Published in final edited form as:

Adv Pharmacol. 2013 ; 68: 405–420. doi:10.1016/B978-0-12-411512-5.00019-1.

Neuropeptide regulation of the locus coeruleus and opiate-induced plasticity of stress responses

Elisabeth J. Van Bockstaele and Rita J. Valentino*

Department of Neuroscience, Thomas Jefferson University, Farber Institute for Neurosciences, Philadelphia, PA 19107

*3615 Civic Ctr Blvd, ARC Suite 402E, Children's Hospital of Philadelphia, Philadelphia, PA 19107

Abstract

Stress has been implicated as a risk factor in vulnerability to the initiation and maintenance of opiate abuse and is thought to play an important role in relapse in subjects with a history of abuse. Conversely, chronic opiate use and withdrawal are stressors and can potentially predispose individuals to stress-related psychiatric disorders. Because the interaction of opiates with stress response systems has potentially widespread clinical consequences, it is important to delineate how specific substrates of the stress response and endogenous opioid systems interact and the specific points at which stress circuits and endogenous opioid systems intersect. The purpose of this review is to present and discuss the results of studies that have unveiled the complex circuitry by which stress-related neuropeptides and endogenous opioids co-regulate activity of the locus coeruleus (LC)-norepinephrine (NE) system and how chronic morphine, or stress, disturbs this regulation.

Keywords

norepinephrine; enkephalin; corticotropin-releasing factor; immunoelectron microscopy; receptor trafficking; hyper-arousal; anxiety; biological psychiatry

I. Introduction

The interaction between the stress axis and endogenous opioid systems has gained substantial clinical interest as it is increasingly recognized that stress predisposes to opiate abuse and chronic stress negatively impacts addiction recovery (Hyman, Fox, Hong, Doebrick, & Sinha, 2007; Kreek & Koob, 1998; Schluger, Bart, Green, Ho, & Kreek, 2003; Sinha, 2007; Stewart, 2003). The locus coeruleus (LC)-norepinephrine (NE) system is reciprocally regulated by endogenous opioids and the stress-related neuropeptide, corticotropin-releasing factor (CRF) (Curtis, Bello, & Valentino, 2001; Curtis, Lechner,

Corresponding Author: Elisabeth J. Van Bockstaele, Ph.D., Department of Neuroscience, Farber Institute for Neurosciences, Thomas Jefferson University, 900 Walnut Street, Suite 400, Philadelphia, PA 19107, Voice: (215) 503-1245, FAX: (215) 503-9238, ejv101@jefferson.edu.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

Pavcovich, & Valentino, 1997; Kawahara, Kawahara, & Westerink, 2000; Page, Berridge, Foote, & Valentino, 1993; Tjounmakaris, Rudoy, Peoples, Valentino, & Van Bockstaele, 2003; Valentino, Page, & Curtis, 1991; R. J. Valentino & E. Van Bockstaele, 2001). Our prior studies have shown that chronic morphine exposure sensitizes the LC-NE system to CRF and stress, providing a potential mechanism that could link opiate use and vulnerability to stress-related psychiatric disorders (Xu, Van Bockstaele, Reyes, Bethea, & Valentino, 2004). Withdrawal from opiates engages CRF and other stress-related systems including noradrenergic pathways, which produce heightened anxiety-like states and dysphoria that can increase susceptibility to relapse (Schluger et al., 2003). The complex circuitry by which CRF and endogenous opioids co-regulate activity of the LC-NE system continues to be elucidated (Fig. 1). The neuropeptides, CRF and enkephalin (ENK, acting at μ -OR), exert a primarily postsynaptic opposing regulation while recent evidence indicates a novel presynaptic regulation of afferent inputs via κ -OR modulation of excitatory (glutamate, Glu) and CRF afferents to the LC. The circuitry that links these peptides to the LC-NE system and the conditions that engage this circuitry have been identified and highlight the central nucleus of the amygdala (CNA) as a key structure in its afferent regulation. Additionally, accumulating evidence demonstrates that chronic morphine disturbs this regulation. The following sections will summarize our current knowledge of the reciprocal regulation of opiates and stress on the noradrenergic system.

II. The Locus Coeruleus-Norepinephrine System

The LC is a compact, homogeneous NE-containing nucleus that innervates the entire neuraxis through a divergent efferent system. It is the sole source of NE in many forebrain regions that have been implicated in cognition (e.g., cortex and hippocampus (Waterhouse, Lin, Burne, & Woodward, 1983)). LC neurons are spontaneously active and their rate of discharge is positively correlated to behavioral and electroencephalographic indices of arousal (Aston-Jones & Bloom, 1981a, 1981b; Ishimatsu & Williams, 1996). LC neurons are also activated by salient sensory stimuli and this response usually precedes orientation to the stimuli, implicating this system in directing attention toward salient stimuli in the environment. LC recordings in unanesthetized monkeys performing operant tasks, suggest that LC neurons fire in different patterns that are related to ongoing behavior (Aston-Jones & Cohen, 2005). Particularly, a pattern characterized by moderate spontaneous discharge rate, robust activation by sensory stimuli and synchronous firing is associated with focused attention and staying on task. In contrast, when cells are firing at a relatively high rate of discharge, they are not synchronous and are relatively unresponsive to sensory stimuli. This mode of LC activity is associated with scanning of the environment, going off task and increased behavioral flexibility. During stress or when LC neurons are exposed to the stress-related neuropeptide, CRF, LC discharge rate is shifted to this high tonic mode (Curtis, Leiser, Snyder, & Valentino, 2012; Valentino, Curtis, Page, Pavcovich, & Florin-Lechner, 1998; Valentino & Foote, 1987; Valentino & Wehby, 1988). This shift towards a state of scanning the environment and behavioral flexibility may be adaptive in a dynamic environment with life-threatening stimuli. However, if LC neurons were persistently in this state or if they were in this state inappropriately, this would be pathological, for example mimicking the hyperarousal-like symptoms that characterize post-traumatic disorder (PTSD)

(Krystal & Neumeister, 2009; O'Donnell, Hegadoren, & Coupland, 2004; Strawn & Geraciotti, 2008).

