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Influence of Perinatal Lesions of the Central Nervous System in Women of Reproductive Age with Hypothalamic Syndrome on the Neuroendocrine Regulation

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ABSTRACT

The hypothalamo-pituitary-adrenocortical (HPA axis) is required for stress adaptation. Activation of the HPA axis causes secretion of glucocorticoids, which act on multiple organ systems to redirect energy resources to meet real or anticipated demand. The HPA stress response is driven primarily by neural mechanisms, invoking corticotrophin releasing hormone (CRH) release from hypothalamic paraventricular nucleus (PVN) neurons. Pathways activating CRH release are stressor dependent: reactive responses to homeostatic disruption frequently involve direct noradrenergic or peptidergic drive of PVN neurons by sensory relays, whereas anticipatory responses use oligosynaptic pathways originating in upstream limbic structures. Anticipatory responses are driven largely by disinhibition, mediated by trans-synaptic silencing of tonic PVN inhibition via GABAergic neurons in the amygdala. Stress responses are inhibited by negative feedback mechanisms, whereby glucocorticoids act to diminish drive (brainstem), promote transsynaptic inhibition by limbic structures (e.g, hippocampus). Glucocorticoids also act at the PVN to rapidly inhibit CRH neuronal activity via membrane glucocorticoid receptors. Chronic stressinduced activation of the HPA axis takes many forms (chronic basal hypersecretion, sensitized stress responses, even adrenal exhaustion), with manifestation dependent upon factors such as stressor chronicity, intensity, frequency and modality. Neural mechanisms driving chronic stress responses can be distinct from those controlling acute reactions, including recruitment of novel limbic, hypothalamic and brainstem circuits. Importantly, an individual's response to acute or chronic stress is determined by numerous factors, including genetics, early life experience, environmental conditions, sex and age. The context in which stressors occur will determine whether an individual's acute or chronic stress responses are adaptive or maladaptive (pathological).

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1. Introduction

Survival is a fundamental priority of all organisms in an ever-changing environmental context. Survival frequently hinges on the ability to adapt to various homeostatic challenges. Over the course of evolution, multiple and overlapping mechanisms are in place to deal with both acute and prolonged threats. The so-called ‘stress response’ represents an integrated reaction to stressors, broadly defined as real or perceived threats to homeostasis or wellbeing. Activation of the hypothalamo-pituitary-adrenocortical (HPA) axis represents a primary hormonal response to homeostatic challenge. In general, some sort of HPA axis change is engendered by all varieties of stressor, and is a hallmark of the physiological HHS Public Access Author manuscript Compr Physiol. Author manuscript; available in PMC 2016 May 14. Published in final edited form as: Compr Physiol.; 6(2): 603–621. doi:10.1002/cphy.c150015. Author Manuscript Author Manuscript Author Manuscript Author Manuscript reaction to stress. Through the release of glucocorticoids, the HPA axis mobilizes energy reserves to insure that the organism has the resources needed to meet a very real physical insult (a ‘reactive’ response), or prepare for a predicted insult (an ‘anticipatory’ response). Proper control of the stress response is of critical importance, as inappropriate or prolonged HPA axis activation is energetically costly and is linked with numerous physiological and psychological disease states Glucocorticoids serve to mobilize the appropriate energy needed for the context at hand [1]. In brain and pituitary, glucocorticoids signal through at least two receptor subtypes, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). The GR and MR are both ligand-gated transcription factors that alter expression of a large arsenal of genes [2]. The MR, which has a higher glucocorticoid binding affinity than GR, regulates basal circadian and ultradian rhythms and is important in dictating HPA axis activity with respect to time of day. In the kidney and other tissues, the MR largely senses aldosterone, due to inactivation of corticosterone (or cortisol) by high levels of 11-β hydroxysteroid dehydrogenase (11-βHSD1) [3]. However, in other tissues, including brain, βHSD1 acts in the opposite direction (as a reductase) in brain, and may indeed amplify glucocorticoid action under some conditions [4]. Higher levels of glucocorticoids (including those seen following stress) activate the lower-affinity GR, which promotes expression of a wide variety of genes and is thought to mediate glucocorticoid effects on mobilization of energy stores (liver, fat and muscle), inflammation and neural function (among others) [5].

2. Conclusion

The HPA axis stress response is one of many bodily systems that is designed to help the organism cope with adversity. The importance of this system is underscored by its conservation across species and maintenance of dynamic responsiveness across the life span. An array of intrinsic regulatory processes governs the activity of hypothalamic CRH neurons, anterior pituitary corticotropes, and steroidogenesis in the adrenal cortex. Further, organismal regulation of the HPA axis can be mediated by mechanisms as diverse as plasma binding proteins, sex steroids, and the autonomic nervous system. Importantly, previous stress history interacts with current environmental demands to regulate HPA axis activity. Critical components of this interaction are the divergent and interconnected forebrain limbic sites that provide substantial regulation of HPA axis stress responding. The dynamics of the HPA axis require a tightly-controlled balance of excitation and inhibition for appropriate stress responding and adaptation to environmental demand. Understanding the mechanisms mediating the beneficial and (potentially) deleterious aspects of glucocorticoid action will certainly advance our understanding of health and disease.

3. References

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