REVIEW ARTICLE

Anxiety and Depression: It All Starts With Stress

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Is stress an issue for your patients? Perhaps the real question is, when is stress not an issue? Everyone is exposed to potential stressors on a daily basis. Stress comes in the form of physical stressors, as in an injury or infection, and emotional stressors, such as loss, change, or trauma. Lack of sleep and skipping meals are also stressful due to the body response that occurs in an attempt to maintain balance. Even the perception of stress stimulates the body's stress response.

No matter the form, recent studies show that stress leads to disruptions in neurotransmitter balance, which, in turn, can cause anxiety, depression, and other problems. Since a variety of nutrients are important to the effective production of neurotransmitters, practitioners can help patients balance their moods using nutritional approaches. To help you as the practitioner identify patients who can benefit, several simple, natural treatment options for neurotransmitter imbalances have become available in recent years—for example, new home urinary test kits can measure neurotransmitter levels, making it easy to pinpoint imbalances.

Therefore, when your patients experience stress, or the resultant anxiety and depression, they don't have to rely only on standard conventional medications. By understanding the cause of anxiety and depression in how the body responds to stress, and recognizing that simple nutrients are important to the effective production of neurotransmitters, practitioners can easily assist patients.

The Body's Response to Stress

- Increases heart rate and blood pressure
- Leads to increased cholesterol levels
- Suppresses the reproductive system
- Hinders growth
- Hinders release of stomach acid
- Delays stomach emptying
- Stimulates the colon, increasing movement
- May lead to change in appetite and weight gain
- Decreases ability to fight infections
- May lead to increased cancer and autoimmunity
- Affects balance of neurotransmitters
- Can result in long-term activation of the stress system
- Activates changes in the hypothalamic-pituitary-adrenal (HPA) axis
- Has other regional brain effects

Other Things to Consider

- Elevated cortisol -> affects neurotransmitters
- By-products of cortisol act as sedatives
- Cytokines affect HPA axis and cortisol
- Neurotransmitters (GABA) affect HPA axis

An Introduction to Stress

The body's stress response can be both helpful and harmful. It gives people the ability to avoid an impending threat, but, when the threat (or perceived threat) persists, stress can put someone at risk for obesity, heart disease, cancer, and a variety of other illnesses.

Over the past 20 years, research by George Chrousos, MD, professor and chairman of the first department of pediatrics at the Athens University Medical School and chief of the pediatric and reproductive endocrinology branch of the National Institute of Child Health and Human Development, National Institutes of Health, has resulted in a better understanding of stress and its effects on the body.[1-3] For example, it is now known the brain responds to stress by sending chemical signals and hormones into the blood that prepare the body to act appropriately—the classic "fight or flight response." When the stressful situation ends, negative feedback by cortisol turns off the stress response. However, in a society where our way of life involves daily stress, the stress response doesn't always stop. Persistent perception of stress results in a continuous stress response that will eventually take a toll upon the body.

What is the stress response? Also known as the hypothalamic-pituitary-adrenal (HPA) axis or "stress circuit," the stress response is a feedback loop between the nervous system and the parts of the endocrine system that release stress hormones. The hypothalamus releases corticotropin-releasing hormone (CRH) in response to stress, which then triggers the pituitary gland to release adrenocorticotropin (ACTH). ACTH stimulates the adrenal glands to produce epinephrine (adrenaline), norepinephrine (noradrenaline), and cortisol, which result in elevated blood pressure and heart rate, increased blood flow to muscles, and a release of glucose into the bloodstream.

In some cases of chronic stress, the stimulus becomes so overwhelming that the HPA axis starts to shut down—it becomes underactive, resulting in low CRH and cortisol levels. These patients are likely to experience fatigue, as with chronic fatigue syndrome, and depression symptoms similar to those seen in seasonal affective disorder and postpartum depression. A lack of cortisol can also lead to a hyperactive immune system; thus, autoimmune problems are more likely to occur in these cases.

