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The role of corticosteroids and stress in chronic pain conditions

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Abstract

The relationship between corticosteroids (endogenous and exogenous) and stress is well known, as is the use of steroids as concomitant treatment in pain management during acute inflammation. In the past, steroids have not been considered the first line of treatment in pain management. In this review, we examine new scientific and clinical evidence that demonstrates the direct role that steroids play in the generation and clinical management of chronic pain. We will discuss the new findings demonstrating the fact that steroids and related mediators produce paradoxical effects on pain such as analgesia, hyperalgesia, and even placebo analgesia. In addition, we will examine the physiologic effect of stress, high allostatic load, and idiopathic disease states such as chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and burnout. The recently observed positive relationship between glutaminergic activity in the insula and clinical pain will be examined in the context of understanding the central role of steroids in chronic pain. The complex role of the hypothalamic-pituitary-adrenal axis in pain will be discussed as well as other heterogeneous forms of chronic pain that involve many components of the central nervous system. Components of the hypothalamic-pituitary-adrenal axis have paradoxical effects on certain types of pain that are dependent on dose and on site (whether peripheral or central) and mode of application. Recent studies on glia have shown that they prolong a state of neuronal hypersensitization in the dorsal root ganglia by releasing growth factors and other substances that act on the immune system. We will discuss the implication of these new findings directly linking pain to steroids, stress, and key higher brain regions in the context of future therapeutic targets.

1. Introduction

The purpose of this article is to examine new data that demonstrate the direct nociceptive and antinociceptive actions of corticosteroids and to evaluate these findings in the context of physiologic stress and disease states that are associated with a high allostatic load [1,2]. We will discuss the paradoxical analgesic and hyperalgesic effects of stress in idiopathic pain conditions such as chronic fatigue syndrome (CFS), fibromyalgia (FM), irritable bowel syndrome (IBS), and burnout. These complex interactions between pain and stress will be examined in the context of the network of mediators involved in stress and adaptation to stress. This review will also summarize the role of corticosteroids and stress and stress hormones in pain. In addition, we will discuss "placebo analgesia," that is, the influence of psychological factors on pain perception [3-5].

Although the history of the clinical use of steroids dates back to several centuries and effective medications for pain control have been available for decades, the direct action of steroids in pain conditions has received little attention. This is mainly because, when dealing with pain, clinicians rely heavily on steroids to control concomitant underlying conditions such as inflammation and have considered steroids as playing only a supplementary role in pain management. However, recent studies in chronic painful disease conditions such as FM and CFS have enabled us to evaluate the direct action of corticosteroids and glutaminergic activity in the insula in chronic pain states [6,7]. These studies have shown that glutaminergic activity in the insula is positively related to clinical pain and have led to a new understanding of the central role of steroids in chronic pain.

1.1. Corticosteroids

Naturally occurring glucocorticoids (cortisol/hydrocortisone) have a number of physiologic effects such as the

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regulation of intermediary metabolism, cardiovascular function, growth, and immunity. In the absence of stress in a normal adult, 10 to 20 mg of cortisol are secreted per day, 90% of which is bound to a globulin (corticosteroid-binding globulin). Exogenous (synthetic) glucocorticoids such as dexamethasone on the other hand are largely bound to albumin [8].

1.2. Pain

The sensation of pain is the result of a complex and interactive network of mediators and mechanisms that involve all levels of the nervous system from the sensory input via the dorsal horn of the spinal cord to higher brain structures such as the medulla, midbrain central gray amygdala, and insula [6,7]. Pain is elicited by the neural activity from injury to sensory fibers or from damage to the brain itself ("neuropathic pain") [9].

1.3. Corticosteroid modulation of spinal nociceptive transmission

Chronic corticosteroid treatment alters the expression of neuropeptides involved in nociceptive transmission at the spinal cord level and confirms that corticosteroid receptors play a crucial role in the mediation of pain transmission at the spinal cord level [10,11]. Nociceptive modulation takes place in laminae I and II of the dorsal horn of the spinal cord where primary nociceptor afferents synapse on interneurons and projection neurons. Nociceptive stimulation releases substance P and calcitonin gene-related peptide (CGRP) and somatostatin. In addition, a high density of glucocorticoid receptors (GR) coexisting with substance P (SP) and CGRP is found in laminae I and II of the dorsal horn and dorsal root ganglia [11]. The loss of the antinociceptive effect of cortisone after 4 weeks of treatment is paralleled by a restoration of CGRP and GABAB2 expression toward control levels. These results may be useful in the pharmacologic management of certain types of pain in which corticosteroids are used as adjuvant analgesics

The results of randomized trials have shown low, short-dose corticosteroid regimens to be safe and effective for reducing postoperative pain [12]. Corticosteroids, with or without local anesthetic agents, have been administered by surgeons across various medical specialties and with different methods; and there is overwhelming evidence that corticosteroids increase the efficacy of pain reduction following surgery in a manner that does not compromise patient safety [12].

