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Review

This can't be stressed enough: The contribution of select environmental toxicants to disruption of the stress circuitry and response

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HIGHLIGHTS

- HPA axis and limbic system function in parallel to mediate the stress response.
- Environmental toxicants have been shown to damage the HPA axis and limbic region.
- Chemicals cause alterations in glucocorticoids and neurotransmitter signaling.
- More work is needed to fill gaps in our understanding of chemicals in stress response.

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ABSTRACT

Integration of the hypothalamic–pituitary–adrenal (HPA) axis and the limbic system through glucocorticoid signaling is imperative in initiating and regulating a suitable stress response following real or perceived threats. Dysfunction of these circuits that results in a persistent or inhibited glucocorticoid secretion can severely affect processing of stressful experiences and lead to risk for developing further psychiatric pathology. Exposure to toxic chemicals found in our environment, including pesticides, metals, and industrial compounds, have been shown to have significant impact on neurological health and disease. Indeed, studies have begun to identify the HPA axis and limbic system as potential targets of many of these environmental chemicals, suggesting a possible environmental risk for damage to the stress circuit and response to stressful stimuli. This review will focus on our current understanding of the impact exposure to environmental toxicants, including bisphenol A and lead, has on the synaptic physiology of the HPA axis and limbic system and how this contributes to an alteration in behavior output. Further, this discussion will provide a starting point to continue to couple novel toxicological and neurological approaches to elaborate our understanding of the influence of environmental chemicals on the stress response and pathology.

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1. Introduction

In situations of physical or perceived adversity, a biological and physiological response is initiated that functions to ensure a context-relevant response that counteracts the challenge and allows an organism to adapt to future stressful encounters. In order for this to occur the body relies on several different, yet highly integrated neural circuits that work in concert to elicit an appropriate action [1]. Under normal conditions, an intact stress circuit will initiate a response that is both physiologically and behaviorally aligned with magnitude and valence of the stressful experience. However, various malfunctions within the stress response circuit could lead to an aberrant response that is not suitable to the situation [2]. While a maladaptive stress response certainly has implications for how someone navigates society and interpersonal interactions, a chronic disruption of this circuit can lead to pathological manifestations, including risk for depression and other psychiatric concerns [3].

It is well established that there are various environmental risk factors for alterations to both the centrally mediated hypothalamic–pituitary–adrenal (HPA) and the peripherally mediated sympatho-adrenomedullary (SAM) axis stress circuitry, including maternal care, psychological and physical traumas, socioeconomic status (SES), that can severely impact normal development and maintenance of the stress response [4–9]. In addition to these concerns, we must also consider the neurological impact of exposure to environmental chemicals on the specific aspects of the stress circuit. These chemical specters encroach, unseen, at various entry points in our day to day lives, either through air pollution, contaminated food and water, or the inclusion of harmful chemicals into many of our consumer products, we are exposed to an extensive and diverse chemical cocktail. Thus, on any given day we are potentially exposed to hundreds of different chemicals, many of which are known to travel to the brain and affect neurological health. With these points in mind, this review will appreciate the most salient aspects of the HPA axis and stress circuitry and will continue this discussion in the context of environmental chemicals by highlighting specific targets of this circuit that have been shown to be altered by environmental exposures. It is hoped that this discussion will serve as a starting point, from which to initiate a greater appreciation for the environmental contribution to neurological disease and facilitate further in-depth investigations to uncover the impact of environmental chemicals in modulating the stress circuit and maladies related to its dysfunction.