III. Co-regulation of the LC by CRF and endogenous opioids

Previous studies have revealed that the LC is finely tuned by co-regulation between the endogenous opioids, ENK and dynorphin (DYN), and CRF (B. A. Reyes, Carvalho, Vakharia, & Van Bockstaele; B. A. Reyes, Chavkin, & van Bockstaele, 2009; B. A. Reyes, Drolet, & Van Bockstaele, 2008; B. A. S. Reyes, Johnson, Glaser, Commons, & Van Bockstaele, 2007; Tjounmakaris et al., 2003; E. J. Van Bockstaele, A. Saunders, K. Commons, X.-B. Liu, & J. Peoples, 2000). During stress (physiological or psychological), CRF is released (likely from the central nucleus of the amygdala CNA, (E. J. Van Bockstaele, Chan, & Pickel, 1996; E. J. Van Bockstaele, Peoples, & Valentino, 1999)) to shift the activity of LC neurons to a high tonic state that would promote scanning of the environment and behavioral flexibility (Curtis, Bello, Connolly, & Valentino, 2002; Curtis et al., 2001; Curtis et al., 2012; A. S. Kreibich et al., 2008; R. J. Valentino & E. J. Van Bockstaele, 2001; Valentino & Van Bockstaele, 2005; E. J. Van Bockstaele, Reyes, & Valentino, 2010; Xu et al., 2004). At the same time, endogenous opioids acting at μ -OR in the LC (via ENK) exert an opposing inhibitory effect that may serve to restrain the excitatory actions of CRF and help to bring neuronal activity back to baseline (Curtis et al., 2001; Curtis et al., 2012). The CRF and ENK that regulate the LC derive from distinct sources (CNA and medulla, respectively) (Drolet, Van Bockstaele, & Aston-Jones, 1992; B. A. Reyes, Carvalho, et al.; E. J. Van Bockstaele, Chan, et al., 1996; E. J. Van Bockstaele, Colago, & Valentino, 1996; E.J. Van Bockstaele, Colago, & Valentino, 1998)) but their axon terminals converge onto common LC neurons (Tjounmakaris et al., 2003) which can respond to both peptides because they co-express μ -OR and CRF receptors (B. A. Reyes, Glaser, & Van Bockstaele, 2007). Both ENK and CRF axon terminals co-localize glutamate (Barr & Van Bockstaele, 2005; Valentino, Rudoy, Saunders, Liu, & Van Bockstaele, 2001), which mediates the short-lived LC activation by sensory stimuli (Valentino, Foote, & Aston-Jones, 1983). Most recently, the dynorphin-k-OR receptor system was shown to exert another layer of regulation on the LC system by presynaptic inhibition of excitatory LC afferents (A. S. Kreibich et al., 2008). Dynorphin was found to be co-localized with CRF (B. A. Reyes et al., 2008) and κ -OR was localized to CRF, Glu (B. A. S. Reyes et al., 2007) and DYN-containing axon terminals (B. A. Reyes et al., 2009). Electrophysiological studies demonstrated selective presynaptic inhibition of glutamatergic and CRF afferent input by selective κ -OR agonists (A. S. Kreibich et al., 2008). By allowing LC neurons to fire spontaneously, but attenuating information from excitatory afferents, the dynorphin-k-OR system takes the LC off-line, preventing adaptive responses to sensory stimuli or stressors. This may serve to protect the LC from over-activation. However, it might also be predicted to promote passive behavior as is characteristic of depression.

IV. Dysregulation of the LC-NE system by an imbalance in endogenous opioids or CRF

Given how LC activity is finely tuned by the integration of CRF and endogenous opioid inputs, upsetting the CRF:opioid balance in the LC could influence the stress-sensitivity of

this system or its sensitivity to opiates. Consistent with this, chronic morphine administration sensitized LC neurons to CRF and this was expressed as increased sensitivity of the neurons to stress (Xu et al., 2004). Importantly, this neuronal plasticity translated to a change in the behavioral repertoire of the animal in response to stress. Thus, when exposed to swim stress, morphine-treated rats were unusual in that they exhibited a strikingly higher incidence of climbing (Xu et al., 2004), an active arousal-related behavior that has been attributed to increased availability of NE activation in this model (Detke, Rickels, & Lucki, 1995). These findings infer that chronic opiate use, whether as a result of abuse or clinical use, predisposes individuals to hyperarousal symptoms of stress-related psychiatric disorders. These are a core feature of PTSD and notably, there is a significant comorbidity between PTSD and opiate abuse (Mills, Lynskey, Teesson, Ross, & Darke, 2005; Mills, Teesson, Ross, & Peters, 2006). In addition to increasing vulnerability to stress-related pathology, opiate-induced sensitization of the LC-NE system may facilitate the maintenance of opiate use in an effort to counteract the hypersensitivity of the LC-NE system.

Most recently, we found that repeated daily exposure to social stress (5 days) using the resident-intruder model, surprisingly decreased spontaneous LC activity of unanesthetized rats recorded 2 days after the last social stress. By 10 days after the last social stress, LC activity of stressed rats was comparable to that of controls. However, administration of naloxone selectively increased LC activity in the stressed rats similar to the cellular opiate withdrawal response described by others after chronic morphine administration (Aghajanian, Alreja, Nestler, & Kogan, 1992; Nestler, Alreja, & Aghajanian, 1994; Zachariou et al., 2008). The results suggest the compelling notion that the engagement of m-OR in the LC during social stress can render the neurons opiate tolerant and dependent, conditions that would promote self-administration. Notably, a body of literature has described tolerance to opioid analgesia following this same stress (Miczek, 1991; Miczek, Thompson, & Shuster, 1986; Thompson, Miczek, Noda, Shuster, & Kumar, 1988).