1.4. Stress

An individual's response to stress, either physical or emotional, includes activation of the hypothalamic-pituitary-adrenal (HPA) axis, which is accomplished by the secretion of corticotrophin-releasing hormone and arginine vasopressin from the paraventricular nucleus of the hypothalamus [13,14]. The interaction of these neurohormones with specific receptors on corticotrophic cells of the anterior pituitary triggers release of adrenocorticotropin (ACTH) that in turn stimulates secretion of cortisol from the adrenal cortex.

1.5. Stress, pain, and stress-induced changes in pain threshold

Psychological stress can turn into physical pain and illness [15]. Acute stress induces analgesia, but the effects of chronic stress in nociception are less predictable: some studies report analgesia after prolonged stress [16], and other studies report hyperalgesia [10,17,18]. Stressful experiences can alter pain thresholds by either reducing pain ("stress-induced analgesia") or exacerbating pain ("stress-induced hyperalgesia"). Members of the HPA axis as well as endorphins appear to be involved in this phenomenon [19,20]. Stress is thought to be the physiologic trigger of the intrinsic pain inhibitory system [21]. The phenomenon of stress-induced analgesia involves both opioid- and non–opioid-mediated mechanisms, usually classified on the basis of their cross-tolerance with morphine and sensitivity to naloxone [21]. Both types of stress-induced analgesia are disrupted by lesions of the spinal dorsolateral funiculus, suggesting involvement of descending inhibitory pathways

1.6. Stress-related pain syndromes

The HPA axis plays a pivotal role in the coordinated physiologic response to stress including inflammatory and pain states of many diseases and "stress-related syndromes" such as CFS, FM, IBS, chronic headaches, dysmenorrhea, and temporomandibular disorder [6,7,22,23], all of which are thought to be associated with stress. There is evidence that the HPA axis is involved in acute and chronic pain. However, it is unclear whether the observed HPA axis abnormalities in stress-related pain syndromes reflect preexisting vulnerability to these syndromes or whether chronic somatic symptoms alter HPA axis activity. At the same time, although the corticotropin-releasing factor (CRF) can produced analgesia [24], CRF is also involved in enhancing neuropathic pain in the amygdala, as will be discussed below [25]. The same is true of glucocorticoids that enhance neuropathic pain but also can be used to reduce certain kinds of pain when given in large systemic doses [26].

2. Central concept of network of mediators of stress and adaptation and biphasic effects

The impact of threatening and adverse experiences, as well as features of the physical environment, is processed by the brain and is usually referred to under the rubric of *stress*. The brain determines what is threatening and produces the behavioral and physiologic responses that lead to fighting, fleeing, helplessness, or engaging in health-damaging and health-promoting behaviors; and it also regulates the activity

