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## Stress and Neuroinflammation

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### Abstract

It has been well established that there is bidirectional communication between the immune and central nervous systems. One context in which this interaction has been extensively studied is that of the stress response. Stress, whether physical or psychological, induces alterations in immune function. Often exposure to a stressor results in pro-inflammatory responses in the brain and periphery. These responses are mediated by a variety of inflammatory molecules including neuropeptides, cytokines, and stress hormones among others. Here, we will discuss several of the more comprehensively studied of these inflammatory mediators and their role(s) in stress-induced neurogenic inflammation.

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Stress is defined as a set of responses to an instigating stimulus (e.g. a stressor). This definition implies that stress is a state of the body (and mind) in which the demands of the situation surpass one's resources available to cope with those demands [1–3]. These responses may be physiological, psychological, or behavioral; the measurement of which have been discussed for several decades [4]. Stressors, which elicit a *stress response*, are often distinguished by severity (e.g. mild vs.

moderate vs. severe), duration (e.g. short-term vs. chronic), time course (intermittent vs. sustained), and predictability (predictable vs. unpredictable) [1–3]. The precise effects of various types of stressors on the body have been debated; however, in many contexts chronic, sustained, unpredictable stressors are the most deleterious, contributing to immune and endocrine dysfunction, altered mood, and several neurobiological and psychological diseases [1, 5]. In contrast, brief, predictable stressors may sometimes be beneficial in terms of enhancing cognition, emotion, and neurobiological systems such as the immune system [6, 7].

Pioneering work by Cannon [8], Selye [9], Mason [10], and Lazarus [11] helped define the concept of the stress response. Selye's concepts of the *general adaptation syndrome* and *diseases of adaptation* [9, 12] have provided a foundation for our current understanding of the body's responses to stressors. The concept of stress is linked to functions of the hypothalamic-pituitary-adrenal (HPA) axis, renin-angiotensin-aldosterone system, and autonomic nervous system, all of which have inter-communication with the immune system. The stress response is an adaptive response

involving physiological, psychological, and behavioral changes to promote survival and reduce the consequences of a threatening situation. For example, the stress response involves changes in blood pressure, heart rate, oxygen delivery, and tissue breakdown, along with down-regulation of neurobiological systems that hinder the adaptive reaction such as digestion, reproduction and growth [13, 14]. Affective and behavioral responses mirror these physiological changes, including exhibiting defensive behaviors, fear, and distress.

Parvocellular neurons in the hypothalamic paraventricular nucleus (PVN) contain corticotropin-releasing factor (CRF), and project to the median eminence to control pituitary adrenocorticotrophic hormone (ACTH) release in response to a stressor. ACTH and the sympathetic nervous system signal the adrenal glands to secrete cortisol and catecholamines, respectively. Adrenal glucocorticoids (GCs) can modulate activity of the HPA axis by providing feedback to the pituitary, hippocampus and hypothalamus [5, 14]. An extensive network of CRF-containing neurons is present in other central nervous system (CNS) structures, and under conditions of stress there is an increase in activity in neurons where CRF is serving as a classic hypothalamic releasing factor as well as in others where it is released in the brain as a neurotransmitter. CRF-containing axons from cell bodies in the hypothalamic PVN project to the ventrolateral medulla and the intermediolateral column of the spinal cord. Extrahypothalamic CRF projections, originating in the central nucleus of the amygdala and the bed nucleus of the stria terminalis, also communicate with the parabrachial and dorsal motor nucleus of the vagus (10th cranial nerve) [15]. Intracerebroventricular (i.c.v.) injections of CRF induce behaviors resembling those of the stress response, including decreased food intake and sexual activity, disturbed sleep, altered motor behavior and impaired learning [16–18]. A heightened arousal to various stimuli may reflect

an action of CRF on the noradrenergic neurons of the locus coeruleus or serotonin neurons in the raphe nuclei [15, 19].

