Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Neurosci Res. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

J Neurosci Res. 2017 June ; 95(6): 1336–1346. doi:10.1002/jnr.23956.

The Noradrenergic Locus Coeruleus as a Chronic Pain Generator

Bradley K. Taylor[*] and **Karin N. Westlund**

Department of Physiology, School of Medicine, University of Kentucky Medical Center, Lexington, KY 40536

Abstract

Central noradrenergic centers such as the locus coeruleus are traditionally viewed as pain inhibitory; however, complex interactions among brainstem pathways and their receptors modulate both inhibition and facilitation of pain. In addition to the well-described role of descending pontospinal pathways that inhibit spinal nociceptive transmission, an emerging body of research now indicates that noradrenergic neurons in the locus coeruleus (LC) and their terminals in the dorsal reticular nucleus (DRt), medial prefrontal cortex (mPFC), spinal dorsal horn and trigeminal spinal nucleus caudalis (spVc) participate in the development and maintenance of allodynia and hyperalgesia after nerve injury. With time after injury, we argue that the balance of LC function shifts from pain inhibition to pain facilitation. Thus, the pain inhibitory actions of antidepressant drugs achieved with elevated noradrenaline concentrations in the dorsal horn may be countered or even superseded by simultaneous activation of supraspinal facilitating systems dependent on α_1-adrenoreceptor in the DRt and mPFC as well as α_2-adrenoreceptors in the LC. Indeed, these opposing actions may account in part for the limited treatment efficacy of tricyclic antidepressants and noradrenaline reuptake inhibitors such as duloxetine for the treatment of chronic pain. We propose that the traditional view of the LC as a pain inhibitory structure be modified to account for its capacity as a pain facilitator. Future studies are needed to determine the neurobiology of ascending and descending pathways and the pharmacology of receptors underlying LC-mediated pain inhibition and facilitation.

INTRODUCTION

Patients describe chronic neuropathic pain as unrelenting, excruciating, and/or burning. Monotherapies such as analgesics, antidepressants, and anticonvulsants offer only modest therapeutic benefit for some types of neuropathic pain, and no efficacy at all for many patients (Finnerup et al. 2015). Efficacy of current therapies for chronic low back and

[*]**Corresponding author:** Bradley K Taylor, University of Kentucky Medical Center, 800 Rose Street, Department of Physiology, Lexington, KY 40536-0298, Tel: 859 323 1870, Fax: 859 323 1070, brad.taylor@uky.edu, http://www.mc.uky.edu/physiology/people/taylor.asp.

Associate Editor: Tuan Trang

Role of Authors

BKT and KNW contributed to literature review, drafting of the manuscript, and critical revision of the manuscript.

Conflict of Interest Statement

Neither author has conflicts to disclose

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

trigeminal neuropathic pain, in particular, remains low (Baron et al. 2016). For example, only 11% of patients with painful traumatic trigeminal neuropathy responded to pharmacotherapy with a greater than 50% reduction in pain intensity (Haviv et al. 2014). Opiates are the most highly efficacious analgesic drugs available, but their use for neuropathic pain in particular remains controversial since they lack efficacy at the doses usually used for other pain syndromes. Their chronic administration can lead to tolerance, physical dependence and opioid-induced hyperalgesia (Mehendale et al. 2013), as well as a constellation of side effects including drowsiness, fatigue, constipation, nausea, organ damage, and even misuse and diversion. Consequently, the management of patients with neuropathic pain remains a significant challenge (Romero-Reyes et al. 2013).

A large body of basic research suggest that pain inhibitory systems, descending from the brainstem, involve noradrenergic inhibition of spinal nociceptive transmission (Fields et al. 1991; Millan 2002). Antidepressants (amitriptyline and duloxetine) and spinal clonidine, thought to target and mimic these noradrenergic analgesic systems, have become first-line treatments for clinical neuropathic pain (Dworkin et al. 2007). For unknown reasons, however, their efficacy has been quite disappointing. Indeed, animal studies suggest that analgesic efficacy, quite powerful soon after an injury, is lost as time goes by (Llorca-Torralba et al. 2016). An important clue for this lack of efficacy is that noradrenergic α_2-adrenoreceptor signaling at the spinal cord does not simply reduce acute nociceptive responses. In the setting of neuropathic pain, they also exert opposing α_2-adrenoreceptor mediated facilitatory signaling by autoreceptors (or indirect activation) at the pontine brainstem level which negates the effectiveness of noradrenergic antagonists during sustained nerve injury (Wei and Pertovaara 2006).

The brainstem centers that provide noradrenergic input are widely thought to be pain inhibitory. The locus coeruleus (LC), containing by far the greatest number of noradrenergic neurons in the brain, could be described by many as a “pain suppressor”. We refer the reader to excellent comprehensive overviews of the basic science that describes the contribution of the LC to the inhibition of acute and chronic pain (Llorca-Torralba et al. 2016; Pertovaara 2013). By contrast, the current review argues that, after traumatic nerve injury, the LC is not an inhibitor but instead becomes a chronic neuropathic “pain generator”. In support of this opposing position, we emphasize two of our own studies, using standard models of neuropathic pain following traumatic injury to the sciatic or trigeminal nerves (Brightwell and Taylor 2009; Kaushal et al. 2016), as well as several others. This topic is interesting given our stance that facilitation increases over time after nerve injury, and the lack of knowledge surrounding the underlying mechanisms that cause the transition from acute to chronic pain. Recognition of the pain facilitatory component of the LC will expedite the development of more efficacious noradrenergic therapies for the treatment of neuropathic pain.

Mechanisms underlying neuropathic pain and its inhibition

Neuroplastic and glial changes after nerve injury increase the CNS expression and/or activity of voltage- and ligand-gated ion channels, peptide receptors, and neuro-immune factors that then drive dorsal horn neuronal hyperexcitability (Taylor 2009). Net

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

hyperexcitability is determined by numerous factors, including alterations in the activity of local excitatory and inhibitory neurotransmitter systems, together with ongoing/evoked primary afferent activity, as well as descending supraspinal controls (Taylor 2009). Supraspinal endogenous inhibitory systems serve as opposing compensatory influences, and are gaining recognition for their powerful capacity to restrain allodynia and hyperalgesia (Taylor 2009). However, we and others propose that excessive down-regulation or defective compensatory up-regulation of these systems at prolonged time points after nerve injury contribute to the maintenance of neuropathic pain. Therefore, a valuable strategy for the development of new and effective analgesics for neuropathic pain is to mimic and enhance inhibitory neurotransmission arising from the brain. While most attention was paid initially to the inhibitory capacity of the rostral ventral medulla (RVM), there has been a resurging interest in other brain systems, including the LC. The studies reviewed here suggest that development of pharmacological agents to diminish noradrenergic NAα1 signaling will effectively reduce chronic neuropathic pain. The rationale for this proposal is provided below.

The LC is anatomically and physiologically poised as a critical modulator of acute and persistent pain

Neuroanatomy of pain-related inputs to and projections from the LC—The neuronal pathways and structures innervated and activated by the noradrenergic system are complex. The major contributor, the LC, is the tightly packed A6 noradrenergic group of neurons located at the lateral edge of the pontine gray matter. The LC is a heterogenous nucleus comprised of distinct subdivisions along the dorsoventral and rostrocaudal axes that project to distinct regional targets (Mason and Fibiger 1979). The dendrites of the LC and other noradrenergic cells are heavily innervated and activated by ascending spinothalamic tract neuron axons as they bring information about pain through the brainstem (Panneton et al. 2011; Westlund and Craig 1996).

LC neurons form an elaborate network of ascending and descending projections (Grzanna and Molliver 1980). Ascending axons of noradrenergic LC neurons project to specific regions of the CNS including thalamus, forebrain limbic medial prefrontal cortex, anterior cingulate cortex, hippocampus, hypothalamus, amygdala, and cerebellum, while descending axons of noradrenergic cell subgroups in the pons target pain pathway circuitry at the spinal dorsal horn and trigeminal nerve entry zone in spinal caudalis (spVc) (Agster et al. 2013; Jones and Moore 1977; Loughlin et al. 1986a; Loughlin et al. 1986b; Mason and Fibiger 1979; Millan 2002; Panneton et al. 2011; Westlund and Coulter 1980; Westlund and Craig 1996). Spinal and trigeminal dorsal horn noradrenaline is derived from the terminals of descending axons originating primarily from the locus coeruleus (A6) noradrenergic pontospinal neurons, but also from the A5 and A7 noradrenergic cell groups in the lateral and ventral pons (Westlund et al. 1983). Spinothalamic tract neurons in the dorsal horn receive direct innervation by noradrenergic terminal endings (Westlund et al. 1990).