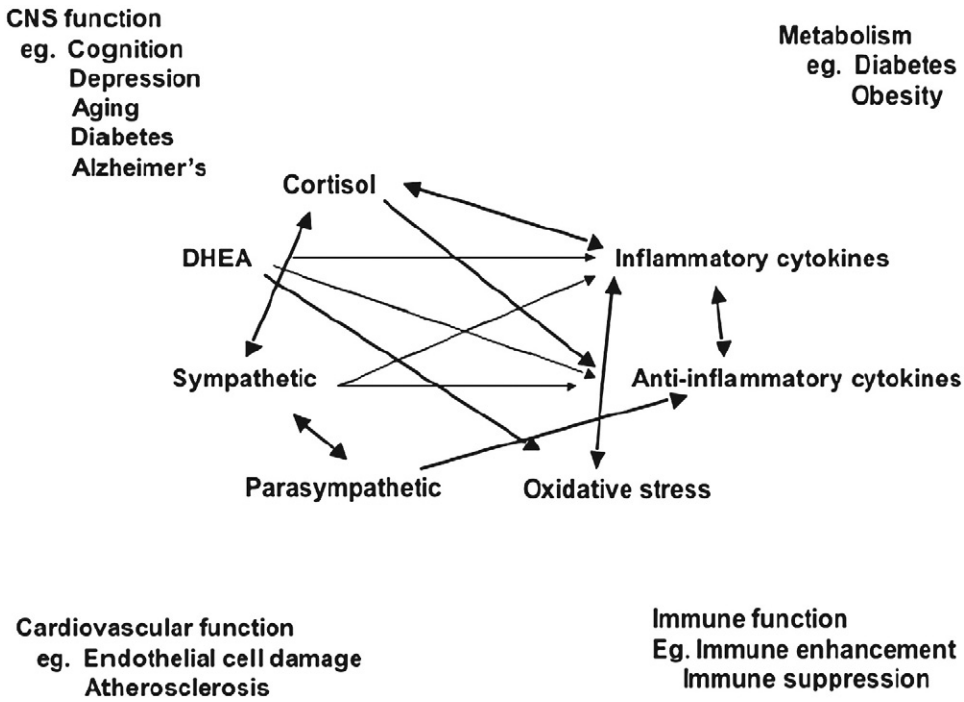

Fig. 1. Nonlinear network of mediators of allostasis involved in the stress response. Arrows indicate that each system regulates the others in a reciprocal manner, creating a nonlinear network. Moreover, there are multiple pathways for regulation; for example, inflammatory cytokine production is negatively regulated via anti-inflammatory cytokines as well as via parasympathetic and glucocorticoid pathways, whereas sympathetic activity increases inflammatory cytokine production. Parasympathetic activity, in turn, contains sympathetic activity. Reprinted from Takasaki et al [38] by permission.

of the autonomic, neuroendocrine, and immune systems that produces adaptation of the body and brain to the stressor [13,27]. Multiple mediators are involved, including hormones of the HPA axis (CRF, ACTH, glucocorticoids), as well as parasympathetic and sympathetic activity and pro- and anti-inflammatory cytokines [28,29]. In the nervous system, excitatory amino acid neurotransmitters, monoaminergic systems, GABA inhibition, endocannabinoids, and other neuromodulators play a role in the response to stressors, as well as in the various aspects of neural response that signal pain [28,29].

One important feature of these mediators is that they regulate each other, sometimes both positively and negatively, in nonlinear networks of allostasis [28,29] (Fig. 1). Allostasis is the active process that leads to adaptation to stressors and other challenges to an individual, whereas overuse of the mediators of allostasis or dysregulation of the network of allostasis leads to a wear-and-tear called *allostatic load* [28,29]. Allostatic load can lead to disease [1,2]. With regard to pain, there are a number of examples of dysregulation of the network associated with neuropathic pain as well as examples of how stress can either decrease or increase nociceptive pain; and these will now be summarized.

3. Complex and paradoxical actions of HPA constituents

The HPA axis and its key members, CRF, ACTH, and glucocorticoids, play somewhat paradoxical roles in different aspects of pain as they are affected by stress. These will be discussed in relation to analgesia, hyperalgesia, and neuropathic pain, followed by a discussion of paradoxical actions of CRF and glucocorticoids in exacerbation and treatment of pain conditions.

3.1. Stress-induced analgesia

Exposure to various stressors can lead to a subsequent decrease in responsiveness to pain [16,21]. "Long-term analgesia," which is opioid mediated and naloxone sensitive [19,20], is blocked by adrenalectomy as well as by hypophysectomy and dexamethasone suppression of corticosterone secretion; and this blockade is overcome by treatment of adrenalectomized (ADX) rats with corticosterone [30,31]. However, there is also nonopioid stress-induced analgesia; and it has been proposed that opioid systems are activated when the stressor is either brief or weak, whereas the nonopioid mechanisms are turned on when the stressor is more intense or lasts longer [21].

There is evidence that other components of the HPA axis are involved in stress-induced analgesia, with some evidence supporting an independent role of CRF and ACTH beyond their ability to cause glucocorticoid secretion. Endocannabinoids are also involved in stress-induced analgesia [32]; and glucocorticoids may be involved in these actions because they are known to modulate the release of endocannabinoids, their receptors, and the endogenous opioids themselves [33,34].

3.2. Stress-induced hyperalgesia

Stress can also cause hyperalgesia depending on the type of stressor as well as its intensity and duration [17]. Repeated exposure to cold, restraint, and forced swim produced hyperalgesia, whereas acute stressors such as restraint, novelty, and vibration can induce a transient hyperalgesia [17]. In humans, whereas stress-induced analgesia is found among athletes injured in games and soldiers injured in battle, increased pain sensitivity is recognized in neurasthenia and in FM, where there is often widely generalized allodynia and hyperalgesia related to stressful life events [17]. The role of stress and stress hormones in FM will be discussed later in this article. Depression and anxiety are also able to intensify pain [17].