Finally, as another example of how upsetting peptide regulation of the LC can have pathological consequences, microarray studies revealed that the WKY rat has a higher level of expression of the κ -OR gene in the LC (Carr et al., 2010; Pearson, Stephen, Beck, & Valentino, 2006). As the κ -OR attenuates LC activation by excitatory inputs (A. S. Kreibich et al., 2008), its over-expression in the WKY rat is consistent with the passive coping, depressive-like phenotype that characterizes this strain (O'Mahony, Clarke, Gibney, Dinan, & Cryan, 2011). In line with this, κ -OR antagonists had antidepressant efficacy selectively in the WKY rat strain (Carr et al., 2010). Together these observations show the importance of maintaining appropriate interactions between ENK- μ -OR, DYN- κ -OR and CRF in the LC and the pathological consequences that can develop from a dysregulation of these systems.

V. Potential mechanisms underlying morphine-induced sensitivity to stress

Previous studies from our laboratory have characterized adaptations in endogenous opioid afferents to the LC-NE system following exposure to chronic morphine (E. J. Van Bockstaele, Menko, & Drolet, 2001). Specifically, we have shown that the endogenous opioid peptide, ENK, is significantly decreased in afferents to the LC following chronic morphine exposure when compared to control (E. J. Van Bockstaele, Peoples, Menko,

McHugh, & Drolet, 2000). Decreases in ENK in the LC were ascribed to decreases in ppENK mRNA in neurons of the nucleus paragigantocellularis (PGi) located in the rostral ventral medulla, a known source of excitatory afferents to the LC (Drolet et al., 1992; Ennis & Aston-Jones, 1988). Our work also demonstrated that ENK co-localizes with glutamate in LC afferents (Barr & Van Bockstaele, 2005; E. J. Van Bockstaele, A. Saunders, K. G. Commons, X. B. Liu, & J. Peoples, 2000) suggesting that a potential imbalance in ENK expression levels in glutamatergic afferents following chronic morphine exposure may have consequences for opiate withdrawal-induced activation of LC neurons (Rasmussen, 1995; E. J. Van Bockstaele, Menko, et al., 2001). Although ENK does not co-exist significantly with CRF in LC afferents (Tjoumakaris et al., 2003), the two converge and regulate LC neurons at a postsynaptic level (B. A. Reyes et al., 2007). A gap in our knowledge exists, however, as it is not known whether, in the same animals under conditions of opiate dependence, increases in CRF mRNA expression, in limbic regions, accompany decreases in ppENK mRNA expression observed in the rostral ventral medulla (E. J. Van Bockstaele, J. Peoples, et al., 2000) and whether these directly impact the LC. Given the reciprocal regulation of the LC-NE system by CRF and opioids, upsetting the CRF:opioid balance in the LC could influence the stress-sensitivity of this system and enhance vulnerability to stress or conversely, vulnerability to opiate abuse. It is tempting to speculate that following chronic exposure to morphine, expression levels of ppENK mRNA will significantly decrease in LC-projecting medullary afferents when compared to control and that this will be accompanied by a concomitant increase in CRF mRNA expression levels in limbic afferents (i.e. CNA) to the LC. However, future studies are required to address this. Adaptations in the endogenous opioid system following chronic morphine exposure suggest that afferent regulation of the LC may not only be affected by alterations in neuropeptide release but also by differences in neural circuit activation. We have previously described the topographic architecture of stress-related pathways impacting the LC (E. J. Van Bockstaele, Bajic, Proudfit, & Valentino, 2001). For example, in studies using lesions and functional neuroanatomy, the CNA was identified as the source of CRF that activates the LC during hypotensive stress (Rouzade-Dominguez, Curtis, & Valentino, 2001). The effect of chronic exposure to opiates not only impacts the LC-NE system on an afferent level but it also involves alterations in postsynaptic receptor effects. We demonstrated that chronic morphine sensitizes LC neurons to CRF and this results in a greater activation by stressors (Xu et al., 2004). LC sensitization to CRF was expressed as increased sensitivity of LC neurons to hypotensive stress. Importantly, this neuronal plasticity translated to a change in the behavioral repertoire of the animal in response to stress. Thus, when exposed to swim stress, morphine-treated rats were unusual in that they exhibited a strikingly higher incidence of climbing (Xu et al., 2004), a behavior that has been attributed to central NE activation in this model (Detke et al., 1995).

Potential mechanisms underlying opioid-induced sensitization of LC neurons to CRF are depicted in Figure 2. Increases in cell surface expression of CRF receptors (CRFr) in the LC could underlie the observed sensitization. Increased trafficking of CRFr to the plasma membrane could be attributed to an increase in protein expression levels or a decrease in internalization (Figure 2). Alternatively, chronic exposure to morphine may alter expression levels of mRNA for CRF and ppENK in LC-projecting neurons. We have previously shown

that LC-projecting neurons in the rostral ventral medulla exhibit decreased expression levels of ppENK mRNA in morphine treated rats when compared to controls (E. J. Van Bockstaele, J. Peoples, et al., 2000) and it is tempting to speculate that this may be accompanied by increases in CRF mRNA expression in CNA neurons that project to the LC (Figure 2). This would provide a potential mechanism whereby upsetting the CRF:opioid balance in the LC, as a result of opiate exposure, influences the stress-sensitivity of this system. It is also feasible that expression levels of ppDYN or κ -OR mRNA in LC afferents will decrease resulting in a reduction of an inhibitory influence on presynaptic modulation of excitatory afferents. Decreases in κ -OR regulation of excitatory afferents (A. Kreibich et al., 2008) would lead to increased stimulus-elicited activation of the LC-NE system potentially leading to hyperarousal. If either CRF or κ -OR is altered after chronic morphine, heightened stimulus- or stress-evoked LC activation would potentially be observed.

