



CALMING DOWN THE HPA AXIS HYPERACTIVITY: IMPLICATIONS FOR NUTRITIONAL THERAPY

Benjamin Brown reviews the facts...

Hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis has been linked to the development of a wide range of mental health issues, including anxiety, depression and memory impairment.

Research suggests that dysfunction of the HPA axis may be in part the result

of nutritional factors, and that dietary change and nutraceutical interventions may help reduce HPA axis hyperactivity and improve mental health and stress-related disorders.

NERVOUS OVERDRIVE

A healthy adaptation to stress is essential for the maintenance of optimal physical and mental health and well-being. One

of the major components of the stress response is the HPA axis, which mediates the stress response from the brain and out into the periphery.

Under stress, the brain secretes neurosteroids such as noradrenaline and glutamate, increasing sympathetic nervous system and causing a signalling cascade from the hypothalamus and pituitary out to the adrenal glands,

ultimately increasing the production of cortisol¹.

While a well-functioning HPA axis is essential to good health, chronic hyperactivity of the HPA axis, over-responsiveness to stressful events and high basal cortisol secretion, may be central to the development of a number of serious health consequences².

Illness associated with HPA axis hyperactivity

Chronic stress

Melancholic depression

Anorexia nervosa

Obsessive-compulsive disorder

Panic disorder

Chronic, active alcoholism

Diabetes mellitus

Central obesity (metabolic syndrome)

Hyperthyroidism

A TOP DOWN VIEW OF STRESS

Excessive activity of the HPA axis may be driven by exaggerated neuronal activity in the brain, as well as stress-induced changes in brain structure. The neurotransmitters Gamma-Aminobutyric Acid (GABA) and glutamate are involved in regulation of the HPA axis. GABAergic neurons in the hypothalamus can directly inhibit HPA axis via the hypothalamus and ultimately reduce cortisol secretion. In contrast, glutamate activates the HPA axis by way of hypothalamus³. Dysfunction of GABA signalling system has long been associated with anxiety⁴. Both GABA and glutamate are produced in the limbic system (e.g. prefrontal cortex, amygdala).

Chronic stress and HPA hyperactivity has also been associated with structural changes in the brain, most notably atrophy of the hippocampus and prefrontal cortex (involved in cognitive function, mood regulation and memory), and hypertrophy of the amygdala (involved in the fear response)⁵. This

is thought to be in part due to the effects of excessive cortisol secretion on brain plasticity and impairment of neurogenesis, the growth of new neurones⁶.

IMPLICATIONS FOR TREATMENT

Reducing hyperactivity of the HPA axis could be an important treatment focus; indeed research suggests that the degree of HPA axis hyperactivity may predict symptom development and treatment response⁷⁻⁸. Furthermore, improvements in HPA function may correlate with treatment with pharmacotherapy, psychotherapy and overall symptom improvement⁹. And most remarkably, reductions in circulating cortisol may allow regeneration and repair of the brain¹⁰.

Dietary change and treatment with nutraceuticals has the potential to improve HPA axis activity and offer a viable and safe approach to the management of stress-related illness. Indeed dietary changes have the potential to reduce HPA axis hyperactivity, and a number of nutraceuticals may be able to improve the GABA signalling system and limit HPA activation.

DIETARY CHANGE

Several dietary changes have been proposed for modification of HPA axis function and the management of stress-related disorders. A plant-based diet rich in monounsaturated and omega-3 fatty acids and complex carbohydrates, can reportedly produce consistent improvements in cortisol levels¹¹. Indeed, women consuming a dietary pattern closer to the traditional Mediterranean diet, with high monounsaturated fatty acid intake, were found to have lower levels of HPA axis activity¹². And a number of phytonutrient-dense foods have also been shown to lower circulating cortisol levels, including cherries, cocoa and pomegranate¹³⁻¹⁵.