There are situations in which initial transient stress-induced hypoalgesia is followed by a longer-lasting hyperalgesia [17]. In rats, a "nonnociceptive environmental stress" (NNES) consisting of 1 hour in a novel environment with a bright light produced a naltrexone-sensitive hypoalgesia lasting only an hour or so; repetition of the NNES produced a longer-lasting hyperalgesia [35]. Interestingly, both a prior inflammation and/or treatment with fentanyl, a powerful opioid analgesic, led to hyperalgesia after NNES exposure, indicating that prior experience and low levels of opioids can cause a pain sensitization [35].

Dysregulated monoaminergic activity is suspected of contributing to hyperalgesia along with substance P, neurokinin receptors, CGRP, vasopressin, and N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors [35]. However, the role of the HPA axis is less clear, although CRF can intensify abdominal pain and anxiety in patients with IBS [36]. Paradoxical actions of CRF will be discussed later in the article.

3.3. Neuropathic pain and the role of GR and CRF2 receptors

Peripheral nerve injury can lead to neuropathic pain; and spinal cord GRs are up-regulated and play a role in increasing expression of NMDA receptors, along with interleukin-6 and protein kinase C γ [37]. Consistent with this, intrathecal injection of the GR antagonist Ru486 blocked allodynia and hyperalgesia caused by nerve injury [38]. Spinal GR also mediates the down-regulation of the spinal glutamate transporter EAAC1 following nerve injury, leading to elevated levels of extracellular glutamate [39]. At the same time, GR activity in spinal cord is responsible for up-regulation of CB-1 receptors in spinal cord, which may contribute to the ability of cannabinoids to reduce the hyperalgesia [31]. Moreover, continuous infusion of a synthetic glucocorticoid, methylprednisolone, for 21 days blocked hyperalgesia due to sciatic nerve injury; but the mechanism, which does not involve substance P or NK1 receptor down-regulation, remains a mystery [40].

Another site of hyperalgesia due to nerve injury is the amygdala, specifically, the laterocapsular division of the central amygdala (CeLC), which receives nociceptive information directly from the parabrachial area through the spino-parabrachio-amygdaloid pain pathway; and it is in CeLC that CRF1 receptors play a key role in the hyperalgesia [26]. Sciatic nerve injury increased CRF messenger RNA in the CeLC but not in the paraventricular nucleus (PVN) or bed nucleus of the stria terminalis (BNST), and it also increased GR messenger RNA in central and medial amygdala. Corticotropin-releasing factor 2 receptors do not appear to be involved, and the mechanism of CRF1 receptor action involves a protein kinase A stimulation of potassium currents highly sensitive to tetraethyl ammonia (TEA) in CeLC [25]. Moreover, NMDA transmission does not appear to be involved in CeLC in the hyperalgesia to nerve damage, whereas NMDA receptors are involved in hyperalgesia related to arthritic and visceral pain, which nevertheless also involves the parabrachial input to CeLC [41].

3.4. Paradoxical aspects of HPA components in relation to pain

Both glucocorticoids and CRF have paradoxical effects on pain. We have noted that both CRF in CeLC amygdala and GRs in both CeLC amygdala and spinal cord dorsal horn are up-regulated in neuropathic pain and appear to contribute to hyperalgesia. We have also noted that continuous infusion of a synthetic glucocorticoid, methylprednisolone, for 21 days blocked hyperalgesia due to sciatic nerve injury; in the same study, a daily regimen of glucocorticoid was ineffective in reducing hyperalgesia, suggesting that timing of glucocorticoid application is important in outcome [40]. For CRF, which appears to act at all levels of the neuraxis, both systemic and local applications frequently have analgesic effects, particularly for prolonged pain conditions [24]. Endorphins do not appear to be involved in the analgesia produced by intravenous or local CRF applications, and inflammation must be present for analgesic actions of CRF to take place [24].

4. HPA activity in neuropathic pain and in chronic fatigue and FM

Altered activity of the HPA axis appears to be part of a number of syndromes that are associated with pain. Chronic fatigue syndrome and idiopathic chronic pain conditions, such as FM and IBS, appear to reflect an imbalance in mediators of allostasis, as depicted in Fig. 1 [42-44]. These conditions are also sometimes associated with symptoms of posttraumatic stress disorder [43] and burnout [45-47]. Prominent among the contributing mediators is dysregulated HPA axis activity.

Two of the prominent conditions are CFS and FM, and life stress has been identified as a major contributor to both [48]. *Chronic fatigue syndrome* is defined as disabling fatigue of 6 months or longer duration, often accompanied by several from among a long list of physical complaints [49]. Multiple investigators have proposed that disruption in the

integrity of the HPA axis may be the proximate cause of many of the somatic, cognitive, and emotional symptoms that characterize CFS and also FM [13,48,50,51].