VI. Stress-induced molecular and cellular plasticity that sensitize LC neurons to naloxone

Repeated social stress has been shown to alter sensitivity to drugs of abuse and to promote self-administration (Covington & Miczek, 2001). With regard to opiates, social stress results in an opioid mediated analgesia that when repeated, becomes cross-tolerant with morphine (Miczek, 1991; Miczek et al., 1986). Interestingly, mice exposed to repeated social stress show withdrawal jumping when challenged with the opiate antagonist, naloxone to a similar extent as mice chronically administered morphine, suggesting that this stress can produce a state of opiate dependence (Miczek et al., 1986). Similar preliminary findings from our group, using rats, suggest that repeated social stress engages opioid inputs to the LC and results in a state of “cellular opiate dependence”.

Exposure to stress is known to alter endogenous opioid levels (Butler & Finn, 2009). The most widespread endogenous opioid in the brain is ENK (Maderdrut, Merchenthaler, Sundberg, Okado, & Oppenheim, 1986; Merchenthaler, Maderdrut, Altschuler, & Petrusz, 1986). Studies that have examined the relationship between stress and ENK expression indicate that stress alters extracellular levels of ENK in numerous structures, including mesolimbic and brainstem nuclei, and that temporal aspects of stress determine either increases or decreases in ENK release or expression (Angulo, Printz, Ledoux, & McEwen, 1991; Dumont, Kinkead, Trottier, Gosselin, & Drolet, 2000; Hebb et al., 2004; Kalivas & Abhold, 1987; Mansi, Laforest, & Drolet, 2000; Mansi, Rivest, & Drolet, 1998; Nankova et al., 1996; Wiedenmayer, Noailles, Angulo, & Barr, 2002). For example, short-term exposure to stress appears to result both in an increase in ENK release (Kalivas & Abhold, 1987) and mRNA levels (Lucas et al., 2004). In contrast, chronic stress is associated with decreased extracellular levels of ENK release as well as decreased ENK-mRNA abundance in striatal structures (Angulo et al., 1991; Lucas et al., 2004). Repeated exposure to social stress has been shown to decrease ENK-mRNA levels in the nucleus accumbens in subordinate adult male rats resulting in diminished dopaminergic tone in motivational circuitry (Lucas et al., 2004). Furthermore, previously socially defeated rats show increased cocaine self-administration compared with non-defeated rats several days after repeated exposure to the stressor suggesting an enhanced vulnerability to drug seeking behaviors (Haney, Maccari,

Le Moal, Simon, & Piazza, 1995; Tidey & Miczek, 1997). Given the preliminary findings that repeated social stress produces a decrease in LC discharge rate that is apparent 2 days after the last stress, we expect that this is due to the engagement of ENK afferents to the LC and so ppENK is predicted to be upregulated in LC afferents of social stressed rats at this time. This would be consistent with studies showing heightened analgesia following social defeat (Miczek, 1991; Rodgers & Randall, 1985) which is thought to reflect an increase in endogenous opioid release in brain regions associated with pain processes (Kulling, Frischknecht, Pasi, Waser, & Siegfried, 1988). Interestingly, ENK is co-localized with Glu in LC afferents (Barr & Van Bockstaele, 2005; E. J. Van Bockstaele, A. Saunders, et al., 2000) and glutamatergic afferents have been implicated in the LC withdrawal response (Akaoka & Aston-Jones, 1991; Rasmussen & Aghajanian, 1989; Rasmussen, Beitner-Johnson, Krystal, Aghajanian, & Nestler, 1990). It is possible that at this time ppENK mRNA is downregulated, leaving glutamate to produce the withdrawal activation.

Conclusion

These studies have broad clinical and therapeutic implications including the potential of certain pharmacological interventions in breaking the link between stress history and opiate abuse liability as well as understanding the neural basis through which repeated stress contributes to vulnerability to substance abuse. Understanding how chronic opiates increase sensitivity to stress and predispose to a spectrum of psychiatric disorders and substance abuse will enable a more targeted approach to novel therapeutic approaches.

Acknowledgments

This work was supported by National Institutes of Health grant DA009082.

Abbreviations

CNA	central nucleus of the amygdala
CRF	corticotropin releasing factor
CRFr	CRF receptor
DYN	dynorphin
ENK	enkephalin
Glu	glutamate
LC	locus coeruleus
NE	norepinephrine
PTSD	post-traumatic disorder

References

Aghajanian GK, Alreja M, Nestler EJ, Kogan JH. Dual mechanisms of opiate dependence in the locus coeruleus. [In Vitro]. *Clinical neuropharmacology*. 1992; 15(Suppl 1 Pt A):143A–144A.