2. Overview of the central and peripheral stress circuitry

Mounting a response to a specific challenge requires equal input from both central as well as peripheral mediators of the stress circuitry. The peripheral stress response circuit is comprised of the SAM axis and is primarily tasked with integrating and transmitting viscero- and somatosensory stress stimuli. Stressful stimuli, such as visceral or somatic pain, loss of blood volume, or respiratory distress, activate sympathetic neurons in the spinal cord, which initiates the release of norepinephrine (NE) onto target organs [10]. An elevation in NE stimulates an adaptive response to the stressor by increasing heart rate and respiration and mobilizing energy stores for use. Stressors that arise from the periphery are concurrently integrated with the central nervous system through ascending signals that synapse onto NE neuron populations in the locus coeruleus as well as other NE-releasing brainstem and medullary cell populations [11]. These cells then transmit stress signals via projections to critical nuclei of the HPA axis and limbic system to further mediate homeostatic imbalance in the body. Thus, physical stressors as well as psychogenic stressors, such as a perceived threat or anticipated adversity are integrated and converge upon the hypothalamus, which initiates the secretion of corticotrophin-releasing hormone (CRH) from the periventricular nucleus (PVN) to the pituitary gland. In turn, adrenocorticotrophic hormone (ACTH) is sent to the adrenal gland in the periphery, stimulating the release of the glucocorticoids, cortisol (in humans) or corticosterone (in rodents) [12–14]. These glucocorticoids signal through the glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs), which are located ubiquitously in the central and peripheral nervous systems [15] and serve as major mediators of the stress response. However, the location of these receptors in the limbic system, including the prefrontal cortex (PFC), hippocampus, and amygdala, make them especially important for responding to stressful stimuli. In addition to glucocorticoids, each of these regions is highly innervated and dependent upon glutamatergic, GABAergic, dopaminergic, and noradrenergic signaling in order to mediate the proper function of the stress pathway (Fig. 1). Moreover, these circuits comprise an important feedback mechanism that communicates with the hypothalamus and serves to modulate glucocorticoid release and ultimately terminate the stress response [1,16,17].

It is important to note that although this represents the conventional stress pathway, stress-induced signaling of CRH and to a lesser degree ACTH have additional functions and targets in the central and peripheral stress circuit as non-endocrine neuromodulators that are independent of CORT activation. In terms of CRH, extensive work has identified the localization and regulation of both CRH and the CRH receptor in the rodent brain [18–20]. Given the role of CRH in the stress response, it is not surprising that dense populations of CRH neurons reside in many of the brain regions associated with the stress circuitry, including the cortex, hippocampus, and amygdala, as well as the PVN in the hypothalamus. Similarly, the CRH receptor is highly expressed in these same brain regions and can be activated by local CRH release or CRH projections from the PVN [21]. Both scenarios contribute to the CRH-mediated regulation of behavioral responses to stress. While usually associated with perceived or impending threats, stress induces the release of CRH in areas like the hippocampus and amygdala, which then activates CRH receptors in these same regions to elicit an increase in anxiety behaviors as well as impair LTP in the hippocampus. Moreover, descending projections that release CRH to the LC in the brainstem, mediate stress-induced alterations in heart rate, blood pressure, and other autonomic outputs.

Although extensively and in many ways seamlessly integrated, regions of the limbic system involved in facilitating the stress response serve discrete functions that are imperative to a normal stress response. For example, the PFC serves an important function in decision making processes and working memory, as it relates to stressful events and plays a critical role in translating stressful events or information into action [22,23]. This is most important when the stressful situation is perceived or anticipated and the PFC must make a "value judgment" related to the magnitude of the threat. By comparing the current threat with prior stressful events an adequate physiological response is initiated. In order to accomplish this, the PFC relies on connectivity with the hippocampus and amygdala, as well as the ventral tegmental area (VTA), which sends projections to the PFC. While the hippocampus plays a critical role in learning and memory processes, the amygdala serves to integrate and consolidate emotionally salient memories for the expression of anxiety, both of which are regulated by glucocorticoids [24–26]. Indeed, emotionally arousing experiences are better remembered, which allows us to recall emotional situations and apply them to future situations that are similar. Neuronal inputs, primarily from the LC to the hippocampus, may further contribute to enhance memory formation and consolidation for emotional events [27]. Thus, the proper integration and functioning of these circuits are imperative to many important aspects of the stress response.

The underlying function of this circuit is extensively mediated by glutamatergic, GABAergic, dopaminergic, and noradrenergic responses and signaling following exposure to glucocorticoids and stress stimuli [1,11,16,28,29]. Indeed, acute release of glucocorticoids facilitates an increase in glutamatergic output from the PFC, as seen by elevated glutamate release, in addition to upregulation and trafficking of NMDA and AMPA receptors to the plasma membrane of the postsynaptic neuron [30,31]. Similar rearrangements to glutamatergic signaling are also

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