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The Noradrenergic Locus Coeruleus as a Chronic Pain Generator

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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of antidepressant drugs achieved with elevated noradrenaline concentrations in the dorsal horn may be countered or even superseded by simultaneous activation of supraspinal facilitating systems dependent on α_1 -adrenoreceptor in the DRt and mPFC as well as α_2 -adrenoreceptors in the LC.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

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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

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 control (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 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 (Ferreton et al. 2011; Westlund and Craig 1996).

LC neurons form an elaborate network of ascending and descending projections (Crismona 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 (Aster et al. 2013; Jones and Moore 1977; Zoughlin et al. 1986; Loughlin et al. 1986; 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

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 intraparenchymal 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

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-DBH-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).

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 pronociceptive 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-D β H-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-

D β H-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

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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.

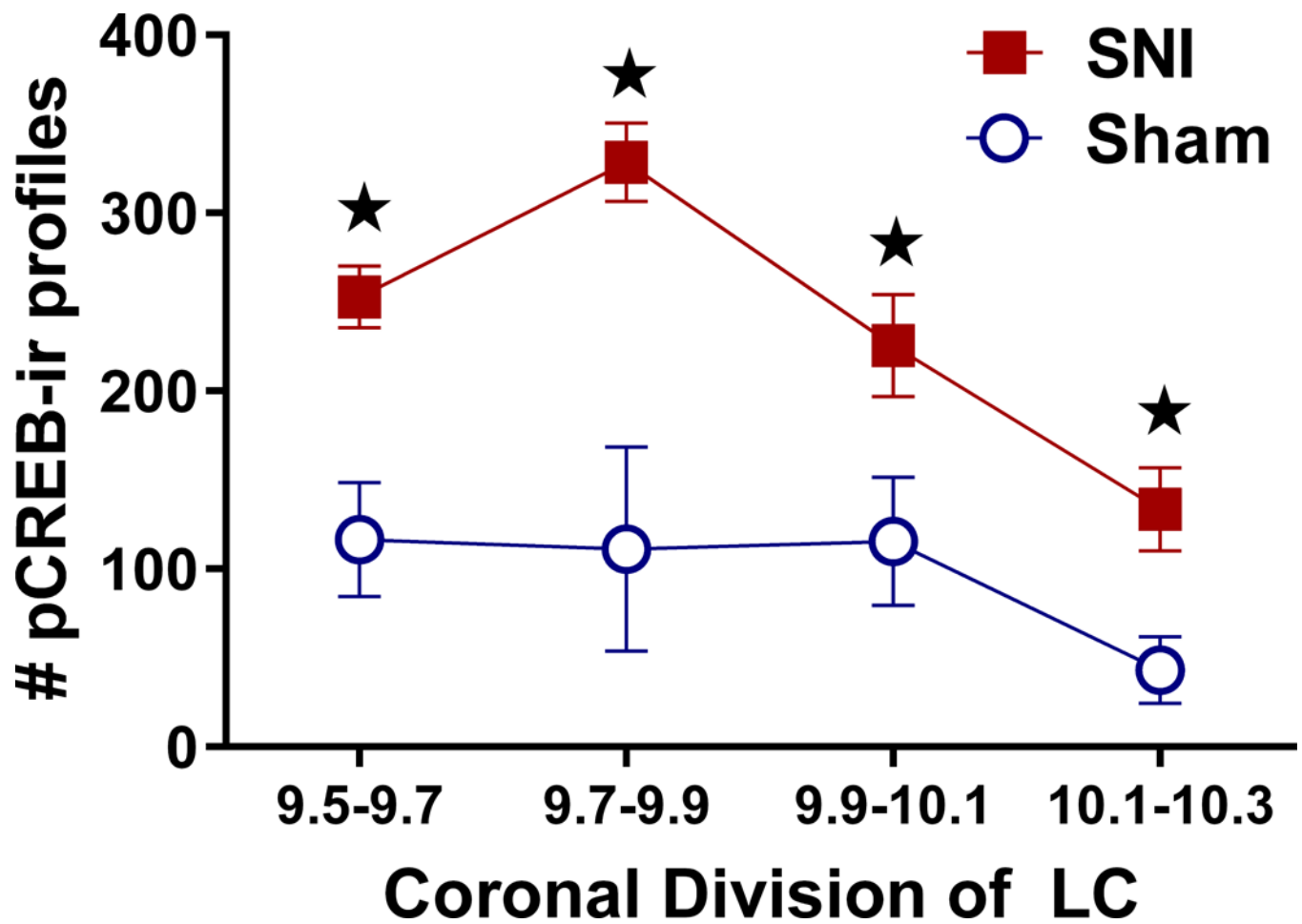


Figure 1. Nerve injury increases stimulus-induced pCREB expression throughout the rostrocaudal extent of the LC

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-ir profiles two weeks after spared nerve injury (SNI) as compared to sham surgery. n=5–12.

★ $p < 0.05$. (Brightwell and Taylor 2009).

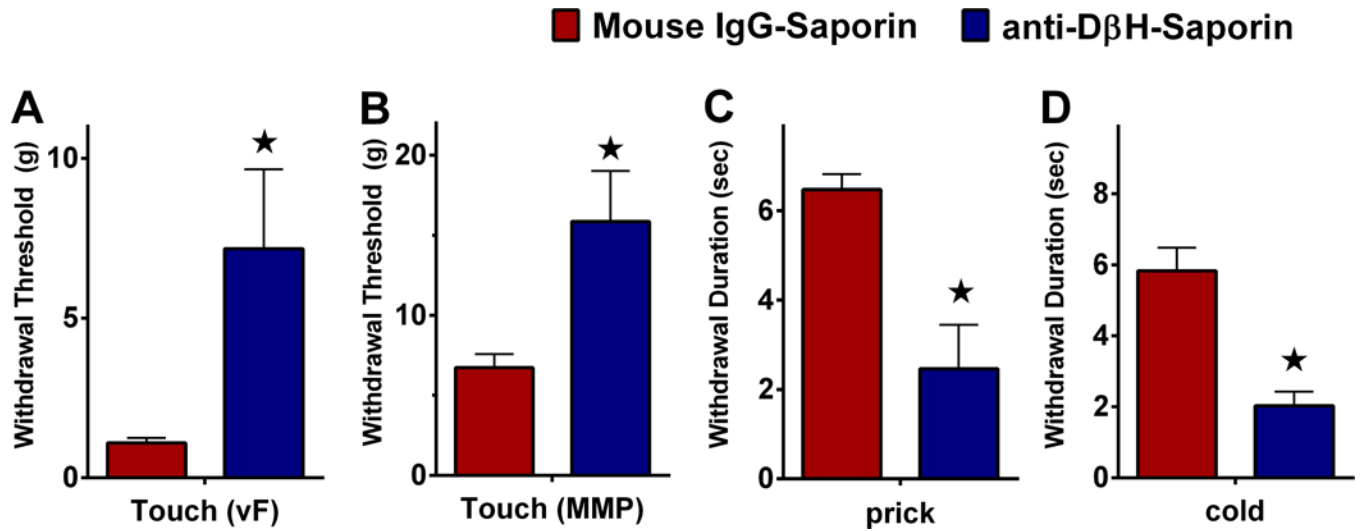


Figure 2. Ablation of noradrenergic neurons reduced multiple somatosensory modalities of nerve injury-induced hypersensitivity

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 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 [$\star p$'s < 0.05, post-hoc Bonferroni subsequent to ANOVA]. Values represent mean \pm SEM. n=4. For further details see Brightwell and Taylor, 2009. (Brightwell and Taylor 2009)

