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Where do triptans act in the treatment of migraine?

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Migraine headache is a pervasive but poorly understood primary pain disorder. Sumatriptan and the ‘triptan’ class of serotonin receptor subtype-selective drugs have well-established efficacy in treating the pain of migraine. Although sumatriptan was originally selected to target vasoactive properties thought to be fundamental to the etiology of migraine, other studies point to an action of triptans at several levels of the nervous system. To this day, however, it is not clear whether the antimigraine activity of the triptans involves an action only in the periphery or in the CNS as well. Because sumatriptan is hydrophilic, it penetrates the blood–brain barrier poorly, suggesting a peripheral site of action. On the other hand, it has been proposed that the barrier is compromised in migraineurs, so a CNS site of action has not been ruled out. Finally, the basis for the apparent selectivity of triptans in the treatment of migraine pain but not other kinds of somatic pain is still not understood. Determining that mechanism of triptan action will likely provide important new insights into the unique and essential features of migraine.

1. Peripheral mechanisms

Graham and Wolff (1938) first proposed that the pain of migraine results from abnormal cranial vascular distention. They were influenced by (1) the association between migraine relieving properties of ergotamine tartrate infusion and arterial vasoconstriction and (2) the finding that compression of the common carotid artery or superficial temporal artery reduces pain in many migraine attacks. Although the relationship between vascular changes and migraine was still uncertain, the vasoactive, serotonergic properties of ergotamine on isolated artery and vein preparations led to the development of sumatriptan, a serotonergic agonist with selective activity on 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors. The vasoconstrictive properties of triptans are mediated by an action on 5-HT_{1B} in arterial smooth muscle. On the other hand, although sumatriptan-mediated vasoconstriction can dose-dependently increase blood flow velocity in middle cerebral vessels, because these vascular changes are not temporally related to the resolution of the migraine attack (Limmroth et al., 1996), it is still unclear whether triptan activation of vascular 5-HT_{1B} receptors is necessary for the treatment of migraine.

The triptans are also thought to inhibit the abnormal activation of peripheral nociceptors. In an experimental model of migraine, called sterile neurogenic inflammation, an abnormal activation of nociceptors in the dura mater triggers vascular changes, including plasma protein

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extravasation (PPE) (Moskowitz and Cutrer, 1993). The triptans reduce PPE, presumably by inhibiting the activation of nociceptors and preventing the peripheral release of vasoactive peptides, including substance P and calcitonin gene related peptide (CGRP). Venous CGRP itself provides another useful measure of peripheral neuronal activation. In animal models and in humans, CGRP is elevated in the external jugular vein after stimulation of the trigeminal ganglion as well as during migraine attacks. Consistent with a peripheral action for triptans, treatment with sumatriptan reduces CGRP levels as the migraine subsides (Goadsby and Edvinsson, 1993).

The localization of 5-HT_{1D} receptors on peptidergic nociceptors also points to a contribution of this receptor subtype in the reduction of peripheral activation by triptans (Potrebic et al., 2003). The 5-HT_{1D} receptor-selective agonist PNU-142633 showed greater potency than sumatriptan in blocking electrically induced PPE, and had little to no detectable vascular activity in carotid, meningeal, or coronary arteries. Although a small single trial of PNU-142633 failed to show benefit in the treatment of migraine (Gomez-Mancilla et al., 2001), concerns over its side effects may have prevented a full investigation of the potential for this 5-HT_{1D} agonist.

2. CNS mechanisms of triptan action

An important model of migraine pathogenesis involves central sensitization, in which peripheral stimulation of dural and vascular afferents by electrical, chemical, or mechanical stimuli cause both excitation and sensitization of neurons in the trigeminal nucleus caudalis (TNC) with dural receptive fields (Goadsby and Zagami, 1991; Strassman et al., 1996). As implied by this model of peripheral and central sensitization, the development of cutaneous allodynia in cranial and non-cranial regions of the body involves the sequential recruitment of spinal and supraspinal nociceptive responses during the evolution of a migraine attack (Burstein, 2001).

