and combined inhibition of tumor necrosis factor, interleukin-1, and RANKL pathways in tumor necrosis factor-induced arthritis: effects on synovial inflammation, bone erosion, and cartilage destruction. *Arthritis Rheum.* 2004. 50(1): 277-90.

¹⁷Wang ZQ, Porreca F, Cuzzocrea S, Galen K, Lightfoot R, Masini E, Muscoli , Mollace V, Ndengele M, Ischiropoulos H, Salvemini D. A newly identified role for superoxide in inflammatory pain. *J Pharmacol Exp Ther.* 2004. 309(3): 869-78.

¹⁸Sakai Y, Dobson C, Diksic M, Aubé M, Hamel E. Sumatriptan normalizes the migraine attack-related increase in brain serotonin synthesis. *Neurology.* 2008. 70(6): 431-9.

¹⁹Drummond PD. Tryptophan depletion increases nausea, headache and photophobia in migraine sufferers. *Cephalgia.* 2006. 26(10): 1225-33.

²⁰<http://www.cfsan.fda.gov/~dms/eafus.html>. Accessed 1/9/09.