Conversely, unhealthy dietary patterns may increase HPA activity and hyper-responsiveness to stress. In a recent

study of type 2 diabetics, it was found that there was a significant correlation between low quality foods high in calories, sugar, and fat and HPA axis disruption¹⁶. Interestingly, lower intakes of potassium and magnesium, as well as a more net acid-producing Western diet have been associated with increased daily cortisol levels and HPA axis activity¹⁷⁻¹⁸.

THE BENEFITS OF MAGNESIUM

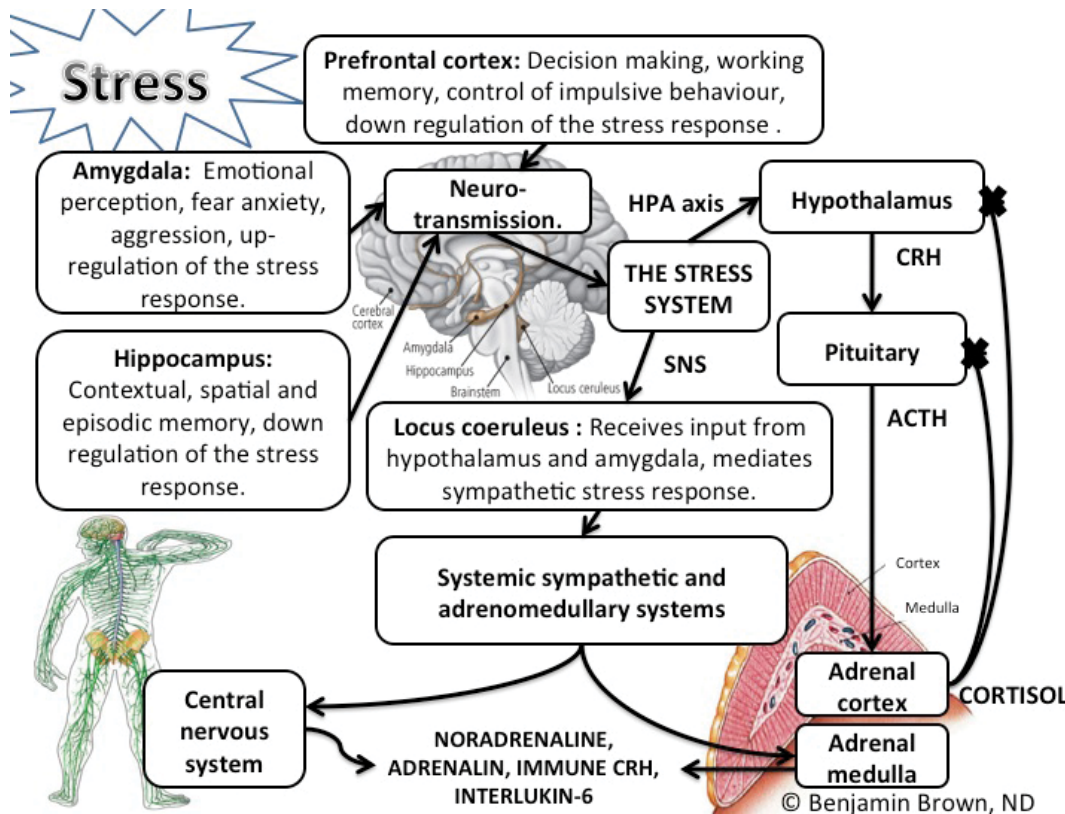
Magnesium deficiency has been associated with anxiety and depression, although the mechanisms for the effects of magnesium on mood are not clearly understood. A recent exploratory study was able to demonstrate that magnesium deficiency reliably induced altered HPA axis function and increases in anxiety-like behaviour¹⁹. Magnesium is able to block glutamate and improve GABA neurotransmission, which may explain its ability to reduce HPA axis activity²⁰.

A research group at the Medical University of Lublin, Poland have been pioneering investigations into the nutritional neuroscience of magnesium, particularly its anti-depressant and anti-anxiety effects. They recently published a comprehensive review of the history, clinical use and science of magnesium, concluding that; "Magnesium preparations seem to be a valuable addition to the pharmacological armamentarium for management of depression²¹."

