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Review

Interleukin-1 (IL-1) in stress-induced activation of limbic-hypothalamic-pituitary adrenal axis

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Abstract:
Proinflammatory cytokine interleukin-1 (IL-1) produced during psychological and immunological stress, plays a significant role in the neuroendocrine and stress responses. Brain IL-1 is an important mediator in stress-induced stimulation of the limbic-hypothalamic-pituitary-adrenal axis and secretion of ACTH and corticosterone. This review aims to describe some signaling pathways between the limbic-hypothalamic-pituitary structures during prolonged stress responses including their sensitization and adaptation. Interleukin-1 represents an important central component operating in neurochemical and immune network for efficient coping in preventing stress-associated psycho- and neuropathology.

Key words:
interleukin-1, limbic-hypothalamic-pituitary-adrenal axis, IL-1 in stress responses, sensitization, immuno-endocrine responses

Introduction

Homotypic daily stressors are associated with increased depressive symptoms and anxiety. Behavioral and hormonal responses to repeated and predictable homotypic stressor, as restraint, develop habituation that is a progressive decrease in the expression of stress responses after repeated application of the same stressor. Habituation is stress-specific, and depends on the interstimulus duration and initial stressor intensity. To promote coping and reduce the impact of stressors, the stress responses are highly organized and tightly regulated. In contrast with the previous notion that the function of stress responses is to restore the stability of internal environment, it is now proposed that stressors elicit well organized complex responses with their own homeostasis, which promote adaptive coping.

The central nervous system (CNS) and immune system are the two major adaptive systems, which respond rapidly to the numerous challenges that can compromise health. Different stressors induce a stereotyped neuroendocrine response in humans and animals, which result in physiological adaptation. Communication between CNS and immune systems include many interactions among the neural, neuroendocrine and immune systems by bidirectional routes. Recent literature provides more detailed information on the molecular signaling, which links the two systems during the integrated response. This bidirectional cross-talk is based on the secretion of cytokines, hormones, neurotransmitters and neuropeptides. Cellular and molecular data present the bidirectional interactions between hormone-hormone and cytokine-hormone interactions at the receptor level.

The changes in gene expression mediated by glucocorticoid hormones and neurotransmitters during stress can dysregulate function of limbic-hypothalamic-pituitary (LHPA) axis. The magnitude of stress-associated neuroendocrine and immune dysregulation is sufficient to elicit health implications.

This article reviews some signaling pathways, which mediate bidirectional communication between the immune and neurons system during stress situations. Particular emphasis is placed on the role of pro-inflammatory cytokine interleukin 1 (IL-1) in mediating psychological stress responses. Interleukin 1β is the first cytokine associated with modulation of the hypothalamic-pituitary-adrenal axis. This cytokine is a critical mediator of adaptive stress response and stress associated psycho- and neuropathology.

The review also presents some molecular insight regarding the pro-inflammatory signal transduction pathways that occur by cells of the blood-brain-barrier and how they are related to the neuroendocrine circuits mediating the increase in plasma glucocorticoid levels immunogenic insults.

Neuroendocrinology of the stress response

Homeostasis threatened by stressors is re-established by various physiological and behavioral adaptation responses. Major roles in the regulation of both basal and challenged homeostasis have neuroendocrine and immune systems [14, 16, 17, 93, 121]. The stress response is subserved by both CNS and peripheral components [62]. The central components of the stress system are located in the hypothalamus and the brainstem, and include the parvocellular neurons of corticotropin-releasing hormone (CRH), the arginine vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus [60], medulla and locus coeruleus (LC) [127, 128] and other mostly noradrenergic (NE) cell groups in the medulla and pons (LC/NE system). CRH stimulates secretion of ACTH *via* CRH type 1 receptor from the corticotrophs of the anterior pituitary. Main role in stimulating CRH synthesis plays cyclic AMP-protein kinase A (PKA) [68]. Also pituitary adenylate cyclase-activating polypeptide (PACAP), a member of the vasoactive intestinal peptide (VIP) and the PACAP receptor type 1 are considerably expressed in the hypothalamic parvocellular and magnocellular subdivisions of the PVN. PACAP stimulate also cAMP production in the anterior pituitary [48, 52]. The peripheral components of the stress system include the peripheral limbs of the hypothalamic-pituitary-adrenal (HPA) axis, the efferent sympathetic-adrenomedullary system; and components of the parasympathetic system [98, 123]. The cholinergic activation of HPA axis is mediated by cholinergic hippocampal system [134, 135].

