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Parsing Pain From Anxiety Within the Locus Coeruleus Noradrenergic System

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The affective and cognitive consequences of chronic pain are often the most difficult dimensions of the condition to endure and treat. There is mounting evidence that the locus coeruleus–noradrenergic (LC-NE) system is a critical mediator of the emotional component of pain (1,2), but the functional details remain unclear. The LC and its near-ubiquitous NE innervation of the brain and spinal cord has long been thought to function as a global gain modulator for the central nervous system. Its extensive efferent system, gap junction coupling, and seemingly universal firing patterns make this a compelling framework for understanding central NE function. However, a growing body of evidence is rapidly redefining the way we view this important neuromodulatory system (2–7) (Figure 1). Rather than functioning as a single homogeneous set of neurons, the LC-NE system appears to operate with projection site–selective modularity. In this issue of *Biological Psychiatry*, Llorca-Torralba *et al.* (8) expand this concept with an important and timely article on the role of LC-NE projections to the basolateral amygdala (BLA) in pain-induced anxiety-like behavior. This detailed study uses chemogenetics to activate and inhibit LC-BLA projections, demonstrating a bidirectional role for this circuit in chronic pain–induced anxiety and cognitive impairment.

As our understanding of the LC-NE system shifts from homogeneous to heterogeneous, its role in anxiety is becoming clearer. Llorca-Torralba *et al.* (8) specifically address its role in anxiety resulting from chronic neuropathic-like pain. To model neuropathic pain in rats, Llorca-Torralba *et al.* (8) use chronic constriction injury (CCI) of the sciatic nerve. This injury produces robust mechanical and cold hypersensitivity for many weeks and ultimately causes increased anxiety-like behavior and decreased discrimination of aversive and neutral stimuli. Most importantly, the development of anxiety-like behavior, modeled here as exploration in either an elevated zero maze or open field test, only occurs after prolonged CCI (5–6 weeks). Following their earlier work with this model that implicated the LC and alpha-2 adrenergic receptors in the prefrontal cortex (PFC) (1), Llorca-Torralba *et al.* (8) use excitatory and inhibitory chemogenetic tools to probe LC-BLA projections in these behavioral adaptations.

We recently demonstrated that optogenetic activation of the LC-BLA projection drives anxiety-like behavior in mice (3), and Llorca-Torralba *et al.* (8) see similar results with local activation of LC-BLA inputs in naïve rats. However, they greatly extend our previous work by manipulating this projection during the pain experience. While short-term pain exposure (2–3 weeks) does not elicit anxiety-like behavior on its own, chemogenetic augmentation of the LC-BLA projection shifts behavior toward anxiety. Conversely, long-term pain exposure (5–6 weeks) does cause an anxiety-like state, which can be reversed with chemogenetic inhibition of LC-BLA fibers or by locally antagonizing beta-adrenergic receptors in the BLA. However, this pain-induced negative affective state is not increased with further stimulation of the projection. Interestingly, inhibition of the LC-BLA projection in a naïve state does not decrease baseline anxiety levels. Therefore, while this pathway can drive anxiety (3) and endogenously drives anxiety during chronic pain (8), it does not seem necessary for regulating state anxiety without some kind of behavioral challenge. Uematsu *et al.* (4) recently showed parallel results where LC-BLA optogenetic inhibition during fear conditioning reduced fear memory formation but did not alter freezing during conditioning.

The succinct role of LC-BLA projections in pain-induced affect and cognition that Llorca-Torralba *et al.* (8) describe is likely too narrow to capture the full role LC-NE circuits in pain. The LC-NE system is known to support both analgesia and hyperalgesia. Hirschberg *et al.* (2) recently used another approach for selective chemogenetic activation to segregate pain-exacerbating projections from the LC to the PFC and analgesic projections to the spinal cord. Hirschberg *et al.* (2) also used a slightly different model of nerve injury, a complete tibial nerve transection, but the finding that LC-PFC projections increase aversive responses to pain is particularly important here because it suggests that pain-related negative affect can arise from two separate LC efferent systems. Though the LC-NE system is emerging to modulate distinct behaviors through discrete projections, both Hirschberg *et al.* (2) and Llorca-Torralba *et al.* (8) suggest that different pathways produce similar, though not identical, behavioral end points. These overlapping observations are not entirely unique given that anxiety-like behaviors have now been driven by the activation of LC inputs to the BLA, PFC, and superior colliculus (2,3,5). Beta-adrenergic antagonists have reversed these behaviors in each region except the PFC, which has yet to be tested. The potential redundancy of the LC-BLA (3,8) and LC-PFC (2) efferent systems in general anxiogenesis is interesting and suggests that further work will be required to understand the nuances of these projections, which might depend on the pain model and will almost certainly depend on the duration after injury. Pain state might begin to explain this overlap. While Hirschberg *et al.* (2) clearly show that anxiety-like behavior can be driven by activating the LC-PFC pathway and that this pathway exacerbates pain-induced aversion and spontaneous nocifensive responses, they did not directly test whether the projection modified pain-induced anxiety. On the

