Published in final edited form as:

Pain. 2011 January ; 152(1): 4–5. doi:10.1016/j.pain.2010.10.026.

Trigeminal TRPs and the scent of pain

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The neurological mechanisms leading to headache pain are complex and poorly understood. Genetic studies of familial migraine conditions have provided important insights into the potential physiological causes underlying headache conditions. Familial cases of hemiplegic migraine have been linked to mutations in genes encoding for calcium channels, sodium-potassium ATPase and for sodium channel subunits [5]. Recently, a dominant negative mutation in the gene that codes for the TRESK potassium channel subunit was linked to a familial form of migraine with aura [14]. Mutations in these genes are likely to lead to heightened excitability of peripheral nociceptors and of CNS pain circuits that contribute to the headache. Monogenic migraine conditions are rare, and genetic association studies have begun mapping migraine susceptibility loci in larger patient populations [1]. Other headache conditions, such as cluster or tension headaches, are less clearly defined and genetic investigations are in early stages.

Environmental factors likely act together with genetic and physiological causes to trigger headache episodes. Indeed, epidemiological studies have associated headaches with environmental air pollution and second hand smoke exposures [12;16] and migraineurs often report that light, sound and olfactory stimuli can trigger episodes. A condition termed “Multiple Chemical Sensitivity”, describing patients who develop heightened sensitivity to chemical irritants following high level exposures, is often associated with headache. Case studies found that certain volatile natural products can trigger cluster headaches [2].

A new study by Kunkler et al. in this issue of *Pain* sheds light on a potential mechanism through which irritants can trigger headache [13]. Using laser Doppler analysis the authors show that application of chemical irritants to the nasal mucosa of rats increases blood flow in meningeal vessels in the dura. The irritants used by the authors are agonists of the sensory neuronal transient receptor potential ion channel, TRPA1, which was recently identified as a target for a broad spectrum of environmental irritants [3]. These include acrolein and croton aldehyde, the major electrophilic irritants in cigarette smoke, oxidants such as chlorine and ozone, formaldehyde, tear gas agents and industrial chemicals. If inhaled, these chemicals activate TRPA1 channels in trigeminal nerve endings in airway mucosa, leading to irritation and pain, as well as sneezing, cough and glandular secretions. Studies investigating the role of TRPA1 in a mouse model of asthma found that the ion channel promotes the local allergic response in the airways, and is essential for the irritant-induced release of calcitonin

Conflict of Interest

Sven-Eric Jordt is serving on the Scientific Advisory Board of Hydra Biosciences (Cambridge, MA), a biopharmaceutical firm developing TRP channel antagonists for the treatment of pain and inflammation..

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gene-related peptide (CGRP) from sensory nerve endings [4]. CGRP is an essential mediator of neurogenic inflammation, causing vasodilation and serving as a chemotactic signal for inflammatory immune cells.

Kunkler *et al.* show that TRPA1-induced CGRP release may also be the key mechanism through which irritants increase meningeal blood flow. They observed that an antagonist of the CGRP receptor, CGRP_{8–37}, prevented irritant-induced dural blood flow increase. CGRP was likely of trigeminal origin, since radioimmunoassay revealed that irritating TRPA1 agonists induced the release of CGRP from cultured trigeminal neurons. The crucial role of TRPA1 in this mechanism was further supported by the finding that nasal application of HC-030031, a TRPA1 antagonist, prior to irritant exposure, also prevented increases in dural blood flow.

How does activation of TRPA1 in nasal nerve endings evoke CGRP release from perivascular nerve endings in the dura? Both ocular and nasal trigeminal nerve endings are derived from the ophthalmic branch of the trigeminal nerve, which also innervates parts of the meninges. Dural CGRP release thus may be triggered through axon reflexes that spread from the ophthalmic to other trigeminal branches innervating the meninges. This mechanism is also triggered by activation of TRPV1, the capsaicin receptor, which is co-expressed with TRPA1 in chemosensory C-fibers. Kunkler *et al.* administered capsaicin to the rat nose, and, similar to TRPA1 agonists, found increased dural blood flow, thereby demonstrating a general, C-fiber driven mechanism of dural CGRP release.

The proposed mechanism of irritant induced headache centering on CGRP shows intriguing parallels with studies linking dural CGRP release to migraine. CGRP dilates human cerebral and meningeal arteries and induces dilation of meningeal vessels in animal models [6]. Intravenous infusion of CGRP was found to trigger migraine episodes in patients suffering from migraine with aura and without aura, but not in familial hemiplegic migraine patients [15;10]. Elevated CGRP levels have also been associated with other primary headaches, including cluster headache and paroxysmal hemicranias [8–9].

While the authors' data provide clear support for a functional link between nasal irritant exposures and dural vasodilation, it is uncertain whether this effect, by itself, will be sufficient to trigger a headache episode. Trigeminal or central sensitization, through either genetic or inflammatory factors, may be required to elicit headache. Olfactory, auditory or visual stimuli may move the system further towards disequilibrium. Interestingly, although mustard, wasabi and horseradish all contain large amounts of TRPA1 agonist and are consumed by millions on a daily basis, these foods have not generally been associated with headache. This is the case even though significant amounts of mustard oil reach the nasal cavity through evaporation during consumption. Exposures to tear gas agents, the most potent TRPA1 agonists known, while inducing intense ocular and airway pain and reflexes, also has not been reported to induce headache. The reason for the lack of documented cases may be a result of prior conditioning, with irritant-sensitive individuals avoiding consumption of and exposures to irritants.

In general, the dearth of clinical studies linking specific chemical exposures to headache conditions is surprising, especially in light of the many subjective reports of chemical sensitivity of individual migraine patients [7]. Hopefully, the interesting mechanistic findings by Kunkler *et al.* will be noticed by clinical and environmental health scientists, and will encourage them to design more detailed studies that examine the sensitivity of headache patients to specific chemical exposures.

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