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Endogenous opioids: opposing stress with a cost

Rita J. Valentino[1,2]* and Elisabeth Van Bockstaele[3]

Addresses: [1]Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, Civic Ctr. Blvd., Philadelphia, PA 19104, USA; [2]University of Pennsylvania, Civic Ctr. Blvd. Philadelphia, PA 19104, USA; [3]Department of Pharmacology, Drexel University College of Medicine, N. 15th St., Philadelphia, PA 19102, USA

* Corresponding author: Rita J. Valentino (rjv@mail.med.upenn.edu or valentino@email.chop.edu)

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Abstract

The stress response is characterized by the coordinated engagement of central and peripheral neural systems in response to life-threatening challenges. It has been conserved through evolution and is essential for survival. However, the frequent or continual elicitation of the stress response by repeated or chronic stress, respectively, results in the dysfunction of stress response circuits, ultimately leading to stress-related pathology. In an effort to best respond to stressors, yet at the same time maintain homeostasis and avoid dysfunction, stress response systems are finely balanced and co-regulated by neuromodulators that exert opposing effects. These opposing systems serve to restrain certain stress response systems and promote recovery. However, the engagement of opposing systems comes with the cost of alternate dysfunctions. This review describes, as an example of this dynamic, how endogenous opioids function to oppose the effects of the major stress neuromediator, corticotropin-releasing hormone, and promote recovery from a stress response and how these actions can both protect and be hazardous to health.

Introduction

In response to perceived life-threatening stimuli, several physiological processes—including the following: glucocorticoid release into the circulation to mobilize energy resources and modulate immune reactions; increases in heart rate, blood pressure, and respiration; changes in gastrointestinal motility; increases in arousal; and modification of behavior—are synchronized in an effort to best cope with the challenge. This complex yet finely coordinated acute stress response is necessary for survival and has been conserved throughout evolution. A built-in component of this response that is essential for health is the ability to terminate the processes once the stressor is no longer present.

Stress exposure is associated with many neuropsychiatric diseases, including depression, post-traumatic stress disorder (PTSD), substance abuse, and Alzheimer's disease as well as medical conditions, including obesity, cardiovascular disease, inflammatory disorders, and irritable bowel syndrome [1–8]. The clinical impact of stress derives from the ability of repeated or chronic stressors to produce enduring dysfunctions in stress response systems or stress neuromediators such that they become overactive or are not counter-regulated. Given the prevalence of stressors in the dynamic environment of an animal, mechanisms that limit activity of stress response systems and promote fast recovery to pre-stress levels are essential. Feedback inhibition of paraventricular hypothalamic corticotropin-releasing hormone (CRH) neurons by rising levels of glucocorticoids is a classic example of an acute stress recovery mechanism [9]. However, in the face of either repeated or chronic stress, other systems or neuromodulators that oppose "pro-stress" systems or neuromediators may be engaged. Examples of opposing factors that have been identified are neuropeptide Y, endocannabinoids, urocortins, and endogenous opioids [6,10–16]. Here, we describe the opposing interactions between the CRH system that initiates many components of the stress response and endogenous opioids that restrain the effects of CRH on a major stress response system, the brain norepinephrine

system. The importance of a balance between these two neuromodulators and the implications of this for individual vulnerability to stress-related disorders are emphasized. Finally, the idea that systems that oppose the stress response can be the basis for alternate pathologies is discussed.