The HPA axis also communicates with the limbic system (affecting motivation and mood), including such areas as the amygdala (relating to fear), the hippocampus (the center for memory formation), and brain regions that control body temperature, appetite, and pain. Along with the HPA axis, the stress response affects many other body systems. Digestive issues, for

example, are quite common among people who suffer from chronic stress. CRH and the autonomic nervous system hinder the release of stomach acid and emptying of the stomach while stimulating the colon. Glandular systems, aside from the adrenal gland, are suppressed by stress. Persistent stress inhibits gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH), which often results in decreased fertility. Release of thyroid hormones, growth hormone, and insulin-like growth factor 1 are also reduced with chronic stress.

Stress hormones also inhibit the function of the immune system. This can lead to a decreased ability to fight infection and contributes to the development and progression of some types of cancer.[4] Multiple studies and clinical evidence have shown that various cellular and molecular immunological parameters, including cytotoxic T cell and natural killer cell activities that govern immune surveillance of tumors, are compromised with chronic stress and depression.[5,6] Evidence also indicates that genetic variations exist in the control of the HPA axis, explaining why some people are more susceptible to strong stress responses than others. Environment further influences HPA axis functioning. Extreme stress at any time, and especially during childhood, permanently alters the HPA axis and increases a person's tendency to mount a strong stress response to future stressors.

According to Chrousos, chronic stress can take 15 to 20 years off a person's life by increasing the risk of health problems.[7] Adverse health outcomes, such as infections and skin disorders—as well as others that are less easily traced—are associated with all types of stress and especially posttraumatic stress disorder and depression.[8] However, if a person decreases stress factors and inhibits the stress response, the damaging effects of stress can be controlled and disorders such as clinical anxiety and depression can be prevented.

As mentioned above, in some cases of chronic stress, the stimulus becomes so overwhelming that the HPA axis starts to shut down, causing low cortisol levels. However, Chrousos's research shows that with constant stress, the brain can also stop responding to the negative feedback message of cortisol, which ordinarily shuts down the stress response when the threat is over—thus, the brain continues to produce CRH, which stimulates yet more cortisol. Chrousos observed this situation in people with depression and found that it can result in anxiety, insomnia, overreaction to stimulation, lack of appetite and motivation, loss of sex drive, rapid heartbeat, high blood pressure, high cholesterol, and high triglycerides. Along with high cortisol levels, these individuals also had high CRH, both of which are associated with anxiety and other mood, eating, and addiction disorders.[7,9] Interestingly, the byproducts of cortisol act as sedatives that may contribute to feelings of depression.

Relapses of major depression have been linked to elevated cortisol levels.[10] And, in fact, antidepressant drugs have been researched for their ability to counteract hypercortisolemia.[11] Classical antidepressants do inhibit corticosteroid-induced gene transcription in cell cultures, while new-generation antidepressant drugs have weaker effects on glucocorticoid receptors.

In the treatment of anxiety and depression, it is important to consider a person's history of stress and measure cortisol levels throughout the day to determine whether increased or decreased cortisol levels are involved. In fact, assessment of adrenal gland functioning in general is key to successfully addressing anxiety and depression. Salivary cortisol sampled 4 different times of day and salivary or serum dehydroepiandrosterone (DHEA) levels are commonly used to assess adrenal function. Natural treatment options for both high and low cortisol include stress reduction, nutrients, herbal therapies, and homeopathic remedies intended to balance dysregulated adrenal responses.

Stress, Depression, and Neurotransmitters

Another hypothesis for the cause of depression predicts deficiencies in norepinephrine and/or serotonin.

Whether the deficiencies are related to altered metabolism, numbers of receptors, affinities, or "cross-talk" between the noradrenergic system (stimulated by or releasing norepinephrine) and serotonergic system (related to the action of serotonin or its amino acid precursor, L-tryptophan), the evidence suggests that depression is related to imbalanced neurotransmitters (see sidebar, "Neurotransmitter Basics" on page 44).

