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# Endogenous opioids: The downside of opposing stress

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ABSTRACT

Our dynamic environment regularly exposes us to potentially life-threatening challenges or stressors. To answer these challenges and maintain homeostasis, the stress response, an innate coordinated engagement of central and peripheral neural systems is initiated. Although essential for survival, the inappropriate initiation of the stress response or its continuation after the stressor is terminated has pathological consequences that have been linked to diverse neuropsychiatric and medical diseases. Substantial individual variability exists in the pathological consequences of stressors. A theme of this Special Issue is that elucidating the basis of individual differences in resilience or its flipside, vulnerability, will greatly advance our ability to prevent and treat stress-related diseases. This can be approached by studying individual differences in "pro-stress" mediators such as corticosteroids or the hypothalamic orchestrator of the stress response, corticotropin-releasing factor. More recently, the recognition of endogenous neuromodulators with "anti-stress" activity that have opposing actions or that restrain stress-response systems suggests additional bases for individual differences in stress pathology. These "anti-stress" neuromodulators offer alternative strategies for manipulating the stress response and its pathological consequences. This review uses the major brain norepinephrine system as a model stress-response system to demonstrate how co-regulation by opposing pro-stress (corticotropin-releasing factor) and anti-stress (enkephalin) neuromodulators must be fine-tuned to produce an adaptive response to stress. The clinical consequences of tipping this fine-tuned balance in the direction of either the pro- or anti-stress systems are emphasized. Finally, that each system provides multiple points at which individual differences could confer stress vulnerability or resilience is discussed.



## 1. Introduction

The stress response is characterized by a synchronized set of endocrine, immunological, autonomic, behavioral and cognitive responses to perceived threats that is necessary for survival and has been conserved throughout evolution. The prevalence of stressors in the dynamic environment of an animal, make it essential to have mechanisms that limit activity of stress response systems and promote rapid recovery to pre-stress levels. For example, activation of the hypothalamic-pituitary-adrenal (HPA) axis by stress is under tight feedback regulation that serves to restrain and terminate the response (Dallman et al., 1972). Dysfunctions in this feedback as a result of repeated or chronic stress or even a single severe stress are thought to underlie the link between stress and 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 (Chrousos, 2000a; Chrousos and Gold, 1992; de Kloet et al., 2005; Goeders, 2003; McEwen, 1998; Larauche et al., 2012; Chrousos, 2000b; McEwen and Stellar, 1993). Individual differences in various components of glucocorticoid feedback mechanisms are points of potential vulnerability or resilience to stress. For example, variations in early life maternal care can determine individual sensitivity of this feedback through epigenetic mechanisms that determine glucocorticoid receptor expression (Weaver et al., 2004).

Although feedback inhibition of the HPA axis by glucocorticoids is critical in restraining the endocrine limb of the stress response, neural circuits underlying other limbs of the stress response are not similarly regulated. For example, whereas glucocorticoids inhibit corticotropin-releasing factor (CRF) mRNA expression in neurons of

*Abbreviations:* CRF, corticotropin-releasing factor; HPA, Hypothalamic-pituitary-adrenal; MOR, μ-opioid receptor; PTSD, post-traumatic stress disorder.

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the paraventricular hypothalamic nucleus that initiate anterior pituitary adrenocorticotropin release, they increase CRF mRNA in neurons of the amygdala and bed nucleus of the stria terminalis that are thought to underlie behavioral aspects of the stress response (Makino et al., 1994a, 1994b). Given the complexity of stress circuitry, there are likely to be multiple mechanisms for counter-regulation of different components of the stress response. Identifying these mechanisms can guide strategies to prevent or treat stress-related neuropsychiatric diseases. Mechanisms for counteracting stress are also potential points at which individual differences can be expressed and thus can be determinants of stress vulnerability and/or resilience.

One mechanism for counteracting stress responses is through stress-elicited engagement of neuromodulators that act in opposition to "pro-stress" systems or neuromediators. Some neuromediators that have been characterized as opposing stress include neuropeptide Y, endocannabinoids, urocortins and endogenous opioids (Bowers et al., 2012; Crowe et al., 2014; Gunduz-Cinar et al., 2013; Heilig and Thorsell, 2002; Hillard, 2014; Kozicz, 2007; Reul and Holsboer, 2002).

This review presents the locus coeruleus (LC)-norepinephrine (NE) system as a model stress-response system that is co-regulated by the opposing influences of the pro-stress mediator, CRF and the opioid neuropeptide, enkephalin during acute stress. We begin with a brief description of the anatomical and physiological characteristics of the LC-NE system with respect to its role in behavioral and cognitive aspects of the stress response (additional detail on anatomical and physiological characteristics of the LC-NE system are reviewed in (Aston-Jones et al., 1995)). This is followed by a discussion of CRF as the orchestrator of the stress response and a neurotransmitter that activates the LC-NE system in response to stress. Endogenous opioids are introduced as "anti-stress" mediators that co-regulate the LC in a manner that opposes CRF. The adaptive nature of maintaining a balance between CRF and endogenous opioid influences in the LC is emphasized. Individual factors that can tip this balance to result in pathology or determine vulnerability are discussed. An underlying theme is that systems that oppose the stress response, while protective, can also be the basis for alternate pathologies.

