The Hypothalamic-Pituitary-Adrenal Axis: The Actions of the Central Nervous System and Potential Biomarkers

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Chapter 10

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ABSTRACT

The adrenal glands are part of an adaptive system involved in the maintenance of a homeostatic biological balance in response to stress. The adrenal glands release cortisol, epinephrine, and norepinephrine to preserve a healthy, but dynamic equilibrium. Specific brain nuclei control adrenal gland function either through the actions of the hypothalamic-pituitary-adrenal (HPA) axis, initiated by traditional HPA drivers like corticotrophin releasing factor (CRF) from the hypothalamus, or through direct innervation by stimulated preganglionic sympathetic nerves. These pathways can be activated by physical or emotional stressors as well as inflammatory processes which can activate adrenal activity through the signaling of various cytokines. The continuum of hyperstimulation of the HPA axis from an acute insult to a chronic saturation of the system is led by varying degrees of adrenal collapse eventually giving way to adrenal fatigue. The functionality of the HPA axis can be evaluated with peripheral biomarkers such as urinary epinephrine and norepinephrine and salivary cortisol. These HPA biomarkers help practitioners identify contributing factors to various clinical conditions and provide insight into potential intervention points. By understanding the pathways that can lead to altered HPA axis activity and by using biomarkers to assess HPA functionality, health care practitioners can make more informed clinical decisions to enhance patient care.

Keywords: HPA axis, neurotransmitter, biomarker, central nervous system, adrenal gland, cortisol

INTRODUCTION

Modern day stressors such as relational dysfunctions or physical challenges constantly threaten the homeostatic balance that a healthy, functioning organism is charged in the maintenance of. However, when jeopardized by excessive or constant stress, the biological system begins to lose ground in its ability to maintain chemical stability and instead allows pathological discord to rule.

Stress is defined as “a state of threatened homeostasis,” and any alterations in the ability to respond to stress may lead to disease.1 During a stress response a number of changes to the physiological functioning of the organism can occur, primarily led by the release of glucocorticoids and the catecholamine neurotransmitters epinephrine and norepinephrine from the adrenal glands.2 Epinephrine and norepinephrine are released from the adrenals as hormones into circulation and act on a variety of different tissues. Their function is dependent on the type of adrenergic receptor that is expressed on the tissues. Typically, these neurotransmitters are described as initiators of the fight or flight response, as they increase respiration and heart rate, and trigger the release of glucose from energy stores.3 The glucocorticoid cortisol contributes to carbohydrate, protein, and fat metabolism, regulates blood glucose, and suppresses the immune system. Excess release of neurotransmitters and glucocorticoids from the adrenal glands, if left unchecked, can advance the development of a number of pathological responses.4

The control and release of these molecules from the adrenal glands is mediated through a network of central nervous system (CNS) neurons with resultant peripheral nervous system (PNS) effects, collectively known as the hypothalamic-pituitary-adrenal (HPA) axis. But what are the key brain nuclei in this intricate central communication and how do they initiate a response? A better understanding of the consequences of stress on the central nervous system and accordingly, HPA axis function and adrenal responses, provide solutions to these questions.

In the human body, the CNS and the PNS function together to coordinate the actions of the endocrine and immune systems, along with all other biological processes. Under healthy conditions, changes in internal and external milieu are received and processed by the nervous system to elicit an appropriate action. When faced with excessive stress, whether physical or emotional, adaptive systems function to maintain a dynamic equilibrium. The autonomic nervous system (ANS) is part of the PNS and
consists of sympathetic and parasympathetic divisions. The HPA axis is an adaptive system in the sympathetic division that regulates the biological response to stress through the release of glucocorticoids, epinephrine, and norepinephrine in the periphery. These hormones and neurotransmitters can be measured as biomarkers to assess HPA activity and the determinant central pathways.5,6

A breadth of research has examined HPA axis function and the relationship between CNS and PNS biochemistry. The physiological consequences of stress and HPA activation appear as enhanced attention, accelerated cardiac output and respiration, increased catabolism, and redirection of blood flow to provide the highest perfusion to the brain, heart, and muscles.7 Interestingly, these resultant physiological actions of the HPA axis are tightly regulated by specific brain circuits.7 Neuronal impairment of these brain circuits prevents adrenal neurotransmitters and hormones from performing their required biological functions, consequently leading to a state of imbalance and various pathological conditions.8 Therefore, measurement of biomarkers has become an important tool to predict the CNS circuitry that underlies the discordance in HPA axis function.

