Review Article

INVOLVEMENT OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND SYMPATHOADRENAL SYSTEM IN THE PATHOGENESIS OF STRESS

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ABSTRACT

The central stress circuitry represents a neural network that includes hypothalamic-pituitary-adrenocortical axis, sympathoadrenal system and limbic areas (medial prefrontal cortex, hippocampus and amygdala). Hypothalamic-pituitary-adrenocortical axis and sympathoadrenal system dysregulation are the important features of the pathogenesis of stress. The following review summarizes the relationship of hypothalamic-pituitary-adrenocortical axis, sympathoadrenal system and limbic structures as well as control of glucocorticoid and norepinephrine/epinephrine release. Medial prefrontal cortex projects nerve input to the amygdala and hypothalamus. Amygdala has stimulatory while hippocampus has inhibitory control over hypothalamic-pituitary-adrenocortical axis. Paraventricular nucleus of hypothalamus further projects to the pituitary gland. The final outputs of this central stress circuit are endocrine system and emotional motor system. These result in the release of corticosterone and norepinephrine/epinephrine through hypothalamic-pituitary-adrenocortical axis and sympathoadrenal system, respectively.

Keywords: hypothalamic-pituitary-adrenocortical axis, glucocorticoid, sympathoadrenal system.

INTRODUCTION

The central stress circuitry represents a neural network that is consisting of integrated brain structures which generate the stress responses. The central stress circuitry includes hypothalamic-pituitary-adrenocortical (HPA) axis, sympathoadrenal system (SAS) and limbic areas. Limbic area comprises mainly of medial prefrontal cortex, hippocampus and amygdala. SAS and HPA axis are the two distinct but interrelated systems, which are involved in the maintenance of homeostasis in stress (1). Stress stimuli activate the HPA axis and SAS. Briefly, stimulation of SAS in stress results in the release of norepinephrine from the sympathetic nerve terminals and adrenal medulla (2). On the other hand, stimulation of HPA axis in stress results in the release of glucocorticoids from the adrenal cortex (3).

Sympathoadrenal system (SAS)

SAS comprises of locus coeruleus, sympathetic nervous system (SNS) and norepinephrine. Locus coeruleus is a nucleus in the pons of the brainstem and involved in the norepinephrine synthesis inside the brain. The sympathetic nerves can be considered as neurochemical transducer that converts electrical impulses in the nervous system to chemical messenger. Chemical messenger released in turn produce physiological response by receptors in the innervated tissue. Activation of SAS results in increased release of norepinephrine and neuropeptide-Y from sympathetic nerve terminals while norepinephrine, epinephrine and dihydroxyphenylalanine from the adrenal medulla. Norepinephrine is accountable for fight-or-flight responses (2).

Hypothalamic–pituitary–adrenal (HPA) axis

The HPA axis is controlled by a discrete set of neurons in the medial parvocellular division of the paraventricular nucleus (PVN) of hypothalamus. These neurons synthesize and release the corticotrophin releasing hormone (CRH) with arginine vasopressin (AVP). CRH and AVP pass through the hypophysial portal veins to access anterior pituitary corticotrophes and then stimulate the adrenocorticotropic hormone (ACTH) release from anterior pituitary into systemic circulation. ACTH binds to the adrenal cortex and results in the synthesis and release of glucocorticoids, mineralocorticoid hormones and dehydroepiandrosterone from the adrenal cortex (4, 5).

The magnitude and duration of glucocorticoid release by HPA axis is controlled by a negative feedback mechanism. In glucocorticoid negative feedback mechanism, the secreted glucocorticoids inhibit further release of ACTH and thus limit the excessive presence of cortisol levels. Multiple feedback mechanisms are involved in modulating HPA axis function by glucocorticoids. Two important types are fast and delayed-feedback mechanisms. Fast-feedback is sensitive to glucocorticoid secretion rate (non-genomic). In contrast, delayed-feedback is sensitive to glucocorticoid levels (genomic actions) (6).

There are two steroid receptors in the brain, glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). GR is highly expressed in brain regions that regulate stress responses and mediates chiefly the negative feedback mechanism upon exposure to stress. In contrast, MR is restricted than GR in its expression and regulates HPA basal tone (7).

Regulation of hypothalamic–pituitary–adrenal axis by limbic brain circuits

The involvement of the limbic system (medial prefrontal cortex, hippocampus and amygdala) in the regulation of HPA axis is complex. Functional alterations in the regulation of HPA axis by limbic system may be responsible for hyper or hyposecretion of glucocorticoids. Stress results in the functional alterations in the regulation of HPA axis by limbic system which in turn leads to allostatic load rather than allostasis and ultimately results in several stress disorders. Thus, the overall connection between alteration in limbic structures, HPA axis dysfunction and affective disorders is associated with impaired integration of hippocampal, amygdala and medial prefrontal cortical information at one or more of the key regulatory nodes.