- Akaoka H, Aston-Jones G. Opiate withdrawal-induced hyperactivity of locus coeruleus neurons is substantially mediated by augmented excitatory amino acid input. [Research Support, U.S. Gov't, P.H.S.]. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1991; 11(12):3830–3839. [PubMed: 1683899]
- Angulo JA, Printz D, Ledoux M, McEwen BS. Isolation stress increases tyrosine hydroxylase mRNA in the locus coeruleus and midbrain and decreases proenkephalin mRNA in the striatum and nucleus accumbens. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Brain research Molecular brain research*. 1991; 11(3–4):301–308. [PubMed: 1684631]
- Aston-Jones G, Bloom FE. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J Neurosci*. 1981a; 1(8):876–886. [PubMed: 7346592]
- Aston-Jones G, Bloom FE. Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. *J Neurosci*. 1981b; 1(8):887–900. [PubMed: 7346593]
- Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci*. 2005; 28:403–450. [PubMed: 16022602]
- Barr J, Van Bockstaele EJ. Vesicular glutamate transporter-1 colocalizes with endogenous opioid peptides in axon terminals of the rat locus coeruleus. *Anat Rec A Discov Mol Cell Evol Biol*. 2005; 284(1):466–474. [PubMed: 15803474]
- Butler RK, Finn DP. Stress-induced analgesia. [Research Support, Non-U.S. Gov't Review]. *Progress in neurobiology*. 2009; 88(3):184–202. [PubMed: 19393288]
- Carr GV, Bangasser DA, Bethea T, Young M, Valentino RJ, Lucki I. Antidepressant-like effects of kappa-opioid receptor antagonists in Wistar Kyoto rats. [Comparative Study Research Support, N.I.H., Extramural]. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2010; 35(3):752–763. [PubMed: 19924112]
- Covington HE 3rd, Miczek KA. Repeated social-defeat stress, cocaine or morphine. Effects on behavioral sensitization and intravenous cocaine self-administration “binges”. [Research Support, U.S. Gov't, P.H.S.]. *Psychopharmacology*. 2001; 158(4):388–398. [PubMed: 11797060]
- Curtis AL, Bello NT, Connolly KR, Valentino RJ. Corticotropin-releasing factor neurones of the central nucleus of the amygdala mediate locus coeruleus activation by cardiovascular stress. *J Neuroendocrinol*. 2002; 14(8):667–682. [PubMed: 12153469]
- Curtis AL, Bello NT, Valentino RJ. Evidence for functional release of endogenous opioids in the locus coeruleus during stress termination. *J Neurosci*. 2001; 21(RC152):1–5.
- Curtis AL, Lechner SM, Pavcovich LA, Valentino RJ. Activation of the locus coeruleus noradrenergic system by intracoeular microinfusion of corticotropin-releasing factor: effects on discharge rate, cortical norepinephrine levels and cortical electroencephalographic activity. *J Pharmacol Exp Ther*. 1997; 281(1):163–172. [PubMed: 9103494]
- Curtis AL, Leiser SC, Snyder K, Valentino RJ. Predator stress engages corticotropin-releasing factor and opioid systems to alter the operating mode of locus coeruleus norepinephrine neurons. *Neuropharmacology*. 2012; 62(4):1737–1745. [PubMed: 22210331]
- Detke MJ, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Psychopharmacology*. 1995; 121(1):66–72. [PubMed: 8539342]
- Drolet G, Van Bockstaele EJ, Aston-Jones G. Robust enkephalin innervation of the locus coeruleus from the rostral medulla. *J Neurosci*. 1992; 12(8):3162–3174. [PubMed: 1379635]
- Dumont EC, Kinkead R, Trottier JF, Gosselin I, Drolet G. Effect of chronic psychogenic stress exposure on enkephalin neuronal activity and expression in the rat hypothalamic paraventricular nucleus. [Research Support, Non-U.S. Gov't]. *Journal of neurochemistry*. 2000; 75(5):2200–2211. [PubMed: 11032909]
- Ennis M, Aston-Jones G. Activation of locus coeruleus from nucleus paragigantocellularis: a new excitatory amino acid pathway in brain. *J Neurosci*. 1988; 8(10):3644–3657. [PubMed: 3193175]

- Haney M, Maccari S, Le Moal M, Simon H, Piazza PV. Social stress increases the acquisition of cocaine self-administration in male and female rats. [Research Support, Non-U.S. Gov't]. *Brain research*. 1995; 698(1–2):46–52. [PubMed: 8581502]
- Hebb AL, Zacharko RM, Gauthier M, Trudel F, Laforest S, Drolet G. Brief exposure to predator odor and resultant anxiety enhances mesocorticolimbic activity and enkephalin expression in CD-1 mice. [Research Support, Non-U.S. Gov't]. *The European journal of neuroscience*. 2004; 20(9): 2415–2429. [PubMed: 15525282]
- Hyman SM, Fox H, Hong KI, Doebrick C, Sinha R. Stress and drug-cue-induced craving in opioid-dependent individuals in naltrexone treatment. [Clinical Trial Research Support, N.I.H., Extramural]. *Experimental and clinical psychopharmacology*. 2007; 15(2):134–143. [PubMed: 17469937]
- Ishimatsu M, Williams JT. Synchronous activity in locus coeruleus results from dendritic interactions in pericoerulear regions. *J Neurosci*. 1996; 16(16):5196–5204. [PubMed: 8756448]
- Kalivas PW, Abhold R. Enkephalin release into the ventral tegmental area in response to stress: modulation of mesocorticolimbic dopamine. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Brain research*. 1987; 414(2):339–348. [PubMed: 3620936]
- Kawahara H, Kawahara Y, Westerink BH. The role of afferents to the locus coeruleus in the handling stress-induced increase in the release of noradrenaline in the medial prefrontal cortex: a dual-probe microdialysis study in the rat brain. *Eur J Pharmacol*. 2000; 387(3):279–286. [PubMed: 10650173]
- Kreek MJ, Koob GF. Drug dependence: stress and dysregulation of brain reward pathways. *Drug Alcohol Depend*. 1998; 51(1–2):23–47. [PubMed: 9716928]
- Kreibich A, Reyes BA, Curtis AL, Ecke L, Chavkin C, Van Bockstaele EJ, et al. Presynaptic inhibition of diverse afferents to the locus coeruleus by kappa-opiate receptors: a novel mechanism for regulating the central norepinephrine system. [Comparative Study Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2008; 28(25):6516–6525. [PubMed: 18562623]
- Kreibich AS, Reyes BAS, Curtis AL, Ecke L, Chavkin C, Van Bockstaele EJ, et al. Presynaptic inhibition of diverse afferents to the locus coeruleus by kappa opiate receptors: a novel mechanism for regulating the central norepinephrine system. *J Neurosci*. 2008; 28(25):6516–6525. [PubMed: 18562623]
- Krystal JH, Neumeister A. Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Review]. *Brain research*. 2009; 1293:13–23. [PubMed: 19332037]
- Kulling P, Frischknecht HR, Pasi A, Waser PG, Siegfried B. Social conflict-induced changes in nociception and beta-endorphin-like immunoreactivity in pituitary and discrete brain areas of C57BL/6 and DBA/2 mice. [Comparative Study Research Support, Non-U.S. Gov't]. *Brain research*. 1988; 450(1–2):237–246. [PubMed: 3401713]
- Lucas LR, Celen Z, Tamashiro KL, Blanchard RJ, Blanchard DC, Markham C, et al. Repeated exposure to social stress has long-term effects on indirect markers of dopaminergic activity in brain regions associated with motivated behavior. [Comparative Study Research Support, Non-U.S. Gov't]. *Neuroscience*. 2004; 124(2):449–457. [PubMed: 14980394]
- Maderdrut JL, Merchantlhaler I, Sundberg DK, Okado N, Oppenheim RW. Distribution and development of proenkephalin-like immunoreactivity in the lumbar spinal cord of the chicken. [Research Support, U.S. Gov't, P.H.S.]. *Brain research*. 1986; 377(1):29–40. [PubMed: 3524750]
- Mansi JA, Laforest S, Drolet G. Effect of stress exposure on the activation pattern of enkephalin-containing perikarya in the rat ventral medulla. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Journal of neurochemistry*. 2000; 74(6):2568–2575. [PubMed: 10820219]
- Mansi JA, Rivest S, Drolet G. Effect of immobilization stress on transcriptional activity of inducible immediate-early genes, corticotropin-releasing factor, its type 1 receptor, and enkephalin in the hypothalamus of borderline hypertensive rats. [Research Support, Non-U.S. Gov't]. *Journal of neurochemistry*. 1998; 70(4):1556–1566. [PubMed: 9523573]