Corticotropin-releasing hormone: initiating the stress response

A major advance in stress neurobiology was the isolation and characterization by Vale and colleagues [17] (1983) of CRH as the paraventricular hypothalamic neurohormone that is released into the median eminence to initiate anterior pituitary adrenocorticotropin secretion into the general circulation, a response that is generally considered a hallmark of stress. This discovery opened a portal that allowed the generation of new hypotheses for how the brain organizes the multicomponent acute response to stressors and how the mechanisms by which it does this underlie stress-related pathology. Anatomical, electrophysiological, and behavioral studies from numerous laboratories provided convergent evidence for a parallel function of CRH as a neuromodulator that is released by stressors in brain regions underlying autonomic, behavioral, and cognitive responses to stress [18,19]. For example CRH-containing axon terminals and CRH receptors were identified in the dorsal vagal complex and brainstem regions that regulate autonomic function and in limbic regions such as the central nucleus of the amygdala and bed nucleus of the stria terminalis that are involved in emotional output [20,21]. Central CRH administration was demonstrated to mimic many of the autonomic and behavioral aspects of the stress response even in hypophysectomized rats [22–32]. Importantly, many stress-elicited effects were demonstrated to be prevented or reversed by administration of CRH antagonists or were found to be absent in animals with genetic deletions of CRH receptors [16,33–44]. Together, the findings led to the compelling notion that coordinated CRH release in specific neural circuits integrates the different limbs of the stress response. Although the autonomic and behavioral processes initiated by CRH are adaptive in responding to life-threatening challenges, if they were engaged in the absence of such a challenge or if they persisted long after the challenge was terminated, this would be considered pathological. Consistent with this, many stress-related disorders, including depression, PTSD, and irritable bowel syndrome, have been attributed to excessive CRH that is not counter-regulated [6,45–47].

Endogenous opioids: opposing the stress response

The endogenous opioids and their receptors were discovered and characterized by several different groups in the early 1970s [48–53]. Four major families that derive from precursors that are encoded by distinct genes have been identified: preproopiomelanocortin, preproenkephalin, preprodynorphin, and proorphanin [52,54–59]. The active peptides that are cleaved from these precursors produce their effects primarily through actions on μ-opioid receptors, κ-opioid receptors, δ-opioid receptors and ORL-1 G-protein coupled receptors [60,61]. Opioids are best recognized for their analgesic activity. In addition to inhibiting sensation, opioid analgesia involves a blunting of the negative affective component of pain [62]. Pain shares characteristics with other stressors in that it signals physical threat, alters autonomic function, increases arousal, redirects attention, induces avoidance behaviors, and generates negative affect [63]. The ability of endogenous opioids to counter cognitive and affective components of pain may represent a more global function to counteract these components of the response to stressors in general. Notably, these opioid actions are attributed primarily to the μ-opioid receptor (MOR), for which β-endorphin, endomorphin, and enkephalins are more selective [64–66]. In contrast, aversive effects that in some ways resemble stress have been attributed to the dynorphin-κ-opioid receptor system [67]. An anti-stress function of endogenous opioids is further supported by substantial evidence that stressors of different modalities elicit their release. For example, many stressors, including those that are non-noxious, elicit an analgesia that is cross-tolerant with morphine and is antagonized by naloxone [68–71]. In subjects with PTSD, combat-related stimuli elicit naloxone-sensitive analgesic responses [72,73]. Repeated social stress releases sufficient endogenous opioids to create a state of opioid dependence that is expressed as withdrawal signs when naloxone is administered (see below). Finally, stressors have also been demonstrated to increase preproenkephalin mRNA in certain brain regions or β-endorphin in plasma [74–78].

The distribution of enkephalin overlaps that of CRH in brain regions that mediate endocrine, behavioral, and autonomic components of the stress response, including the paraventricular hypothalamic nucleus, central amygdalar nucleus, bed nucleus of stria terminalis, parabrachial nucleus, and nucleus tractus solitaries [21,66,79]. Taken with their opposing "pro-stress" and "anti-stress" effects, respectively, the anatomical overlap between CRH and endogenous opioids in the brain positions these neuromodulators to work in concert to fine-tune neuronal activity in response to stressors. In this situation, an imbalance favoring either neuromodulator may have pathological consequences. A specific example of this is seen with brain locus coeruleus (LC)-norepinephrine (NE) neurons, which are targeted by

both CRH and enkephalin inputs that have opposing actions that are engaged during stress [80–82].

