

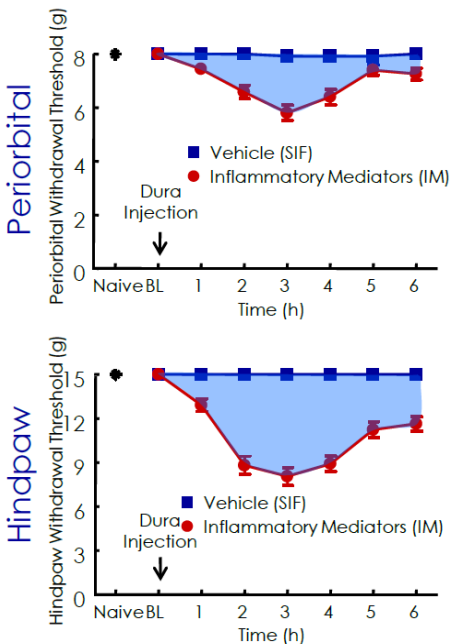
Central Modulation of Cephalic Nociception

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Migraine is characterized as an episodic, unilateral throbbing cephalic pain and that may be accompanied by nausea, vomiting, photophobia and phonophobia that may occur with, or without, aura.¹ Whereas multiple mechanistic hypotheses of migraine have been proposed—including cortical spreading depression, vasodilation, plasma protein extravasation, and sensitization of nociceptive dural afferents—the underlying pathophysiology of this disorder remains unclear. Despite high prevalence in the general population, a unified concept of migraine has not emerged.

A central mechanism hypothesized to drive migraine is that migraine represents a dysfunction of brainstem mechanisms of pain modulation, or more generally, sensory gating.² This idea is attractive because a central dysfunction would explain the multiple triggers and the range of symptoms associated with migraine attacks. Functional imaging studies performed with migraineurs showed activation of pontine brainstem structures that became active with the onset of a migraine headache, and remained active when the pain was resolved with triptans, and suggested the possible existence of a "brainstem generator" or a "migraine center."^{2,3} Although the concept of a brainstem generator of migraine is not universally accepted, it is intriguing that the sites include the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM), which are prominent components of the pain modulatory pathways. The RVM receives inputs from the PAG and exerts bi-directional control over nociception under different physiological and pathophysiological conditions. A facilitating influence from the RVM has been implicated in models of hyperalgesia and persistent pain.⁴ Based on our observations, we have explored the hypothesis that the pronociceptive role of the RVM in sensitized pain states is also implicated in cutaneous allodynia associated with migraine headache. This suggestion is consistent with the observations that electrical stimulation of the PAG or microinjection of naratriptan into the PAG inhibits responses of trigeminal neurons to dural stimulation.^{5,6}

To develop and validate a model of cutaneous allodynia triggered by dural inflammation for pain associated with headaches, as well as to explore neural mechanisms underlying cephalic and extracephalic allodynia, we applied inflammatory mediators (IM) to the dura of unanesthetized rats via previously implanted cannulas, and then we characterized sensory thresholds of the face and hind-paws.⁷ IM elicited robust facial and hind-paw allodynia, which peaked within 3 hours.



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The effects, which resembled the cutaneous allodynia seen in migraineurs, were reversible with sumatriptan, naproxen, and a calcitonin gene-related peptide (CGRP) antagonist, but they did not respond to a neurokinin-1 antagonist. The data indicate that facial and hind-paw allodynia associated with dural stimulation is a useful surrogate of pain associated with primary headache—one that may be exploited for development of novel therapeutic strategies for headache pain.⁷

Although frequent use of headache medications causes some patients to develop medication overuse headache (MOH), the underlying neural mechanisms of this phenomenon remain unknown. We recently treated rats with subcutaneous sumatriptan 0.6 mg/kg daily or saline for 6 days to determine if sustained exposure would cause neural adaptations or alterations in responses to migraine triggers.⁸ Sumatriptan caused a time-dependent decrease in withdrawal threshold in both the face and hindpaws within one day of exposure—a finding maintained throughout the infusion period and for 18 days after termination of treatment. Sumatriptan also significantly increased the expression of neuronal nitric oxide synthase or CGRP in trigeminal ganglion cells on day 6 and on day 20 after the termination of therapy. We concluded that sustained sumatriptan exposure increases the likelihood of developing primary headache by causing pronociceptive neural adaptations that persist even after treatment is stopped and sensory thresholds return to baseline. The triptan-induced neural adaptations and behavioral hypersensitivity we observed may serve as a useful model to explore mechanisms underlying medication overuse headache and, possibly, chronic migraine.⁸

References

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