- Merchenthaler I, Maderdrut JL, Altschuler RA, Petrusz P. Immunocytochemical localization of proenkephalin-derived peptides in the central nervous system of the rat. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. *Neuroscience*. 1986; 17(2):325–348. [PubMed: 3517687]
- Miczek KA. Tolerance to the analgesic, but not discriminative stimulus effects of morphine after brief social defeat in rats. [Research Support, U.S. Gov't, P.H.S.]. *Psychopharmacology*. 1991; 104(2): 181–186. [PubMed: 1876662]
- Miczek KA, Thompson ML, Shuster L. Analgesia following defeat in an aggressive encounter: development of tolerance and changes in opioid receptors. [Research Support, U.S. Gov't, P.H.S. Review]. *Annals of the New York Academy of Sciences*. 1986; 467:14–29. [PubMed: 3524377]
- Mills KL, Lynskey M, Teesson M, Ross J, Darke S. Post-traumatic stress disorder among people with heroin dependence in the Australian treatment outcome study (ATOS): prevalence and correlates. [Research Support, Non-U.S. Gov't]. *Drug and alcohol dependence*. 2005; 77(3):243–249. [PubMed: 15734224]
- Mills KL, Teesson M, Ross J, Peters L. Trauma, PTSD, and substance use disorders: findings from the Australian National Survey of Mental Health and Well-Being. [Comparative Study Research Support, Non-U.S. Gov't]. *The American journal of psychiatry*. 2006; 163(4):652–658. [PubMed: 16585440]
- Nankova B, Kvetnansky R, Hiremagalur B, Sabban B, Rusnak M, Sabban EL. Immobilization stress elevates gene expression for catecholamine biosynthetic enzymes and some neuropeptides in rat sympathetic ganglia: effects of adrenocorticotropin and glucocorticoids. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Endocrinology*. 1996; 137(12):5597–5604. [PubMed: 8940389]
- Nestler EJ, Alreja M, Aghajanian GK. Molecular and cellular mechanisms of opiate action: studies in the rat locus coeruleus. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Brain research bulletin*. 1994; 35(5–6):521–528. [PubMed: 7859110]
- O'Donnell T, Hegadoren KM, Coupland NC. Noradrenergic mechanisms in the pathophysiology of post-traumatic stress disorder. [Review]. *Neuropsychobiology*. 2004; 50(4):273–283. [PubMed: 15539856]
- O'Mahony CM, Clarke G, Gibney S, Dinan TG, Cryan JF. Strain differences in the neurochemical response to chronic restraint stress in the rat: relevance to depression. [Research Support, Non-U.S. Gov't]. *Pharmacology, biochemistry, and behavior*. 2011; 97(4):690–699.
- Page ME, Berridge CW, Foote SL, Valentino RJ. Corticotropin-releasing factor in the locus coeruleus mediates EEG activation associated with hypotensive stress. [Research Support, U.S. Gov't, P.H.S.]. *Neuroscience letters*. 1993; 164(1–2):81–84. [PubMed: 8152620]
- Pearson KA, Stephen A, Beck SG, Valentino RJ. Identifying genes in monoamine nuclei that may determine stress vulnerability and depressive behavior in Wistar-Kyoto rats. [Comparative Study Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2006; 31(11):2449–2461. [PubMed: 16710313]
- Rasmussen K. The role of the locus coeruleus and N-methyl-D-aspartic acid (NMDA) and AMPA receptors in opiate withdrawal. [Review]. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 1995; 13(4):295–300. [PubMed: 8747753]
- Rasmussen K, Aghajanian GK. Withdrawal-induced activation of locus coeruleus neurons in opiate-dependent rats: attenuation by lesions of the nucleus paragigantocellularis. *Brain Res*. 1989; 505(2):346–350. [PubMed: 2598056]
- Rasmussen K, Beitner-Johnson DB, Krystal JH, Aghajanian GK, Nestler EJ. Opiate withdrawal and the rat locus coeruleus: behavioral, electrophysiological, and biochemical correlates. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1990; 10(7):2308–2317. [PubMed: 2115910]
- Reyes BA, Carvalho AF, Vakharia K, Van Bockstaele EJ. Amygdalar peptidergic circuits regulating noradrenergic locus coeruleus neurons: linking limbic and arousal centers. *Exp Neurol*. 230(1):96–105. [PubMed: 21515261]
- Reyes BA, Chavkin C, Van Bockstaele EJ. Agonist-induced internalization of kappa-opioid receptors in noradrenergic neurons of the rat locus coeruleus. *J Chem Neuroanat*. 40(4):301–309. [PubMed: 20884346]