Neurophysiology of noxious stimulus-evoked activation of the LC—Noxious stimulation activates LC neurons, and their excitability is particularly high in the setting of neuropathic pain (Martins et al. 2015). Sensory signal processing is continually altered over

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the range of tonic LC discharge frequency with phasic bursts establishing a relationship to sensory-stimulus intensity (Devilbiss and Waterhouse 2004; Devilbiss and Waterhouse 2011). In the absence of injury, noxious heat or chemical stimulation increases the firing of LC neurons, most recently described by Pickering and colleagues (Hickey et al. 2014). These authors also reported previously that noxious intraplantar injection of dilute formalin-evoked Fos expression in 16% of noradrenergic coeruleospinal neurons, identified upon co-labeling with eFGP that had been retrogradely transported following intraparencymal injection of AVV-PRS-EGFP adenoviral vector into the L4–L5 dorsal horn (Howorth et al. 2009a). As illustrated in Figure 1, we reported that activation was increased throughout the rostro-caudal extent of the LC denoted by the increased expression of phosphorylated CREB (pCREB) and Fos (Brightwell and Taylor 2009). This followed non-noxious tactile hindpaw stimulation of the spared sural nerve innervation territory after a spared nerve injury (SNI) involving transection of the tibial and common peroneal branches of the sciatic nerve, leaving the sural nerve intact. Indeed, the pCREB and Fos markers of neuronal activity correlated with the intensity of the tactile allodynia, suggesting a strong relationship between LC function and neuropathic pain (Brightwell and Taylor 2009).

Descending noradrenergic projections from the LC provide endogenous inhibition of neuropathic pain

In the absence of injury, descending noradrenergic projections to the spinal cord were described anatomically (Kwiat and Basbaum 1992; Westlund and Coulter 1980) and were neurophysiologically characterized as pain inhibitory by Jones and Gebhart, who reported that electrical stimulation of the LC reduced heat stimulus-evoked activity of dorsal horn neurons in anesthetized rats (Jones and Gebhart 1986; Jones and Gebhart 1987). Subsequent studies in awake animals often conclude that tonic or transient activation of pontospinal noradrenergic brain centers reduces acute nociception (Martin et al. 1999), as reviewed extensively by Millan (Millan 2002). There is notable exception to this. Extensive depletion of NE with electrolytic or noradrenergic lesions of the LC often do not increase transient reflex responses to noxious stimulation in uninjured rats, arguing against the idea that tonic noradrenergic transmission has an effect in non-pathological pain states (Hayashida et al. 2012; Jasmin et al. 2003; Martin et al. 1999; Taylor et al. 2000; West et al. 1993).

In contrast to the debatable contribution of tonic CNS noradrenergic transmission to transient nociception, it is well accepted that the LC is capable of engaging systems that promote the feedback inhibition of the persistent nociception that arises after tissue or nerve injury. For example, electrolytic lesions of the LC and subcoeruleus increases inflammation-induced behavioral and dorsal horn neuronal responsiveness to heat stimulation (Tsuruoka et al. 2003; Tsuruoka and Willis 1996a; Tsuruoka and Willis 1996b; Wei et al. 1999). More recently, Pickering and colleagues reported that molecular genetic silencing of pontospinal noradrenergic neurons with an AVV-PRS-hKir$_{2.1}$ adenoviral vector produced heat (but not mechanical) hypersensitivity, and increased the heat (but not mechanical) hypersensitivity associated with the inflammation produced by the intraplantar injection of complete Freund's adjuvant (Howorth et al. 2009b). Similarly, the AVV-PRS-hKir$_{2.1}$ vector increased noxious stimulus-evoked behavior and Fos expression in the dorsal horn following intraplantar injection of dilute formalin (Howorth et al. 2009b). They concluded that

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

pontospinal noradrenergic neurons (the specific contribution of the LC was not assessed) contribute to the tonic inhibition of specific types and modalities of pain, e.g. heat and chemical nociception as well as heat hypersensitivity after inflammation. By contrast, however, Martin *et al* and Taylor *et al* found that the selective destruction of noradrenergic neurons with intrathecal or intracerebroventricular administration of the neurotoxin saporin conjugated to anti-dopamine-beta-hydroxylase (anti-DBH-saporin) reduced rather than increased formalin-induced nociception (Martin et al. 1999; Taylor et al. 2000). At the time, these findings were quite unexpected, and suggested that the LC could serve a pain facilitatory function. Further studies are still needed to distinguish the neuroanatomical characteristics of the pain-reducing and pain-enhancing actions of the LC in the modulation of inflammatory pain.

As with inflammatory pain, there is strong consensus that an important neuropathic pain-related function of the LC is to promote feedback inhibition. One premise for this is that targeted ablation of descending noradrenergic neurons with the intrathecal administration of anti-DBH-saporin produced an increase in mechanical hypersensitivity after nerve injury (Hayashida et al. 2012; Jasmin et al. 2003; Llorca-Torralba et al. 2016). Another premise is that spinal delivery of α_2-adrenergic receptor agonists reduce signs of neuropathic pain in both animals and humans (Baba et al. 2000; Kawasaki et al. 2003). Intrathecal injection of the α_2-adrenoreceptor antagonist yohimbine produced hyperalgesia on the limb contralateral to tibial nerve transection as well as Fos expression in the dorsal horn, suggesting that pontospinal noradrenergic inhibition masks contralateral hyperalgesia (Hughes et al. 2013). This mechanism is likely restricted to the spinal cord.

Unlike the opioids which produce both analgesic effects in the uninjured subject (increased response threshold to a noxious stimulus above baseline threshold), as well as antihyperalgesic effects in the injury state (return of response threshold to baseline), the effects of amitryptaline and duloxetine only exert antihyperalgesic effects. To explain the targeting of these drugs specifically to the injured state, Hayashida and Eisenach proposed that nerve injury induces the spinal release of BDNF, which then drives sprouting of terminals from descending noradrenergic fibers (Hayashida et al. 2008a). In addition, nerve injury increases the efficacy of G-protein coupling to spinal α_2-adrenoceptors (Bantel et al. 2005). An intriguing idea is that nerve injury leads to a pharmacological plasticity, whereby increased inhibitory noradrenergic innervation, release, and receptor efficacy would lead to the antihyperalgesic effects of duloxetine.

Hayashida and others have posited that gabapentin activates noradrenergic neurons in the locus coeruleus (LC) to induce spinal noradrenaline release that in turn stimulates α_2-adrenoreceptors, leading to analgesia (Hayashida et al. 2007a; Hayashida et al. 2008b; Hayashida et al. 2007b; Takasu et al. 2006). Recently they discovered that gabapentin decreased extracellular GABA and increased extracellular glutamate in the LC, the latter by a glutamate transporter-1 dependent mechanism, to stimulate descending noradrenergic inhibition in neuropathic rats (Suto et al. 2014; Yoshizumi et al. 2012). Furthermore, they found that glutamate transporter GLT-1 expression is decreased several weeks after peripheral nerve injury (Kimura et al. 2015), thus explaining in part the loss of gabapentin's antihyperalgesic efficacy over time after nerve injury (Kimura et al. 2016).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

As alluded to above, however, not all studies agree with the tenet that nerve injury is necessarily and only associated with an upregulation of descending pain inhibitory noradrenergic controls. For example, some studies indicate that there is a deficit in the activity of the descending noradrenergic system in neuropathic pain models. Spinal antinociception induced by electrical stimulation of the LC was significantly weaker in nerve-injured than control animals (Viisanen and Pertovaara 2007). Furthermore, peripheral nerve injury resulted in the suppression of noradrenergic spinal α_2-adrenoceptor-mediated inhibition of spinal dorsal horn neuronal activity evoked by low-intensity mechanical stimuli (Rahman et al. 2008). These results suggest that nerve injury may enhance inhibition of the LC, thereby suppressing noradrenergic pain inhibition and promoting neuropathic pain. Most recently, expression of inwardly rectifying K+ channel $hKir_{2.1}$ in the pontospinal noradrenergic neurons before SNI did not have a demonstrable hyperalgesic effect (Howorth et al. 2009b). These results led Pickering and colleagues to suggest that the level of ongoing tonic activity in the noradrenergic system may be insufficient to suppress established neuropathic allodynia, but may be able to play a role in ameliorating the expression of less severe neuropathic pain phenotypes (Howorth et al. 2009b). Alternatively, based on the finding that intrathecal injection of the α_2-adrenoreceptor antagonist yohimbine suppressed hyperalgesia only when injected at early time points after SNI (Days 3–5), but had little effect on established hyperalgesia when delivered at later timepoints (days 10–17), the contribution of descending noradrenergic pain inhibitory controls may be transient, restricted to the earlier periods of neuropathic pain (Hughes et al. 2013). Taken together with the results of our laboratories, described below, we propose that the net effect of the noradrenergic LC activation on neuropathic pain shifts over time, beginning with a profound inhibition mediated by descending projections from the ventral LC to the DRt and dorsal horns, and ending with pain chronicity mediated by cerebral projections from the dorsal LC to the mPFC. This shift to pain facilitation ostensibly contributes as an underlying mechanism in the transition from acute to chronic pain.