There are multiple sites of interaction among the various components of the stress system [45, 54, 57]. Reciprocal neural connections exist between the CRH and noradrenergic neurons of the central stress system, with CRH and norepinephrine stimulating each other primarily through CRH type 1 and α_1-noradrenergic receptors, respectively [36]. Autoregulatory negative feedback loops are also present in both the hypothalamic paraventricular nucleus CRH and brainstem noradrenergic neurons, with collateral fibers inhibiting CRH and catecholamine secretion *via* presynaptic CRH and α_2-noradrenergic receptors. Both the CRH and the noradrenergic neurons also receive stimulatory innervation from the serotoninergic and cholinergic system and inhibitory input from the γ-aminobutyric acid (GABA)-benzodiazepine (BZD) neuronal systems of the brain as well as from the end-product of the HPA axis, the glucocorticoids. Certain stress related affective disorders are associated with changes in the amygdalas excitability, inducing a possible dysfunction of the GABAergic system. Norepinephrine is an important central modulator of the stress response and also of the GABAergic synaptic transmission. Stress impairs the noradrenergic modulation of GABAergic transmission in the basolateral amygdala (BLA). In control rats, noradrenaline (10 μM) facilitated spontaneous, evoked, and miniature inhibitory post synaptic potentials *via* the α_{1A} agonist, A61 603 (1 μM). In restrained tail-shocked rats, noradrenaline or A61 603 had no significant effects on GABAergic transmission. Thus, in the BLA, norepinephrine acting *via* presynaptic α_{1A} adrenoceptors facilitates GABAergic inhibition, and this effect is severely impaired by stress [12]. Although many components of the biological response to emotional stressors enable the individual to cope with stress, excessive or repeated stress can have detrimental effects on health due to functional alterations in the systems involved in the stress response.

Axons from the paraventricular nucleus of the hypothalamus project widely to autonomic nuclei in the

brain stem, to the LC, which neurons have receptors for CRH [54]. During stress, CRH enhances the synthesis and secretion of noradrenaline. Autonomic CRH further stimulates the release of noradrenaline from peripheral sympathetic nerve terminals and particularly adrenaline in the adrenal medulla [106]. Elevated noradrenaline and adrenaline levels are consistently present during stress and represent the second major class of stress hormones. Intraventricular infusion of CRH produces all of these changes, i.e. the increases in corticosteroids, noradrenaline, and adrenaline and the arousal behavior.

Peripheral symphatetic nerves and brainstem noradrenergic neurons of the LC respond in parallel to a variety of stress-related stimuli which result in peripheral and central noradrenaline release [128]. During stress numbers of adrenergic receptors decrease (downregulation) due to reduced expression of the receptor gene and proteolytic degradation of receptor molecules. A reduced number of functional receptors results in "desensitization" mainly by phosphorylation of the receptor molecule through protein kinases [18, 54]. After phosphorylation, the receptor uncouples from its effector unit, is internalized into the cell, and undergoes intracellular trafficking. During stress, internalization of β-ARs occurs more frequently or is accelerated [36, 37]. Chronic stress-induced downregulation of brain β-ARs is an important mechanism of adaptation [45] though increased β-AR binding sites in rats were also evidenced. Effects on brain β-ARs are stress-time dependent, β_1- and β_2-ARs are differentially regulated with variations among brain regions [37]. Stress-evoked activation of the central nervous noradrenergic system may induce depressive disorders. Chronic psychosocial stress persistently upregulates α_{2A} subtype heteroreceptor, which is also upregulated in depressed patients [37]. Functional changes in neurons carrying noradrenaline receptors may activate the HPA system and increases release of corticosterone, the prevailing hormone in most rodents or cortisol in humans, which due to their lipophilic nature easily enter the brain. Within the brain, glucocorticoid hormone acts at those sites where receptors are enriched [63].

Chronic homotypic stress induces adaptation of temporally functional and autonomically distinct changes in signaling components within stress-responsive brain regions [97]. Habituation is stressor-specific and depends upon the stimulus duration and intensity [19]. In the mechanism of stress adaptation, corticosteroid hormones are considerably involved by both rapid non-genomic effects on neurons in the hypothalamus and by classical mineralocorticoid receptors acting on CA1 region [20, 21]. Repeated immobilization stress elicited reduction of glucocorticoid receptor (GR) mRNA in the hippocampus and the hypothalamic PVN. Tumor suppressor p53, which represses the promoter activity of GR gene, may negatively regulate GR mRNA expression in the PVN, the hippocampus and the anterior pituitary during repeated stress [90]. Glucocorticoid hormones may affect peptide genes in CRH producing neurons and almost all structures involved in the LHPA axis regulation in normal and stress conditions [107, 114, 131].