When considering peripheral biomarkers to assess CNS activity, the validity of such an approach is called into question. Due to the presence of the blood-brain-barrier limiting the transport of neurotransmitters from the periphery to the CNS, it is often assumed that the transport of neurotransmitters from the CNS to the periphery is also limited, when in fact, central neurotransmitters are carried via transporters to the periphery.9 Additionally, research has clearly illustrated the relationship and crosstalk between the CNS and PNS.10-14 Therefore, understanding the neural circuits that mediate this crosstalk and viewing peripheral biomarkers as a reflection of central activity can provide practitioners with powerful insight into CNS function and a better understanding of the etiology and treatment of HPA axis dysfunction.

In this review, information will be presented on brain circuits that regulate HPA axis activity, the use of biomarker measurements to delineate specific neural circuits that control HPA axis function, and the association between neuronal impairment, biomarkers, and stressful challenges that lead to impaired HPA axis function and eventual adrenal dysregulation.

THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The Neurocircuitry of the HPA Axis

The HPA axis is organized into three distinct regions: the hypothalamus, pituitary gland, and adrenal glands. Specifically, the paraventricular nucleus (PVN) is the hypothalamic region that uses corticotrophin-releasing hormone (CRH) to stimulate the pituitary.15 Upon stimulation, the anterior pituitary releases adrenocorticotrophin hormone (ACTH), which is transported in general circulation to the adrenal cortex of the adrenal glands.16 The adrenal glands rapidly synthesize and release cortisol into the blood where it participates in the response to stress and maintenance of homeostasis throughout the body.15

The adrenal gland is the effector organ of the HPA axis and its actions are essential to maintaining homeostasis. Although much research has focused on the hypothalamic-pituitary regulation of adrenal function, other pathways exist that can alter adrenal activity. Neural projections from the CNS affect adrenal activity by acting at different levels of the HPA axis.

Sympathetic Innervation of Adrenal Gland

One pathway that regulates adrenal function involves sympathetic preganglionic fibers that project to the adrenal medulla to elicit the release of epinephrine and norepinephrine as hormones into circulation (Fig. 1).17 The neural pathways that innervate the adrenal medulla are mediated by the stimulation of sympathetic preganglionic neurons that originate in the intermediolateral (IML) cell column.18 The IML cell column extends from the first thoracic through the third lumbar segment and receives excitatory projections from specific brainstem and hypothalamic regions which can alter adrenal activity.18 Specifically, the IML receives excitatory projections originating in the lateral hypothalamus (LH) and rostral ventrolateral medulla (RVLM). Stress can initiate this pathway through the activation of the LH and RVLM.
Figure 1. Sympathetic preganglionic fibers, activated by various brain nuclei in response to stress, project directly to the adrenal medulla to elicit the release of epinephrine and norepinephrine into circulation.

**Neural Input to Hypothalamic Paraventricular Nucleus**

Stimulation of the adrenal glands via the classical hypothalamic-pituitary pathway is also under stringent control by the CNS. Specifically, the PVN can be stimulated by excitatory projections from specific brainstem nuclei, limbic centers, the basal forebrain, and circumventricular organs. The brainstem nuclei that send excitatory projections to the PVN include the locus coeruleus (LC) and dorsal raphe (DR). During times of stress, the LC and DR use norepinephrine and serotonin, respectively, to stimulate the PVN. From the limbic system, the areas involved include the amygdala and hippocampus, which are important for emotion, behavior, and memory. Strong emotions or emotional memories can trigger the amygdala and hippocampus to stimulate the PVN. Increased PVN activity causes enhanced cortisol release leading to a rise in vigilance to deal with the stressor (Fig. 2).