Noradrenergic projections from the LC facilitate neuropathic pain

Although coeruleospinal activity has been predominantly associated with inhibition of neuropathic pain, there is growing evidence to suggest that descending and ascending projections from the LC contribute to an opposing facilitation of neuropathic pain, particularly at later time points after nerve injury. An early clue came from studies of autotomy (self-destructive behavior thought by some to reflect neuropathic pain, though this is controversial) following transection of the sciatic and saphenous nerves. Systemic ablation of noradrenergic neurons with intraperitoneal injection of DSP4 reduced autotomy (Al-Adawi et al. 2002). To rigorously test the hypothesis that noradrenergic neurons contribute to the development of neuropathic pain, we selectively destroyed these neurons with delivery of anti-dopamine-β-hydroxylase saporin (anti-DβH-saporin) into the intracerebroventricular space. Anti-DBH-saporin is taken up by noradrenergic nerve endings, resulting in selective ablation of noradrenergic neurons (Wrenn et al. 1996). Anti-DBH-saporin was administered either two weeks before SNI, or three weeks after induction of a model of trigeminal neuropathic pain involving chronic constriction injury of the infraorbital nerve (CCI- ION), the second branch of the trigeminal nerve coursing across the maxillary bone under the orbit (Vos and Strassman 1995; Vos et al. 1994). Pre-SNI treatment with anti-DβH-saporin but not

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

control IgG-saporin reduced behavioral signs of mechanical and cold allodynia (Figure 2), a preventative effect that lasted for at least one month after SNI (Brightwell and Taylor 2009).

These findings support the idea that central noradrenergic neurons contribute to the development of neuropathic pain. To test the hypothesis that these neurons also contribute to the maintenance of neuropathic pain, we performed the SNI model, waited two weeks for maximal allodynia and hyperalgesia to develop, and then disrupted synaptic activity with the microinjection of the local anaesthetic (lidocaine) directly into the LC parenchyma. As illustrated in Figure 3, from (Brightwell and Taylor 2009), lidocaine reduced all behavioral signs of neuropathic pain in a reversible manner, suggesting that the LC contributes to pain facilitation.

Similarly, intracerebroventricular administration of anti-DβH-saporin but not control IgG-saporin, given three weeks ***after*** CCI-ION surgery, reduced behavioral signs of mechanical hypersensitivity for at least one month after initiation of treatment (Kaushal et al. 2016). Taken together, these data indicate that the LC facilitates both the development and maintenance of neuropathic pain following injury to the sciatic or trigeminal nerves (Brightwell and Taylor 2009; Kaushal et al. 2016). However, because intracerebroventricular injection of anti-DBH saporin will disrupt both ascending (e.g. A1 and A2) as well as descending (A5, A6, A7) noradrenergic pathways, further studies were required to determine if the LC contributes to allodynia or hyperalgesia via ascending projections, lateral projections to other brainstem sites, or descending projections to the spinal cord. Emerging studies are beginning to answer this question, as outlined in the next section.

Neural pathways of neuropathic pain facilitation by the LC: Projections to DRt, mPFC, and the spinal trigeminal nucleus

Some of the complex interactions among brainstem pathways that modulate both inhibition and facilitation of pain are detailed below.

Facilitation via the dorsal reticular nucleus (DRt)—A pain facilitatory circuit comprised of the LC, DRt, and spinal cord plays an important role in descending pain facilitation. The DRt receives noradrenergic innervation from the LC and the A5 noradrenergic cell groups (Almeida et al. 2002). Noradrenergic innervation of DRt contributes to the facilitation of pain transmission at the dorsal horn (Lima and Almeida 2002). Local manipulations to the DRt that decreased noradrenaline levels (with viral vector-mediated delivery of tyrosine hydroxylase antisense) or increased noradrenaline levels (with the reuptake inhibitory nomifensine) attenuated or augmented neuropathic pain induced nociceptive behaviors, respectively (Martins et al. 2010; Martins et al. 2013). Microinjection of the α_1-adrenoceptor antagonist prazosin but not the α_2-adrenoceptor antagonist atipamezole decreased SNI-induced hypersensitivity to noxious mechanical or cold stimulation, indicating α_1- but not α_2-adrenoreceptors mediate pain facilitation from the DRt (Martins et al. 2015). These data demonstrate that noradrenergic innervation is involved in triggering descending facilitation from the DRt (Martins et al. 2010; Martins et al. 2013), and raise the interesting idea that the LC exerts an indirect pro-nociceptive effect due to its projections to the DRt (Martins et al. 2013).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Facilitation via ascending noradrenergic pathways—A major noradrenergic efferent pathway from the locus coeruleus includes the projection to the medial prefrontal cortex (mPFC) (Aston-Jones and Cohen 2005; Aston-Jones et al. 1984), an important site of activation in chronic pain patients. In humans, the mPFC is a key neural region activated by sustained nociceptive input during the transition from acute nociceptive processing to central generation of pain based on numerous fMRI studies (Apkarian et al. 2013; Baliki et al. 2006; Baliki et al. 2012). In rodents, unilateral electrical stimulation of the LC elicits bilateral LC activation and sustained activation of the mPFC (Marzo et al. 2014). Therefore, to determine the contribution of LC ➔ mPFC projections to trigeminal neuropathic pain, α_1- and α_2-adrenergic receptor antagonists (benoxathian and idazoxan hydrochloride, respectively) were microinjected directly into the mPFC to block the effects of noradrenergic input (Kaushal et al. 2016). Benoxathian but neither vehicle nor idazoxan alleviated mechanical hypersensitivity associated with CCI-ION, suggesting that α_1-adrenoreceptors in the medial prefrontal cortex contribute to the facilitative effect of noradrenergic LC neurons in chronic orofacial neuropathic pain (Kaushal et al. 2016).

The LC regulates numerous interlinked functions including attention, sleep– wake cycles, mood, cognitive performance, and motivation (Berridge and Waterhouse, 2003; Jones, 2003; Sara, 2009). Within this framework, Pickering and colleagues hypothesized that the pro-nociceptive actions of the LC may be mediated by a subset of neurons that are also responsible for promoting wakefulness and attention (Carter et al., 2010), as part of a system to focus cognitive resources (Hickey et al. 2014); indeed, the LC-mPFC circuit optimizes behaviorally-relevant, cognitive functions (Aston-Jones and Cohen 2005; Marzo et al. 2014). For example, salient internal or external events can alter function or “reset” large-scale neural populations. This can be mediated by the targeted release of noradrenaline in the mPFC and can then shift the excitatory/inhibitory balance of the mPFC to a more excitable state. Therefore, we speculate that trigeminal nerve injury shifts pain modulation within the noradrenergic LC-mPFC circuit from inhibition to excitation; that perhaps while the LC typically functions through α_2-adrenoreceptors to assist in homeostatic recovery and inhibition of pain, excess stress and noradrenaline release shifts noradrenergic binding to lower-affinity α_1-adrenoreceptors, resulting in pain facilitation and chronification.

Facilitation via descending noradrenergic pathways to the trigeminal spinal nucleus caudalis—As discussed earlier, tissue injury or nerve damage triggers early neuroplastic changes in descending noradrenergic projections from the brainstem to the dorsal horn that contribute to an endogenous feedback inhibition of pain. Normally, such mechanisms aid in the prevention of further injury, serving as a beneficial, adaptive mechanism in times of stress and/or danger (Millan 1999; Millan 2002). Most of the previous studies evaluated behavior for only 1–3 weeks after nerve injury, and none of them evaluated the contribution of descending noradrenergic systems in a model of trigeminal neuropathic pain. To address these questions, we ablated noradrenergic projection from the LC to the spinal trigeminal nucleus caudalis (spVc) with local microinjection of anti-DβH-saporin directly into the spVc. This was performed 2–3 weeks after CCI-ION, and then followed with the measurement of mechanical sensitivity to vibrissal stimulation with von Frey hairs for an additional 4 weeks (Kaushal et al. 2016). As illustrated in Figure 4, anti-

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

DβH-saporin significantly reduced mechanical hypersensitivity throughout the testing sessions, suggesting that descending noradrenergic projections to the trigeminal spinal nucleus caudalis contribute to the maintenance of chronic orofacial neuropathic pain.

Bidirectional modulation of pain by the LC

Based on all of the studies reviewed here, we propose that during intense or long-term activation after nerve injury, both descending pain modulatory outflows from the LC to the DRt, spinal cord and trigeminal dorsal horns, as well as ascending pain modulatory outflows from the LC to the mPFC become predominantly facilitatory (Figure 5). In summary, under certain conditions intense or long-term sensory stimulation invokes mechanisms that are yet to be determined to produce CNS nociceptive facilitation that can persist long after the injury has healed; thereby intense or long-term sensory activation contributes as an underlying mechanism to pathological central sensitization that drives the neural and behavioral manifestations of chronic pain.

In the absence of injury, Pickering and colleagues used an optogenetic approach to reveal a bidirectional modulation of neuronal responses in LC to heat stimuli (Hickey et al. 2014). They concluded that the pronociceptive and antinociceptive actions are mediated by distinct subpopulations of LC neurons, with the antinociceptive effect originating from neurons in the ventral region of the LC and subcoeruleus that project to the dorsal horn of the spinal cord (Bruinstroop et al. 2012; Howorth et al. 2009a; Loughlin et al. 1986a; Westlund et al. 1983). This implies that pronociceptive effects would originate from neurons localized more dorsally in the LC. By contrast, both inhibitory and facilitatory effects of the RVM, another structure responsible for the bidirectional modulation of pain, are thought to be mediated by interspersed bulbospinal projections from pain inhibitory (OFF-cell) and excitatory (ON-cell) projection neurons that both receive direct noradrenergic innervation (Heinricher et al. 2009; Meng et al. 1997; Porreca et al. 2002; Suzuki et al. 2004).