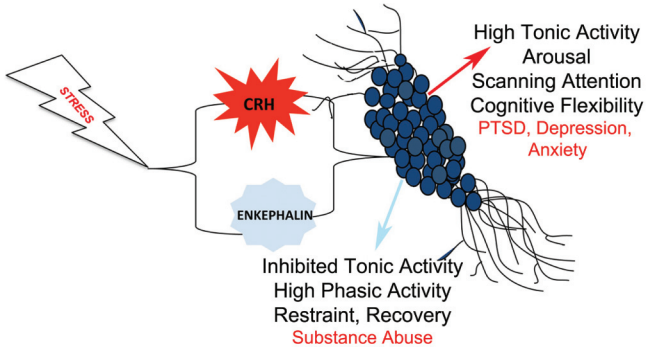
The locus coeruleus-norepinephrine stress response system

The LC-NE system is activated by stressors in parallel with the hypothalamic-pituitary-adrenal axis and this activation plays an integral role in initiating and maintaining arousal and facilitating certain behavioral and cognitive responses to stress [83]. The LC is a compact pontine nucleus of norepinephrine-containing neurons [84,85]. Through an extensive axonal projection system, the LC serves as the primary source of brain norepinephrine [86]. The physiological characteristics of LC neurons have implicated this system in arousal, particularly in response to salient stimuli [87–89]. LC neurons exhibit different patterns of firing that are associated with different cognitive states [90,91]. For example, a phasic pattern of LC neuronal discharge, when the overall rate is moderate but the cells are highly activated by sensory stimuli, is associated with focused attention and staying on-task. In contrast, a high tonic mode of LC discharge is characterized by high-frequency spontaneous discharge and minimal activation by discrete sensory stimuli and is associated with scanning attention and behavioral flexibility, a mode of activity that would be adaptive in coping with a stressor. The ability of LC neurons to switch between phasic and tonic modes of discharge facilitates rapid behavioral adjustments in a dynamic environment.

Co-regulation of the locus coeruleus-norepinephrine system by opposing CRH and opioid influences: a fine balance

LC neurons are poised for co-regulation by CRH and enkephalin because they receive convergent input from CRH- and enkephalin-containing axon terminals [80,81]. Activation of CRH1 and MOR on LC neurons has opposing electrophysiological effects. CRH1 signaling increases LC neuronal discharge frequency and favors a high tonic mode of activity [92,93], whereas MOR signaling inhibits LC neurons and favors a phasic mode of activity [94] (Figure 1). Acute stressors, such as a hypotensive challenge or exposure to predator odor, mimic the electrophysiological effects of CRH on LC neurons [95–98]. The increased arousal and cognitive flexibility associated with a shift toward high tonic LC activity would be adaptive in coping with a life-threatening stimulus. Administration of a CRH antagonist into the LC during stress blocks stress-induced LC activation, indicating that it is mediated by CRH neurotransmission [95–98]. Moreover, it reveals a prominent inhibition that can be prevented by opioid antagonists [95,97]. In the presence of opioid antagonists

Figure 1. Schematic depicting the consequences of opposing corticotropin-releasing hormone (CRH)-opioid interactions on locus coeruleus (LC) neurons



Stress engages both CRH and enkephalin inputs that converge on LC neurons. CRH increases tonic and decreases phasic LC discharge and this is associated with increased arousal, a shift from focused to scanning attention, and enhanced cognitive flexibility, effects that would be adaptive in response to an acute stressor. Activation of μ-opioid receptors on LC neurons inhibits LC tonic discharge and facilitates phasic activity. These opposing effects serve to restrain the effects of CRH and facilitate recovery after the stressor is terminated. Shifts in the CRH-opioid balance can promote different pathology. An imbalance in favor of CRH would increase vulnerability to stress-related disorders characterized by hyperarousal. An imbalance in favor of endogenous opioids would increase vulnerability to substance abuse. Abbreviations: PTSD, post-traumatic stress disorder.

alone, stressors produce an enhanced LC activation and one that takes longer to recover to baseline after stressor termination [95,97]. These findings indicate that stressors engage both CRH and opioid inputs to the LC (Figure 1). The net effect of acute stress on LC activity is dominated by CRH excitation and this is adaptive in the acute situation. The co-release of endogenous opioids serves to restrain stress-induced excitation and also promotes recovery when the stressor is no longer present (Figure 1).