Cytokines from an inflammatory response can also contribute to PVN activation. Research has thoroughly described the relationship between pro-inflammatory cytokines mediated by immune system activation and adrenal function. Upon insult or injury, cytokines released by immune cells can alter brain chemistry in two ways. The first is a humoral pathway, whereby cytokines are released into systemic circulation and can act on circumventricular organs such as the area postrema (AP). The circumventricular organs are areas of the brain that have incomplete blood-brain barriers and can therefore detect and relay chemical signals (e.g. pro-inflammatory cytokine responses) to the brain. In this way, cytokines can directly alter CNS function without the use of transport systems. Upon activation, the AP transmits signals to the nucleus tractus solitarius (NTS). From there, the NTS stimulates the PVN, which leads to enhanced adrenal gland activity.
Figure 2. The paraventricular nucleus of the hypothalamus (PVN) receives input from several areas of the brain, including brainstem nuclei, limbic centers, and circumventricular organs. The PVN integrates these signals and activates the HPA axis cascade, resulting in the release of cortisol from the adrenal cortex.

The second way cytokines can alter brain activity is via a neural pathway, whereby cytokines released by immune cells in lymphoid tissue activate the vagus nerve to signal to the brain that an inflammatory process is occurring. The vagus nerve projects to the NTS, causing stimulation of the PVN, which again leads to enhanced adrenal activity and cortisol release. Cortisol acts on glucocorticoid receptors expressed on immune cells to inhibit pro-inflammatory cytokine production and stimulate anti-inflammatory cytokine production. Epinephrine and norepinephrine effect a similar response by binding to β-adrenergic receptors. The anti-inflammatory response of glucocorticoids and catecholamines released from HPA activation can decrease pro-inflammatory cytokine levels as a protective mechanism to avoid tissue damage.

**Specialized Stress Pathways**

It is interesting to note that different types of stress, (physiological and emotional), activate the HPA axis through separate, but convergent, pathways. That is, although different types of stress are involved in different circuits, the end result culminates in HPA activation and glucocorticoid release.

Physiological or ‘real’ stress is detected by somatic, visceral, or circumventricular pathways. True, physical changes in the body, including respiratory and cardiovascular changes, pain, and elevated levels of circulating inflammatory mediators, represent a current, tangible threat to homeostasis. This sensory information is communicated through ascending vagus nerves and circumventricular organs that converge on the NTS, which integrates the sensory input and passes it along to the PVN.

Unlike the physiological stress response, which is a reaction to an actual disturbance to homeostasis, an emotional, or anticipated, stress response can happen without a primary sensory stimulus. Emotional stress elicits HPA activation in anticipation of a potential homeostatic disruption. As mentioned above, limbic brain regions such as the amygdala and hippocampus are heavily involved in...
emotional processing, behavior, and memory, and will stimulate the PVN when activated. A fear response triggered by climbing a ladder, for example, would evoke glucocorticoid release, consequently increasing vigilance to prevent a fall.

**Chronic Stress Effects**

The HPA axis is an innate system adept at compensating for the detrimental effects of acute stressors, reining the system back into equilibrium. The system is meant to respond to an acute stressor and then terminate that response via negative feedback mechanisms. This ebb and flow adaptive effect is crucial to the survival of an organism (for review see Ziegler & Herman20). However, chronic HPA stimulation due to ongoing physical or emotional stress can lead to unresponsiveness of hypothalamic nuclei.28 Additionally, if the adrenals maintain a high level of activity to mobilize cortisol, epinephrine, and norepinephrine, the stores of these hormones may become depleted. Taken together, these events lead to adrenal insufficiency, which reduces the gland’s ability to maintain homeostasis. An insufficient adrenal response to stress or an immune challenge prevents the body from being able to deal with the stress or fight off infection.26, 29

Overall, the HPA axis receives input from a variety of central and peripheral sources, and it is the integration of these signals that allows this system to produce the appropriate homeostatic response. However, excessive stimulation of the HPA axis by one or more of these inputs can disrupt its ability to maintain homeostasis, which could then lead to a disease state.

**Biomarkers of HPA Activity**

Neurotransmitter and hormone measurements can be used as indicators of biological imbalances and may help improve our understanding of complex disease states. In many areas of medicine, biomarkers aid in diagnosis, prognosis, and predicting treatment efficacy.30 For example, cholesterol is commonly assessed to determine the risk of cardiovascular disease and subsequently re-tested to monitor treatment efficacy, and prostate-specific antigen (PSA) is used in the detection of prostate cancer.