Another contrast between the LC and RVM are differences in the time-dependent features of their activity. Porreca and colleagues reported that dermorphin-saporin ablations of RVM neurons containing the mu opioid receptor (Porreca et al. 2001) or lidocaine inactivation of the RVM (Burgess et al. 2002) reduced mechanical hypersensitivity at late but not early time points after spinal nerve ligation. By contrast, the results of LC neurotoxin and microinjection studies suggest that the LC instead contributes to both the maintenance and initiation of neuropathic pain (Brightwell and Taylor 2009; Kaushal et al. 2016). Regardless of these differences, a dynamic balance between inhibitory and excitatory outflows from pain modulatory centers including the LC, RVM, periaqueductal gray, DRt, and ventrolateral medulla likely set the gain of nociceptive processing (Heinricher et al. 2009), thereby determining the presence or absence of neuropathic pain after nerve injury. Additionally, we proposed above that the net effect of the noradrenergic LC activation on neuropathic pain shifts over time, beginning with inhibition mediated by descending projections from the ventral LC to the dorsal horn, and then, within a month, switching to facilitation mediated by ascending projections from the dorsal LC to the mPFC (Brightwell and Taylor 2009; Kaushal et al. 2016). This is analogous to the thesis of Ren and Dubner, who argued that descending modulatory RVM neurons undergo a time-dependent phenotypic switch

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

following persistent inflammaton (Dubner 2004; Ren and Dubner 2002). These shifts to pain facilitation ostensibly contribute to the transition from acute to chronic pain.

It is well known that the LC is compartmentalized within its rostrocaudal extent – descending noradrenergic neurons are primarily localized in the caudal LC while ascending projections primarily originate in more rostral LC (Jones and Moore 1977; Millan 2002). While highly disputed, the possibility remains that caudally-located, spinally-projecting LC neurons send collateral projections to supraspinal sites such as the mPFC, or, that dorsal rostrally-projecting LC neurons send collaterals to spinal sites such as the dorsal horn (Guyenet, 1980; Leanza et al., 1989; Howorth et al. 2009a) (Figure 5). Alternatively, others postulate that activation in one part of the LC can spread throughout the LC through membrane-to-membrane cellular electrotonic coupling (Ishimatsu and Williams, 1996). Moreover, as noted above, peripheral nerve injury is associated with stimulus-induced activation of both caudally- and rostrally-located neurons within the LC (Brightwell and Taylor 2009) (Figure 1, 4). An incomplete understanding of multilevel influences across the rostrocaudal extent of the LC during pain processing and its resultant multireceptor impact on both ascending and descending CNS systems poses a particularly interesting but challenging problem for future research.

Clinical Implications

The contribution of central noradrenergic systems to the modulation of neuropathic pain has attracted considerable attention as noradrenergic reuptake inhibitors such as duloxetine are sometimes effective (Brecht et al. 2007) and are amongst the most highly prescribed drugs for chronic pain (Attal et al. 2010; Sindrup et al. 2005). However, the LC α_2-adrenoreceptors can no longer be considered as a “pure” target for inhibitory pain modulation. The pain inhibitory actions of antidepressant drugs achieved with elevated noradrenaline concentrations in the dorsal horn may be opposed by simultaneous activation of supraspinal facilitating systems dependent on α_1-adrenoceptors in the DRt and mPFC (Kaushal et al. 2016) and α_2-adrenoceptors in the LC (Wei and Pertovaara 2006). Indeed, these opposing actions may account in part for the limited efficacy of tricyclic antidepressants and noradrenaline reuptake inhibitors in the treatment of chronic pain (Finnerup et al. 2010). Recognition of the pain facilitatory component of the LC will expedite the development of more efficacious therapies targeted to α_1- and α_2-adrenoceptors for the treatment of neuropathic pain.

Acknowledgments

This review is dedicated to the memory of Jennifer Brightwell, a talented young neuroscientist and pioneer in the study of noradrenergic pain facilitation.

Grant Information: NIH DA37621 to BKT and VA Merit BX002695 to KW

References

Agster KL, Mejias-Aponte CA, Clark BD, Waterhouse BD. Evidence for a regional specificity in the density and distribution of noradrenergic varicosities in rat cortex. J Comp Neurol. 2013; 521(10): 2195–2207. [PubMed: 23184811]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Al-Adawi S, Dawe GS, Bonner A, Stephenson JD, Zarei M. Central noradrenergic blockade prevents autotomy in rat: implication for pharmacological prevention of postdenervation pain syndrome. Brain Res Bull. 2002; 57(5):581–586. [PubMed: 11927359]

Almeida A, Cobos A, Tavares I, Lima D. Brain afferents to the medullary dorsal reticular nucleus: a retrograde and anterograde tracing study in the rat. Eur J Neurosci. 2002; 16(1):81–95. [PubMed: 12153533]

Apkarian AV, Neugebauer V, Koob G, Edwards S, Levine JD, Ferrari L, Egli M, Regunathan S. Neural mechanisms of pain and alcohol dependence. Pharmacology, biochemistry, and behavior. 2013; 112:34–41.

Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annual review of neuroscience. 2005; 28:403–450.

Aston-Jones, G., Foote, SL., Bloom, FE. Anatomy and physiology of locus coeruleus neurons: functional implications. Baltimore: Williams and Wilkins; 1984. p. 92-116.

Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, European Federation of Neurological S. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010; 17(9):1113–e1188. [PubMed: 20402746]

Baba H, Shimoji K, Yoshimura M. Norepinephrine facilitates inhibitory transmission in substantia gelatinosa of adult rat spinal cord (part 1): effects on axon terminals of GABAergic and glycinergic neurons. Anesthesiology. 2000; 92(2):473–484. [PubMed: 10691235]

Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, Apkarian AV. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2006; 26(47):12165–12173. [PubMed: 17122041]

Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci. 2012; 15(8):1117–1119. [PubMed: 22751038]

Bantel C, Eisenach JC, Duflo F, Tobin JR, Childers SR. Spinal nerve ligation increases alpha2-adrenergic receptor G-protein coupling in the spinal cord. Brain research. 2005; 1038(1):76–82. [PubMed: 15748875]

Baron R, Binder A, Attal N, Casale R, Dickenson AH, Treede RD. Neuropathic low back pain in clinical practice. European journal of pain. 2016; 20(6):861–873. [PubMed: 26935254]

Brecht S, Courtecuisse C, Debieuvre C, Croenlein J, Desaiah D, Raskin J, Petit C, Demyttenaere K. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. J Clin Psychiatry. 2007; 68(11):1707–1716. [PubMed: 18052564]

Brightwell JJ, Taylor BK. Noradrenergic neurons in the locus coeruleus contribute to neuropathic pain. Neuroscience. 2009; 160(1):174–185. [PubMed: 19223010]

Bruinstroop E, Cano G, Vanderhorst VG, Cavalcante JC, Wirth J, Sena-Esteves M, Saper CB. Spinal projections of the A5, A6 (locus coeruleus), and A7 noradrenergic cell groups in rats. J Comp Neurol. 2012; 520(9):1985–2001. [PubMed: 22173709]

Burgess SE, Gardell LR, Ossipov MH, Malan TP Jr, Vanderah TW, Lai J, Porreca F. Time-dependent descending facilitation from the rostral ventromedial medulla maintains, but does not initiate, neuropathic pain. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2002; 22(12):5129–5136. [PubMed: 12077208]

Devilbiss DM, Waterhouse BD. The effects of tonic locus ceruleus output on sensory-evoked responses of ventral posterior medial thalamic and barrel field cortical neurons in the awake rat. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2004; 24(48): 10773–10785. [PubMed: 15574728]

Devilbiss DM, Waterhouse BD. Phasic and tonic patterns of locus coeruleus output differentially modulate sensory network function in the awake rat. Journal of neurophysiology. 2011; 105(1):69–87. [PubMed: 20980542]

Dubner R. The neurobiology of persistent pain and its clinical implications. Suppl Clin Neurophysiol. 2004; 57:3–7. [PubMed: 16106600]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007; 132(3):237–251. [PubMed: 17920770]

Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. Annu Rev Neurosci. 1991; 14:219–245. [PubMed: 1674413]

Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015; 14(2):162–173. [PubMed: 25575710]

Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010; 150(3):573–581. [PubMed: 20705215]

Grzanna R, Molliver ME. The locus coeruleus in the rat: an immunohistochemical delineation. Neuroscience. 1980; 5(1):21–40. [PubMed: 6988734]

