Editorial

What does the pathophysiology of migraine tell us about treatment?

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"When given early, triptans not only relieve headache, but prevent the development of allodynia."

Migraine is a primary brain disorder resulting from altered modulation of normal sensory stimuli. It was previously believed that the migraine aura is caused by cerebral vasoconstriction and that the headache is associated with cerebral or meningeal reactive vasodilation [1]. It is now believed that the migraine aura is due to cortical spreading depression, not vasoconstriction; ischemia rarely occurs, if it does at all. Headache starts when cerebral blood flow is reduced, but not to ischemic levels and it is not due to reflex vasodilation [2,3]. Woods and coauthors reported on a PET study of a patient with migraine that showed propagated hypoperfusion during the pain phase of a migraine attack [4]; Denuelle *et al.* investigated migraine patients using PET and also found cortical hypoperfusion during the pain phase of migraine [5].

The aura is triggered in the hyperexcitable cortex. The fortification spectrum of the visual aura corresponds to an event moving across the cortex at 2–3 mm/min, similar to cortical spreading depression. Cortical spreading depression, originally described by Leão [6], is an intense depolarization of neuronal and glial membranes accompanied by a massive disruption of ionic gradients and loss of membrane resistance.

Headache and its associated neurovascular changes are subserved by the trigeminal vascular system [7]. Headache probably results from activation of meningeal and blood vessel nociceptors combined with a change in central pain modulation. Trigeminal sensory neurons contain the neuropeptides substance P, calcitonin gene-related peptide and neurokinin A, as well as glutamate [8]. Trigeminal nerve activation is accompanied by the release of vasoactive neuropeptides from the nerve terminals. These mediators produce mast cell activation, sensitization of the nerve terminals, extravasation of fluid into the perivascular space (plasma protein extravasation) around the dural blood vessels and

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platelet activation (neurogenic inflammation) [9,10]. Neurogenic inflammation sensitizes peripheral nociceptors (peripheral sensitization). Neurons show increased responsiveness to both painful and nonpainful, previously innocuous, stimuli. The receptive fields expand and pain is felt over the greater part of the head. This results in hyperalgesia (increased sensitivity to pain) and cutaneous allodynia (the perception of pain when ordinarily nonpainful stimuli are applied to the skin). The normal rhythmic pulsation of the meninges, which are innervated by peripheral trigeminal neurons, is interpreted as painful.

Central sensitization of trigeminal nucleus caudalis neurons (the central relay of the trigeminal nerve) results in muscle tenderness and cutaneous allodynia during a migraine attack. Cutaneous allodynia, which can either be confined to, or occur both within and outside of, the pain-referred area, is experienced by more than 70% of migraineurs [11]. The development of cutaneous allodynia during migraine can be studied by measuring the pain thresholds in the head and forearms of a patient at several points during the attack [12] and comparing the pain thresholds in the absence of an attack [13]. Patients who develop cutaneous allodynia have progression from local allodynia to extended allodynia over a 1–2 h period during the course of an attack. This progression may reflect the sequential recruitment and sensitization of peripheral and central pain pathways [11,13–16]. Central sensitization can occur as early as 1 h after the onset of migraine pain. Central sensitization initialization depends on input from sensitized peripheral pathways; later, central sensitization can be maintained independently of peripheral input [13].

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Triptans can prevent, but not reverse, cutaneous allodynia [13]. The presence of allodynia predicts the effectiveness of triptans [17]. When given early, triptans not only relieve headache, but prevent the development of allodynia. When given late with established allodynia, triptans are not as effective for pain relief and do not control allodynia, but do decrease throbbing pain (due to peripheral sensitization) [17]. Early intervention may work by preventing cutaneous allodynia and central sensitization, which may play a key role in maintaining the headache. Clinical therapeutic success is greater when migraine attacks are treated early, while pain is mild, rather than later, when pain has progressed to moderate or severe. Giving a triptan before cutaneous allodynia has been established is more likely to produce a pain-free response [15]. In a study of 31 migraineurs treating 34 allodynia-associated migraine attacks and 27 attacks not associated with allodynia, patients were pain free within 2 h of dosing with a triptan in 93% of nonallodynic attacks compared with 15% in allodynic attacks [14]. In the presence of allodynia, triptan treatment was similarly ineffective for migraine attacks treated 1 versus 4 h after pain onset, whereas in its absence, it was similarly effective. The presence or absence of allodynia predicted the ability of a triptan to render a patient pain free with 90% accuracy. Consistent with these results, administering sumatriptan in conjunction with an inflammatory soup topically applied to the rodent dura prevented the development of central sensitization, whereas sumatriptan administered 2 h later did not [14].

Patient differences in cutaneous allodynia may result from differences in trigeminal nociceptive sensitization [18]. Peripheral sensitization of trigeminal meningeal nociceptors results in intracranial hypersensitivity (manifested as pain intensification triggered by bending over, sneezing or coughing). This may occur alone or be followed by central sensitization of central trigeminal (second-order) neurons in the brainstem, resulting in cutaneous allodynia [18].

Between-patient triptan responsiveness, such as responsiveness within a given migraine attack, may be predicted by the degree of cutaneous allodynia experienced. Those who never experience allodynia may always respond to triptans. In the 31-patient study described above, patients who never developed allodynia were, in fact, highly likely to become pain free after using a triptan, regardless of the time of triptan administration relative to the onset of pain [14]. Those who develop allodynia during the later phase of the migraine attack may respond particularly well to triptans administered early during the course of the attack, while pain is mild. Those who experience constant allodynia, both during and between migraine attacks, may constitute a group that never responds to triptans. These possibilities warrant evaluation in clinical studies. Allodynia is prevalent in patients with migraine, and its presence is 90% accurate at predicting pain-free triptan efficacy.

Conclusion

Peripheral sensitization can lead, in a time-dependent manner, to central sensitization.

Treating early with a triptan, while the pain is mild, produces better outcomes, in part by preventing central sensitization.

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