Through this communication, the HPA axis interacts with the autonomic nervous system, renin-angiotensin-aldosterone system, and other visceral functions. CRF activation of the locus coeruleus stimulates the release of norepinephrine (NE) [14, 20]. For instance, CRF produces an increase in blood pressure and heart rate via sympathetic activation [21, 22]. The locus coeruleus also inhibits the parasympathetic nervous system as well as certain neurovegetative functions such as sleep [23]. When the balance of the autonomic nervous system shifts to increased sympathetic drive, this stimulates the kidneys to release renin. This in turn initiates the renin-angiotensin-aldosterone system cascade whereby angiotensin II is produced in part to cause vasoconstriction and a further increase in heart rate.

The CNS not only controls the stress response via the mechanisms mentioned above, but it also has the capacity to induce an inflammatory response to both physiological and psychological stressors [24, 25]. It is widely accepted that nerves containing inflammatory neuropeptides participate in both local inflammatory reactions in response to tissue trauma or infection, and also in response to stress [24]; the relationship between stress and the development of inflammatory diseases (e.g. cardiovascular diseases, inflammatory bowel disorders) has been well-documented [26, 27]. The following sections will focus on several neuropeptides, steroid hormones, cytokines, and other inflammatory factors that play important roles in the inflammatory stress response.

## Neurogenic Inflammation

Both somatic and autonomic nerves are associated with inflammation; however, the majority of data providing evidence for neurogenic inflammation comes from studies of the unmyelinated

sensory nerve fibers, or 'C' fibers [24]. Electrical, mechanical, heat, and chemical stimulation of somatic nerves containing C fibers results in an inflammatory response [28]. The response includes vasodilatation of arterioles (flare), and swelling (wheal) caused by the extravasation of plasma from postcapillary venules [24]. This inflammatory reaction is brought about by neuropeptides (e.g. substance P; SP) that are released from the peripheral sensory nerve terminals [24, 27]. This response requires an intact peripheral nervous system, as cutting the nerves or blockade by a local anesthetic will prevent this inflammatory response [24].

## Substance P

One of the more potent neuropeptides involved in neurogenic inflammation is SP [24]. SP is a member of the tachykinin family of bioactive peptides and functions as a neurotransmitter/neuromodulator in the CNS [29, 30]. This 11 amino acid peptide is not only widely distributed in the CNS but in the peripheral and enteric nervous systems as well [24, 30, 31]. Both SP and its primary binding site, the neurokinin-1 receptor, are found in areas of the brain that are important for processing and responding to physiological and psychological stressors (i.e. amygdala, prefrontal cortex) [24, 30]. SP is involved in sensory pathways, including nociceptive signaling, within the dorsal horn of the spinal cord. In the peripheral nervous system and throughout most of the body, SP has been found in both autonomic afferents and in C-type (i.e. unmyelinated) sensory fibers [24, 30, 31]. Based on where this peptide is located it is, perhaps, not surprising that SP has been shown to play an important role in the stress response as well as to contribute to stress-induced inflammation.

SP is elevated in the brain in response to a variety of psychological stressors including restraint stress, and as a result of anxiety [24, 30]. The regions in which SP shows the greatest increase are

in the limbic system, specifically the amygdala [24, 30]. Additionally, SP interacts with the HPA axis, leading to increases in CRF and ACTH during psychological stressors and SP is essential for the activation of the HPA in response to somatosensory stress [24]. Typical stress responses, such as isolation-induced vocalizations in guinea pigs, can be triggered by treatment with SP and abolished by treatment with a SP receptor antagonist [24, 32].

SP has repeatedly been shown to play an important role in both the neurogenic and non-neurogenic inflammatory response. For example, SP receptors have been found in a variety of immune cell types (e.g. leukocytes, lymphocytes and mast cells), and SP can trigger the release of cytokines from these cells [24]. Generally, however, SP is released to a site of tissue damage from primary afferent fibers that have been activated by the injury; SP then acts on mast cells to release serotonin and histamine, promoting vasodilatation [31]. Inoculation of the skin with SP alone, however, can also induce many of the signs of an acute inflammatory response including vasodilatation, contributing to the production of swelling and urticaria [33]. Treatment with an SP antagonist can block this response [33].