Haviv Y, Zadik Y, Sharav Y, Benoliel R. Painful traumatic trigeminal neuropathy: an open study on the pharmacotherapeutic response to stepped treatment. J Oral Facial Pain Headache. 2014; 28(1):52–60. [PubMed: 24482788]

Hayashida K, Clayton BA, Johnson JE, Eisenach JC. Brain derived nerve growth factor induces spinal noradrenergic fiber sprouting and enhances clonidine analgesia following nerve injury in rats. Pain. 2008a; 136(3):348–355. [PubMed: 17822849]

Hayashida K, DeGoes S, Curry R, Eisenach JC. Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. Anesthesiology. 2007a; 106(3):557–562. [PubMed: 17325515]

Hayashida K, Obata H, Nakajima K, Eisenach JC. Gabapentin acts within the locus coeruleus to alleviate neuropathic pain. Anesthesiology. 2008b; 109(6):1077–1084. [PubMed: 19034104]

Hayashida K, Parker R, Eisenach JC. Oral gabapentin activates spinal cholinergic circuits to reduce hypersensitivity after peripheral nerve injury and interacts synergistically with oral donepezil. Anesthesiology. 2007b; 106(6):1213–1219. [PubMed: 17525597]

Hayashida K, Peters CM, Gutierrez S, Eisenach JC. Depletion of endogenous noradrenaline does not prevent spinal cord plasticity following peripheral nerve injury. J Pain. 2012; 13(1):49–57. [PubMed: 22155404]

Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: Specificity, recruitment and plasticity. Brain Res Rev. 2009; 60(1):214–225. [PubMed: 19146877]

Hickey L, Li Y, Fyson SJ, Watson TC, Perrins R, Hewinson J, Teschemacher AG, Furue H, Lumb BM, Pickering AE. Optoactivation of locus ceruleus neurons evokes bidirectional changes in thermal nociception in rats. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2014; 34(12):4148–4160. [PubMed: 24647936]

Howorth PW, Teschemacher AG, Pickering AE. Retrograde adenoviral vector targeting of nociresponsive pontospinal noradrenergic neurons in the rat in vivo. J Comp Neurol. 2009a; 512(2):141–157. [PubMed: 19003793]

Howorth PW, Thornton SR, O'Brien V, Smith WD, Nikiforova N, Teschemacher AG, Pickering AE. Retrograde viral vector-mediated inhibition of pontospinal noradrenergic neurons causes hyperalgesia in rats. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2009b; 29(41):12855–12864. [PubMed: 19828800]

Hughes SW, Hickey L, Hulse RP, Lumb BM, Pickering AE. Endogenous analgesic action of the pontospinal noradrenergic system spatially restricts and temporally delays the progression of neuropathic pain following tibial nerve injury. Pain. 2013; 154(9):1680–1690. [PubMed: 23707289]

Jasmin L, Boudah A, Ohara PT. Long-term effects of decreased noradrenergic central nervous system innervation on pain behavior and opioid antinociception. J Comp Neurol. 2003; 460(1):38–55. [PubMed: 12687695]

Jones BE, Moore RY. Ascending projections of the locus coeruleus in the rat. II. Autoradiographic study. Brain research. 1977; 127(1):25–53. [PubMed: 301051]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Jones SL, Gebhart GF. Quantitative characterization of coeruleospinal inhibition of nociceptive transmission in the rat. J Neurophysiol. 1986; 56:1397–1410. [PubMed: 3025380]

Jones SL, Gebhart GF. Spinal pathways mediating tonic, coeruleospinal, and raphe-spinal descending inhibition in the rat. J Neurophysiol. 1987; 58:138–159. [PubMed: 3612222]

Kaushal R, Taylor BK, Jamal AB, Zhang L, Ma F, Donahue R, Westlund KN. GABA-A receptor activity in the noradrenergic locus coeruleus drives trigeminal neuropathic pain in the rat; contribution of NAalpha1 receptors in the medial prefrontal cortex. Neuroscience. 2016

Kawasaki Y, Kumamoto E, Furue H, Yoshimura M. Alpha 2 adrenoceptor-mediated presynaptic inhibition of primary afferent glutamatergic transmission in rat substantia gelatinosa neurons. Anesthesiology. 2003; 98(3):682–689. [PubMed: 12606912]

Kimura M, Eisenach JC, Hayashida KI. Gabapentin loses efficacy over time after nerve injury in rats: role of glutamate transporter-1 in the locus coeruleus. Pain. 2016

Kimura M, Suto T, Morado-Urbina CE, Peters CM, Eisenach JC, Hayashida K. Impaired Pain-evoked Analgesia after Nerve Injury in Rats Reflects Altered Glutamate Regulation in the Locus Coeruleus. Anesthesiology. 2015; 123(4):899–908. [PubMed: 26244888]

Kwiat GC, Basbaum AI. The origin of brainstem noradrenergic and serotonergic projections to the spinal cord dorsal horn in the rat. Somatosens Mot Res. 1992; 9(2):157–173. [PubMed: 1354402]

Lima D, Almeida A. The medullary dorsal reticular nucleus as a pronociceptive centre of the pain control system. Prog Neurobiol. 2002; 66(2):81–108. [PubMed: 11900883]

Llorca-Torralba M, Borges G, Neto F, Mico JA, Berrocoso E. Noradrenergic Locus Coeruleus pathways in pain modulation. Neuroscience. 2016

Loughlin SE, Foote SL, Bloom FE. Efferent projections of nucleus locus coeruleus: topographic organization of cells of origin demonstrated by three-dimensional reconstruction. Neuroscience. 1986a; 18(2):291–306. [PubMed: 3736860]

Loughlin SE, Foote SL, Grzanna R. Efferent projections of nucleus locus coeruleus: morphologic subpopulations have different efferent targets. Neuroscience. 1986b; 18(2):307–319. [PubMed: 3736861]

Martin WJ, Gupta NK, Loo CM, Rohde DS, Basbaum AI. Differential effects of neurotoxic destruction of descending noradrenergic pathways on acute and persistent nociceptive processing. Pain. 1999; 80(1–2):57–65. [PubMed: 10204718]

Martins I, Carvalho P, de Vries MG, Teixeira-Pinto A, Wilson SP, Westerink BH, Tavares I. Increased noradrenergic neurotransmission to a pain facilitatory area of the brain is implicated in facilitation of chronic pain. Anesthesiology. 2015; 123(3):642–653. [PubMed: 26146901]

Martins I, Costa-Araujo S, Fadel J, Wilson SP, Lima D, Tavares I. Reversal of neuropathic pain by HSV-1-mediated decrease of noradrenaline in a pain facilitatory area of the brain. Pain. 2010; 151(1):137–145. [PubMed: 20637543]

Martins I, de Vries MG, Teixeira-Pinto A, Fadel J, Wilson SP, Westerink BH, Tavares I. Noradrenaline increases pain facilitation from the brain during inflammatory pain. Neuropharmacology. 2013; 71:299–307. [PubMed: 23602988]

Marzo A, Totah NK, Neves RM, Logothetis NK, Eschenko O. Unilateral electrical stimulation of rat locus coeruleus elicits bilateral response of norepinephrine neurons and sustained activation of medial prefrontal cortex. Journal of neurophysiology. 2014; 111(12):2570–2588. [PubMed: 24671530]

Mason ST, Fibiger HC. Regional topography within noradrenergic locus coeruleus as revealed by retrograde transport of horseradish peroxidase. J Comp Neurol. 1979; 187(4):703–724. [PubMed: 90684]

Mehendale AW, Goldman MP, Mehendale RP. Opioid overuse pain syndrome (OOPS): the story of opioids, prometheus unbound. J Opioid Manag. 2013; 9(6):421–438. [PubMed: 24481931]

Meng XW, Budra B, Skinner K, Ohara PT, Fields HL. Noradrenergic input to nociceptive modulatory neurons in the rat rostral ventromedial medulla. J Comp Neurol. 1997; 377(3):381–391. [PubMed: 8989653]

Millan MJ. The induction of pain: an integrative review. Prog Neurobiol. 1999; 57(1):1–164. [PubMed: 9987804]

Millan MJ. Descending control of pain. Prog Neurobiol. 2002; 66(6):355–474. [PubMed: 12034378]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Panneton WM, Gan Q, Livergood RS. A trigeminoreticular pathway: implications in pain. PloS one. 2011; 6(9):e24499. [PubMed: 21957454]

Pertovaara A. The noradrenergic pain regulation system: a potential target for pain therapy. Eur J Pharmacol. 2013; 716(1–3):2–7. [PubMed: 23500194]

Porreca F, Burgess SE, Gardell LR, Vanderah TW, Malan TP Jr, Ossipov MH, Lappi DA, Lai J. Inhibition of neuropathic pain by selective ablation of brainstem medullary cells expressing the mu-opioid receptor. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2001; 21(14):5281–5288. [PubMed: 11438603]

Porreca F, Ossipov MH, Gebhart GF. Chronic pain and medullary descending facilitation. Trends in neurosciences. 2002; 25(6):319–325. [PubMed: 12086751]

