CellPress

Neuron
Previews

Pontospinal control of nociception via a negative feedback loop

Andrew D. Vigotsky,[1,2,3] Adrien Tassou,[1,2,3] and Grégory Scherrer[1,2,3,*]
[1]Department of Cell Biology and Physiology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[2]UNC Neuroscience Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[3]Department of Pharmacology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
*Correspondence: gregory_scherrer@med.unc.edu
https://doi.org/10.1016/j.neuron.2025.05.007

The nociceptive apparatus has the remarkable ability to regulate itself by amplifying and attenuating nociception and thus pain in a context-dependent way. In this issue of *Neuron*, Li et al.[1] identified a subpopulation of pontospinal projection neurons that dampen nociception in mice.

Nociception subserves survival by detecting bodily threats and initiating responses that prevent or reduce harm. These protective or *nocifensive* responses begin in dorsal root/trigeminal ganglion neurons in the peripheral nervous system, where primary afferent nociceptors detect and transduce noxious stimuli into nociception and transmit this information to neurons in the spinal/trigeminal dorsal horn. Dorsal horn interneurons integrate nociceptive signals and relay this information, including to initiate immediate nocifensive responses such as withdrawal reflexes.[2] In contrast, dorsal horn ascending projection neurons transmit nociception to the brain, including to the thalamus, lateral parabrachial nucleus, and periaqueductal gray (PAG). These regions distribute nociception to numerous cortical and subcortical regions, which mediate higher-level nocifensive responses such as attending, coordinated escape behavior, and learning associated with pain experience.[3,4] As the above aptly illustrates, nociception is widespread across the neuraxis[4] and neurons that specifically process nociception, no matter how they receive the signal or where they reside, can be considered *nociceptive* neurons.

Importantly, ascending nociceptive pathways alone cannot account for several well-documented phenomena. For example, Hippocrates[5] astutely observed that, "Of two pains occurring together, not in the same part of the body, the stronger weakens the other." Although Hippocrates' account is intuitive, its implications are paradoxical: how could nociception have anti-nociceptive effects? One parsimonious explanation entails descending modulatory pathways, which originate from the brain and exert powerful control over nociceptive processing in the spinal cord. Several descending systems balance the inhibition and facilitation of nociception,[6,7] including (1) ON/OFF cells in the rostral ventromedial medulla (RVM); (2) descending serotonergic projections from nucleus raphe magnus; and (3) descending noradrenergic projections from the pons, including locus coeruleus (Figure 1). Intriguingly, these three pathways are at least partly governed by the PAG.[6,7] Moreover, descending inhibitory projections from these regions to the dorsal horn are activated by noxious stimuli,[6] providing a clear explanation for Hippocrates' anecdote—that is, noxious inputs drive descending inhibition of nociception, meaning that nociception is self-regulated via negative feedback loops. Understanding these negative feedback loops may pave a pathway to treat a host of chronic pain conditions.

Of course, pathways that modulate nociception via negative feedback loops must be activated by nociception. Li et al.[1] exploited this logic and set out to identify descending projections that are activated by noxious stimuli and elucidate how they modulate nociceptive processing in healthy and neuropathic (spared nerve injury) mice. To do so, the authors combined genetic trapping in TRAP2 mice and retrograde labeling with a Cre-dependent adeno-associated GFP virus injected into the lumbar dorsal horn (retro-TRAP). This method induced GFP expression in spinally projecting brain neurons that become active in response to pain-inducing stimuli. Ultimately, the authors observed prominent GFP expression in an area typically associated with the pontine micturition center (PMC).

Next, Li et al.[1] assessed the molecular identity of these GFP$^+$ neurons, for which they combined retro-TRAP with single-nucleus RNA sequencing. Interestingly, two identified cell types—both of which expressed corticotropin-releasing hormone (encoded by the *Crh* gene)—mapped to an Allen Brain Cell Atlas cell type in the pontine that is typically associated with Barrington's nucleus, which contains PMC neurons. In contrast, the TRAPed neurons did not colocalize with other neurons that are typically associated with micturition (i.e., defined by expression of the estrogen receptor 1 gene, *Esr1*). The authors called the nociceptive TRAPed neurons Bar^{Crh+}. Are these nociceptive Bar^{Crh+} neurons actually part of the PMC, and if not, what is their function?