## 2. The locus coeruleus and stress

The following section reviews anatomical and physiological characteristics of the LC-NE system that have implicated the system in stress. More detailed information about this system and its other putative functions that are outside the scope of this review can be found in (Aston-Jones et al., 1995; Foote et al., 1983; Berridge and Waterhouse, 2003). The LC is a compact cluster of NE neurons in the pons that serves as the primary source of brain NE (Grzanna and Molliver, 1980). A distinguishing anatomical feature of the LC is its widespread, highly collateralized projection system that innervates the entire neuraxis (Aston-Jones et al., 1995; Swanson and Hartman, 1976). Through this axonal system the nucleus LC can broadly influence neuronal activity throughout the brain. Notably, the LC serves as the primary source of NE in forebrain regions such as the hippocampus and cortex that govern cognition, memory and complex behaviors.

The physiological characteristics of LC neurons have been studied in vivo in rodents and non-human primates and in vitro in slice preparations and have implicated this system in arousal, attention and behavioral flexibility (Aston-Jones and Bloom, 1981a, 1981b; Foote et al., 1980; Williams and Marshall, 1987; Aston-Jones and Cohen, 2005). LC neurons discharge spontaneously and their tonic rate is positively correlated to arousal state (Aston-Jones and Bloom, 1981b; Foote et al., 1980). However, the relationship between neuronal activity and arousal is more than just correlation because selective activation or inhibition of LC neurons results in cortical and hippocampal electroencephalographic (EEG) activation or inhibition, respectively, indicating causality between LC discharge rate and arousal (Berridge and Foote, 1991; Berridge et al., 1993). As described below, LC activation is necessary for cortical EEG activation by stress (Page et al., 1993).

In addition to spontaneous firing, LC neurons are phasically activated by salient, multimodal stimuli that elicit a burst of discharge followed by a period of inhibition (e.g., Fig. 1) (Aston-Jones and Bloom, 1981a)' (Aston-Jones and Bloom, 1981a; Foote et al., 1980). The phasic response precedes orientation to the eliciting stimuli, suggesting that the LC-NE system redirects attention towards salient sensory stimuli. LC neurons are thought to discharge synchronously during phasic activation as a result of electrotonic coupling through gap junctions between dendrites outside of the nucleus, in the peri-coerulear (peri-LC) region (Ishimatsu and Williams, 1996). In contrast, during spontaneous or tonic LC discharge, the neurons are thought to be uncoupled (Usher et al., 1999). When LC neurons are discharging at a relatively high spontaneous rate (high tonic mode), phasic LC activation by stimuli is greatly attenuated so that high tonic discharge precludes phasic activity (Valentino and Aulisi, 1987).

LC neurons switch between phasic and high tonic discharge modes to bias behavior differently and these shifts facilitate adaptation in a dynamic environment (Fig. 1) (see for reviews (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005)). LC neuronal recordings in monkeys performing operant tasks suggest that phasic LC discharge is associated with focused attention and staying on-task whereas high tonic discharge is associated with labile attention and going off-task (Usher et al., 1999; Rajkowski et al., 1994). A shift from phasic to high tonic LC discharge has been suggested to promote behavioral flexibility, disengaging animals from attention to specific stimuli and ongoing behaviors and favoring scanning the environment for stimuli that promote alternate, more rewarding behaviors (Aston-Jones and Cohen, 2005). The ability to shift between phasic and tonic firing modes would promote rapid adjustments in response to a stressor or after stressor termination (Fig. 1).

Convergent lines of evidence suggest that stressors that initiate the HPA response to stress also activate the LC-NE system and the parallel engagement of these two systems serves to coordinate endocrine and cognitive limbs of the stress response (Valentino and

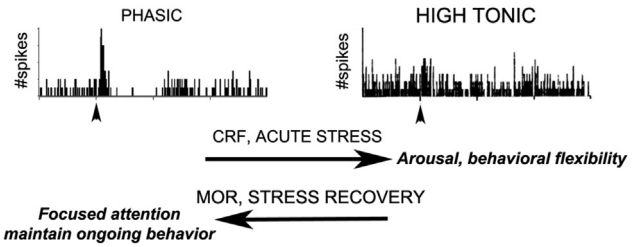


**Fig. 1.** Schematic depicting the relationship between phasic and high tonic LC activity. Shown are representative peri-stimulus time histograms (PSTHs) of LC neuronal activity during a trial of repeated auditory stimulation occurring at the arrowhead. In the phasic mode LC neurons are more responsive to sensory stimuli and fire with a burst of spikes followed by a period of inhibition before activity returns to pre-stimulus frequency. In the high tonic mode, LC neurons fire faster throughout the trial of sensory stimulation and show little response to the sensory stimuli. These histograms were generated before (PHASIC) and after (HIGH TONIC) CRF administration. Exposure of LC neurons to CRF or exposure of animals to acute stress biases LC activity towards the high tonic mode that is associated with increased arousal, scanning attention and behavioral flexibility. Activating MOR in the LC as occurs during stress recovery biases discharge towards lower tonic and increased phasic activity and this is associated with focused attention and maintenance of ongoing behavior.