The presence of triptan binding sites and triptan receptor mRNA within the CNS, notably in the dorsal raphe and periaqueductal gray of the midbrain (Bonaventure et al., 1998), leaves little doubt as to the potential for CNS effects of the triptans. But the relatively low brain penetration of sumatriptan called into question whether CNS effects were at all necessary for its antimigraine activity (Humphrey et al., 1991). Disruption of the blood-brain barrier by hyperosmolar mannitol infusion was used to study possible CNS actions of sumatriptan. Only under those conditions did systemic sumatriptan infusion inhibit evoked responses of single units in the TNC (Kaube et al., 1993), and suppress Fos protein expression, a marker of neuronal activity (Shepherd et al., 1995). Consistent with these observations, iontophoresis of triptans in the TNC also potently inhibited both evoked and spontaneous activity of neurons with dural receptive fields (Storer and Goadsby, 1997).

The potential benefits of triptan activity in the CNS, not surprisingly, became more apparent with the introduction of more lipophilic triptans. For example, zolmitriptan and rizatriptan block the dura-evoked activation of TNC neurons in both electrophysiological and *c-fos* studies (Cumberbatch et al., 1997; Hoskin and Goadsby, 1998). It is noteworthy however, that despite the evidence for central modulatory effects of lipophilic triptans, the greater lipophilicity and better brain penetration of the various triptans do not correlate with significantly greater clinical efficacy over sumatriptan (Ferrari et al., 2002).

As to the possible action of triptans in the TNC, there is an important distinction between a possible presynaptic action, on the central terminals of nociceptors, and a postsynaptic action, on the second order 'pain' transmission neuron. Two studies argue for a significant central, presynaptic mechanism. The first used single unit recordings from both presynaptic trigeminal afferents and postsynaptic neurons with dural receptive fields (Levy et al., 2004). As measured

by afferent activity at the trigeminal ganglion, sumatriptan was unable to inhibit peripheral sensitization produced by dural application of inflammatory mediators, but recordings from the second order neurons showed that sumatriptan had, in fact, inhibited the transmission of sensitized afferent activity to the central target. Interestingly, central neurons that had already been sensitized were not further modulated by sumatriptan. Using an in vitro trigeminal ganglion-TNC preparation, Jennings et al. (2004) showed that sumatriptan dose-dependently reduced the spontaneous firing rate of postsynaptic miniature excitatory postsynaptic currents (mEPSC's), without changing the amplitude of the mEPSC. Taken together these data argue that sumatriptan is a potent inhibitor of neurotransmitter release at the central terminal of the nociceptor.

To isolate the postsynaptic action of triptans, Goadsby and colleagues bypassed the primary afferent and focused on the regulation of postsynaptic responses to microiontophoretic application of glutamate or the NMDA receptor agonist DL-homocysteate. These agonists increased the spontaneous firing rate of TNC neurons with receptive fields in the sagittal sinus; co-administration of pulses of sumatriptan reduced that firing activity (Goadsby et al., 2001). The authors acknowledged that this experiment did not exclude the interesting possibility of triptan action on an intrinsic interneuron that modulates the activity of the neuron in question. Perhaps the most direct evidence for multiple CNS sites of triptan action is the report that microinjection of naratriptan into the periaqueductal gray selectively inhibits durally-evoked nociceptive responses of TNC neurons with shared dural and facial receptive fields (Bartsch et al., 2004).