The PMC is functionally defined by its role in micturition: a neuron is a part of the PMC if and only if it is involved in micturition.[8] To assess whether the retro-TRAPed neurons were involved in micturition or if they were purely nociceptive, Li et al.[1] used fiber photometry recordings while applying different stimuli and during urination. In healthy mice, *Crh*$^+$ and retro-TRAPed *Crh*$^+$ neurons, but not *Esr1*$^+$ neurons, responded to noxious heat and pinprick stimuli but not low-force von Frey filaments. In neuropathic mice, *Crh*$^+$ and TRAPed *Crh*$^+$ neurons, but not *Esr1*$^+$ neurons, responded to low-force von Frey filaments and brush stimuli, typically associated with allodynia. Both *Crh*$^+$ and *Esr1*$^+$ activated during urination, indicating that these populations contain PMC neurons. In contrast,

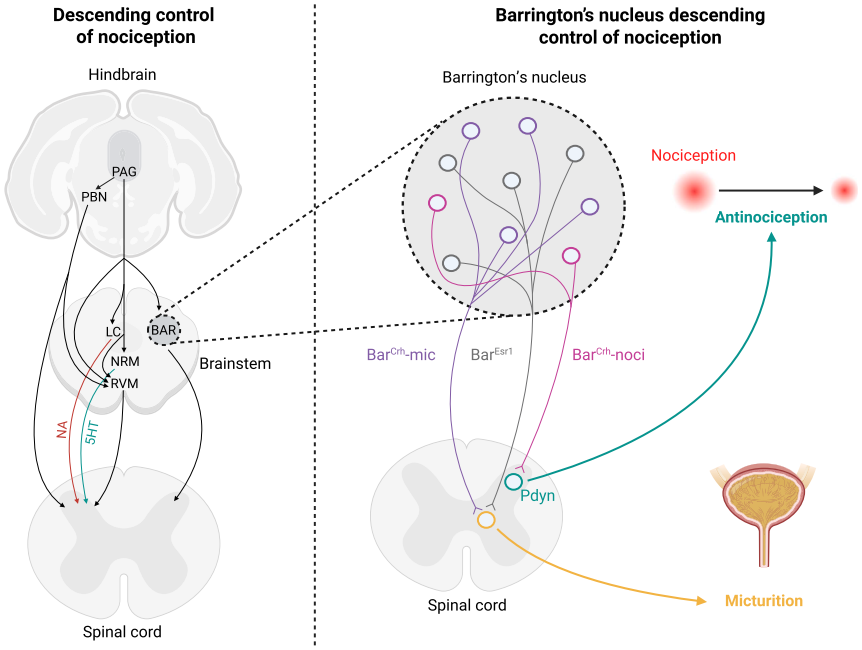

Figure 1. Neural circuits for descending control of nociception

The left side of the brain and spinal cord depicts previously established descending modulatory pathways, including those stemming from the rostral ventromedial medulla (RVM), nucleus raphe magnus (NRM), and locus coeruleus (LC), which receive input from the periaqueductal gray (PAG); the right side of the brain and spinal cord illustrates the novel descending inhibitory mechanism mediated by *Crh*$^{+}$ neurons in Barrington's nucleus (Bar) discovered by Li et al. The *Crh*$^{+}$ neurons exert their antinociceptive effects by exciting prodynorphin-expressing inhibitory interneurons in the dorsal horn. Importantly, the *Crh*$^{+}$ neurons involved in antinociception are distinct from those involved in micturition.