In psychiatry, diagnostic and treatment decisions are made by evaluating subjective measures such as clinical signs and symptoms. With the development of biomarkers for particular psychiatric disorders, it is anticipated that more objective criteria for those disorders can be achieved, which would reduce evaluator bias due to emotions or personal prejudices.30 Schwarz and Bahn31 established the need for biomarkers in psychiatry to monitor responses to treatment and to predict clinical outcome. These authors stated that the efficacy of a medication for a particular patient should be assessed using biomarkers to reduce the chance of selecting unsuccessful treatment for complex diseases.31 In terms of the HPA axis, urinary epinephrine and norepinephrine and salivary cortisol can serve as indicators to detect a dysfunctional state and aid in the selection of various treatments to either increase or decrease adrenal activity.

In the past, biomarker assessments have been viewed as irrelevant to symptomatology because measures had included peripheral biological fluids, such as blood, urine, and saliva, but not CNS markers, such as cerebrospinal fluid and brain tissue.32 A common misconception about peripheral biochemistry is that it cannot serve as a biological indicator of CNS activity due to dissociation of the systems.33 Although this is a reasonable argument as peripheral biomarkers, such as circulating neurotransmitters and hormones, are markers of PNS activity, compelling evidence exists to support the crosstalk between the peripheral and central nervous systems.34 The CNS and PNS must not be viewed as separate entities. We have demonstrated above that specific CNS nuclei can manipulate peripheral neurochemistry, and peripheral neurochemistry can affect central pathways (e.g. vagal afferents from periphery to CNS).35 The pathways described above demonstrate that the CNS and PNS communicate via direct neuronal projections. Therefore, it is possible to obtain inferences on central profiles through the measurement of peripheral biomarkers such as urinary neurotransmitters and salivary hormones.36

**Using HPA Biomarkers to Assess Clinical Symptoms**

Altered HPA axis activity has widespread effects throughout the body, and can contribute to changes in energy, sleep, mood, cognition, weight, and the cardiovascular system, among others. More specifically, HPA axis hypoactivity has been associated with chronic fatigue syndrome (CFS), possibly due to blunted ACTH and CRH responses.37 Studies have shown that there is an association between the
development of obesity and adrenal activity, evident by elevated urinary norepinephrine and lower urinary epinephrine. Another study demonstrated that in older patients, higher salivary cortisol levels are correlated with impaired declarative memory. These studies support the use of HPA biomarker measurements to understand the biochemical contributors to various clinical conditions.

Altered HPA axis activity has also been found to have profound effects on mood and behavior that are characteristic of a variety of psychiatric disorders. In fact, literature supports the relationship between psychiatric disorders and abnormal HPA axis activity and has demonstrated the utility of urinary measures of epinephrine, norepinephrine, and salivary cortisol to assess HPA axis function. For example, patients with panic disorder were found to have higher morning cortisol levels compared to controls, but also lacked a significant cortisol increase in response to psychosocial stress. Whilst Hughes demonstrated a positive correlation between elevated urinary norepinephrine and cortisol levels and depression and anxiety symptoms. Assessment of epinephrine, norepinephrine, and cortisol, given their neurochemical involvement in HPA axis activity and their association with psychiatric disorders, could provide the necessary biochemical targets to determine underlying cause and predict treatment outcome.

Adrenal function can also vary according to the nature of the stressor. Miller and colleagues conducted a meta-analysis to determine why differences in adrenal responses exist among individuals exposed to chronic stress. They discovered that stress which threatens physical integrity, for example combat, elicits higher cortisol output throughout the day. Whereas stress that poses a threat to social self, such as divorce, is associated with higher cortisol in the morning and evening. It is hypothesized that the body increases adrenal activity to mobilize resources when necessary to efficiently evade a stressor. The question remains as to how these different stressors affect specific brain regions. Much of the research that examines specific stressors is confounded by the inability to control other stressors initiated by inflammatory processes or injury. Because the HPA axis plays an integral role in responding to different types of stressors and incorporating signals from the CNS and PNS, it serves as a biological “middleman” that utilizes specific neurotransmitters and hormones as chemical signals. By understanding the interactions between these brain pathways and the HPA axis, one can gain a better understanding of how stress mediated by CNS pathways can provoke alterations in urinary neurotransmitter and salivary cortisol measurements.