Social stress

Social experience alters the response to social stress and may impair individual vulnerability in animals and humans. Depending on the circumstances, social interactions can be stressful or provide a buffer against stress. Chronic psychosocial stress, or the lack of predictability and control over social environment, can chronically elevate HPA axis activity and deteriorate health. In contrast, a positive social interaction and social-bonding phenomena can preserve homeostatic control and improve health and well-being. The physiological mechanisms mediating positive social interaction which influences health are not known but may involve oxytocin-induced suppression of the HPA axis [26].

In an experimental system, in which a dominance hierarchy is established, subordinate male rats exhibit sustained increase in plasma glucocorticosteroid hormone levels with decreased GR, mineralocorticoid receptor (MR) and GAP-43 mRNAs in the CAl region of the hippocampus. Therefore, social stress in the rats elicits both subordination and changes in hippocampal gene expression that are consistent with their regulation by adrenal steroids. The link between low social status and the development of GC resistance was associated with increased chances to develop GC resistance in mice [3]. Environmental stressors in animal can alter neurogenesis, which may contribute to the pathophysiology of affective disorders such as major depression. An acute psychosocial stressor of dominance at the time of cell generation can decrease number of newly generated cells in the hippocampus,

indicating that an acute episode of social stress is sufficient to induce long-lasting reduction of the incorporation of new hippocampal neurons and their survival [120]. In contrast, social bonds protect against stress-induced injuries and decrease stroke-induced neuronal death and improve functional recovery, by suppressing the inflammatory response during stroke. Although an exposure to stress is a universal experience in all living organisms, the impact of different stressor on health is considerably individualistic. Acute stress can improve some important indices of health, while chronic stress can exert deleterious effects on stroke, cardiac arrest or wound healing, which in these models depend on corticosteroids acting on glucocorticoid receptors [25].

Conventional models of stress in laboratory rodents show little similarity with the chronic human psychopathologies. In naturalistic and ethologically-oriented model of chronic psychosocial stress of animals, their status and territory ownership are major factors determining the vulnerability to chronic stress exposure [6]. Elucidation of the relationships between social factors and individual vulnerability to chronic social stress exposure allowed to determine the significance of the factors for individual disease susceptibility. Although stress response is adaptive in the short-term, it can become highly maladaptive in the long-term. A chronic elevation of glucocorticoids can induce a remodeling of the hippocampus, which is involved in the development of several psychopathologies. Reduction in the inhibitory feedback exerted by the hippocampus over the hypothalamic CRH-producing paraventricular nucleus cells and a consequent hyperproduction of CRH induces hyperactivation of the HPA-axis. Mice under chronic stress develop a clear adrenal hyperactivity, likely due to an altered inhibitory feedback of the corticosterone on the hippocampus, which would lead to increased hypothalamic release of CRH. HPA axis alterations develop in all stressed animals independently of whether they were dominants, subordinates, residents or intruders. This may indicate that the HPA axis is sensitive to the stressful nature of the situation *per se* and less modulated by the individual differences in the appraisal of the situation.

Brain IL-1 location, receptors, expression

Cytokines are both immunoregulators and modulators of various neural functions and neural integrity [50, 51]. The central and peripheral nervous system exerts tonic control of cytokine synthesis and release from nonsynaptic varicosities. The sympathetic nerve system is an integrative interface between the brain and the immune systems [30]. Cytokines and their receptors are constitutively expressed by neurons in the CNS under both normal, stress and pathological conditions [11, 64, 84, 117, 124]. There are two forms of IL-1, IL-1α and IL-1β, that share less than 30% homology. The IL-1 family consists of three different genes located in human on the long arm chromosome 2, which encode three distinct proteins with structural homologies. IL-1α and IL-l β bind to the same receptors and act as agonist molecules, whereas the third member of the family – IL-1 receptor antagonist (IL-1ra) that binds to the same receptors as IL-1α and IL-1β, does not induce any intracellular signal [23] and therefore acts as an endogenous inhibitor of IL-1 activity [46, 119]. In most situations, IL-1ra is secreted in the extracellular environment in the form of a 22 kDa glycosylated protein, which biological activity is analogous to that of the 17 kDa non-glycosylated protein. In contrast to IL-1β that has two binding sites for its receptor, IL-1ra has only one what may be responsible for absence of signal transmission and inhibition of IL-l activity.

