

## **New Mechanism of Action Behind Nutritional Mood Enhancers**

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Our well-being is one of the most important aspects of our health. If we do not experience the joy of living, than receiving an otherwise clean bill of health does us no good. The reality is, however, that individuals suffering from depression are also more likely to be afflicted with other diseases. One of the strongest connections made is the link that exists between depression, heart disease and diabetes. Depression occurs in up to one-quarter of patients with cardiovascular disease and diabetes.<sup>1</sup> In fact, depression is ranked with heart disease and diabetes as the most common chronic illnesses affecting the aging population. Depressed heart disease patients have poorer medical outcomes including increased risk of another myocardial infarction and all-cause mortality. Patients with diabetes and depression have poorer glycemic control, more diabetes symptoms, and greater all-cause mortality.<sup>1</sup> Clearly, depression is linked to some of the most common degenerative diseases and plays an outcome in the progression of those diseases.

Furthermore, depression is associated with actual physical symptoms that may play a role in making the cardiovascular system more vulnerable to adverse events. From a physical standpoint, depression dysregulates the hypothalamic-pituitary-adrenal axis. Depression also influences an individual's lifestyle choices and depressed patients may undertake behavior such as poor diet and exercise that may predispose them to cardiovascular disease.<sup>1</sup>

Studies have uncovered, however, that the simultaneous occurrence of heart disease and depression is not random but rather that depression is a risk factor for the occurrence and progression of coronary heart disease. A number of studies have investigated this link. In one study, 2,403 men and women aged 55 and over without cardiac disease were followed for just over 7 years to assess the onset of cardiac disease or cardiac death. The results indicated that subjects with major depression had an increased risk of cardiac events compared with nondepressed respondents, especially cardiac events that were of ischemic origin (angina pectoris and non-fatal myocardial infarctions).<sup>2</sup>

Researchers believe the link between heart disease and depression is partly due to the effect that depression has on neuroendocrine pathways, which leads to increased platelet activation as well as an excess of cortisol and catecholamines. Depression also alters autonomic nervous system function, which influences the development and progression of coronary atherosclerosis and subsequent heart disease.<sup>3</sup>

Another disease linked with depression is dementia. In vitro and animal studies show that inflammatory changes in the brain are pathological features of both depression and dementia and epidemiological studies show that there is a correlation between chronic depression and the likelihood of dementia in later life. This suggests that an increase in inflammation-induced cell death may play a role in the development of both of these disorders. In both depression and dementia, there is a reduction in the brain of neuroprotective components and an increase in neurodegenerative components. Such pathological changes are thought to cause neuronal damage and thereby predispose chronically depressed patients to dementia.<sup>4</sup>

The connection between depression and these other conditions illustrates the importance of taking steps to bolster our mental health in order to ensure our overall well being.

## **Serotonin—The First Piece of the Puzzle**

Serotonin deficiency has long been recognized as a primary cause of depression. Serotonin promotes feelings of well being, calm, personal security, relaxation, confidence and concentration. Deficiencies of serotonin in the brain have been linked to a number of conditions, including: depression (especially the agitated, anxious, irritable type), anxiety, suicide, alcoholism, violent behavior, PMS, obesity, compulsive gambling, insomnia, carbohydrate craving, SAD (seasonal affective disorder), and migraine headaches.

Serotonin is made from the amino acid tryptophan. When neurons convert tryptophan into serotonin, they first use a vitamin B3-dependent enzyme to convert tryptophan into 5-HTP. A vitamin B6-dependent enzyme is then used to convert 5-HTP into serotonin. This process ensures that the body is nourished with proper levels of a neurotransmitter integral to mental health.

Serotonin circuits help counterbalance the tendency of two other major neurotransmitters in the brain—dopamine and noradrenaline—to encourage overarousal, fear, anger, tension, aggression, violence, obsessive-compulsive actions, overeating, anxiety and sleep disturbances. Many people suffer from various degrees of brain serotonin deficiency, leading to a host of mental, emotional and behavioral problems.

The conventional way to treat depression and serotonin deficiency is to prescribe a class of antidepressant drugs known as selective serotonin reuptake inhibitors (SSRIs). However, these drugs are associated with certain side effects, most notably an increased risk of gastrointestinal bleeding.

## **Natural Mood Enhancers**

A number of natural substances are used to help improve mental outlook. These substances work in a variety of ways including boosting levels of serotonin, regulating circadian rhythm, preventing the atrophy of the hippocampus and reducing the inflammation that has now been linked to depression.