Van Bockstaele, 2008). This has been studied using different stressors including shock, auditory stress, immunological stress, autonomic stressors, restraint and social stress and different endpoints including NE turnover, NE release, LC neuronal activity, c-fos expression or tyrosine hydroxylase expression (Cassens et al., 1981, 1980; Korf et al., 1973; Thierry et al., 1968; Beck and Fibiger, 1995; Bonaz and Tache, 1994; Britton et al., 1992; Campeau and Watson, 1997; Chan and Sawchenko, 1995; Chang et al., 2000; Curtis et al., 2012; Dun et al., 1995; Duncan et al., 1993; Funk and Amir, 2000; Graham et al., 1995; Ishida et al., 2002; Kollack-Walker et al., 1997; Lacosta et al., 2000; Makino et al., 2002; Rusnak et al., 2001; Sabban and Kvetnansky, 2001; Smagin et al., 1994; Smith et al., 1992, 1991; Valentino et al., 1991).

In response to acute stress LC spontaneous discharge increases and this is temporally correlated to cortical EEG activation indicative of arousal (Curtis et al., 2012; Lechner et al., 1997; Page et al., 1992). Moreover, LC activation is necessary for forebrain EEG activation by stress because selective bilateral inactivation of LC neurons with clonidine microinfusions prevents this response (Page et al., 1992). As LC spontaneous discharge rate increases, responses to discrete sensory stimuli are attenuated (Curtis et al., 2012; Valentino and Wehby, 1988a). Thus, acute stressors bias LC discharge towards a high tonic mode that would facilitate disengagement from ongoing tasks, scanning attention and behavioral flexibility, all of which would be adaptive in coping with an immediate threat (Fig. 2A). Notably, in the absence of stress, high tonic LC activity would not be adaptive and would translate to hyperarousal and an inability to concentrate or to maintain performance on tasks that require focused attention. These are characteristic symptoms of stress-related psychiatric disorders such as PTSD and major depression, both of which also show evidence of LC-NE hyperactivity (Southwick et al., 1999; Wong et al., 2000).

## 3. Corticotropin-releasing factor, the locus coeruleus and stress

Substantial evidence now implicates the stress-related neuropeptide, CRF as a primary mediator of stress-induced LC activation. CRF was initially characterized as the paraventricular hypothalamic neurohormone that initiates anterior pituitary adrenocorticotropin secretion in response to stressors (Vale et al., 1981). This discovery inspired a body of research from diverse laboratories that ultimately provided convergent evidence for a parallel function of CRF as a brain neuromodulator that coordinates autonomic, behavioral and cognitive responses to stress with the endocrine limb (See for Review (Bale and Vale, 2004; Owens and Nemeroff, 1991)). CRF-containing axon terminals and CRF receptors were regionally localized in brain areas that regulate autonomic functions, emotional expression and cognition (Sakanaka et al., 1987; Swanson et al., 1983). Central CRF administration was demonstrated to mimic many of the autonomic and behavioral aspects of the stress response even in hypophysectomized rats (Britton et al., 1982; Brown and Fisher, 1985; Brown et al., 1982; Tache et al., 1983; Tache and Gunion, 1985; Cole and Koob, 1988; Snyder et al., 2012; Heinrichs et al., 1995; Koob and Heinrichs, 1999; Sutton et al., 1982; Swerdlow et al., 1986). The most convincing evidence that CRF serves as the major molecule that organizes the different components of the stress response came from the numerous studies demonstrating that stress-elicited effects are prevented or reversed by central administration of CRF antagonists or are absent in animals with genetic deletions of CRF receptors (Reul and Holsboer, 2002; Contarino et al., 1999; Lenz et al., 1988; Kawahara et al., 2000; Heinrichs et al., 1992; Korte et al., 1994; Smagin et al., 1996; Tazi et al., 1987; Martinez et al., 1997; Bueno and Gue, 1988; Gutman et al., 2003; Keck et al., 2004; Muller et al., 2004). Together, the findings led to the compelling notion that coordinated CRF release in specific neural circuits integrates the different limbs of the stress response. Although the autonomic and behavioral processes initiated by CRF 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 CRF that is not counterregulated (Larauche et al., 2012; Bremner et al., 1997; Gold and Chrousos, 2002; Tache et al., 1993).

