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RVM circuits regulate both the sensory and affective dimensions of neuropathic pain: A commentary on Dogrul et al

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There is now considerable evidence that the brain is not only the locus of pain percepts but by engaging powerful descending modulatory mechanisms that can inhibit or facilitate the transmission of nociceptive information, the brain can also regulate the experience of pain.[6] In the setting of acute pain, there is normally a dynamic balance between both processes. However, dysfunction of this modulatory system can result in reduced pain inhibition and/or enhanced pain facilitation, either of which can exacerbate pain and contribute to its chronicity.[6,7,21.]

A key structure in this regulatory system is the rostral ventral medulla (RVM), a brainstem region that serves as the major output in the relay of descending controls.[4] The antinociceptive and pronociceptive outputs from the RVM are mediated by molecularly distinct, physiologically definable, classes of spinally-projecting neurons. These classes include OFF, ON, and Neutral cells, which are characterized based on their firing rate during a reflex withdrawal to a noxious stimulus.[12] Via an action on spinal cord nociceptive processing, ON and OFF cells mediate descending facilitation and descending inhibition of pain, respectively. The contribution of Neutral cells is not entirely clear, however, they are serotonergic[22] and have also been implicated in descending modulation of pain.[1,9,17,23] Interestingly, the majority of both ON cells and OFF cells are GABAergic[7,20]. Although a detailed characterization of the molecular identity of RVM neuronal subtypes is still needed[7], some markers distinguish them. For example, ON cells express the μ-opioid receptor (MOR) and can be inhibited by μ-opioid agonists, such as morphine[3]. Indeed, selective ablation of MOR-expressing-RVM neurons in a rat model of chronic pain reverses mechanical allodynia[5], suggesting that RVM^{MOR+} neurons facilitate and maintain chronic pain. Of note, however, most studies of RVM descending controls used approaches that monitor spinal cord reflexes, which assess the sensory dimension of pain[20]. Much less studied is whether RVM descending modulation also influences the affective component of pain.[11,13,20.]

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In this issue of Pain, Dogrul et al, in the Porreca group, tested the hypothesis that descending facilitation derived from RVM^{MOR+} neurons maintains neuropathic pain and influences both its sensory and affective dimensions.[8] These authors used chemogenetics to selectively inhibit RVM^{MOR+} neurons in male Oprm1^{Cre} mice that underwent partial sciatic nerve ligation (PSNL), to generate a model of neuropathic pain. After expressing a Cre-dependent inhibitory DREADD (designer receptor activated by designer drugs) into the RVM, they administered systemic clozapine N-oxide (CNO), a DREADD agonist, to selectively silence RVM $^{MOR+}$ neurons. The authors then assessed both the sensory and affective components of pain, by measuring mechanical sensitivity and performing a conditioned place preference (CPP) test, respectively. In the PSNL model, they found that acute chemogenetic silencing of RVM^{MOR+} relieves both the neuropathic pain-associated mechanical allodynia as well a measure of pain affect.

Interestingly, they also demonstrated that intrathecal administration of CNO transiently reduced mechanical allodynia, confirming the contribution of RVM^{MOR+} spinal terminals to the sensory dimension of pain.[8] The authors hypothesized that RVM^{MOR+} neurons also influence pain affect via an action at the level of the spinal cord, however, additional analyses of the effect of intrathecal CNO is needed to assess whether this results entirely from descending projections. Particularly relevant to this question is a recent preprint[10] demonstrating that some spinally projecting RVM GABAergic neurons have significant ascending collaterals. Rostral RVM targets include the lateral parabrachial nucleus (LPb) and periaqueductal grey (PAG), both of which receive ascending nociceptive information from the spinal cord.[10] This ascending pattern of RVM innervation introduces the possibility that RVM GABAergic neurons regulate the aversive and affective components of pain at supraspinal sites. As both ON and OFF cells are predominantly GABAergic[7,20], it will be important to address whether the RVM^{MOR+} population also has collaterals projecting to supraspinal sites. Conceivably, the affective component of pain can be regulated by both descending and ascending RVM connections.

Dogrul et al also chronically silenced RVM^{MOR+} neurons via sustained CNO administered in drinking water, before PSNL. This manipulation reduced the expression of chronic mechanical allodynia, but did not affect the acute allodynia observed after PSNL, suggesting that RVM^{MOR+} neurons predominantly facilitate and maintain chronic neuropathic pain.[8] The authors also examined the contribution of RVM^{MOR+} neurons to loss of diffuse noxious inhibitory controls (DNIC), a mechanism of endogenous descending pain modulation[19] that is altered in neuropathic pain conditions, both pre-clinically, such as after PSNL, and clinically.[2] Through DNIC, LeBars et al demonstrated that dorsal horn wide dynamic range neurons are strongly inhibited by noxious stimuli applied to a remote location of the body, distinct from their excitatory receptive fields.[19] To test DNIC, Dogrul et al performed a tail-flick assay after injection of capsaicin into the forepaw of mice with PSNL. They found that silencing RVM^{MOR+} neurons restored DNIC. This result supports the hypothesis that there is enhanced descending facilitation by RVM^{MOR+} neurons in the setting of neuropathic pain, which might promote pain by competing with descending inhibitory controls. However, as DNIC does not result in the inhibition of lamina I nociceptive specific neurons[18,19], the output of which does contribute to the affective pain dimension,[15] there clearly is a need for further neuroanatomical and functional dissection of RVM^{MOR+} regulation of

superficial and deep dorsal horn neurons. Furthermore, as there is considerable evidence that descending and ascending noradrenergic mechanisms can independently regulate pain processing,[14] it is conceivable that a component of the RVM-derived circuitry engages noradrenergic controls.

As noted above, although most studies build upon the premise that there are three distinct classes of RVM neurons, it is also likely that these three populations are molecularly heterogeneous. Thus, RVM^{MOR+} neurons may represent multiple overlapping subpopulations that include ON, OFF, and Neutral cells, which could independently exert even more complex, opposing pain modulatory effects. Importantly, with the introduction of calcium imaging, chemogenetic, and optogenetics tools, the field can now address specifically how molecularly distinct RVM descending projections modulate pain behaviors and spinal cord projection neuron properties, before and after pain is provoked in neuropathic or inflammatory pain models. The development of new tools that allow pain researchers to make more accurate predictions of the animal's pain state is also significant. For example, PAWS[16], an automated pain assessment platform, can successfully distinguish spinally (e.g. withdrawals) versus centrally (e.g. licking) mediated behaviors. Unquestionably, a better understanding of RVM influences on both sensory and affective components of the pain experience is critical to the development of novel chronic pain management therapies.

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