The opposing influences of CRH and endogenous opioids on LC activity must be finely tuned for the system to maintain homeostasis. An imbalance between CRH and opioid influences can have different clinical consequences and this may be a basis for individual resilience/vulnerability to stress. For example, a decreased opioid influence in this circuit would be expressed as an exaggerated and more enduring arousal response to stressors. Consistent with this, in rats that are morphine-dependent and presumably tolerant, acute stress produced a greater excitation of LC neurons and an enhanced behavioral response to a stressor [81]. Because many stress-related psychiatric disorders are characterized by symptoms of hyperarousal, conditions that decrease opioid function would render individuals

more vulnerable to these disorders. This could occur as a result of opioid tolerance from chronic use or an innate low sensitivity to opioids because of polymorphisms in the MOR gene [99]. The lower sensitivity of females to MOR agonists [100–102] implicates this as a factor contributing to their increased vulnerability to stress-related psychiatric disorders [103,104].

Repeated stress creates a state of opioid dependence

Although acute stress-induced opioid release is adaptive in curbing the excitatory effects of CRH, its persistence with either repeated or chronic stress can produce enduring modifications in neural circuits that result in opioid tolerance and dependence. This may be an underlying basis for the link between stress and substance abuse. For example, mice and rats exposed to repeated social stress exhibit mild opiate withdrawal signs when administered the opiate antagonist, naloxone, even though they have never been administered opiates [105]. This phenomenon is apparent at a cellular level and can be attributed to an imbalance between endogenous opioids and CRH in favor of opioids [106]. In contrast to the characteristic acute stress-induced activation of LC neurons, repeated social stress inhibits LC neuronal activity [106]. This is due both to a loss of the CRH-elicited excitation as a result of CRH1 internalization and to increased opioid release and MOR signaling. Naloxone administration up to 10 days after the last social stress exposure produces a robust activation of LC neurons resembling that which occurs in opiate-dependent animals and this is associated with mild signs of physical opiate withdrawal. This effect likely generalizes to other stressors because LC neurons were also unexpectedly inhibited in an animal model of PTSD that involves exposure to three different severe stressors [107]. Thus, repeated stress switches the predominant regulation of the LC from CRH-mediated activation to opioid-mediated inhibition (Figure 1). Although this switch may protect against the negative consequences of LC hyperactivity, the bias toward opioid regulation may increase vulnerability to opioid abuse in an effort to avoid negative effects of mild opioid withdrawal. Consistent with this, subjects with PTSD have a higher use of analgesics, show tolerance to opiate analgesia, and have a high comorbidity of opiate addiction [108–110]. These neuronal mechanisms at the level of the LC and perhaps in other brain regions may underlie the significant co-morbidity between PTSD and opiate addiction. This is an example of how a system designed to oppose stress can itself result in stress-related pathology.

Conclusions

Stress is implicated in diverse psychiatric and medical disorders. Stress-related pathology is generally thought to arise from a dysfunction in stress mediators as a consequence of either repeated or chronic stress. This review introduced the concept that pathological consequences of stress can also result from a dysfunction of systems that are engaged during stress but are designed to restrain the stress response. Although this review focused on opposing opioid/CRH interactions at the level of the LC, similar interactions can occur at other sites where opioids and CRH converge. For example, the dorsal raphe nucleus is a point of convergence between CRH and enkephalin, and evidence points to CRH1-MOR interactions in the serotonergic dorsal raphe nucleus as being somewhat analogous to the interactions in the LC [111]. Moreover, there are other endogenous neuromediators that have actions opposite to those of CRH or that have been proposed as protecting against the effects of stress. Individual differences in endogenous mechanisms that oppose the stress response can potentially determine the degree of vulnerability/resilience to stress-related pathology. Similarly, sex differences or age differences in stress-opposing systems can account for sex differences or developmental differences in stress vulnerability, respectively. Future studies designed to identify and characterize endogenous systems that oppose stress would advance our understanding of stress-related disorders and guide the development of therapeutics to treat these diseases.

Abbreviations

CRH, corticotropin-releasing hormone; LC, locus coeruleus; MOR, μ-opioid receptor; NE, norepinephrine; PTSD, post-traumatic stress disorder.

Disclosures

The authors declare that they have no disclosures.

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