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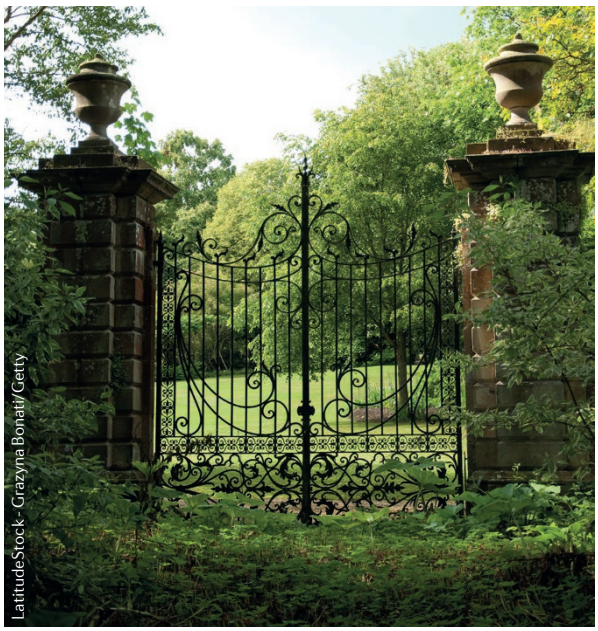
PAIN

A gatekeeper circuit

> RVM neurons that project to the spinal enkephalinergic interneurons are primarily GABAergic and act to facilitate mechanical pain processing

Emotions and expectations can alter sensitivity to pain, as seen in cases of analgesia in response to placebo and anxiety-driven pain exacerbation. This modulation of pain processing is driven by descending input to the spinal cord, yet little is known about the cell types and circuits involved. In their recent study, Scherrer and colleagues identify and dissect a circuit for the descending modulation of mechanical pain thresholds in mice in response to internal states such as stress.

Endogenous opioids such as enkephalins are important modulators of pain processing in the spinal cord dorsal horn, but the cell types involved in their effects are unclear. The authors combined genetic labelling with chemogenetic inhibition to identify a population of GABAergic dorsal horn interneurons that generate enkephalins and act to modulate sensitivity to noxious mechanical stimulation in mice. By optogenetically stimulating enkephalin and GABA release from spinal enkephalinergic neurons, the authors showed that these cells mediate their effects on mechanical pain thresholds by inhibiting presynaptic transmitter release from primary sensory afferents.



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Hypothesizing that these spinal enkephalinergic interneurons could be executors of descending pain modulation pathways, the authors used rabies virus-mediated tracing to determine whether these cells receive input from the brain. They identified a monosynaptic input from the rostral ventromedial medulla (RVM), a known component of descending pain control pathways. The authors further showed that the RVM neurons that project to the spinal enkephalinergic interneurons are primarily GABAergic and act to facilitate mechanical pain processing, suggesting a disynaptic pathway through which RVM neurons inhibit the antinociceptive actions of spinal enkephalinergic interneurons. Indeed, electrophysiological recordings showed that activation of this population of RVM neurons reduces the excitability of the spinal enkephalinergic interneurons to which they project.

These findings demonstrate a circuit through which the brain — and thus internal states — could influence pain processing. Indeed, the authors showed that the RVM neurons that project to the spinal enkephalinergic interneurons receive inputs from several brain regions known to be involved in stress responses. To determine whether stress acts through this pathway to modulate nociception, the authors subjected mice to acute or chronic restraint stress. Chronic stress resulted in increased mechanical hypersensitivity and reduced activity (as indicated by FOS expression) of spinal enkephalinergic interneurons. By contrast, acute stress reduced mechanical hypersensitivity and increased the activity of these neurons.

In this study, the authors have described a pathway through which descending input from the brain can act as a 'gatekeeper' to modulate mechanical pain transmission through the release of endogenous opioids by a key population of interneurons in the spinal cord. It is possible that similar and parallel pathways may modulate other forms of nociceptive information processing.

Katherine Whalley

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