IL-1α and IL-1β have different mechanisms of expression, synthesis, secretion and localization. IL-lα gene does not contain sequences corresponding to the classical transcription initiation motif, known as "TATA box", whereas this motif is found in the IL-1β gene. IL-1α remains mainly intracellular, whereas IL-1β is secreted after cleaving by a specific enzyme responsible for this cleavage, IL-1β-converting enzyme (ICE) caspase-1. ICE is constitutively present in most cells as a 45 kDa inactive precursor that requires two endo-cleavages to become an active heterodimer, composed of a 10- and a 20-kDa chain containing the enzyme site. Following cleavage, IL-1β can circulate in the bloodstream and after binding to its type I receptor acts on distant organs to trigger different physiological responses. Pro-IL-1α is as active as the mature form and remains intracellular, and is rarely found in the circulation or extra-cellular liquids only during serious illnesses when it may originate from the damaged cells. Under normal physiological conditions, IL-1β and its mRNA are present in the CNS in low amounts in specific regions of the brain in a time of day difference manner [15], but are significantly induced in response to diverse stress and pathological

conditions. Both types of IL-1 receptors IL-1RI (activating) and IL-IRII (decoy) mRNA and protein have been detected in the mouse brain. In the mouse, high levels of IL-1RI mRNA expression are found in the hippocampus, the midline raphe system, the choroid plexus, and endothelial cells of postcapillary venules throughout the brain. However, only a minor signal for IL-1RI mRNA has been detected in the median eminence (ME), and no signal in the hypothalamus.

In the rat, constitutive expression of interleukins and IL-1RI mRNA are in major part localized in neurons, in the hypothalamus and hippocampus [125], whereas induced central IL-1's are mainly produced by glial cells, especially microglia [118] and also by neurons [115]. In the injured CNS, microglia are considered as primary source for the production IL-1β. Also infiltrating macrophages may participate in the production of IL-1 in the damaged CNS at the interface of the vascular wall and perivascular glia and on endothelial cells of the rat brain. Interleukin-1 mediates the activation of hypothalamus-pituitary-adrenal axis and interleukin 6 *via* IL-1 type I but not *via* type II receptor, irrespective of the location of the relevant IL-1 receptors [129]. The brain cytokines network can interact with their receptors in regions involved in HPA axis regulation, including the hypothalamus PVN and the hippocampus, which provides negative feedback regulation on PVN activity [72, 73]. In addition, many of the brain regions involved in signaling the message of circulating cytokine to the PVN express cytokine receptors. The density of IL-1 receptor on the cell surface is negatively regulated by IL-1 in hippocampus like in monocytes and fibroblasts.

Activation of neuronal IL-1 receptors induces efferent signals transmitted *via* second messengers, such as prostaglandin E_2, which mediates cellular effects of IL-1β on hypothalamic PVN neurons [33, 82]. Prostaglandins are released by hippocampal slices following exposure to LPS or IL-l *in vivo* or *in vitro*. Since the hippocampus is involved in memory and integration processes [104], the localization of interleukin receptors in this structure may be related to these functions and to the well established immune conditioning.

Cytokines penetration to brain structures

Proinflammatory cytokines may gain access to the brain, in limited concentrations, though cytokines and their receptors have been identified in a variety of brain regions. Cytokines are too large to readily pass the blood-brain barrier to activate CRH-producing neurons in the PVN [29]. Possible mechanisms by which cytokines may affect the brain have been identified [102, 116, 117, 130]. Cytokines could act on the brain regions that lack a functional barrier, the circumventricular organs (CVO's), such as the median eminence, organum vasculosum laminae terminalis (OVLT), or the area postrema [118], which may convey IL-1-mediated signals. IL-1 in the general circulation may also act directly on CRH-containing terminals in the median eminence to initiate HPA axis activation [117]. Local application of IL-1 in the median eminence elevates plasma ACTH and corticosterone in rats.