Antidepressant therapy is commonly prescribed to reverse neurotransmitter alterations. Selective serotonin reuptake inhibitors (SSRIs), as reflected in their name, block the reuptake of serotonin from the synapse into the neuron, thus enabling their continued transmission. Studies show the effectiveness of SSRIs is dependent on adequate serotonin. However, SSRIs do not add to the body's total serotonin supply, which may explain why research shows the medications lose effectiveness over time.[12]

Fortunately, there is another option for balancing neurotransmitters. Since neurotransmitters are produced in the body from amino acids with the assistance of nutrient cofactors, providing the body with an increased supply of these precursors increases the body's ability to synthesize its own supply of transmitters—and can correct neurotransmitter imbalances, according to recent research.[13] In addition, non-neurotransmitter amino acids, like theanine and taurine, act as neuromodulators. The term coined to describe this clinical approach is "targeted amino acid therapy."

Considering the stress response and subsequent disruption in cortisol levels and neurotransmitter balance, it makes sense to approach the treatment of anxiety and depression by reducing stress, regulating the stress response by supporting adrenal function, and balancing neurotransmitters using precursors.

Amino Acid Therapy

Once a patient's neurotransmitter levels are determined using such tests as the urine test (see sidebar), any imbalances can be corrected with amino acid therapy. The key to this therapy is to target several neurotransmitters at once instead of just 1 or 2. It is important to support inhibitory neurotransmitters first, followed by support for excitatory neurotransmitters; otherwise, the patient may experience symptoms of over-stimulation (anxiety, sleeplessness, agitation).

Understanding the biochemical pathways by which amino acids are converted to neurotransmitters and neuromodulators provides insight into the nutrients necessary for treatment. Serotonin, for example, is synthesized from tryptophan (5-HTP

is an intermediary). Dopamine, norepinephrine, epinephrine, and phenylethylamine are synthesized from phenylalanine.

Whole-food protein sources, such as eggs, meat, and dairy products, are not the best sources of amino acids for therapy because only negligible amounts of amino acids in these foods cross the blood-brain barrier for conversion to neurotransmitters in the nervous system. Instead, micronutrients are an important factor in amino acid therapy because the enzymes that convert amino acids to neurotransmitters require certain nutrients and minerals. For instance, the conversion of dopamine to norepinephrine is vitamin C dependent, as is the conversion of 5-HTP to serotonin in the nervous system. Calcium and zinc are also involved in the enzymatic production of neurotransmitters.

Other amino acids may be used to support neurotransmitter function. Theanine and taurine, for example, enhance GABA function by 2 different mechanisms. Glutamine contributes to GABA synthesis, while phosphatidylserine, a phospholipid, increases cortisol receptor function within the HPA axis.

The risk of side effects with amino acid therapy is quite low. Some people experience nausea, particularly with use of 5-HTP when serotonin levels are very low. It is believed that a significant rise in serotonin may stimulate a receptor in the brain that regulates the vomit response. Luckily, symptoms subside within 1 to 2 weeks of use, particularly if the dose of 5-HTP is lowered or taken with food to help prevent nausea. Sedation can occur when inhibitory therapies outweigh excitatory support, and agitation results from the opposite scenario, when inhibitory neurotransmitters are insufficient.

Targeted amino acid therapy can be used with most psychotropic medications without negative consequences, as long as neurotransmitter levels are monitored closely. The 1 exception is monoamine oxidase (MAO) inhibitors. The contraindication of MAO inhibitors with amino acid therapy is related to the risk of hypertension with sympathomimetic potentiation, so caution is needed.

Proper dosage depends on the individual and the amino acid. For example, 5-HTP dosages commonly range from 50 to 500 mg/day. Theanine, often used along with 5-HTP, may be given at a dosage of 100 to 200 mg, 2 to 4 times/day.

Looking at the Two Hypotheses Together

Is it possible that depression and anxiety are related to HPA axis dysregulation, including abnormal cortisol levels and neurotransmitter levels? From what we've seen here, yes. Thus, it makes sense to address neurotransmitter levels as well as the HPA axis and adrenal gland functioning in patients with anxiety and depression.

The fields of psychoneuroimmunology and psychoneuroendocrinology embrace the evidence of communication between the brain and body as a multidirectional flow of information that consists of hormones, neurotransmitters/neuropeptides, and cytokines. A study of 140 depressed and control subjects compared plasma cortisol levels in relation to dexamethasone administration (a catabolic steroid that is a member of the glucocorticoid class of hormones) with cerebrospinal fluid and norepinephrine metabolites in plasma and urine. The study concluded that dysregulation of the noradrenergic system and the HPA axis occur together in depressed patients.[15]

Other similar studies have found that neurotransmitters (specifically GABA) influence the HPA axis at the hypothalamus,[16] suggesting cross talk between the 2.