- Reyes BA, Chavkin C, van Bockstaele EJ. Subcellular targeting of kappa-opioid receptors in the rat nucleus locus coeruleus. *J Comp Neurol.* 2009; 512(3):419–431. [PubMed: 19009591]
- Reyes BA, Drolet G, Van Bockstaele EJ. Dynorphin and stress-related peptides in rat locus coeruleus: contribution of amygdalar efferents. *J Comp Neurol.* 2008; 508(4):663–675. [PubMed: 18381633]
- Reyes BA, Glaser JD, Van Bockstaele EJ. Ultrastructural evidence for co-localization of corticotropin-releasing factor receptor and mu-opioid receptor in the rat nucleus locus coeruleus. *Neurosci Lett.* 2007; 413(3):216–221. [PubMed: 17194545]
- Reyes BAS, Johnson AD, Glaser JD, Commons KG, Van Bockstaele EJ. Dynorphin-containing axons directly innervate noradrenergic neurons in the rat nucleus locus coeruleus. *Neuroscience.* 2007; 145:1077–1086. [PubMed: 17289275]
- Rodgers RJ, Randall JI. Social conflict analgesia: studies on naloxone antagonism and morphine cross-tolerance in male DBA/2 mice. [Research Support, Non-U.S. Gov't]. *Pharmacology, biochemistry, and behavior.* 1985; 23(5):883–887.
- Rouzade-Dominguez ML, Curtis AL, Valentino RJ. Role of Barrington's nucleus in the activation of rat locus coeruleus neurons by colonic distension. [Research Support, U.S. Gov't, P.H.S.]. *Brain research.* 2001; 917(2):206–218. [PubMed: 11640906]
- Schluger JH, Bart G, Green M, Ho A, Kreek MJ. Corticotropin-releasing factor testing reveals a dose-dependent difference in methadone maintained vs control subjects. *Neuropsychopharmacology.* 2003; 28(5):985–994. [PubMed: 12700714]
- Sinha R. The role of stress in addiction relapse. [Research Support, N.I.H., Extramural Review]. *Current psychiatry reports.* 2007; 9(5):388–395. [PubMed: 17915078]
- Stewart J. Stress and relapse to drug seeking: studies in laboratory animals shed light on mechanisms and sources of long-term vulnerability. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* 2003; 12(1):1–17. [PubMed: 12623736]
- Strawn JR, Geraciotti TD Jr. Noradrenergic dysfunction and the psychopharmacology of posttraumatic stress disorder. [Review]. *Depression and anxiety.* 2008; 25(3):260–271. [PubMed: 17354267]
- Thompson ML, Miczek KA, Noda K, Shuster L, Kumar MS. Analgesia in defeated mice: evidence for mediation via central rather than pituitary or adrenal endogenous opioid peptides. *Pharmacology, biochemistry, and behavior.* 1988; 29(3):451–456.
- Tidey JW, Miczek KA. Acquisition of cocaine self-administration after social stress: role of accumbens dopamine. [Research Support, U.S. Gov't, P.H.S.]. *Psychopharmacology.* 1997; 130(3):203–212. [PubMed: 9151353]
- Tjoumakaris SI, Rudoy C, Peoples J, Valentino RJ, Van Bockstaele EJ. Cellular interactions between axon terminals containing endogenous opioid peptides or corticotropin-releasing factor in the rat locus coeruleus and surrounding dorsal pontine tegmentum. *J Comp Neurol.* 2003; 466(4):445–456. [PubMed: 14566941]
- Valentino RJ, Curtis AL, Page ME, Pavcovich LA, Florin-Lechner SM. Activation of the locus coeruleus brain noradrenergic system during stress: circuitry, consequences, and regulation. *Adv Pharmacol.* 1998; 42:781–784. [PubMed: 9328014]
- Valentino RJ, Foote SL. Corticotropin-releasing factor disrupts sensory responses of brain noradrenergic neurons. [Research Support, U.S. Gov't, P.H.S.]. *Neuroendocrinology.* 1987; 45(1):28–36. [PubMed: 3492683]
- Valentino RJ, Foote SL, Aston-Jones G. Corticotropin-releasing factor activates noradrenergic neurons of the locus coeruleus. *Brain Res.* 1983; 270(2):363–367. [PubMed: 6603889]
- Valentino RJ, Page ME, Curtis AL. Activation of noradrenergic locus coeruleus neurons by hemodynamic stress is due to local release of corticotropin-releasing factor. *Brain Res.* 1991; 555(1):25–34. [PubMed: 1933327]
- Valentino RJ, Rudoy C, Saunders A, Liu XB, Van Bockstaele EJ. Corticotropin-releasing factor is preferentially colocalized with excitatory rather than inhibitory amino acids in axon terminals in the peri-locus coeruleus region. *Neuroscience.* 2001; 106(2):375–384. [PubMed: 11566507]
- Valentino RJ, Van Bockstaele E. Opposing regulation of the locus coeruleus by corticotropin-releasing factor and opioids. Potential for reciprocal interactions between stress and opioid sensitivity.