3. Are triptans migraine-selective?

5-HT_{1B} and 5-HT_{1D} receptors are not only localized to afferents of the head but are found throughout the body (Potrebic et al., 2003; Wotherspoon and Priestley, 2000). This is puzzling in light of the purported specificity of triptans for migraine pain. In fact, there is only limited controlled clinical data to support a migraine-selective activity for triptans. On the one hand, sumatriptan failed to treat the indomethacin-responsive primary headache disorders, chronic paroxysmal hemicrania and hemicrania continua (Antonaci et al., 1998), nor was it effective in a study of myofascial temporal muscle pain (Dao et al., 1995), or in a small series with atypical facial pain (Harrison et al., 1997). On the other hand, cluster headache is a distinct primary headache disorder that clearly responds to triptans (Ekbom et al., 1993). Nociceptive thresholds are modulated by sumatriptan in patients with extracranial allodynia during a migraine attack, but the mechanism of action for that change is presumed to be due to the alteration of the underlying central mechanism of migraine, rather than a direct action on non-trigeminal nociceptive systems (Burstein, 2001). What is clearly needed is a study of triptan treatment in patients with a well-defined non-cranial somatic pain disorder, in which nociceptive thresholds can be assessed in addition to self-reported pain relief scores.

In electrophysiological studies in animals, sumatriptan selectively inhibited acute responses to dural stimulation in the TNC and was without an effect on nociceptive responses in the spinal cord (Cumberbatch et al., 1998). Behavioral models of triptan action also argue selectivity for cranial pain, with some exceptions. For example, a preliminary study of acute somatic thermal or mechanical pain in rodents did not detect an antinociceptive effect of sumatriptan (Skingle et al., 1990). In another study, sumatriptan reduced pain-related behaviors following acute intracarotid injection of bradykinin in rats (Ottani et al., 2004) but the study did not include a comparable model of somatic pain. Finally, a detailed study comparing neuropathic models of trigeminal and sciatic pain did detect a selective antinociceptive effect for trigeminal pain with both sumatriptan and zolmitriptan (Kayser et al., 2002). In contrast, evidence for the non-selective activity of triptans was reported in an inflammatory model of pain, where sumatriptan

dose-dependently reduced behavioral signs of hyperalgesia after carageenan injection of the mouse hindpaw (Bingham et al., 2001).

One hypothesis for the selectivity of triptan action arose from studies of the distribution of 5-HT_{1D} receptor in primary afferent terminals. Rather than being localized on the plasma membrane, the receptors are concentrated in the dense core vesicles that store peptide neurotransmitters (Potrebic et al., 2003). This model of activation-dependent 5-HT_{1D} receptor availability is consistent with the fact that triptans do not prevent the pain of migraine, and predicts that triptans would only be effective in experimental models of pain in which a prior stimulus has activated nociceptors and externalized the triptan receptor to the presynaptic membrane. Much as for clinical studies, we clearly need additional studies of triptans as putative analgesics in well-accepted animal models of acute and chronic somatic pain.

4. The blood–brain barrier and migraine

Whether there are transient changes in blood–brain barrier permeability during migraine is as important to understanding the mechanism of triptan actions on the CNS as it is to understanding the pathophysiology of migraine in general. Changes in blood–brain barrier are hypothesized to occur in the migraine model of sterile neurogenic inflammation (Moskowitz and Cutrer, 1993). In the migraine model of cortical spreading depression, changes in meningeal metalloprotease-9 activity are thought to reflect such changes in the maintenance of blood–brain barrier integrity (Gursoy-Ozdemir et al., 2004). Preliminary and anecdotal radiographic reports of blood–brain barrier permeability, using magnetic resonance imaging during the migraine attack, are, however, not consistent (Friedenberg and Dodick, 2000; Nissila et al., 1996) and underscore the need for a more systematic study of this question.

A recent study that indirectly suggests a CNS action of oral sumatriptan reported electroencephalogram changes in normal healthy volunteers (van der Post et al., 2002). An alternative approach would be to use positron emission tomography to map the absorption of ¹¹C-sumatriptan into the human brain, and to determine whether this pattern is modified by a migraine attack. These studies will not only determine which brain regions are targeted by triptans, but taken together with further analysis of the respective contributions of the different triptan receptors, will provide important information on the complex pathophysiology of migraine.

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