Multiple CRF receptors have been identified, with the CRF1 subtype being the most predominant in brain and the subtype considered to be responsible for most effects attributed to the stress response, although some rodent models of anxiety and depression also implicate a role for CRF2 (Dautzenberg and Hauger, 2002; Hauger et al., 2009; Maier and Watkins, 2005; Risbrough et al., 2009, 2004). For the purpose of this review, the CRF effects discussed will be those mediated by CRF1 unless otherwise noted.

The LC-NE system is a target of CRF neurotransmission. CRF-immunoreactive axon terminals synaptically contact LC dendrites, particularly those that extend into the peri-LC (Tjoumakaris et al., 2003; Van Bockstaele et al., 1996). The majority of these synapses are asymmetric or excitatory-type and approximately one third co-

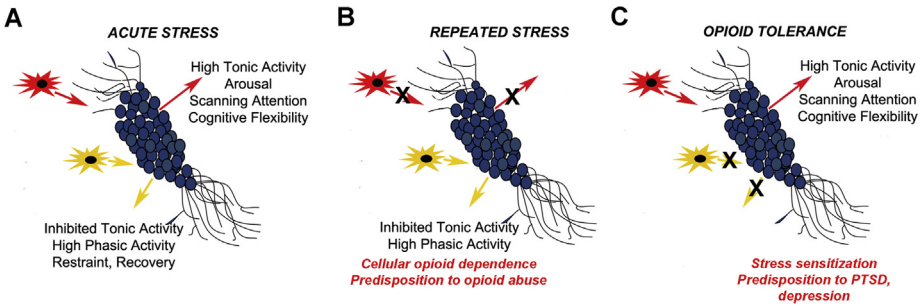


**Fig. 2.** Schematic depicting the net effect of different conditions on LC activity and associated cognitive effects. A) During acute stress both CRF (red cell) and endogenous opioid (yellow cell) afferents to the LC are engaged. The net effect is a shift of LC activity towards high tonic activity that is associated with increased arousal, scanning attention and behavioral flexibility. Endogenous opioids act as a restraint and facilitate recovery of neuronal activity to pre-stress levels after the stress is terminated. B) With repeated stress, the CRF influence is attenuated because CRF1 internalizes and the opioid effect predominates. In this condition, the cells are in a mild state of opioid dependence and individuals may be susceptible to opioid abuse. C) A decreased opioid influence as would occur with tolerance would enhance the neuronal and cognitive effects of CRF and these would be more enduring. The enhanced arousal-like state could account for symptoms of PTSD and depression. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

localize glutamate, whereas few co-localize GABA (Valentino et al., 2001). Additionally, CRF axon terminals are apposed to non-labeled axon terminals that synapse with LC dendrites suggesting that CRF can affect LC neuronal activity through both direct and indirect effects. CRF afferents to LC dendrites in the peri-LC derive from the central amygdalar nucleus (CeA) and the paraventricular hypothalamic nucleus (Reyes et al., 2005; Valentino et al., 1992; Van Bockstaele et al., 1998; Van Bockstaele et al., 1999), whereas those to the nuclear LC include the nucleus paragigantocellularis, Barrington's nucleus and the paraventricular hypothalamic nucleus (Reyes et al., 2005; Valentino et al., 1992, 1996). Hypothalamic CRF neurons that project to the LC are a distinct population from those that project to the median eminence to regulate adrenocorticotropin release (Reyes et al., 2005).

In slice preparations in vitro, CRF increases LC discharge rates in the presence of tetrodotoxin or cadmium, suggesting that these are direct effects on LC neurons (Jedema and Grace, 2004). These actions are mediated by CRF1 Gs-protein coupled receptors, are cyclic AMP dependent and are mediated by a decreased potassium conductance (Jedema and Grace, 2004; Schulz et al., 1996). In vivo, CRF mimics the effects of stressors on LC neuronal activity when administered intracerebroventricularly or directly into the LC. Thus, CRF increases LC spontaneous discharge rate and attenuates sensory-evoked phasic discharge, thereby shifting discharge to a high tonic mode that would promote increased arousal, going off-task, scanning the environment and behavioral flexibility (Curtis et al., 1997; Valentino and Foote, 1987; Valentino et al., 1983). Consistent with this, bilateral intra-LC CRF injections activate forebrain EEG activity (Curtis et al., 1997), behavioral arousal (Butler et al., 1990) and enhance behavioral flexibility in a rat attention set shifting task (Snyder et al., 2012). The increased CRF-elicited LC neuronal activation also translates to elevated forebrain NE release (Page and Abercrombie, 1999).