[Research Support, U.S. Gov't, P.H.S. Review]. *Psychopharmacology*. 2001; 158(4):331–342. [PubMed: 11797054]

- Valentino RJ, Van Bockstaele EJ. Opposing regulation of the locus coeruleus by corticotropin releasing factor and opioids: potential for reciprocal interactions between stress and opioid sensitivity. *Psychopharmacology*. 2001; 158:331–342. [PubMed: 11797054]
- Valentino, RJ.; Van Bockstaele, EJ. Functional interactions between stress neuromediators and the locus-coeruleus noradrenaline system. In: Kalin, N.; Steckler, T.; Reul, JMHM., editors. *Handbook of stress and the brain*. Amsterdam: Elsevier; 2005. p. 465–486.
- Valentino RJ, Wehby RG. Corticotropin-releasing factor: evidence for a neurotransmitter role in the locus coeruleus during hemodynamic stress. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. *Neuroendocrinology*. 1988; 48(6):674–677. [PubMed: 2908000]
- Van Bockstaele EJ, Bajic D, Proudfit H, Valentino RJ. Topographic architecture of stress-related pathways targeting the noradrenergic locus coeruleus. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Physiology & behavior*. 2001; 73(3):273–283. [PubMed: 11438352]
- Van Bockstaele EJ, Chan J, Pickel VM. Input from central nucleus of the amygdala efferents to pericoerulear dendrites, some of which contain tyrosine hydroxylase immunoreactivity. *J Neurosci Res*. 1996; 45(3):289–302. [PubMed: 8841990]
- Van Bockstaele EJ, Colago EEO, Valentino RJ. Corticotropin-releasing factor-containing axon terminals synapse onto catecholamine dendrites and may presynaptically modulate other afferents in the rostral pole of the nucleus locus coeruleus in the rat brain. *J Comp Neurol*. 1996; 364:523–534. [PubMed: 8820881]
- Van Bockstaele EJ, Menko AS, Drolet G. Neuroadaptive responses in brainstem noradrenergic nuclei following chronic morphine exposure. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Molecular neurobiology*. 2001; 23(2–3):155–171. [PubMed: 11817217]
- Van Bockstaele EJ, Peoples J, Menko AS, McHugh K, Drolet G. Decreases in endogenous opioid peptides in the rat medullo-coerulear pathway after chronic morphine treatment. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000; 20(23):8659–8666. [PubMed: 11102471]
- Van Bockstaele EJ, Peoples J, Valentino RJ. A.E. Bennett Research Award. Anatomic basis for differential regulation of the rostralateral peri-locus coeruleus region by limbic afferents. *Biol Psychiatry*. 1999; 46(10):1352–1363. [PubMed: 10578450]
- Van Bockstaele EJ, Reyes BA, Valentino RJ. The locus coeruleus: A key nucleus where stress and opioids intersect to mediate vulnerability to opiate abuse. *Brain Res*. 2010; 1314:162–174. [PubMed: 19765557]
- Van Bockstaele EJ, Saunders A, Commons KG, Liu XB, Peoples J. Evidence for coexistence of enkephalin and glutamate in axon terminals and cellular sites for functional interactions of their receptors in the rat locus coeruleus. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *The Journal of comparative neurology*. 2000; 417(1):103–114. [PubMed: 10660891]
- Van Bockstaele EJ, Colago EEO, Valentino RJ. Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites: substrate for the co-ordination of emotional and cognitive limbs of the stress response. *J Neuroendocrin*. 1998; 10:743–757.
- Van Bockstaele EJ, Saunders A, Commons K, Liu X-B, Peoples J. Evidence for co-existence of enkephalin and glutamate in axon terminals and cellular sites for functional interactions of their receptors in the rat locus coeruleus. *J Comp Neurol*. 2000; 417:103–114. [PubMed: 10660891]
- Waterhouse BD, Lin CS, Burne RA, Woodward DJ. The distribution of neocortical projection neurons in the locus coeruleus. *J Comp Neurol*. 1983; 217(4):418–431. [PubMed: 6886061]
- Wiedenmayer CP, Noailles PA, Angulo JA, Barr GA. Stress-induced preproenkephalin mRNA expression in the amygdala changes during early ontogeny in the rat. [Research Support, U.S. Gov't, P.H.S.]. *Neuroscience*. 2002; 114(1):7–11. [PubMed: 12207949]
- Xu G, Van Bockstaele EJ, Reyes B, Bethea T, Valentino RJ. Chronic morphine sensitizes the brain norepinephrine system to stress. *Journal of Neuroscience*. 2004; 24:8193–8197. [PubMed: 15385601]

Zachariou V, Liu R, LaPlant Q, Xiao G, Renthal W, Chan GC, et al. Distinct roles of adenylyl cyclases 1 and 8 in opiate dependence: behavioral, electrophysiological, and molecular studies. [In Vitro]. Biological psychiatry. 2008; 63(11):1013–1021. [PubMed: 18222416]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

The LC is finely tuned by co-regulation between the endogenous opioids, ENK and DYN, and CRF. Our previous studies have characterized the anatomical, physiological and behavioral basis for interactions between endogenous opioids and the LC-NE system. Specifically, we have shown that NE activity is regulated via distinct CRF and ENK afferents targeting postsynaptically distributed CRF and μ -opioid receptors (μ -OR). We identified the source of DYN afferents to the LC as originating from the CNA (B. A. Reyes et al., 2008) and demonstrated that DYN and CRF are co-transmitters in monosynaptic afferents to the LC where they are poised to coordinately impact LC functions (B. A. Reyes, Carvalho, et al.). We discovered that the DYN- κ -OR system regulates LC neurons at a presynaptic level, inhibiting excitatory afferent input (A. S. Kreibich et al., 2008). In addition to presynaptic modulation of glutamatergic and CRF afferents (A. S. Kreibich et al., 2008), we further demonstrated that κ -ORs modulate DYN afferents to the LC (B. A. Reyes et al., 2009) and that exposure to a κ -OR agonist induces internalization of κ -ORs and impacts cortical catecholaminergic expression levels (B. A. Reyes, Chavkin, & Van Bockstaele).

Figure 2.

Potential mechanisms underlying sensitization to stress following exposure to chronic morphine include: (1) increased CRFr on the plasma membrane arising from increased synthesis (1a), or altered trafficking to the membrane (1b) or decreased internalization (1c); (2) more efficient CRFr signaling by enhanced Gs coupling or stronger affinities for RGS-binding to positive regulators; or (3) increased CRF release from LC afferents. Future studies are required to establish which mechanism is involved.