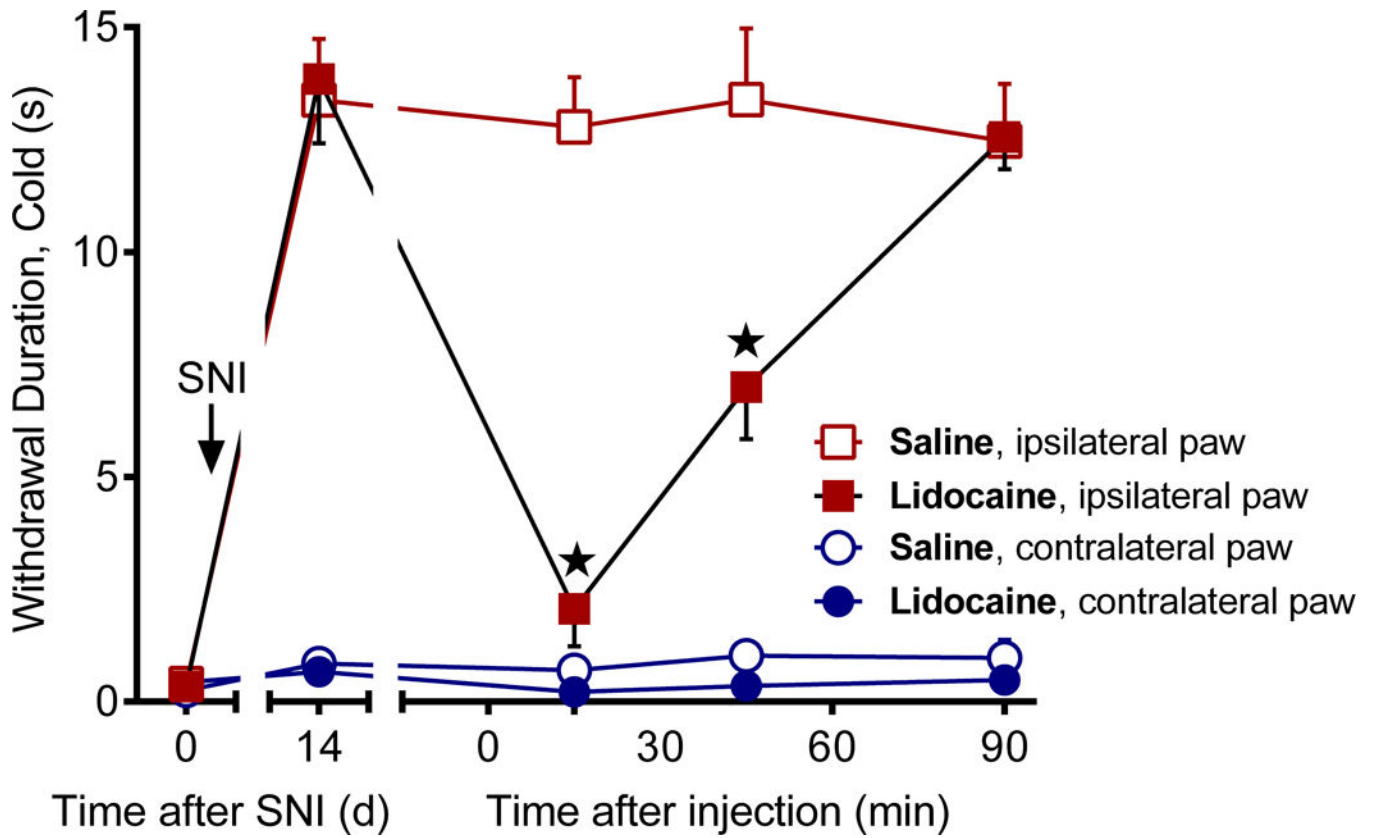


Figure 3. Intra-LC lidocaine reduced nerve injury-induced mechanical hypersensitivity
 Bilateral microinjection of lidocaine (4%), but not saline, reduced all signs of neuropathic pain, including hypersensitivity to application of von Frey hairs, at the paw ipsilateral (but not contralateral) to SNI. Data is expressed as mean \pm SEM. $n=3-6$. $\star p < 0.01$. (Brightwell and Taylor 2009).