SP has also been identified as a possible contributor to tissue damage in chronic inflammatory diseases including arthritis [31]. For example, treatment of a peripheral nerve with capsaicin, which depletes SP, also reduces swelling in an experimentally induced arthritic limb [34]. Additionally, in animals that are injected with Freund's adjuvant – an antigen that induces a syndrome in rats that is similar to human rheumatoid arthritis – the ankles are more severely affected than the knee joints [31]. The synovial fluid from the ankle joints has significantly higher levels of SP, and denervation significantly reduced the amount of SP in the ankle [31, 35]. Recent data suggest that psychological stress, such as social isolation, can trigger mast cell degranulation, which releases several inflammatory mediators

[36]. The mast cell degranulation appears to be mediated, in part, by SP released from sensory nerve fibers [27, 36].

## Neuropeptide Y

Neuropeptide Y (NPY) is a peptide secreted from postganglionic sympathetic nerve fibers [37, 38]. NPY is considered a stress hormone and is released from sympathetic nerves and the adrenal medulla during various stressful conditions in animals (e.g. acute cold, immobilization, foot shock) [24, 37, 39] and humans (e.g. psychological/uncontrollable stress) [40]. NPY has been found to have anxiolytic effects in animal models of anxiety [41], and human studies suggest that post-stress levels of NPY are negatively correlated with psychological distress, suggesting that NPY may buffer against psychological stress [40]. NPY is a nonadrenergic co-mediator of catecholamine action [39]. Specifically, NPY amplifies NE's actions, including regulation of vasoconstriction [37, 39]. NPY also participates in other physiological and behavioral processes such as energy balance, feeding and anxiety [38]. NPY receptors are widely distributed in the CNS and are also found on immune cells including T cells, B cells, dendritic cells, mast cells and NK cells [38]. NPY helps to modulate some T cell responses, chemotaxis, and adhesion of leukocytes, platelet aggregation, and macrophage activation [38]. The latter effect on the immune system, as well as NPY's role in vasoconstriction and as a vascular mitogen, have led to the hypothesis that it may be involved in the inflammatory processes that are involved in atherosclerosis [39, 42]. For example, chronic cold water stress accelerated rat carotid stenosis after a vascular injury via angioplasty [43], and these stress-induced changes could be mimicked by the implantation of a NPY pellet. Administration of NPY receptor antagonists prevented the development of stress-induced or NPY-induced occlusions [43].

## Glucocorticoids

GCs are steroid hormones that are produced by the zona fasciculata of the adrenal cortex [44]. The synthesis and secretion of these hormones is regulated by pituitary ACTH [44]. GCs diffuse into the brain and can then bind to two types of intracellular receptors, mineralocorticoid receptors (MR; type I) and glucocorticoid receptors (GR; type II). The MR has a much higher affinity for GCs than does the GR [45]. As such, at basal GC levels GCs bind predominantly to MRs [46, 47]. It is only when GC levels rise in response to a stressor, i.e. when MRs become saturated with GCs, that GRs become occupied [47]. GRs become heavily occupied only after moderate-to-severe stress exposure and during the GC circadian peak [45, 46]. GRs and MRs are expressed differently across different brain regions, and overall the concentration of GR in the brain is greater than that of MR [25]. The distribution of these receptors can be altered, however, by stress and early experience [48]. The differences in GC affinity and distribution have led to the suggestion that MR and GR may have independent functions [46, 47]. For example, the MR is responsible for much of the effects GCs have at low-stress or basal levels (permissive effects) whereas the GR is responsible for the effects of GCs at high-stress levels [47].

The actions of GCs (i.e. cortisol, corticosterone) are numerous and varied, however, one of their primary roles is to control and modulate the stress response in the period following exposure to a stressor, specifically providing feedback inhibition of the HPA axis [47]. GCs, along with catecholamines, serve to mobilize energy stores to provide a ready source to the skeletal muscles, presumably to allow an organism to effect an escape from or face a stressor [47, 49]. At this point, GCs are also reducing the activity of less immediately necessary functions [49]. One of the functions in which activity is reduced is the immune system; as such GCs have been shown to actively suppress inflammation [49].