Using HPA Biomarkers to Assess Treatment

Convincing data suggests that urinary neurotransmitters and salivary hormones can predict treatment outcome and monitor treatment efficacy. Mooney and colleagues assessed the effects of antidepressants in depressed patients by monitoring urinary neurotransmitter levels. Depressed patients with a favorable antidepressant response to alprazolam, a benzodiazepine, were found to have significantly higher pretreatment urinary catecholamine levels than control subjects. The antidepressant response of alprazolam was monitored in responders and non-responders with subsequent urinary neurotransmitter analysis. The data demonstrated a significant decrease in urinary catecholamines after eight days of alprazolam treatment, which was consistent with improvements in depressive symptoms. Additionally, non-responders to alprazolam did not display significant elevations in pretreatment urinary catecholamine levels compared to control subjects. Alprazolam possesses clear inhibitory effects on the HPA axis in both animals and humans by suppressing hypothalamic and suprahypothalamic levels of corticotrophin-releasing hormone. The activity of alprazolam in the CNS would predicatively change circulating levels of catecholamines by manipulation of HPA axis function. Thus, changes in circulating levels of catecholamines could be used to monitor the efficacy of alprazolam, a centrally active compound.

Another study showed that after one month of Pycnogenol® treatment, a bioflavonoid extract from pine bark, norepinephrine levels decreased significantly, which correlated with improvements in ADHD symptoms. HPA biomarkers can also be used to monitor non-pharmacological treatment. In a study using cognitive-behavioral therapy to treat major depressive disorder, salivary cortisol decreased significantly more in patients treated in the forest compared to patients treated in a hospital setting, and the decrease in cortisol corresponded with symptom improvements. These findings further illustrate the fundamental usefulness of urinary neurotransmitter and salivary cortisol measurements in the determination of treatment selection and effectiveness.
The fact that there is a direct involvement of the CNS in the release of neurotransmitters in the periphery explains why the CNS and PNS must be viewed as parts of a single integrated system. Although there are clear anatomical separations between the CNS and PNS, their functional roles cannot be viewed separately. By understanding the neurocircuitry that enables centrally acting compounds to manipulate peripheral markers and the correlative parallels between the neurotransmitters in the CNS and the periphery, predictions on treatment choice as well as outcome can be made via the measurement of peripheral biochemistry.

CONCLUDING REMARKS

The HPA axis is influenced by a variety of brain nuclei in response to stress. Stress is typically associated with emotional or social demands; however, a broader definition can be applied to stress to include inflammatory processes due to infection or injury. Whether stress occurs due to a traumatic event, divorce, or a severe burn, brain pathways are initiated to activate the HPA axis. The coordinated actions of the brain and HPA axis in response to stress results in the release of cortisol, epinephrine, and norepinephrine into the periphery. The production of these hormones from the adrenal gland is essential to overall health and wellbeing. They provide a mechanism in which humans and other organisms exposed to many different forms of stress can regain homeostasis. However, continuation of stressors can leave an individual at risk for developing mood disorders or infections caused by pathophysiological functioning of the adrenal gland. Urinary epinephrine and norepinephrine and salivary cortisol can be used as HPA biomarkers to help identify contributing factors to various clinical conditions and provide insight into potential intervention points.

The evidential support from the current literature suggests that urinary epinephrine and norepinephrine and salivary cortisol testing have an important role in clinical practice as representative biomarkers of HPA axis activity. There is growing evidence that the central pathways that alter HPA axis activity are important in the interpretation of these biomarkers. By understanding the mechanism(s) for treatment and the factors leading to changes in urinary neurotransmitter and salivary hormone balance, health care practitioners will benefit from these tools to assist in making more informed therapeutic decisions and monitoring treatment regimens with enhanced patient care.

REFERENCES

ABOUT THE AUTHORS

Dr. Kelly Olson’s background as a neuropharmacologist began with a Masters in Science from the University of North Dakota in 1999. She received her Ph.D. in 2007 from the University of Manitoba, Winnipeg, MB, Canada in Pharmacology and Therapeutics. She accepted a position as Director of Research and Development with NeuroScience, Inc., a company based out of Wisconsin, focusing primarily on systems biology. Currently, Kelly works as the Clinical Director of Research and Development at SleepImage in Denver, CO., examining molecular aspects of sleep neurocircuitry, developing patents, investigating clinical data, giving presentations to the medical community and coordinating global research for a sleep monitoring medical device.

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