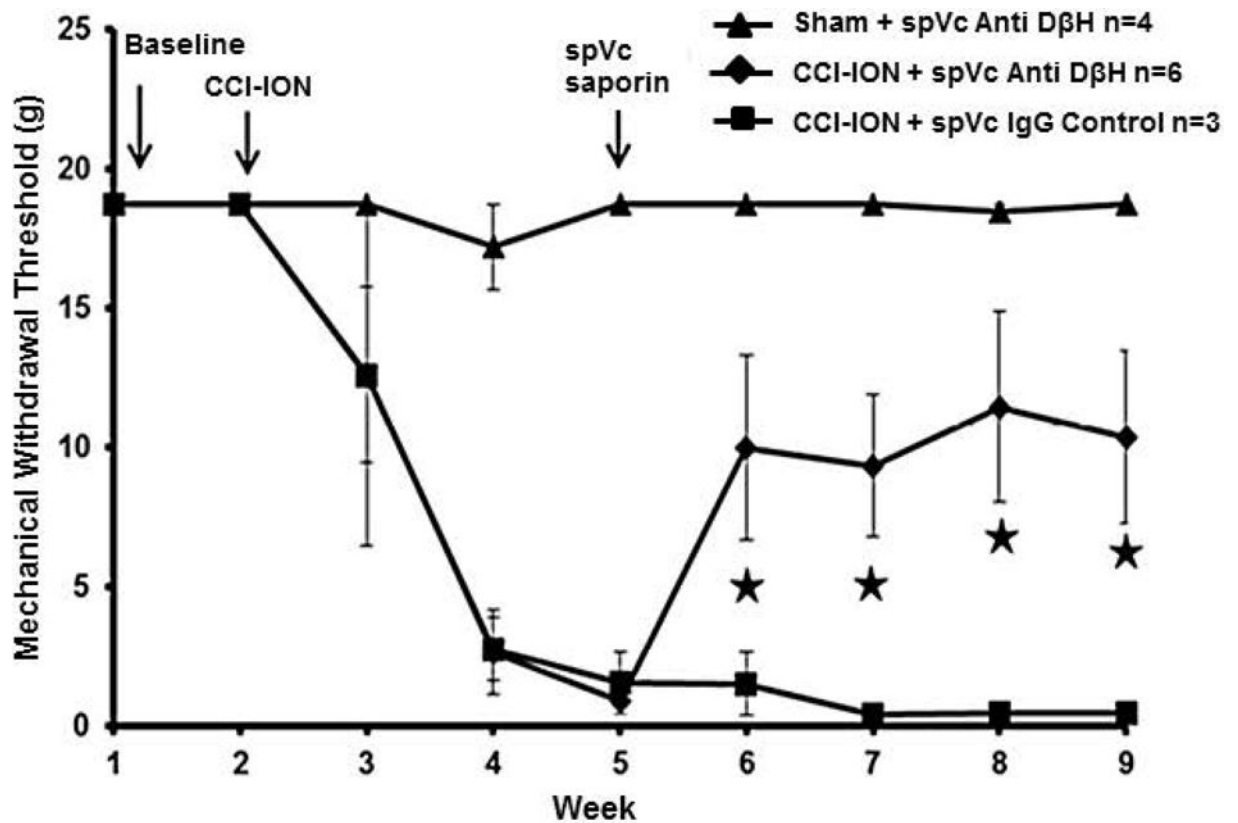


Figure 4. Anti-DβH-saporin alleviated mechanical hypersensitivity induced by CCI-ION but not the control IgG saporin

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).