They note, "The first information on the beneficial effect of magnesium sulphate given hypodermically to patients with agitated depression was published almost 100 years ago." And that since this early observation, "numerous pre-clinical and clinical studies confirmed the initial observations, as well as demonstrated the beneficial safety profile of magnesium supplementation."

LEMON BALM

Lemon balm (*Melissa officinalis*) is a food and medicine with a long traditional use for relaxation, a use supported by a number of pre-clinical and clinical studies. An experimental study found that by



directly increasing GABA in the brain, lemon balm was able to lower serum cortisol levels²². The same report also found a direct effect of lemon balm on neurogenesis. Perhaps not surprisingly, human clinical studies have demonstrated an anti-anxiety effect of lemon balm.

In an extemporaneous study, just 15 days of treatment with 300mg per day of a lemon balm extract "reduced anxiety manifestations by 18 per cent, ameliorated anxiety-associated symptoms by 15 per cent and lowered insomnia by 42 per cent. As much as 95 per cent of subjects responded to treatment, of which 70 per cent achieved full remission for anxiety, 85 per cent for insomnia, and 70 per cent for both²³." This is a rather striking clinical effect.

THEANINE

The mechanism of action of theanine, an amino acid found in tea, appears to be in part related to its influence on neurotransmitters, and it has been shown to inhibit glutamate reuptake, block glutamate receptors, increase GABA concentration, decrease noradrenaline and increase serotonin levels²⁴. In a human clinical study, theanine improved the Dehydroepiandrosterone sulphate (DHEAS) to cortisol ratio, suggesting a

mechanism for theanine's therapeutic effect²⁵.

A recent clinic study demonstrated rapid anti-stress effects of theanine (200mg twice daily). A group of 5th-year university students who were preparing for a pharmacy practice placement took theanine or placebo for one week before the practice started and then for 10 days over the practice period. They also had their morning salivary α -Amylase Activity (sAA) measured as a marker of sympathetic nervous system activity. Compared to the placebo-group, sAA was lower in theanine-group and subjective stress was also significantly lower. These results suggest that theanine can effectively reduce feelings of stress, a benefit that may be in part due to theanine's ability to calm down your sympathetic nervous system²⁶.

SAFFRON

Saffron (*Crocus sativus*) has a long history of use for improving mood and mental health. A traditional Chinese medicine text from the Mongol dynasty for example, states that; "...long-term ingestion causes a person's heart to be happy," and considerable modern research supports this traditional mood-enhancing use of saffron²⁷. Interestingly, simply smelling saffron has been shown to lower the stress

hormone cortisol and reduce symptoms of anxiety²⁸.

A number of possible mechanisms of action may explain the mood enhancing effects of saffron, including; improvements in the action of the neurotransmitter serotonin, enhancement of brain functions such as of memory and learning, antioxidant effects, protecting the brain against the damaging effects of chronic stress and modulating the GABBA receptor²⁹⁻³³.

There are several human clinical studies that have tested the effects of saffron as a natural anti-depressant and mood stabiliser, with some impressive results³⁴⁻⁴¹. Saffron is not only as effective as anti-depressant medications; it was as well or significantly better tolerated, with no more side-effects than placebo. Furthermore,

when used alongside anti-depressant medication, saffron reduced the incidence of sexual side-effects that commonly occur with these drugs. All these studies used just 30mg of saffron extract daily.

HEALTHY MIND, HEALTHY BODY

Beyond the effects of psychological and physical stress, hyperactivity of the HPA axis may be the result of poor dietary practices, and the adoption of a healthy diet may improve adaptation and resilience to stress. In particular, a diet that emphasises dietary sources of polyunsaturated fatty acids, and alkaline, phytonutrient-dense fruits and vegetables, has shown promise. Further, the use of nutraceuticals that modulate activation of the HPA axis via the brain, such as magnesium, lemon balm, theanine and saffron, may help cool down the stress response and improve mental and physical health. ●

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