Herbalism helps headache

Migraine is a common, complex and certainly fascinating disorder of the brain (Lipton et al., 2001; Goadsby et al., 2002), which most active clinicians would agree needs more treatments (Goadsby and Sprenger, 2010). Over the last two decades we have seen substantial advances in migraine therapeutics with the development of triptans, serotonin 5-HT<sub>1B/1D</sub> receptor antagonists (Ferrari et al., 2001), gempants, calcitonin gene-related peptide (CGRP) receptor antagonists (Ho et al., 2010), and most recently ditans, serotonin 5-HT<sub>1F</sub> receptor agonists (Ferrari et al., 2010). Each targets, among other sites the trigeminovascular system, the trigeminal afferent innervation of the pain-producing meninges (Feindel et al., 1960; McNaughton and Feindel, 1977) that projects to second order afferents in the trigeminocervical complex (Akerman et al., 2011). This issue of Brain illustrates yet another target, weaving a very engaging tale of biology, herbalism and therapeutics (Nassini et al., 2012).

Nassini and colleagues (2012) studied a candidate compound, the monoterpenic ketone umbellulone, a volatile component of the leaves of the California Bay Laurel (Umbellularia californica). The tree is said by the authors to be a ‘headache tree’ since inhalation of its vapours can cause headache, a story reminiscent of the origins (Laws, 1898) of the now well established concepts on the role of nitric oxide in migraine (Thomsen and Olesen, 2001). It is remarkable that the tree is said to be both headache provoking, and used to relieve headache by binding the leaves and twigs around the head (Barrett and Gifford, 1933). The latter fact is cited by Wikipedia on the same page that already cites Nassini and colleagues (http://en.wikipedia.org/wiki/Umbellularia), a sobering thought concerning the modern dissemination of knowledge. The authors then set out to study what umbellulone may target to produce headache.

They hypothesized, based on its rapid binding of thiols, an action on the transient receptor potential ankyrin 1 (TRPA1) channel located on peptidergic, nociceptive trigeminovascular neurons. TRPA1 is part of the temperature-sensitive transient receptor (release) potential (TRP) ion channel family (Story et al., 2003), which is crucially involved in thermal detection. First identified by the pioneering work of Julius and colleagues, the capsaicin receptor was heat-activated (Caterina et al., 1997), and called the vanilloid receptor, before being renamed the TRPV1 receptor. It has been known for some time that these receptors are involved in pain as well as thermal sensation (Tominaga et al., 1998). Of the nearly 30 TRP channels, eight sense hot or warm temperatures (TRPV1–4, TRPM2, 4 and 5) and two are activated by cold (TRPA1 and TRPM8), covering a remarkable range of temperatures from 10°C to 53°C (Ramsey et al., 2006).

The TRPV1 channel has been considered as a therapeutic target in migraine (Levy, 1995) and cluster headache (Sicuteri et al., 1989; Fusco et al., 1994), although effective blinding of studies has been very problematic (Marks et al., 1993). Moreover, using an antagonist approach with SB-705498 (Rami et al., 2006), which was not found useful in the laboratory using a different compound (Summ et al., 2011), a clinical trial was conducted (http://clinicaltrials.gov/ct2/show/NCT00269022), which seems to have been finished for more than 2 years without any announcement or progress report—it seems likely to have failed. On this background the new findings are all the more encouraging and exciting.

Nassini et al. (2012) show that umbellulone selectively activates the TRPA1 channel as expressed in HEK293 cells but not in untransfected cells. They describe activation of rat trigeminal ganglion neurons that can be blocked by the TRPA1 receptor.
antagonist HC-030031. Given the role of CGRP in migraine (Ho et al., 2010), this indicates that umbellulone blocks calcium-dependent CGRP release from rat trigeminal nerve terminals in dura mater. Given that CGRP is elevated in migraine during severe attacks (Goadsby et al., 1990), that CGRP release is blocked by sumatriptan in humans (Goadsby and Edvinsson, 1993), and CGRP receptor antagonists are effective in acute migraine (Olesen et al., 2004), this pattern of change seems promising. The authors should be congratulated in harnessing modern molecular biological methods to show that the CGRP effect of umbellulone was absent in TRPA1–/– deficient mice. Moreover, nociceptive behaviour after umbellulone was also absent in the TRPA1–/– deficient mice. Furthermore, intranasal and intravenous administration of umbellulone caused a dose-dependent increase in dural blood flow that could be blocked by either a TRPA1 receptor antagonist or a CGRP receptor antagonist. Taken together the authors consider one potential action of the ‘headache tree’ vapour is to activate TRPA1 channels on nociceptive trigeminal afferents with consequent release of CGRP and presumed activation of trigeminovascular pathways to produce headache. It does not seem unreasonable at least to test this target in humans if suitable TRPA1 receptor antagonists can be identified.

Aspirin came to us from nature. There is much to be learned from deconstructing herbalist approaches; to understand their basis, study their biology and examine the potential for carefully constructed new therapies. Headache remains such a remarkably stimulating field, a rich biology of brain science to be tapped and a marvellous clinical opportunity to double and redouble our ability to help some of our most disabled patients.

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