LC neurons are not under tonic CRF regulation because CRF antagonists typically do not affect LC discharge rate (Curtis et al., 1994). Rather, CRF is released in the LC by acute stressors to shift the mode of activity to a high tonic state. This is evidenced by the ability of local microinfusions of CRF antagonists into the LC to prevent LC activation elicited by the acute stressors, hypotension and colonic distention (Page et al., 1993; Valentino et al., 1991; Lechner et al., 1997). Central administration of CRF antagonists also prevented LC activation by acute exposure to predator odor, which also shifts the mode of LC discharge to a high tonic state (Curtis et al., 2012). Other endpoints of stress-induced LC activation, such as forebrain NE release and cortical EEG activation are also prevented by intra-LC microinfusion of CRF antagonists (Page et al., 1993; Kawahara et al., 2000). Together, these studies support a model whereby acute stress engages CRF inputs to the LC to bias activity towards a high tonic state that would favor increased arousal, scanning attention and behavioral flexibility (Fig. 2A). Studies combining retrograde tracing from the LC and immunohistochemistry to localize CRF and the immediate early gene, c-fos implicate the central nucleus of the amygdala and Barrington's nucleus as sources of CRF that activate the LC during hypotensive stress and colonic distention, respectively and suggest that CRF circuits activating the LC are stressor-specific (Curtis et al., 2002; Rouzade-Dominguez et al., 2001). Similar functional neuroanatomy approaches may be used to delineate the CRF-related circuitry underlying LC activation by psychogenic stressors that are more common in humans.

## 4. Endogenous opioids: counteracting stress

Endogenous opioids have long been implicated in the stress response based on evidence for their release by stressors and their ability to either attenuate or mimic stress responses depending on the specific opioid receptor that is activated. Several laboratories were involved in the discovery and characterization of the endogenous “morphine-like” peptides and their receptors in the early 1970's (Goldstein et al., 1979; Hughes et al., 1975; Ling et al., 1976; Bradbury et al., 1976; Meunier et al., 1995; Pert and Snyder, 1973). Distinct genes were identified that encode for the precursors of the three major endogenous opioid peptide families, preproopiomelanocortin, preproenkephalin and preprodynorphin (Meunier et al., 1995; Comb et al., 1982; Kakidani et al., 1982; Nakanishi et al., 1979; Noda et al., 1982; Nothacker et al., 1996; Pan et al., 1996). The active peptides cleaved from these precursors, endorphin, enkephalin and dynorphin, produce their effects through actions on μ-, δ and κ- G-protein coupled receptors, respectively (Mogil and Pasternak, 2001; Pasternak, 2004).

Opioids are best recognized for their ability to blunt pain. However, this may be an expression of a broader function to counter stress. Pain can be considered a stressor because it signals physical threat and it elicits many of the same responses as non-noxious stressors, including increased arousal, changes in autonomic activity, avoidance behaviors and negative affect (Ribeiro et al., 2005). Although opioid analgesia attenuates the sensory aspects of pain, a major component of the analgesic response involves a blunting of the negative affective component of pain (Zubieta et al., 2001). An “anti-stress” activity of endogenous opioids may be specifically mediated by the μ-opioid receptor (MOR), the receptor that shows greater selectivity for β-endorphin, endomorphin and the enkephalins (Akil et al., 1984; Sora et al., 1997; Drolet et al., 2001). In contrast, a stress-like aversion has been associated with the dynorphin-κ-opioid receptor system (Chavkin, 2013). Support for an anti-stress function of endogenous opioids comes from studies showing evidence for stress-elicited opioid release. In animal studies, many stressors, including those that are non-noxious, produce an analgesia that is cross tolerant with morphine and is antagonized by naloxone (Girardot and Holloway, 1984; Lewis et al., 1980; Miczek et al., 1982; Rodgers and Randall, 1985). This is also apparent in humans. For example, the presentation of combat-related stimuli to PTSD patients produces naloxone-sensitive analgesic responses (Pitman et al., 1990; van der Kolk et al., 1989). Stress also increases preproenkephalin mRNA in certain brain regions and β-endorphin in plasma (Ceccatelli and Orazzo, 1993; Dumont et al., 2000; Mansi et al., 2000; Lightman and Young, 1987; Rossier et al., 1977).

One mechanism by which endogenous opioids can counteract stress is through actions that oppose those of CRF. Enkephalin and CRF are co-localized in many hypothalamic neurons, in the medial preoptic nucleus and in the bed nucleus of the stria terminalis (Sakanaka et al., 1989). The cellular targets of these neurons are potential sites of interaction between CRF and enkephalin. Additionally, CRF and enkephalin distribution overlaps in brain regions underlying behavioral and autonomic components of the stress response including the CEA, parabrachial nucleus and nucleus tractus solitarias (Swanson et al., 1983; Drolet et al., 2001; Sakanaka et al., 1989). That these neuromodulators act in an organized fashion to fine-tune neuronal activity in response to stressors is particularly evident in their co-regulation of the LC-NE system during stress (Valentino and Van Bockstaele, 2001).