Rahman W, D'Mello R, Dickenson AH. Peripheral nerve injury-induced changes in spinal alpha(2)-adrenoceptor-mediated modulation of mechanically evoked dorsal horn neuronal responses. J Pain. 2008; 9(4):350–359. [PubMed: 18226963]

Ren K, Dubner R. Descending modulation in persistent pain: an update. Pain. 2002; 100(1–2):1–6. [PubMed: 12435453]

Romero-Reyes M, Akerman S, Nguyen E, Vijjeswarapu A, Hom B, Dong HW, Charles AC. Spontaneous behavioral responses in the orofacial region: a model of trigeminal pain in mouse. Headache. 2013; 53(1):137–151. [PubMed: 22830495]

Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol. 2005; 96(6):399–409. [PubMed: 15910402]

Suto T, Severino AL, Eisenach JC, Hayashida K. Gabapentin increases extracellular glutamatergic level in the locus coeruleus via astroglial glutamate transporter-dependent mechanisms. Neuropharmacology. 2014; 81:95–100. [PubMed: 24495399]

Suzuki R, Rygh LJ, Dickenson AH. Bad news from the brain: descending 5-HT pathways that control spinal pain processing. Trends in pharmacological sciences. 2004; 25(12):613–617. [PubMed: 15530638]

Takasu K, Honda M, Ono H, Tanabe M. Spinal alpha(2)-adrenergic and muscarinic receptors and the NO release cascade mediate supraspinally produced effectiveness of gabapentin at decreasing mechanical hypersensitivity in mice after partial nerve injury. British journal of pharmacology. 2006; 148(2):233–244. [PubMed: 16582934]

Taylor BK. Spinal inhibitory neurotransmission in neuropathic pain. Curr Pain Headache Rep. 2009; 13(3):208–214. [PubMed: 19457281]

Taylor BK, Roderick RE, Basbaum AI. Brainstem noradrenergic control of nociception is abnormal in the spontaneously hypertensive rat. Neuroscience letters. 2000; 291(3):139–142. [PubMed: 10984626]

Tsuruoka M, Matsutani K, Inoue T. Coeruleospinal inhibition of nociceptive processing in the dorsal horn during unilateral hindpaw inflammation in the rat. Pain. 2003; 104(1–2):353–361. [PubMed: 12855345]

Tsuruoka M, Willis WD. Descending modulation from the region of the locus coeruleus on nociceptive sensitivity in a rat model of inflammatory hyperalgesia. Brain research. 1996a; 743(1–2):86–92. [PubMed: 9017234]

Tsuruoka M, Willis WD Jr. Bilateral lesions in the area of the nucleus locus coeruleus affect the development of hyperalgesia during carrageenan-induced inflammation. Brain research. 1996b; 726(1–2):233–236. [PubMed: 8836566]

Viisanen H, Pertovaara A. Influence of peripheral nerve injury on response properties of locus coeruleus neurons and coeruleospinal antinociception in the rat. Neuroscience. 2007; 146(4):1785–1794. [PubMed: 17445989]

Vos BP, Strassman AM. Fos expression in the medullary dorsal horn of the rat after chronic constriction injury to the infraorbital nerve. J Comp Neurol. 1995; 357(3):362–375. [PubMed: 7673473]

Vos BP, Strassman AM, Maciewicz RJ. Behavioral evidence of trigeminal neuropathic pain following chronic constriction injury to the rat's infraorbital nerve. The Journal of neuroscience: the official journal of the Society for Neuroscience. 1994; 14(5 Pt 1):2708–2723. [PubMed: 8182437]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Wei F, Dubner R, Ren K. Nucleus reticularis gigantocellularis and nucleus raphe magnus in the brain stem exert opposite effects on behavioral hyperalgesia and spinal Fos protein expression after peripheral inflammation. Pain. 1999; 80(1–2):127–141. [PubMed: 10204725]

Wei H, Pertovaara A. Spinal and pontine alpha2-adrenoceptors have opposite effects on pain-related behavior in the neuropathic rat. Eur J Pharmacol. 2006; 551(1–3):41–49. [PubMed: 17027962]

West WL, Yeomans DC, Proudfit HK. The function of noradrenergic neurons in mediating antinociception induced by electrical stimulation of the locus coeruleus in two different sources of Sprague-Dawley rats. Brain research. 1993; 626(1–2):127–135. [PubMed: 7904225]

Westlund KN, Bowker RM, Ziegler MG, Coulter JD. Noradrenergic projections to the spinal cord of the rat. Brain research. 1983; 263(1):15–31. [PubMed: 6839168]

Westlund KN, Coulter JD. Descending projections of the locus coeruleus and subcoeruleus/medial parabrachial nuclei in monkey: axonal transport studies and dopamine-beta-hydroxylase immunocytochemistry. Brain research. 1980; 2(3):235–264. [PubMed: 7470856]

Westlund KN, Craig AD. Association of spinal lamina I projections with brainstem catecholamine neurons in the monkey. Exp Brain Res. 1996; 110(2):151–162. [PubMed: 8836680]

Westlund KN, Sorkin LS, Ferrington DG, Carlton SM, Willcockson HH, Willis WD. Serotoninergic and noradrenergic projections to the ventral posterolateral nucleus of the monkey thalamus. J Comp Neurol. 1990; 295(2):197–207. [PubMed: 2358512]

Wrenn CC, Picklo MJ, Lappi DA, Robertson D, Wiley RG. Central noradrenergic lesioning using anti-DBH-saporin: anatomical findings. Brain research. 1996; 740(1–2):175–184. [PubMed: 8973812]

Yoshizumi M, Parker RA, Eisenach JC, Hayashida K. Gabapentin inhibits gamma-amino butyric acid release in the locus coeruleus but not in the spinal dorsal horn after peripheral nerve injury in rats. Anesthesiology. 2012; 116(6):1347–1353. [PubMed: 22487864]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

SIGNIFICANCE STATEMENT

Conventional wisdom suggests that the locus coeruleus, which contains 80% of noradrenaline-containing neurons in the brain, provides intrinsic inhibition of both acute and persistent pain. The present review challenges this tenet, arguing instead that, under conditions of nerve injury, the LC acquires additional functions including the facilitation of chronic pain. Such opposing mechanisms may explain the limited therapeutic efficacy of noradrenergic reuptake inhibitors, such as duloxetine, or tricyclic antidepressants, such as amitriptyline, for neuropathic pain. The studies presented here support the hypothesis that LC may be a pain generator important in the transition from acute to chronic pain, as well as during the maintenance of chronic pain. The determination of chronic pain generator mechanisms will aid in the development of non-opiate drugs that are effective, safe, non-addictive, and have few side effects. Long-term blockade of descending and ascending LC facilitation is proposed as a therapeutic goal with potential to speed recovery from chronic pain states, aid back-to-work rates, and decrease long-term health care costs.