TRAPed *Crh*$^{+}$ nociceptive neurons did not activate during urination. Thus, the nociceptive TRAPed *Crh*$^{+}$ neurons identified by Li et al.[1] reside by but are not part of the functionally defined PMC—rather, they are perhaps better described as nociceptive *Crh*$^{+}$ Barrington's nucleus neurons, which is defined neuroanatomically rather than functionally.[8] If these neurons are not involved in micturition, what is their function?

To functionally interrogate Bar^{Crh+} neurons, Li et al.[1] principally relied on chemogenetic experiments. In healthy mice, chemogenetic activation increased withdrawal latency in response to heat, decreased licking in response to pinch, and decreased withdrawal probabilities from high-force von Frey filaments without affecting responses to innocuous stimuli. Likewise, in neuropathic mice, withdrawal to tactile stimuli improved, and the animals no longer displayed conditioned place aversion (CPA) to tactile stimuli. Importantly, chemogenetic inhibition had opposite effects. Thus, nociceptive Bar^{Crh+} neurons have antinociceptive effects.

Since the antinociceptive action of Bar^{Crh+} neurons seems to depend on incoming nociceptive signals, they must receive nociceptive input and transmute it into an antinociceptive output, but from where? To identify nociceptive inputs to Bar^{Crh+}, the authors combined retro-TRAP with monosynaptic retrograde tracing with rabies virus in neuropathic (and sham control) mice. After tactile stimulation, the virus labeled nociceptive Bar^{Crh+} descending projections in neuropathic but not sham mice, permitting the monosynaptic rabies virus to infect the inputs to nociceptive Bar^{Crh+} neurons. The authors identified the ventrolateral PAG (vlPAG) as the principal source of nociceptive input. To test the function of vlPAG→Bar^{Crh+}, the authors optogenetically activated Bar^{Crh+}-projecting vlPAG neurons while applying tactile stimuli. Remarkably, activation of these vlPAG neurons induced time-locked antinociceptive effects, suppressing nociensive behavior. In addition, vlPAG activation blunted CPA. To ensure that the antinociceptive effects were mediated by nociceptive Bar^{Crh+} neurons, the authors showed that ablating Bar^{Crh+} neurons reversed the antinociceptive effects—the antinociceptive effects of vlPAG→Bar^{Crh+} are indeed mediated by Bar^{Crh+}.

Next, the authors tried to identify the spinal neurons downstream of Bar^{Crh+} through which they exert their antinociceptive effects. First, they used a transsynaptic anterograde virus to label the targets of Bar^{Crh+}, from which they collected electrophysiological recordings. They found that neurons preferentially receiving Bar^{Crh+} input displayed tonic firing, a hallmark of inhibitory interneurons. Next, the authors optogenetically stimulated Bar^{Crh+} axons in the spinal cord and stained for *Fos* expression across five different types of inhibitory interneuron subtypes. Bar^{Crh+} activation preferentially caused *Fos* expression in prodynorphin (*Pdyn*) neurons. Finally, the authors ablated spinal^{Pdyn+} neurons and repeated their chemogenetic activation experiments. Intriguingly, spinal^{Pdyn+} ablation reversed the antinociceptive effects of Bar^{Crh+} activation during mechanical but not heat stimulation, suggesting Bar^{Crh+}→spinal^{Pdyn+} selectively mediates mechanical antinociception, as previously described for other descending modulatory pathways.[9]

In summary, Li et al.[1] identified a negative feedback loop that transmutes nociception into an antinociceptive signal via a vlPAG→Bar^{Crh+}→spinal^{Pdyn+} pathway, which inhibits dorsal horn nociceptive processing. In doing so, they provide evidence and a circuit mechanism for another descending pathway that modulates spinal nociception. This work raises several important questions and avenues for future research.