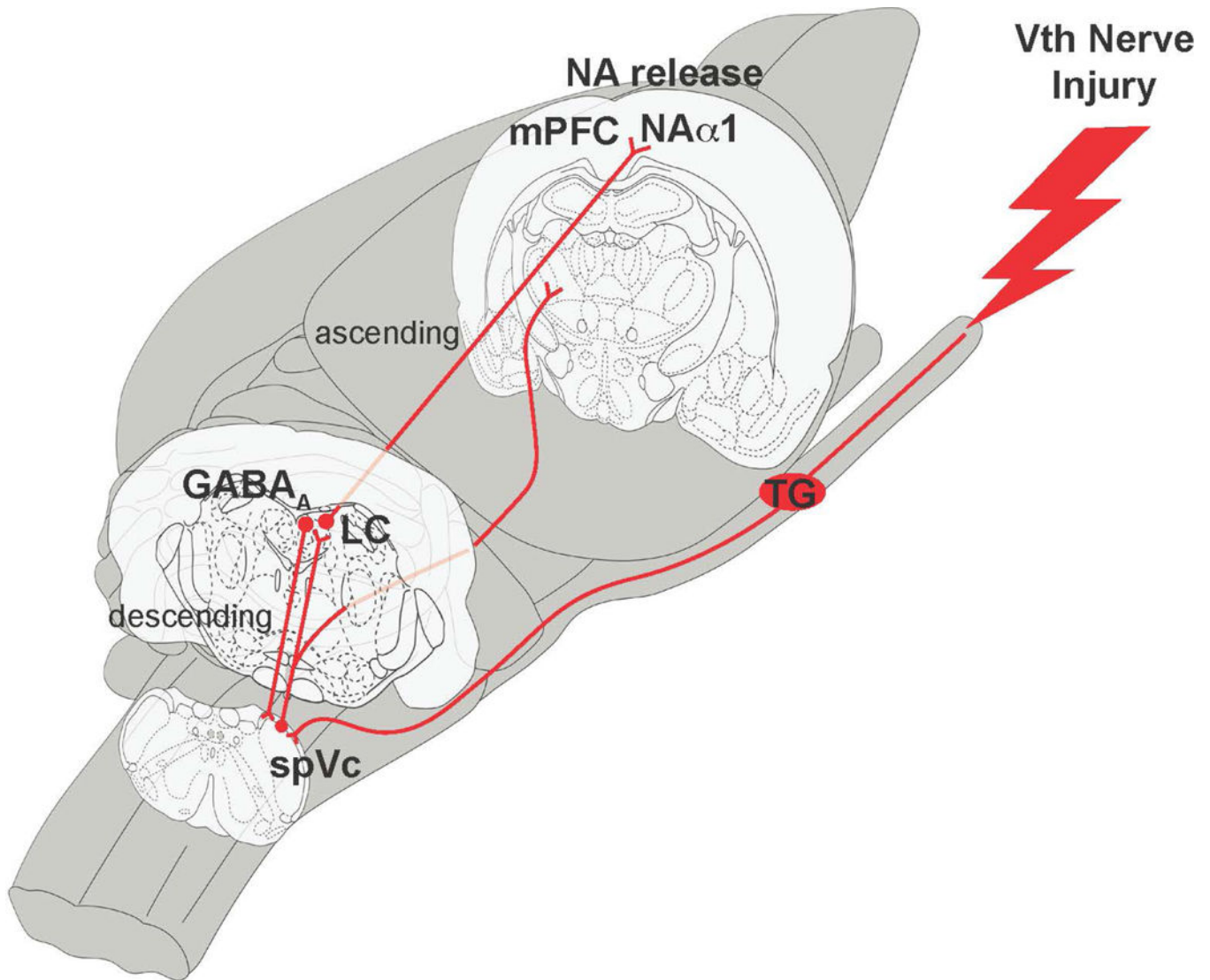


Figure 5. New functional pathways of ascending and descending modulation

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 α_2 inhibition and noradrenergic α_1 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. $\text{NA}\alpha_1$ – noradrenergic alpha1 receptor. spVc = trigeminal spinal nucleus caudalis. TG = trigeminal ganglia. (Kaushal et al. 2016).