## 5. CRF and opioid co-regulation of the locus coeruleus during acute stress

LC neurons are anatomically poised for co-regulation by CRF and enkephalin. Although few axon terminals in the LC and peri-LC region co-localize CRF and enkephalin, LC dendrites receive convergent input from CRF- and enkephalin-containing axon

terminals and co-localize MOR and CRF1 (Tjoumakaris et al., 2003; Xu et al., 2004). Enkephalin innervation of the LC derives from rostral medullary nuclei including the nucleus paragigantocellularis and nucleus prepositus hypoglossi (Drolet et al., 1992). Lesions of the central nucleus of the amygdala that substantially diminish CRF innervation of the LC and peri-LC region have little effect on enkephalin innervation of the LC (Tjoumakaris et al., 2003). Moreover, few (2%) LC-projecting paraventricular hypothalamic nucleus neurons are enkephalin-containing, whereas 30% are immunoreactive for CRF (Reyes et al., 2005). Together these findings suggest that enkephalin and CRF axon terminals that converge onto LC neurons derive from different sources.

Opioids acting at MOR on LC neurons have effects that are directly opposite to those of CRF1 activation. MOR activation inhibits the formation of cyclic AMP and hyperpolarizes LC neurons through an increase in potassium conductance (Williams and North, 1984; Aghajanian and Wang, 1987). In vivo MOR agonists bias LC activity towards a phasic mode, increasing synchrony and decreasing tonic discharge rate without changing or slightly increasing phasic evoked responses (Valentino and Wehby, 1988b; Zhu and Zhou, 2001). Like CRF, opioids do not tonically regulate LC activity because neither MOR antagonists nor κ-opioid antagonists affect LC activity of unstressed rats (Chaijale et al., 2013; Curtis et al., 2001; Kreibich et al., 2008).

The initial evidence for stress-induced opioid regulation of LC activity came from the demonstration that systemic administration of the opioid antagonist, naloxone increased LC discharge rates of cats undergoing restraint stress, but not control cats (Abercrombie and Jacobs, 1988). Later studies using exposure to predator odor as a stress, provided evidence for CRF and enkephalin co-release during stress (Curtis et al., 2012). During this stress LC neurons shifted from a phasic to a high tonic mode, such that spontaneous discharge increased and LC and auditory-evoked discharge decreased. Administration of a CRF antagonist prior to the stress changed this response to a large inhibition of tonic activity with slightly increased auditory-evoked activity, reminiscent of the effects of morphine administration and this was prevented by prior naloxone administration. Thus, in the presence of a CRF antagonist, exposure to the stressor unmasked an opioid inhibition, suggesting that both CRF and enkephalin were co-released during the stress to regulate LC discharge rate. Notably, removal of both the CRF and opioid influence in the LC by prior administration of both a CRF antagonist and naloxone rendered these neurons completely unresponsive to stressors suggesting that these afferents are the primary regulators of LC activity during acute stress (Curtis et al., 2012). CRF and opioid regulation of LC activity was also demonstrated during a physiological stressor, hypotensive stress, although the temporal aspects of opioid release during this stress were less clear (Valentino et al., 1991; Curtis et al., 2001). During hypotensive stress, LC discharge rate increased and when the stressor was terminated and blood pressure returned to baseline LC discharge was robustly inhibited for several minutes (Valentino and Wehby, 1988a; Curtis et al., 2001). Intra-LC administration of a CRF antagonist during the stress prevented the stress-induced excitation and revealed a greater post-stress inhibition that is naloxone-sensitive (Valentino and Wehby, 1988a; Curtis et al., 2001). Additionally, LC administration of naloxone alone increased the time taken for LC excitation to recover to pre-stress levels. This study suggested that opioid inhibition was important in recovery of LC activity from this physiological stressor.

Together these findings support a model whereby acute stressors engage both CRF and opioid inputs to the LC (Fig. 2A). CRF is the predominant afferent and shifts LC discharge to a high tonic mode that favors increased arousal, scanning attention and behavioral flexibility, effects that would be adaptive coping responses to an acute threat. At the same time endogenous opioid afferents that have opposing actions are engaged. These function to restrain the CRF excitation and to promote recovery after stressor termination. These CRF/opioid interactions adjust the activity and reactivity of LC neurons so that level of arousal and processing of sensory stimuli are optimized to facilitate adaptive behavioral responses to stressors. The protective effects of opioids are apparent in the many studies documenting that morphine administration shortly after a single traumatic event reduces the incidence of PTSD (Bryant et al., 2009; Holbrook et al., 2010).