IL-1 may stimulate perivascular cells in the medulla oblongata, in which IL-1 receptors are abundantly expressed [32], and these perivascular cells may activate ascending aminergic neurons to eventually stimulate CRH neurons. Induction of cyclooxygenase (COX)-2 expression by IL-1 was also reported in perivascular cells, and systemic administration of indomethacin, a COX inhibitor, attenuated IL-1 effects in the hypothalamus and medulla and the HPA axis [13]. The inflammatory signaling molecule nuclear factor kappa B (NF-κB), a primary transcription factor in the initiation of the inflammatory response participates in the CRH induced regulation of pituitary propiomelanocortin gene [71]. A second possibility is that many cytokines may cross the blood-brain barrier using specific uptake systems [4]. Uptake has been demonstrated for interleukin-1, however, the capacity of these uptake systems is quite low to accumulate sufficient concentrations of cytokines in the appropriate brain regions [120].

Afferent vagal system and visceral sensory inputs have an important role in cytokine to brain communication and endocrine hypothalamus stimulation [9, 101, 126]. Corticosterone secretion induced by interleukin-1β and accompanied hypothalamic noradrenaline depletion is vagally mediated [35]. Vagotomy can also block the induction of IL-1β mRNA in the brain of rats in response to systemic IL-1β [53]. Electrical stimulation of afferent vagus nerve induces IL-1β expression in the brain and stimulates HPA axis [59]. Subdiaphragmatic vagotomy affects dorsal motor nucleus of the vagus [61] and inhibits intra-abdominal stimulation of ACTH secretion [70]. Vagus nerve affects also physiological and behavioral response in

animals [133] and was proposed as a new tool for brain research and therapy [42].

Cytokines bind to their receptors associated with peripheral afferent vagus nerve fibers that then relay cytokine signals to relevant brain regions, nucleus of the solitary tract and hypothalamus [100]. IL-1 binding sites are present in vagus nerve paraganglia, which may be stimulated by circulating endogenous or exogenously administered IL-1β and signal transmitted by afferents of vagus nerve to its respective brain regions [19]. NF-κB is an essential mediator at the blood-brain barrier interface that communicates peripheral inflammatory signals to the CNS [69]. Central blockade of NF-κB inhibits c-fos activation in multiple brain regions following IL-1β administration and also inhibits the IL-1β and LPS-induced behavioral changes [43].

Neuropeptides and neurotransmitters in LHPA axis activation by interleukins

In examining the effects of cytokines on HPA axis function, the innate proinflammatory cytokine IL-1β is the most potent and studied. IL-1β influences excitability of the hypothalamic parvocellular neurons in whole-cell patch clamp recordings, suggesting a cellular effect on CRH secretion in rat [33]. IL-1β significantly modulate central synaptic transmission and is modulated by stress [91, 92, 94]. In well established potent stress-induced activation of the LHPA axis [62], interleukins can act at the level of the hypothalamus, to induce expression and release of CRH, and at the pituitary to release adrenocorticotrophic hormone or through both of these mechanisms [72, 79, 81]. Interleukins can also directly stimulate the adrenal gland [24, 31, 83] to stimulate glucocorticoid release [1]. Glucocorticoids feed back as potent inhibitors of cytokine expression and action on neuroendocrine responses. Interleukin receptors were detected at all HPA axis levels, and therefore, each level can serve as a target point for neuroendocrine signals [28]. The locally synthesized cytokines in the brain, the anterior pituitary [10], and the adrenal gland may function in paracrine manner to amplify and maintain elevated HPA activity during chronic stimulation. Therefore, each level of HPA axis contains a local cytokine network, which can be stimulated by a variety of circulating cytokines [72]. Hypothalamic CRH is established a primary mechanism, by which cytokines stimulate glucocorticoid release. In addition to CRH, arginine vasopressin (AVP) may contribute to cytokine-HPA axis interactions. Arginine vasopressin in the presence of permissive levels of CRH acts synergistically with CRH to stimulate ACTH release from the anterior pituitary [64, 132]. Proinflammatory cytokines influence AVP synthesis or release. This AVP response may in part originate from the magnocellular cells of the PVN and be transported to the posterior pituitary and the general circulation. AVP derived from parvocellular neurons may exert primarily cytokine effects on HPA axis activity during chronic inflammation, such as rheumatoid arthritis.

IL-1 is the most potent cytokine influencing effects on neurotransmitters in the brain, especially the catecholamines [78], serotonin [77] and acetylcholine, and the amino acid neurotransmitters. Only norepinephrine appeared to be essential in the IL-1-induced activation of the HPA axis. However, IL-1 is able to stimulate the HPA axis by other mechanism. This redundancy may reflect the importance of the HPA activation when secretion of IL-1 occurs as the effect of tissue damage or infection or during stress conditions [29].