First, Li et al.[1] demonstrated that spinal^{Pdyn+} neurons mediate mechanical but not heat antinociception, which raises the question of how Bar^{Crh+} activation produces heat antinociception. Are there distinct Bar^{Crh+} neurons (and associated inhibitory interneurons) for different modalities? Second, how does the vlPAG→Bar^{Crh+}→spinal^{Pdyn+} pathway relate to other descending pathways, particularly PAG→RVM→spinal? Do their inhibitory

mechanisms overlap? Are there any facilitatory aspects of the vlPAG→Bar^{Crh+}→spinal^{Pdyn+} pathway, much like there are in other descending modulatory pathways? Third, several details of the vlPAG→Bar^{Crh+}→spinal^{Pdyn+} circuit are unclear. Specifically, what are the molecular identities of the vlPAG and Bar^{Crh+} neurons involved in this circuit, and what transmitters do they release? Which molecules differentiate nociceptive Bar^{Crh+} neurons from micturition Bar^{Crh+} neurons? Knowing their molecular identities can facilitate intersectional genetic approaches to more precisely study these neurons, as opposed to examining only neurons in which *Fos* is induced (TRAP), and help to identify drug targets. Fourth, spinal *Pdyn*$^{+}$ neurons are best known for their role in itch.[10] Are there distinct populations of *Pdyn*$^{+}$ neurons mediating pruriception (and thus itch) and descending inhibition of nociception, or are the same *Pdyn*$^{+}$ neurons part of overlapping circuits by which spinal pruriception and descending nociceptive inputs can reduce pain? Finally, what happens to this circuit when pathology is present? Do the molecular, cellular, or circuit properties of the Bar^{Crh+} pathway change over time, leading to a hyperexcitability of secondary afferents or facilitating central sensitization? Understanding the molecular, cellular, and synaptic properties of these descending nociceptive regulatory systems may provide valuable insights, based on which potent analgesics can be developed to alleviate pathological pain.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Li, T., Zhou, W., Ke, J., Chen, M., Wang, Z., Hayashi, L., Su, X., Jia, W., Huang, W., Wang, C.-S., et al. (2025). A pontine center in descending pain control. Neuron *113*. https://doi.org/10.1016/j.neuron.2025.02.028.

2. Basbaum, A.I., Bautista, D.M., Scherrer, G., and Julius, D. (2009). Cellular and molecular mechanisms of pain. Cell *139*, 267–284.

3. Palmiter, R.D. (2018). The parabrachial nucleus: CGRP neurons function as a general alarm. Trends Neurosci. *41*, 280–293.

4. Coghill, R.C. (2020). The distributed nociceptive system: A framework for understanding pain. Trends Neurosci. *43*, 780–794.

5. Hippocrates and Adams, F. (1849). The Genuine Works of Hippocrates, *2* (The Sydenham Society), pp. 685–774.

6. Basbaum, A.I., and Fields, H.L. (1978). Endogenous pain control mechanisms: review and hypothesis. Ann. Neurol. *4*, 451–462.

7. Heinricher, M.M., Tavares, I., Leith, J.L., and Lumb, B.M. (2009). Descending control of nociception: Specificity, recruitment and plasticity. Brain Res. Rev. *60*, 214–225.

8. Verstegen, A.M.J., Vanderhorst, V., Gray, P.A., Zeidel, M.L., and Geerling, J.C. (2017). Barrington's nucleus: Neuroanatomic landscape of the mouse "pontine micturition center.". J. Comp. Neurol. *525*, 2287–2309.

9. François, A., Low, S.A., Sypek, E.I., Christensen, A.J., Sotoudeh, C., Beier, K.T., Ramakrishnan, C., Ritola, K.D., Sharif-Naeini, R., Deisseroth, K., et al. (2017). A brainstem-spinal cord inhibitory circuit for mechanical pain modulation by GABA and enkephalins. Neuron *93*, 822–839.e6.

10. Kardon, A.P., Polgár, E., Hachisuka, J., Snyder, L.M., Cameron, D., Savage, S., Cai, X., Karnup, S., Fan, C.R., Hemenway, G.M., et al. (2014). Dynorphin acts as a neuromodulator to inhibit itch in the dorsal horn of the spinal cord. Neuron *82*, 573–586.