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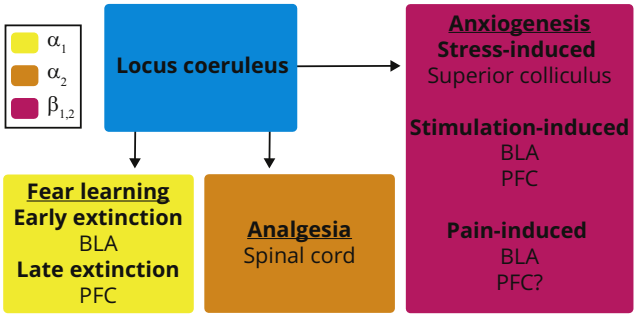

Figure 1. Recent circuit-based insights into locus coeruleus–noradrenergic function in behaviors. Divergent coeruleus–noradrenergic efferent projections mediate distinct behaviors through select adrenergic receptors. Generally, circuit-based coeruleus–noradrenergic anxiety-related behaviors have been reversed by beta-adrenergic blockade (3,5,8), pure analgesia through spinal alpha-2 receptors (2), and divergent effects on fear conditioning were both mediated by alpha-1 receptors. This figure focuses on recent circuit-based advances and does not account for the vast published literature characterizing these behaviors with elegant behavioral pharmacology (e.g., beta-adrenergic receptors in fear). BLA, basolateral amygdala; PFC, prefrontal cortex.

other hand, Llorca-Torralba *et al.* (8) repeatedly show that activation of the LC-BLA pathway is anxiogenic in naïve animals, and either inhibiting this pathway or blocking downstream beta-adrenergic receptors after chronic pain is anxiolytic.

Contemporaneously and separate from the study by Llorca-Torralba *et al.* (8), Corder *et al.* (9) used a multidisciplinary approach to decode affective pain information from the BLA. Specifically, Corder *et al.* (9) showed that pain recruits an ensemble of BLA neurons that encode the affective valence of the pain experience. When this ensemble was inhibited during the sciatic nerve injury model of neuropathic pain, animals still experienced mechanical hypersensitivity and cold allodynia, but had diminished escape and aversion behaviors to painful stimuli. How does the LC interreact with this nociceptive BLA ensemble? Future studies should seek to molecularly define the BLA pain ensemble. Expression of adrenergic receptors within this ensemble could explain, at least in part, how the LC-BLA projection tunes anxiety and cognitive impairment during chronic pain.

Though Llorca-Torralba *et al.* (8) mostly use chemogenetic approaches to modulate the LC-BLA projection, two critical findings emerge from unmodified, wild-type Long Evans rats—highlighting translational potential. First, Llorca-Torralba *et al.* (8) find that pain-induced anxiety-like behavior is time dependent. In other words, the CCI neuropathic model appears to generate anxiety-like behavior and cognitive impairment only after a long-term, persistent neuropathic challenge. These effects are in stark contrast to the increased mechanical hypersensitivity that emerges early after CCI and is maintained at a constant level at subsequent timepoints. This aligns with previous studies (1,10) and further suggests that the emotional component of pain is the dynamic variable defining a chronic pain state. The second and perhaps most important overall finding is that systemic beta-adrenergic blockade reverses chronic pain-induced anxiety-like behavior. After the chemogenetic experiments, suggesting that inhibition of LC-BLA blunts anxiety from chronic pain, Llorca-Torralba *et al.* (8) first used local, site-specific delivery of the prototypical beta-adrenergic antagonist propranolol into the BLA. This local blockade reversed the anxiety seen after long-term nerve injury. The next, and possibly most important experiment demonstrated that this same behavioral outcome can be achieved with systemic propranolol administration. Propranolol, of course, is already approved by the United States Food and Drug Administration and is widely prescribed for a variety of cardiac and anxiety-related disorders. Though a limited number of clinical trials have looked at efficacy for beta-adrenergic blockade in pain, this new observation suggests the need for a well-designed study directly examining anxiety in patients with nerve injury.

Chronic neuropathic pain and anxiety are inextricably linked at both the behavioral and neurobiological levels. Likewise, the role of the LC-NE system in the modulation of pain and anxiety is clearly critical, yet complex. Llorca-Torralba *et al.* (8) advance our understanding of what may be a single module of LC-NE function that helps parse anxiety from pain. The study raises new questions of how we might interpret what appears to be a modular and target-based efferent system while simultaneously offering useful preclinical data with the true potential for translation. As the field moves forward to dissect the circuits and the behavioral features that define the pain experience, the LC-NE system will remain a key focus. Through these and future studies we begin to see how "partly differentiated" (6) the potential "loci coeruleus" (2) are when it comes to the intersection of anxiety and pain.

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Article Information

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