Increased production of pro-inflammatory cytokines plays an important role in the ethiology of depression. Antidepressant fluoxetine, a selective serotonin reuptake inhibitor and amantadine (AMA), an NMDA receptor agonist, had stronger immunomodulatory effect on cytokine production than amantadine alone [75]. These drugs can normalize the stress of forced swimming-induced immunoneuroendocrine alterations [103]. The data are in line with the hypothesis that the disfunction of HPA axis reactivity may be involved in the pathogenesis of depression [85].

Limbic stress processive pathways

Psychological and neurogenic stressors requiring higher-order sensory processing of signals prior to initiation of a stress response recruit the limbic stress processive pathway. Depending on previous experience or ongoing activation, the information is assembled within limbic circuits connecting the hippocampus, amygdala and prefontal cortex [2, 12, 104] to induce neuroendocrine and behavioral responses. Dif-

ferent types of emotional stressors may activate different neuronal circuits [38]. Limbic circuits connecting, e.g., the hippocampus, amygdala, and prefrontal cortex are sensitive to stressors such as restraint, fear or exposure to a novel environment. Common to these stressors is that, before the activation of the stress response, they stimulate an intralimbic processing of information received from different sensory organs. Activation of limbic and hypothalamic brain structures is a major component of the stress reaction that integrates neuroendocrine, autonomic and emotional components and thus determines the magnitude and duration of the hormonal, neural and behavioral stress response.

In contrast, the limbic-insensitive pathway is recruited by systemic stressors, that represent an immediate threat to homeostasis like respiratory, cardiovascular or immune stimuli that require immediate reactions and do not require limbic structures. Both the hippocampus and the medial prefrontal cortex (mPFC) play an important role in the negative feedback regulation of HPA activity during physiological and behavioral stress. Chronic restraint and psychosocial stress can induce atrophy of hippocampal apical dendrites of CA3 pyramidal neurons, depletion of sympatic vesicles in mossy fiber terminals learning tasks. Chronic elevations in corticosterone also induce a suppression in synaptic plasticity in the CA1 hippocampal field. Acute episode of a social stress produces long-lasting effects on the incorporation of new neurons in the hippocampus by reducing their survival [120]. Limbic brain structures are involved in chronic social stress neurohormonal regulations [38, 47]. Immunoregulatory cytokines are expressed in neurons of the lateral hypothalamic area and amygdaloid complex of rats [39]. Aggression enhances monoaminergic activities of limbic structures [74]. Social stress affects hippocampal gene expression. Inescapable stress decreases cell proliferation in adult hippocampus, which is reversed by fluoxetine treatment [80]. Amygdala plasticity, stress and CRH play a role in chronic anxiety [113]. The amygdala is also a major extrahypothalamic source of CRH-1 and CRH-2 receptors. Psychological stressors can activate the amygdala CRH system without evident activation of the hypothalamic CRH system and the amygdala CRH system is much more sensitive to psychological stressors than the hypothalamic paraventricular nucleus. The hippocampus is an important target of circulating adrenal cortical hormones that act on their receptors and are abundant in this structure. Chronic exposure to high corticosteroid levels during prolonged stress, may have a detrimental effect on hippocampal integrity and function and its excitation and plasticity.

The LHPA system, which combines both brain and endocrine components, can be regarded as a classic neuroendocrine circuit. It is activated in concert with other neurohormonal components of the stress system such as the sympathico-adrenomedullary system and the adrenocortical system [127, 128]. The classic neuroendocrine stress circuit, the LHPA axis interacts with a variety of monoaminergic systems, including brainstem noradrenergic [106], serotonergic [77] and GABAergic systems [12]. Neuroendocrine and central brainstem monoaminergic systems responses to stressful stimuli are precisely coordinated to generate adaptive physiological responses. The amygdala is a key structure of the brains neuronal network that generates emotions, consolidates the memory of emotionally significant events, and coordinate the behavioral response to these events.

The target effect of LHPA axis stimulation is the secretion of glucocorticoid hormones secretion from the adrenal cortex. By influencing gene transcription and altering the electrical activity of excitable cells, these steroid hormones are potent modulators of cell physiology and behavior [20]. Their action is not restricted to peripheral organs, but due to their high lipophilicity, they cross the blood-brain barrier and affect many brain structures, especially within the limbic system that expresses high numbers of corticosteroid receptors.