## 6. Repeated stress tips the balance towards opioid regulation

During acute stress MOR regulation of the LC serves as an adaptive counterbalance that curbs the excitatory effects of CRF and protects against the consequences of a hyperactive brain norepinephrine system. However, tipping the balance in favor of a MOR influence incurs alternative costs (Fig. 2B). Like the CRF response to stress, the opposing opioid response must be limited. The persistence of an opioid influence can produce enduring modifications in neural circuits that result in opioid tolerance and dependence. Indeed, this may be an underlying basis for the association between stress and substance abuse.

A bias toward opioid regulation of the LC was recently demonstrated to occur with repeated social stress, which diminishes CRF function and enhances MOR function in the LC (Chaijale et al., 2013). Unlike acute stressors, repeated social stress decreased LC neuronal discharge rate by 48 h after the last stress and this inhibition was naloxone-sensitive indicating that MOR receptors were occupied. Analysis of CRF1 and MOR protein levels and receptor trafficking in the LC demonstrated that this paradoxical stress-induced inhibition is due to both a loss of CRF-elicited excitation as a result of CRF1 internalization and to increased opioid release and MOR signalling (Chaijale et al., 2013). Importantly, the magnitude of the naloxone-elicited LC excitation was greater than that which could be explained by reversal alone and was similar to that observed with naloxone administration to morphine-dependent rats (Valentino and Wehby, 1989). By 10 days after the last social stress, LC neurons were not inhibited and naloxone produced an even greater activation suggesting that the neurons were opioid tolerant and dependent. Notably, naloxone administration to rats exposed to repeated social stress was also associated with mild signs of physical opioid withdrawal. These findings were consistent with previous reports that repeated social stress in mice results in analgesia that is cross tolerant with morphine and in opioid dependence as determined by naloxone precipitated withdrawal signs (Miczek et al., 1986; Miczek, 1991). Together the results suggest that repeated social stress shifts the balance of LC activity towards inhibitory opioid regulation by engaging endogenous opioid afferents to the LC and by downregulating CRF receptors. The opioid imbalance in the LC produced by repeated social stress may generalize to other stressors. For example, in an animal model of PTSD that involves exposure to three different severe stressors (the single prolonged stress model) LC neurons were also paradoxically inhibited (George et al., 2013). For both of these stress models the temporal aspects of opioid release in the LC have yet to be determined and it is not clear whether there is concurrent release of both peptides, or whether opioids are released at a later time.

Thus, in contrast to acute stress, where CRF excitation predominates and opioids act to temper this response and promote recovery, with repeated stress the influence of CRF is diminished and the balance is tipped in favor of opioid regulation (Fig. 2B). Although this protects against the negative consequences of a hypernoradrenergic state, it comes with its own cost. The

dysfunctional bias towards opioid neuronal regulation may render individuals tolerant to opioid analgesia and vulnerable to opioid abuse in an effort to avoid negative effects associated with mild withdrawal. These effects are clinically relevant with respect to PTSD. Individuals with PTSD are tolerant to opioid analgesics and in general have a higher use of analgesics (Schwartz et al., 2006; Jacobsen et al., 2001; Fareed et al., 2013). Importantly substantial co-morbidity exists between PTSD and opioid abuse (Schwartz et al., 2006; Fareed et al., 2013b; Mills et al., 2007; Clark et al., 2001). At the basis of this comorbidity may lie an over responsive opioid system that was initially engaged to counteract responses to trauma. This is an example of stress-related pathology arising from a dysfunction in a system designed to oppose stress.

## 7. Chronic opioid administration tips the balance towards CRF regulation

In contrast to the consequences of repeated stress, conditions that decrease the opioid influence in the LC would bias regulation towards CRF-mediated excitation by removing restraint on the CRF system and hindering recovery of neuronal activity after stress termination (Fig. 2C). This would be expressed as an exaggerated and more enduring activation of the LC-NE system that would translate to exaggerated hyperarousal that is characteristic of PTSD and other stress-related psychiatric disorders. A decrease in opioid influence could occur in individuals who become opioid tolerant as a result of chronic medical use or abuse. Consistent with this, in rats chronically treated with morphine, LC neurons respond with a greater excitation to hypotensive stress (Xu et al., 2004). This is due in part to sensitization of LC neurons to CRF because the CRF dose-response curve for LC activation is shifted to the left and has a greater maximum response in these animals. Importantly, enhanced LC sensitivity to CRF in rats chronically treated with morphine translated to exaggerated stress-induced behavioral activation (Xu et al., 2004). For example, morphine-treated rats exposed to swim stress show excessive climbing behavior (Xu et al., 2004), a response that has been linked to brain NE (Detke et al., 1995) and that is similar to the effects of CRF injected locally into the LC (Butler et al., 1990).

These basic studies imply that chronic opioid administration by humans can sensitize the LC-NE arousal system to stressors and this can also be a basis for comorbidity of opioid abuse and PTSD. However, in contrast to repeated stress, where the stress leads to adaptive mechanisms that predispose to opioid abuse, here opioid abuse would be responsible for a predisposition to the hyperarousal symptoms of PTSD. Either case could account for the high comorbidity of opioid abuse and PTSD (Fareed et al., 2013b; Clark et al., 2001).