Role of hippocampus

The involvement of hippocampus in the inhibition of the HPA axis has been shown in many studies. The ventral subiculum (vSUB) sends excitatory projections to numerous subcortical regions, including the posterior bed nucleus of the striaterminalis (BST), peri-PVN region, ventrolateral region of the medial preoptic area (vlPOA) and ventrolateral region of the dorsomedial hypothalamic nucleus (vlDMH). All these send γ-amino butyric acid (GABA)ergic projections to the PVN and are likely to communicate transsynaptic inhibition. Lesions in the hippocampus cause the accumulation of the corticosterone, ACTH and CRH/AVP mRNA levels. This implies hippocampus inhibits the HPA axis and decreases the secretion of glucocorticoids on stimulation (8-14). The role of the hippocampus in negative feedback processes is not yet clear. However, hippocampus highly expresses GR and MR. The excessively produced glucocorticoids during the stress conditions cause the destruction of the hippocampus and alteration of HPA axis. In contrast, some lesion studies on the dorsal hippocampus reported that some hippocampal regions upon stimulation increase the release of corticosterone and activates HPA axis (7).

Role of medial pre-frontal cortex (mPFC)

The mPFC also plays a crucial role in the regulation of stress. Evidence shows both inhibitory and excitatory effect of mPFC on HPA (7). Lesion in the right infralimbic cortex decreases glucocorticoid secretion. On the contrary left-sided lesions do not affect glucocorticoid secretion (15). Thus, organization of PFC and its effect on HPA axis are complicated. The anatomy of mPFC efferent may explain the inhibitory as well as excitatory influence of mPFC on HPA axis. The mPFC include neurons of the prelimbic, anterior cingulate and infralimbic cortices. These appear to have different actions on the HPA axis stress response. The prelimbic and anterior cingulate send excitatory projections to regions such as the dorsomedial hypothalamus, peri-PVN zone, BST and ventrolateral preoptic area. Both peri-PVN zone and BST send direct GABAergic (negative) projections to the medial parvocellular PVN. Thus, these regions are involved in stress inhibition. In contrast, the infralimbic cortex projects to the

medial and central amygdala, anterior BST and the nucleus of the solitary tract (NTS). These send excitatory projections to the PVN implying a means of PVN excitation from this cortical region. All of these regions are involved in stress excitation (16-18). Hence, different regions of the PFC play different roles in HPA axis regulation. The mPFC also highly expresses GR (19, 20). These excessive GR are involved in the glucocorticoid feedback mechanism. Therefore, mPFC is a site for glucocorticoid negative feedback regulation to defined stress modalities (7).

Role of amygdala

The amygdala is considered to activate the HPA axis. This activation is mainly mediated by the medial and central amygdaloid parts. The neurons from amygdala are projected to basal forebrain, hypothalamic and brainstem structures (21). Various studies show that lesions of the central (CeA) or medial amygdaloid (MeA) nuclei reduce ACTH and/or corticosterone secretion following stress and decreases HPA axis output (22-24), whereas activation of CeA or MeA nuclei increases HPA axis output (25, 26). The MeA nucleus sends inhibitory projections to BST, vlPOA and peri-PVN which in turn send GABAergic projection to PVN, thus eliciting a transsynaptic disinhibition. Similarly, CeA nucleus sends GABAergic innervations to the ventrolateral BST, upto a lesser extent to vlDMH and in the NTS. This may disinhibit ascending projections to the PVN.

The CeA and MeA nuclei also express GR and MR (7, 27). Expression of MR is notably less than GR. Amygdala is also a potential target for glucocorticoids like other limbic regions. The role of the CeA and perhaps MeA in glucocorticoid signalling may differ substantially from that of the hippocampus/PFC. In contrast to the inhibitory effects of glucocorticoids on CRH production in the PVN (12, 28), glucocorticoids increase CRH expression in the CeA (29). Moreover, implants of glucocorticoids into the CeA do not affect acute stress responsiveness, while augment autonomic responses to chronic stress exposure (30). Therefore, these finding led to the interesting hypothesis that amygdalar GR play a "feed forward" role in stress regulation, serving to augment rather than attenuate HPA responses (31).

SAS and HPA axis interaction

SAS and HPA axis are reciprocally innervated. The most well-studied and pronounced interaction of SAS and HPA axis is the bidirectional regulation of CRH and norepinephrine systems. The feedforward system consisting of CRH and norepinephrine acts at different levels of the CNS and promotes the activation of each other (32). Increased norepinephrine and epinephrine secretion tends to reduce serum leptin levels. On the other hand leptin from adipose tissue directly inhibits secretion of glucocorticoids (33). This feedforward cycle is hypothesized to coordinate the biological response of an organism to environmental challenge. Any dearrangement in its function would lead to the collapse of the stress response and increase the vulnerability to stress disorders (32).

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