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

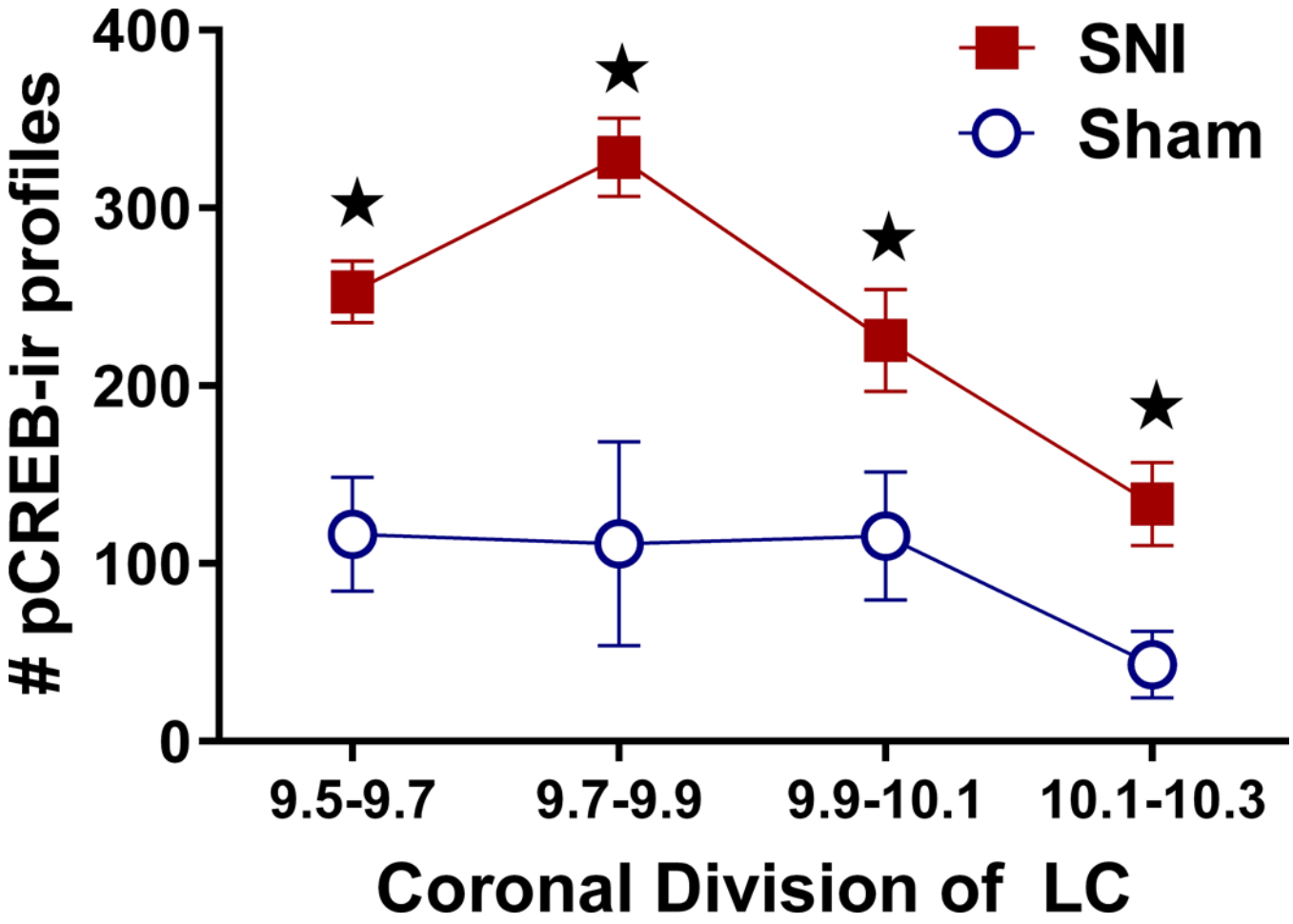

Figure 1. Nerve injury increases stimulus-induced pCREB expression throughout the rostrocaudal extent of the LC

Quantification of pCREB-immunoreactivity (pCREB-ir) in rat transverse slices was segregated by rostral-caudal level of the LC according to the stereotaxic atlas of Paxinos and Watson, relative to bregma (−9.48 to − 9.65; −9.65 to −9.0; −9.9 to −10.15; −10.15 to −10.32). Innocuous tactile stimulation of the footpad increased the number of pCREB-irprofiles two weeks after spared nerve injury (SNI) as compared to sham surgery. n=5–12. ★$p < 0.05$. (Brightwell and Taylor 2009).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

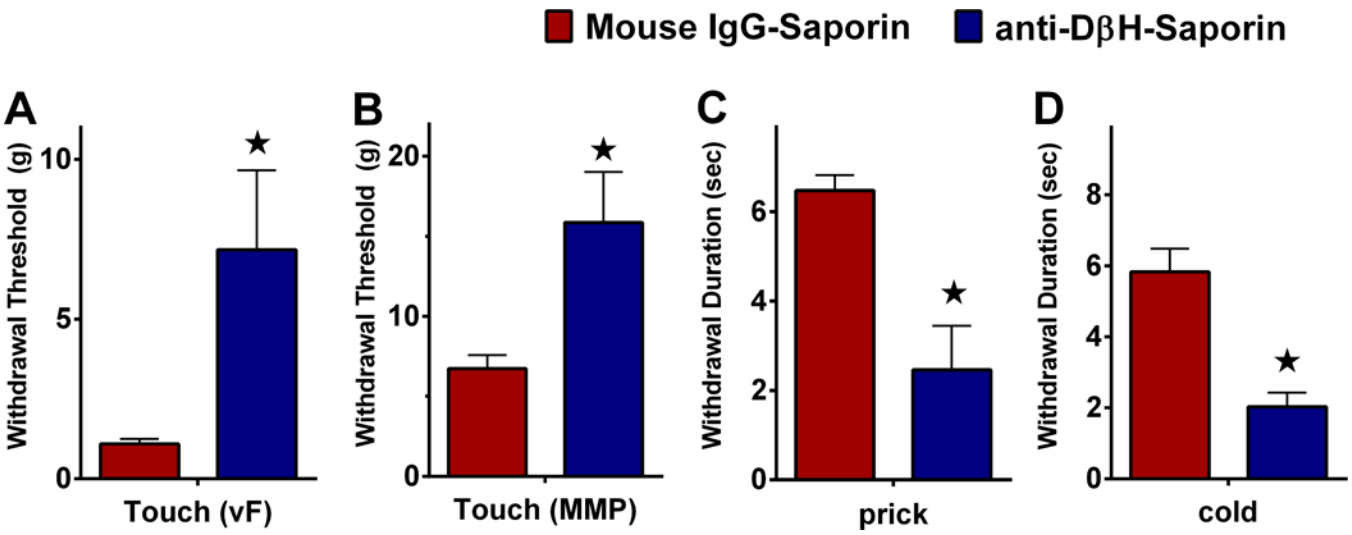

Figure 2. Ablation of noradrenergic neurons reduced multiple somatosensory modalities of nerve injury-induced hypersensitivity

Touch sensitivity was assessed as threshold response to plantar application of (A) von Frey hairs or (B) a machine-mounted probe, MMP, also known as a dynamic plantar anesthesiometer. Noxious tactile sensitivity sensitivity was assessed as paw withdrawal response duration to gentle application of the sharp edge of a diaper pin. Cold sensitivity was assessed as paw withdrawal duration to topical plantar acetone. Intracerebroventricular injection of anti-DβH-saporin but not IgG control reduced all behavioral signs of neuropathic pain [★*p*'s < 0.05, post-hoc Bonferroni subsequent to ANOVA]. Values represent mean ± SEM. n=4. For further details see Brightwell and Taylor, 2009. (Brightwell and Taylor 2009)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

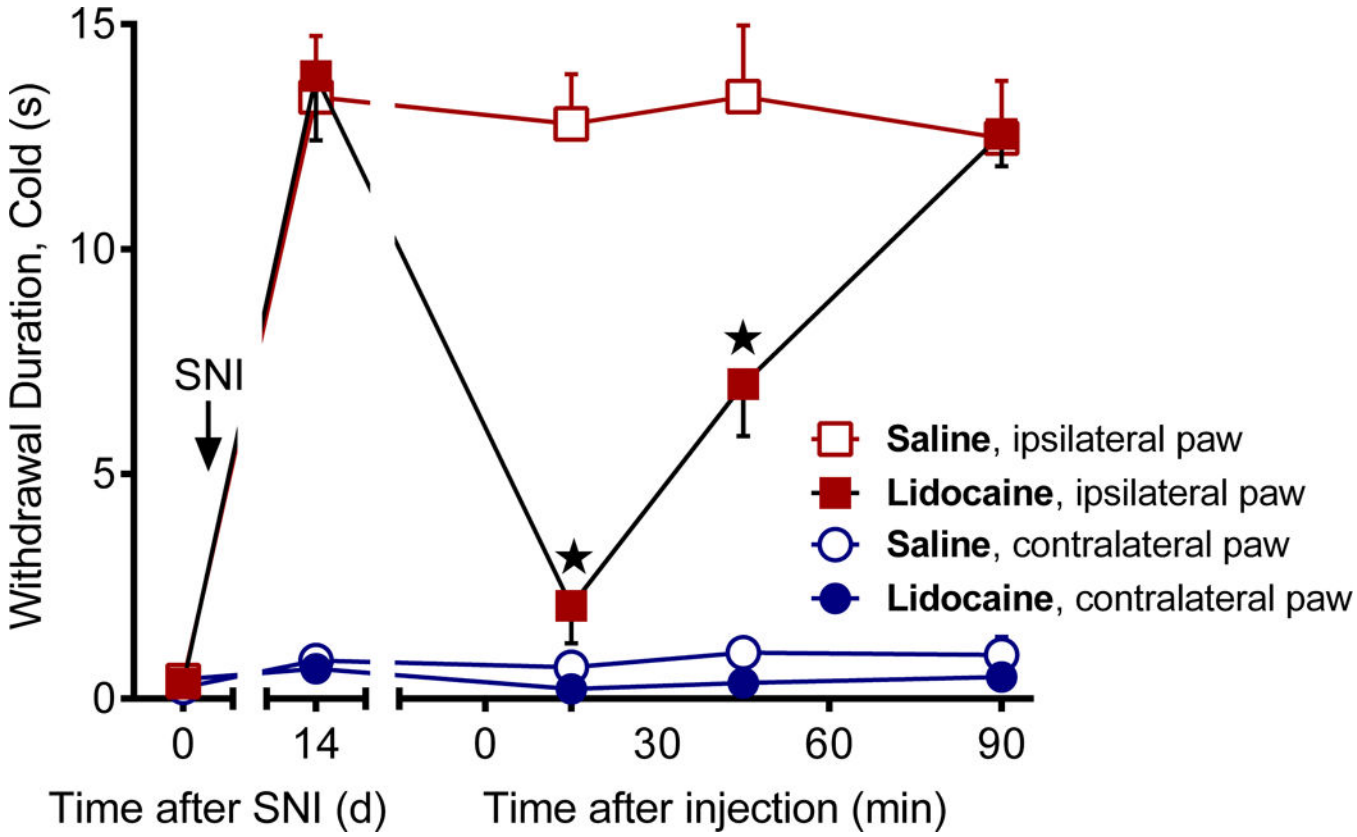

Figure 3. Intra-LC lidocaine reduced nerve injury-induced mechanical hypersensitivity