## **5-HTP**

5-Hydroxytryptophan (5-HTP) is the immediate precursor in the production of serotonin from the essential amino acid L-Tryptophan. Unlike tryptophan, intestinal absorption of 5-HTP does not require the presence of a transport molecule, and is not affected by the presence of other amino acids; therefore it may be taken with meals without reducing its effectiveness. In the body 5-HTP is converted to serotonin. Whereas the pharmaceutical drugs selective serotonin reuptake inhibitors (SSRIs) affect only serotonin reuptake, not serotonin synthesis, 5-HTP effectively increases central nervous system synthesis of serotonin.<sup>5</sup>

5-HTP is well absorbed from an oral dose, with about 70 percent ending up in the bloodstream. It easily crosses the blood-brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin. In the CNS, serotonin levels have been implicated in the regulation of sleep, depression, anxiety, aggression, appetite, sexual behavior, and pain sensation. Administration of 5-HTP has been shown to be effective in a wide variety of conditions, including depression, fibromyalgia, binge eating associated with obesity, chronic headaches, and insomnia.<sup>6</sup>

## **Melatonin**

Melatonin is another mood-supporting substance. Many studies have explored how this important hormone, which is produced at night, plays a role in supporting well being.

The cyclic nature of depressive illness, the daily variations in its symptomatology and the existence of disturbed sleep-wake and core body temperature rhythms, all suggest that dysfunction of the circadian time keeping system may underlie the development of depression. Measurement of melatonin either in saliva or plasma, or of its main metabolite 6-sulfatoxymelatonin in urine, has documented significant alterations in melatonin secretion in depressive patients during the acute phase of illness. Not only the levels but also the timing of melatonin secretion is altered in bipolar affective disorder and in patients with seasonal affective disorder (SAD). A delay of melatonin secretion takes place in SAD, as well as changes in the onset, duration and offset of melatonin secretion.<sup>7</sup>

Because melatonin is so intimately tied to well-being and because it is produced primarily at night, sleep loss has been strongly associated with depression. Sleep loss, in our hectic world, has become a hallmark of modern society, leading to a reduction of melatonin levels that may explain why depression is such a common problem. In one study, healthy young males underwent 6 days of sleep restriction (a 4-hour bedtime) and 6 days of sleep recovery (a 12-hour bedtime). At the end of the sleep restriction period, researchers observed some of the same abnormalities in the subjects that are usually observed in depression. The amount of melatonin secreted in the subjects also was reduced.<sup>8</sup>

According to the researchers, "Since these alterations are qualitatively and quantitatively similar to those observed during aging and sometimes during depression, a state of sleep debt, as is experienced by a substantial fragment of the population in modern societies, is likely to increase the severity of depression and widespread age-related chronic conditions such as obesity, diabetes and hypertension."

## **St. John's Wort**

St. John's wort is well known for its ability to improve well-being in patients with mild to moderate depression. In a review of the medical literature published summer 2006, researchers analyzed randomized, controlled trials of St. John's wort to determine its efficacy. All studies demonstrated a significant drop in the Hamilton Depression Rating Scale scores for clients taking St. John's wort compared with a placebo or pharmaceutical antidepressants.<sup>9</sup>

According to the reviewers, "Practitioners may find Saint John's wort a viable complementary treatment alternative to traditional medical treatment."

## **Tyrosine and Phenylalanine**

The amino acids tyrosine and phenylalanine work with 5-HTP to balance brain neurotransmitters. Durk Pearson and Sandy Shaw were the first to popularize the use of phenylalanine and tyrosine to increase the synthesis of catecholamine neurotransmitters. These two stimulatory, mood-boosting amino acids are designed to be taken during the early part of the day to mimic the body's natural rhythm.

## **Lithium Orotate**

A discussion about natural mood enhancers would not be complete without mentioning lithium orotate. Although this safe, natural form of this mineral is more commonly known for its ability to support the health of individuals with bipolar disorder, many clinicians have found it equally effective in other individuals seeking to improve mental health and well being. Dr. Ward Dean, in particular, has achieved a great deal of success using lithium in patients with standard depression.