## 8. Individual differences in opioid regulation of the LC: potential determinants of resilience

Given the role of opioids in buffering LC-NE activation during stress and the pathological implications of excessive or insufficient opioid influence described above, individual differences in either enkephalin expression or MOR sensitivity are potential determinants of stress resilience/vulnerability or the form of pathology that is expressed. For example, whereas decreased MOR function may predispose to hyperarousal symptoms of stress-related disorders because of a decreased ability to counteract CRF effects, it may protect against substance abuse because the neurons won't become opioid-dependent. In contrast, individuals with greater MOR sensitivity would be predicted to be protected from hyperarousal symptoms but more prone to substance abuse. Thus, how the balance is tipped will determine how the stress-related pathology is expressed. In this regard MOR density, sensitivity and trafficking, as well as enkephalin expression are affected by sex and hormonal status (Torres-Reveron et al., 2008, 2009; Van Kempen et al., 2013; Milner et al., 2013; Craft, 2008). The relationships are not clear-cut and may be dependent on the species, the endpoint and brain region studied. Nonetheless, studies documenting decreased MOR sensitivity in females (Kepler et al., 1991; Ji et al., 2006; Wang et al., 2006) would be consistent with reports that stress-related diseases characterized by hyperarousal are more prevalent in females whereas substance abuse is more prevalent in males (Kessler et al., 2005, 1994; Breslau, 2002).

Like sex, age is a potential determinant of individual resilience/vulnerability. Developmental differences in enkephalin innervation of the LC or MOR expression by LC neurons will determine the balance of CRF-opioid regulation of the LC-NE system at different ages and can contribute to age-related determinants of stress vulnerability. Although developmental differences in the enkephalin-MOR system that regulates the LC have not specifically been investigated, differences in enkephalin expression and MOR signalling have been reported in other brain regions during postnatal development (Kwok et al., 2014). Preliminary findings in our laboratory suggest that LC neurons of adolescent male rats (42–47 day old) are activated by social stress to a similar magnitude as seen in adults but do not recover as well, suggesting that the opioid system is not completely developed and this may increase vulnerability to the hyperarousal components of stress-related pathology.

Another potential determinant of individual variability lies in the MOR gene. A single nucleotide polymorphism (SNP) A118G occurring in exon 1 of the MOR gene is relatively common in individuals of European ancestry (15–30%) and Asian ancestry (40–50%) (Kwok et al., 2014). Individuals with the G118 allele exhibit less sensitivity to morphine analgesia and in vitro studies suggest that this SNP confers a loss of function although this is not a uniform finding of all studies (Mague and Blendy, 2010). For example, HPA inhibition is greater in animals with this SNP, suggesting increased opioid inhibitory tone. Notably, there is evidence for an interaction of this SNP with sex in certain endpoints (Mague et al., 2009). Elucidating the impact of this MOR SNP on LC responses to stressors may identify this as a genetic source of variability that interacts with sex to determine resilience/vulnerability to stress.

## 9. Conclusions

Stress-related pathology is generally thought to result from a dysfunction in the mediators of the stress response as a consequence of repeated or chronic stress. This review introduced the concept that a dysfunction of systems that are engaged during stress but are designed to restrain the stress response produce alternate pathological consequences. Although this review focused on the LC as a target for opposing opioid/CRF interactions, there are other potential points of opioid/CRF convergence in brain at which an altered balance between the systems could result in pathology. Thus far, the preponderance of evidence points to CRF1-MOR interactions in the serotonergic dorsal raphe nucleus (DRN) as being somewhat analogous to the interactions in the LC (Staub et al., 2012). CRF1 and MOR have opposing effects on GABA neurons in the DRN, with CRF1 activating GABA and indirectly inhibiting 5-HT-DRN neurons and MOR inhibiting GABA neurons and indirectly exciting 5-HT-DRN neurons (Kirby et al., 2000, 2008; Jolas and Aghajanian, 1997). Similar to the effects on LC neurons described above, chronic morphine sensitizes DRN-5-HT neurons to CRF and that has been proposed to underlie vulnerability to stress-induced

relapse (Staub et al., 2012). Notably, these studies used male subjects.

In addition to opioids, there are other endogenous neuromediators that are proposed to protect against the effects of stress. Innate individual differences in endogenous mechanisms that oppose the stress response can determine vulnerability/resilience to the pathological consequences of stress. Likewise, sex differences or age differences in stress-opposing systems are potential contributors to sex differences or developmental differences in stress vulnerability, respectively. Identifying and characterizing the stress-opposing neuromediators such as the endogenous opioids and their circuitry would be a major advance in approaching the treatment of stress-related disorders.

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