Neurotransmitter Basics

Neurotransmitters are chemical messengers in the nervous system. They communicate between neurons throughout the body, not just in the brain. The study of neurotransmitters—neurobiology—began more than 50 years ago and included research on the use of 5-hydroxytryptophan (5-HTP) to increase serotonin levels. The effect of neurotransmitters has much to do with determining mood, energy level, focus/concentration, food cravings, digestion, sleep patterns, and metabolism. More than 100 chemicals in the body are currently known to act as neurotransmitters or neuromodulators.[14]

Neurotransmitters are either inhibitory or excitatory. Inhibitory neurotransmitters decrease the likelihood that a signal will be relayed across the synaptic cleft, while excitatory neurotransmitters increase the likelihood of transmission. More specifically, glutamate neurons are excitatory and γ-aminobutyric acid (GABA) neurons are inhibitory. All the other neurons and transmitters modulate the glutamate and GABA neurons, enhancing or inhibiting their effects.[14] The balance between excitatory and inhibitory neurotransmitters contributes to optimal health.

A number of other substances, including biogenic amines (epinephrine, norepinephrine, dopamine, and serotonin), peptides (endorphins and enkephalins), and hormones (estrogens, androgens, and corticosteroids), modulate and alter the efficiency of neurotransmission. Excitatory neuromodulators include epinephrine, norepinephrine, phenylethylamine, histamine, and aspartic acid. Inhibitory neurotransmitters include serotonin, glycine, taurine, and agamatine. Dopamine can be both excitatory and inhibitory.

Neurotransmitter-related disorders, such as anxiety and depression, occur when neurotransmitter levels are out of balance and unable to properly relay nervous system messages from one neuron to the next. Neurotransmitter levels can become decreased from prolonged stress, genetic predisposition, and diets low in amino acid precursors. Decreased neurotransmitter receptor levels, caused by heavy metals, pesticides, amphetamines, and some other prescription drugs, can also influence transmission.[14]

The development of enzyme immunoassays and radioimmunoassays has made it possible to accurately measure and analyze neurotransmitter levels in the urine.[15] Several laboratories have made these tests available and relatively easy to complete. The patient collects a single, timed, at-home urine sample, which is mailed to the lab for analysis. The results provide information about neurotransmitter levels compared to optimal levels and observed ranges.

Furthermore, hormones, including those produced by the stress response, affect neurotransmitter levels. Estrogens are neuroprotective, inducing the creation of more synapses. Estradiol decreases MAO, subsequently allowing for the availability of more serotonin and dopamine. Progesterone, instead, potentiates GABA receptors, reducing neurotransmitter activity. Cortisol inhibits the excitatory response by reducing catecholamines and their effect; cortisol also potentiates GABA receptors. DHEA enhances the effects of serotonin and norepinephrine.

The Bottom Line is Stress Reduction

No matter how you look at the research, stress influences depression and anxiety. It seems obvious, then, to treat depression and anxiety with stress management techniques such as yoga, massage therapy, and exercise, in addition to any other treatments or modalities employed.

A study of 24 emotionally distressed women showed that participation in a 3-month Iyengar yoga class significantly reduced stress and improved psychological outcomes.[17] Another study found sufficient evidence that yogic breathing reduced stress, anxiety, and depression.[18] A review of research on the positive effects of massage concluded that massage decreases cortisol ("stress-alleviating effects") and increases serotonin and dopamine ("activating effects").[19] Furthermore, several studies found regular exercise is associated with lower anxiety and depression.[20]

We can't ignore stress and how it affects the body. When my patients talk to me about their symptoms and want to know why they feel terrible, I always reply that it's all about stress and how the body responds to it. When practitioners and patients better understand the stress response and how neurotransmitter levels come into play, we will more effectively be able to address anxiety and depression. Then the tests available for identifying adrenal and neurotransmitter imbalances can be used as tools to determine the most appropriate treatment. No matter what, stress reduction should be at the top of that list.

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