IL-1 in stress-induced LHPA axis response

Cytokines other than IL-1, were almost undetectable in CNS tissue following stressor exposure due to their extremely low expression under basal conditions. Considerable increases in mRNA for IL-1 following tailshock were found, but no changes in TNF or IL-6 mRNA. Thus, IL-1 appears to be particularly inducible in CNS tissue by stressors, both at the mRNA or protein levels [23]. Stressors such as footshock, tailshock, immobilization and psychological stressors can induce hypothalamic IL-1 production [55], while other stressors such as restraint, maternal separation

and social isolation have no marked effect on hypothalamic IL-1 levels. Chronic stress increases proinflammatory cytokine production and impairs neurogenesis in brain structures important to cognition and behavior [5, 80]. Some stressors-induced responses can be blocked by potent anti-inflammatory agents such as IL-1 receptor antagonist, α-MSH [25], and indomethacin [13], but not all stressors-induced increase in central IL-1 expression and neuroendocrine and behavioral responses were prevented by IL-1 inhibition [6, 25, 34]. Since the hypothalamus IL-1 is produced in neurons, microglia, and astrocytes and the diencephalon contains bioactive IL-1 under non-pathological conditions [36], it is unlikely that blood-born IL-1 contributes to the IL-1 detected in the hypothalamus. Since *icv* IL-1 causes c-fos expression in CRH-producing parvocellular neurons in the PVN, stress-induced intrinsic IL-1β production in the PVN definitely contributes to the activation of HPA axis [112].

Stress-induced increases in hypothalamic IL-1 may impair neuronal function and subsequent neurodegenerative disease and elevated central cytokines may decrease damaging processes in affective, cognitive and neurodegenerative diseases [44, 58, 105]. The potential relationship between stress and brain IL-1β has not been elucidated [89]. Intracerebroventricular administration of IL-1β induces many of the same neural, behavioral, and physiological alterations as are produced by stress. The *icv* and regional injection of the IL-1 receptor antagonist blocks or attenuates many of the brain-mediated responses to stress and blocks the brain monoamine and pituitary-adrenal response to immobilization and the alterations produced by inescapable tailshock (IS). The induction of IL-1β in brain regions by stressors is accompanied by an increase in IL-1β mRNA in hypothalamus and an increase in IL- 1β protein levels in a number of brain regions 2 h after IS. Diverse stressors such as inescapable tailshock, social isolation, immobilization and restraint increased IL-1 in both peripheral tissues such as blood, pituitary and spleen as well as in the CNS hypothalamus, hippocampus, and cortex [38]. The regional specificity of these effects within the CNS depends upon the nature of the stressor employed [46]. Psychological stressors can induce pro-inflammatory cytokine production both centrally and peripherally. Forced swim stress does not increase central production of IL-1 [22, 99], suggesting that the central IL-1 system is unlikely to play a role in mediating behavioral consequences of this stressor. Psychosocial stress of crowding for 7 days markedly impaired the IL-1β induced ACTH and corticosterone secretion. Under basal conditions, IL-1β is not markedly involved in the α_1-adrenergic agonist-induced stimulation of the HPA axis. During social crowding stress, IL-1β and prostaglandins are significantly involved in this stimulation [40]. Nitric oxide plays crucial role in the IL-1β-induced HPA axis stimulation under basal and stress conditions. Nitric oxide generated by eNOS is also involved in the stress-induced alterations of HPA axis activity by nicotine [41].

Sensitization of IL-1 response in LHPA axis

Proinflammatory cytokines often sensitize various neuronal, hormonal, and behavioral responses to subsequent stimulation [86, 87]. Single administration of IL-1 increased CRH mRNA in the hypothalamic PVN, which paralleled long-lasting sensitization to emotional stress [108]. HPA axis responsiveness to IL-1 β undergoes individual variation [76]. Prior stressor exposure enhances peripheral and central pro-inflammatory cytokine and HPA axis responses to subsequent immune challenge up to 4 days later [65–67]. Exposure to stressful life events can sensitize various neuronal and hormonal responses including sympathetic nervous system activation and hypothalamic-pituitary-adrenal responses. Cross-sensitization appears between stress and the production of proinflammatory cytokines induced by peripheral immune stimulation. Elevations in central IL-1β, induced by stress or exogenous administration are sufficient for sensitizing central IL-1β and corticosterone responses to subsequent immune stress challenge. Interleukin-1 is able to induce plasticity of hypothalamic CRH neurons and long-term stress hyperresponsiveness [122]. Central and systemic administration of IL-1β increased release of ACTH and corticosterone upon subsequent IL-1β stimulation 11–22 days later [111]. The enhancement in HPA activation following IL-1β administration might be due to increased stores of vasopressin [89, 110] in terminals of corticotropin releasing hormone containing neurons in the median eminence and/or enhanced release of noradrenaline into the hypothalamus upon subsequent challenge. Elevated levels of