Studies show that lithium in general inhibits the atrophy of the hippocampus. Atrophy of the human hippocampus is seen in a variety of psychiatric and neurological disorders including recurrent depression, schizophrenia, bipolar disorder, post-traumatic stress disorder, epilepsy, head injury, and Alzheimer's disease.<sup>10</sup>

Lithium orotate also has been found useful in subjects with alcoholism. In one study of 42 patients (33 males and 9 females), researchers treated the subjects with 150 mg per day of lithium orotate during an alcohol rehabilitation program for at least six months. The results indicated that 10 of the patients had no relapse for over three and up to 10 years, 13 patients remained without relapse for 1 to 3 years, and the remaining 12 had relapses between 6 to 12 months. The researchers noted that lithium orotate was safe and the side effects noted were minor. Eight patients developed muscle weakness, loss of appetite or mild apathy, but these symptoms subsided when the daily dose was reduced to 4 to 5 times weekly.<sup>11</sup>

People often confuse lithium orotate with the prescription version of this mineral. However, lithium orotate is considered safer and better absorbed by the body. Dr. Dean has written extensively on lithium orotate's mechanism of action and how lithium orotate prevents the enzyme reactions responsible for the sodium depletion and dehydration effects of other lithium salts. Because of the superior bioavailability of lithium orotate, the therapeutic dosage is much less than prescription forms of lithium (150 mg/day compared to 900-1800 mg of the prescription forms.) In this dosage range of lithium orotate, there are no adverse lithium side reactions and no need for monitoring blood serum measurements.<sup>12</sup> Individuals who are taking other forms of lithium for depression should only discontinue them while under the supervision of a physician.

## **Inflammation's Emerging Role**

Scientists are beginning to realize that the mechanism behind treating depression is more complex than they first thought. In fact, they are now discovering that there might be an inflammatory cause behind depression and that many of the natural mood enhancers mentioned above may work partly due to their ability to reduce inflammation. A body of evidence indicates that the therapeutic activity of natural mood enhancers is connected with their modulatory effect on the inflammatory response system.

Recently, researchers have widely investigated the link between depression and inflammation. Major depression in male patients with increased early life stress is associated with enhanced inflammatory responsiveness to psychosocial stress, providing preliminary indication of a link between major depression, early life stress and adverse health outcomes in diseases associated with inflammation.<sup>13</sup>

In addition, a recent study found higher levels of the inflammatory marker C-Reactive Protein (CRP) in patients with bipolar disorder compared to healthy controls.<sup>14</sup>

Interestingly, over the last five years, scientists have begun to explore the possible anti-inflammatory actions of St. John's wort. In a recent study, researchers decided to test St. John's wort on an animal model of acute inflammation. They injected carrageenan, an inflammatory substance, into the lung cavity of mice. This caused an acute inflammatory response characterized by fluid accumulation in the pleural cavity and a build up of various markers of inflammation. All these markers of inflammation were attenuated by St. John's wort. In addition, the carrageenan triggered increased production of nuclear factor-kappaB (NF-kappaB), an inflammatory substance, in the lung. St. John's wort significantly inhibited NF-kappaB. The researchers concluded that St. John's wort extract potentially reduces the development of acute inflammation.<sup>15</sup>

In addition to its ability to control circadian rhythm, melatonin modulates the expression of a number of genes related to inflammation.<sup>16</sup> In addition, it lowers levels of the inflammatory marker NF-kappaB.<sup>17</sup> It may therefore have a two-pronged effect in improving mood—its ability to regulate our daily cycle and its ability to control inflammation. Because melatonin is such a potent anti-inflammatory hormone, the reason why sleep debt elicits depression-like changes may be due to the low levels of melatonin in sleep-deprived people, which triggers an inflammatory response.

Like St. John's wort and melatonin, 5-HTP is now also thought to support mental health not only through its ability to influence serotonin metabolism but also through its anti-inflammatory actions. Studies have shown that 5-HTP increases levels of Interleukin-6 (IL-6) and Interleukin-10 (IL-10). IL-6 and IL-10 are cytokines, proteins produced by white blood cells important in the body's inflammatory and immune response.<sup>18-19</sup> The anti-inflammatory ability of 5-HTP has led researchers to state "We speculate that the therapeutic activity of these antidepressants is at least partly connected with their effect on the cytokine network and IL-6 production."

Although lithium orotate per se has never been investigated for its anti-inflammatory actions, this would be an interesting area for researchers to explore since other forms of lithium have been shown to reduce inflammation in animal studies.<sup>20</sup> It is possible that one of lithium's mechanisms of actions is through a possible anti-inflammatory effect.

## **Conclusion**

Melatonin, 5-HTP, St. John's wort, phenylalanine, tyrosine and even the mineral lithium have proved to be effective natural mood elevators. By influencing serotonin metabolism, circadian rhythm and even the health of the hippocampus, each of these substances plays a role in enhancing well being. Furthermore, scientists have recently discovered that many of these substances may work to improve mood and mental outlook through their ability to lower inflammation, indicating a surprising new mechanism of action.

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