Bilateral microinjection of lidocaine (4%), but not saline, reduced all signs of neuropathic pain, including hypersensitivity to application of von Frey hairs, at the paw ipsilateral (but not contralateral) to SNI. Data is expressed as mean ± SEM. n=3–6. ★$p < 0.01$. (Brightwell and Taylor 2009).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

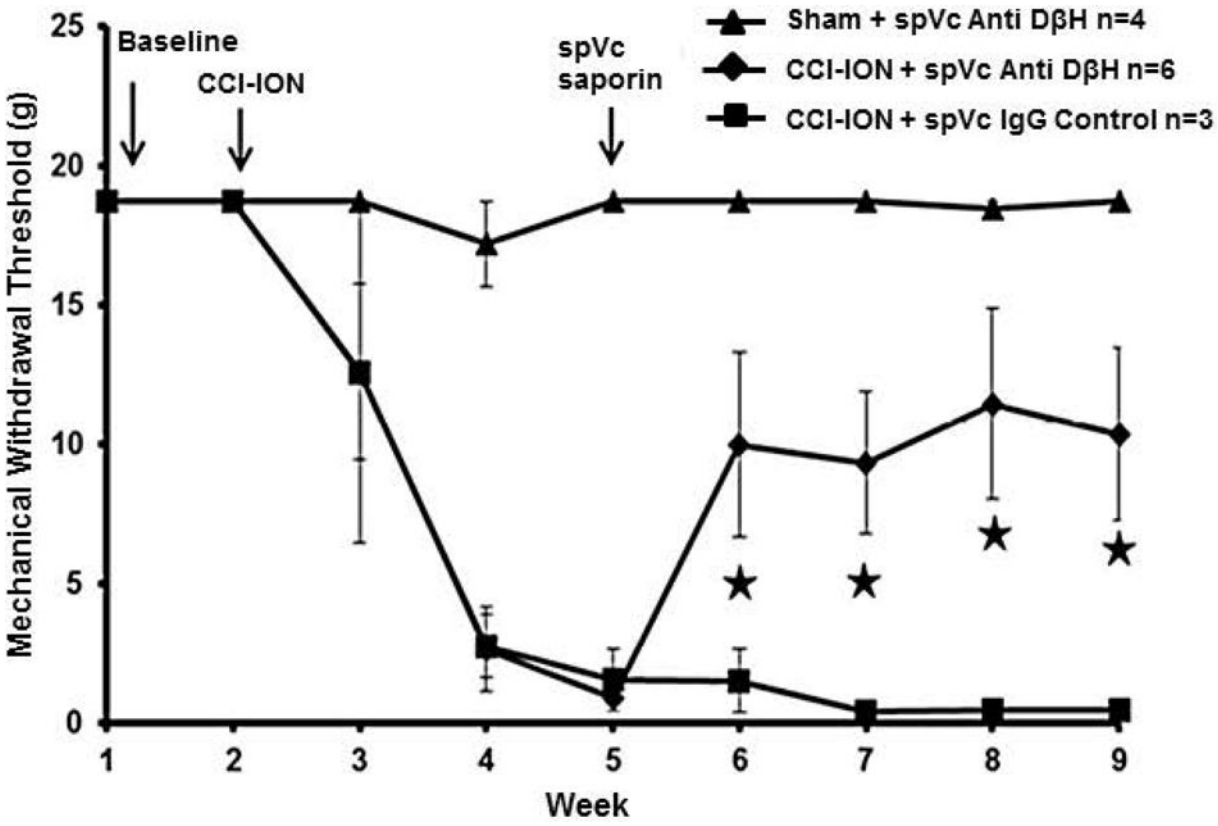

Figure 4. Anti-DβH-saporin alleviated mechanical hypersensitivity induced by CCI-ION but not the control IgG saporin

The time course of mechanical hypersensitivity at the ipsilateral vibrissal whisker pad in rats following constriction of the trigeminal infraorbital nerve (ION), with and without microinjection of anti-DβH-saporin into the spinal trigeminal nucleus caudalis (spVc) is shown as 50% mechanical withdrawal threshold to von Frey hairs applied to the whisker pad (g). ★$p<0.05$ ION + spVc anti-DβH-saporin vs. ION + spVc blank IgG. One-way ANOVA, Tukey's multiple comparisons test. (Kaushal et al. 2016).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

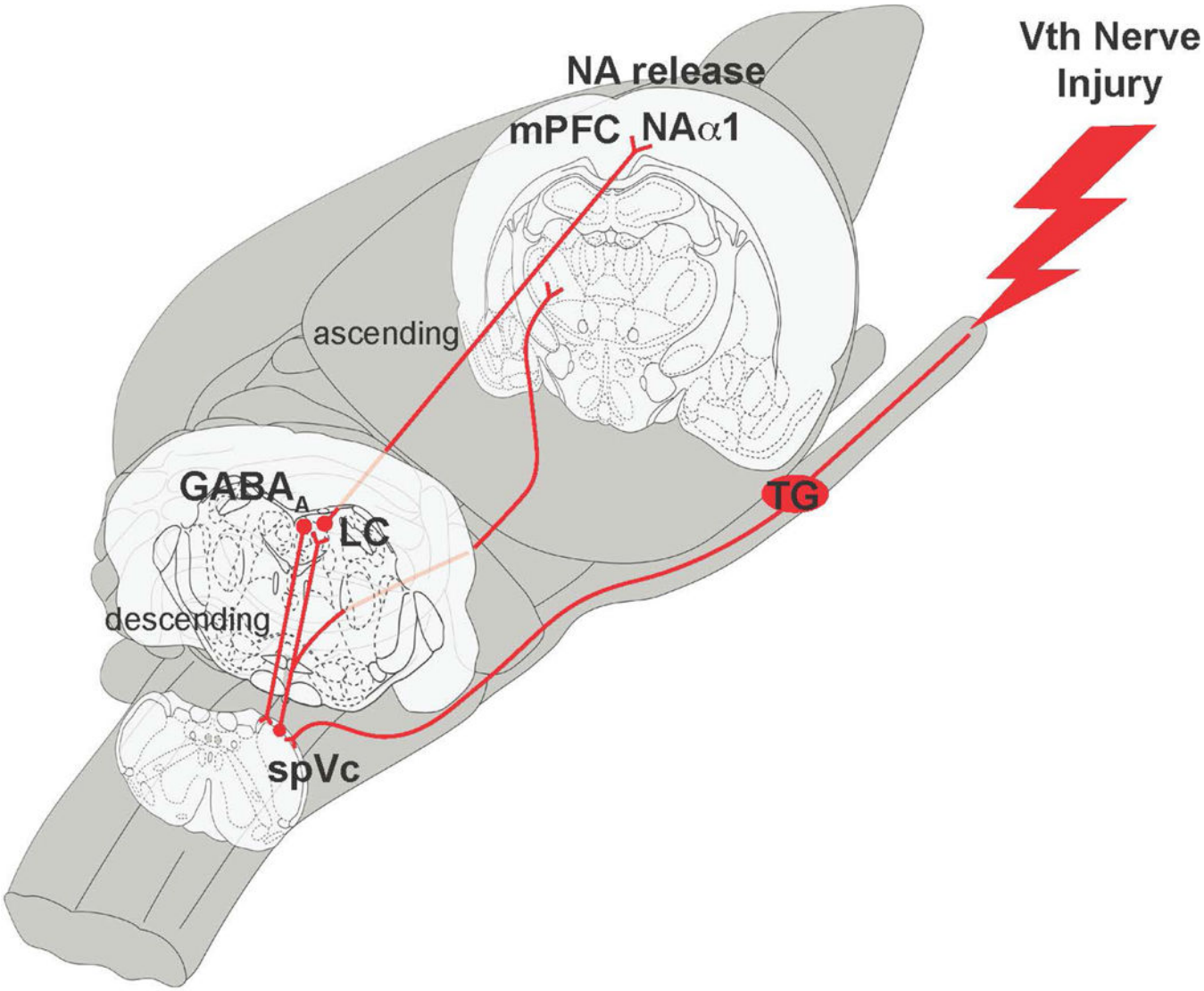

Figure 5. New functional pathways of ascending and descending modulation

The spinothalamic tract (dashed lines) innervates the LC as it passes through the brainstem. In response to noxious stimulation of the peripheral terminal fields of TG and DRG neurons, particularly in the setting of nerve injury (red lightning bolts connected to solid lines), LC neurons modulate pain through descending and ascending pathways (solid lines). Noradrenergic α2 inhibition and noradrenergic α1 facilitation influences pain sensation at various sites in the pain modulatory circuitry. This includes direct LC projections to both the spinal and trigeminal dorsal horns and the mPFC. DRG = dorsal root ganglia. LC = locus coeruleus. mPFC = medial prefrontal cortex. NAα1 – noradrenergic alpha1 receptor. spVc = trigeminal spinal nucleus caudalis. TG = trigeminal ganglia. (Kaushal et al. 2016).