central IL-1β during stress exposure are necessary for proinflammatory cytokine sensitization. Systemic administration of hrIL-1β in animals under basal conditions results in sensitization of IL-1β responses in limbic structures, hypothalamus, hippocampus, and cortex involved in HPA axis activity to subsequent cytokine challenge. Sensitization of various brain regions produced by IL-1β is capable to potentially alter an organism's behavior, even after IL-1β levels have returned to normal. Elevated levels of central IL-1β are critical for the development of at least some of the long-lasting behavioral changes induced by tailshock. Systemic and central IL-1 administration augments the response to stressors or further cytokine exposure and IL-1ra attenuated the effects of the stressor [65–67]. Stressors, and IL-1 increased time-dependently co-expression of CRH and AVP within the external zone of the median eminence, which synergistically stimulated ACTH secretion from the anterior pituitary [109]. Thus exposure to stressful events may sensitize animals to greater vulnerability to stressor related pathology [56].

IL-1 in central neuro-endo-immune systems interactions

IL-1β is produced in the periphery by a variety of cell types and plays a number of roles in immune and inflammatory processes [85, 88, 89]. It is now well established that communication occurs between the immune, endocrine and central nervous systems [19, 30, 49, 50, 96]. Central neurochemical and endocrine alterations influence immune functioning and, conversely, immune challenge affects endocrine and central neurotransmitter processes. The existence of a bidirectional regulatory circuit between the central nervous and immune systems is well established. This regulation is mediated in part through neuroendocrine hormones and cytokines and involves the interaction of common cofactors. Both systems have receptors for both types of signal molecules. The nervous system has receptors for cytokines and it also synthesizes cytokines. Cytokines are endogenous to the brain, endocrine and immune systems. The immune system synthesizes and responds to cytokines [7]. Neuroendocrine peptide hormones could bind to leukocytes and modulate immune functions and the immune system also synthesizes functional neuropeptide hormones, like ACTH and CRH [51, 119]. The similarity between the endocrine and central neurochemical changes elicited by antigenic challenge, suggests that immune activation may be interpreted by the CNS as a stressor [27, 95]. The immune system by affecting central transmitter activity is the part of regulatory mechanisms of brain structures that are involved in regulation of the LHPA axis activity under basal and stress conditions.

CRH not only induces leukocytes to produce proopiomelanocortin (POMC), but is also produced by leukocytes. The accepted role of CRH is its release from the hypothalamus during stress and in circadian regulation for activation of HPA axis but CRH's physiological role is modulation of immune responses [116]. CRH is also associated with major depression and other behavioral disorders. The proinflammatory cytokines – IL-1, IL-6, and TNFα stimulate HPA axis activity *in vivo* in various species. A primary pathway by which cytokines stimulate the HPA axis is the release of CRH from PVN neurons into the ME, indicated by the IL-1-induced expression of c-fos mRNA, a cellular marker of neuronal activation, and an increase in CRH mRNA in the PVN. Cytokines can directly stimulate ACTH release from the pituitary gland since IL-1 induces POMC transcription and ACTH release from cultured rat anterior pituitary cells. However, another studies failed to demonstrate a direct action of IL-1 on cultured anterior pituitary cells to stimulate ACTH release. Therefore, CRH-dependent ACTH release may mediate the rapid onset of an acutely induced glucocorticoid response, whereas a direct action of cytokines on the anterior pituitary may be involved in persistent glucocorticoid responses during chronic inflammation.

Endotoxin, systemic immunological stressor elicits a prolonged activation of the HPA axis mainly due to released cytokines from stimulated peripheral immune cells. Immune activation of adrenal gland by endotoxin occurs by cytokine stimulation of CRH in the median eminence, which in turn stimulates ACTH secretion from the pituitary. Prolonged endotoxemia in response to a large dose of LPS can develop tolerance of both immune and HPA function [8]. HPA activation in response to LPS challenge may be an important immunoregulatory response, suppressing this response by inhibiting production of acute-phase proteins [112] and pro-inflammatory cytokines which prevents septic shock.

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