Fibromyalgia is characterized by widespread musculoskeletal pain associated with low pain threshold as detected by pain on palpation of at least 1 of 28 well-defined tender points [52]. Fibromyalgia patients not only show a reduced threshold for pain stimuli, but also have a heightened sensitivity to stress [48]. Fibromyalgia has been reported to be associated with elevated cortisol levels [14], although it is not clear whether HPA axis changes are the cause or the consequence of the chronic pain of FM. However, the pain in FM cannot be explained by the presence of inflammation. This has led to the conclusion that the central nervous system (CNS) must be contributing to the symptoms of chronic pain and that both the CNS and other mediators of allostasis are likely to be involved.

5. Involvement of other mediators of allostasis in CFS, FM, IBS, burnout, and idiopathic pain disorders, and placebo analgesia

Besides the HPA axis, multiple mediators of allostasis and end points of allostatic load are reported to be altered in these conditions. For example, in CFS, there are reported to be low aldosterone, low urinary cortisol, and elevated waist-hip ratio, as well as increased bodily pain and poor physical functioning [1,2,53]. Lower-than-normal cortisol and aldosterone are associated with higher-than-normal levels of proinflammatory cytokines in CFS [54]. However, a specific and uniform dysfunction of the HPA axis is unlikely to be a key feature of CFS; rather, imbalances in other hormones such as dehydroepiandrosterone and abnormal serotonergic function are also implicated, along with the above-mentioned elevations in cytokines, pointing to a broader disruption of the network of allostasis [54]. Yet, certain alleles of the GR have been associated with CFS [37].

There is also an overlap of these symptoms with those of ‘burnout,” a condition associated with emotional exhaustion, depersonalization, lack of satisfaction with personal accomplishment, and low self-esteem [45-47]. Although lower-than-normal cortisol has been reported in burnout along with higher-than-normal sensitivity to dexamethasone suppression of the HPA axis, this is not always reported; and the underlying physiology is undoubtedly more complex, as it appears also to be for CFS and idiopathic chronic pain disorders [55-57]. Increased risk for type 2 diabetes mellitus has been reported in chronic burnout in otherwise healthy individuals [58].

Psychological distress and strong emotions play an important role in promoting the symptoms of idiopathic pain disorders such as IBS, FM, and temporomandibular joint disorder [59-61]. However, HPA abnormalities in FM are not fully explained by psychological distress but may have another basis. In contrast to the evidence that elevated cortisol is involved [48], it has been suggested that FM is accompanied by mild hypocortisolemia, increased resistance to cortisol feedback, and reduced CRF synthesis and release in the PVN [48]. What about the involvement of abnormal brain activity? In IBS, as also in other chronic pain conditions, there are alterations in activation of brain regions associated with central arousal, pain, and strong emotions, including the brainstem, insula, amygdala, hippocampus, and cingulate cortex, among other brain regions [36,44,62]. Reduction in dopaminergic activity in the nucleus accumbens may play a key role along with elevated NMDA receptor-mediated activity in brain regions, including the hippocampus [62,63].

Elevated CRF is associated with sensory and emotionally driven pain symptoms, although not with CFS [64,65]. One of the unanswered questions is whether there is structural remodeling of brain areas involved in these processes, which, along with chemical imbalances in 5HT-, CRF-, dopamine-, and NMDA-mediated neural activity, would help explain the apparent sensitization of the brain to pain stimuli. Moreover, when considering pain and brain activation associated with pain, it is important to recognize the role of brain mechanisms in the placebo effect, in which perceptions of pain can be manipulated by expectations [4,5,66]. This further emphasizes the importance of cognitive processes in top-down regulation of the body.

6. Conclusion

The role of the HPA axis in pain is complex, just as the forms of chronic pain are heterogeneous and involve many components of the CNS. Components of the HPA axis have paradoxical effects on certain types of pain that are dependent on dose and on site and mode of application, whether peripheral or central. In addition, besides the HPA axis, other mediators of the nonlinear network of allostasis are implicated. The experience of pain is determined at multiple levels of the neuraxis, and higher cognitive processes appear to play a major role. Recent studies by Fields [67] have shown that, following injury, several factors facilitate/disinhibit neuronal transmission of pain signals. This leaves the dorsal root ganglion cells in a state of neuropathic pain. Glia have been found to prolong this state of neuronal hypersensitization by releasing growth factors and other substances that act on the immune system. The possibility of therapeutically targeting glial-induced hypersensitivity could be of interest in pain management. Future studies should also look carefully at structural and functional alterations in key higher brain regions that are likely to contribute to increased sensations of pain.

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