Parthenolide inhibits nociception and neurogenic vasodilatation in the trigeminovascular system by targeting TRPA1 channel

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While feverfew has been used for centuries to treat pain and headaches and is recommended for migraine treatment, the mechanism for its protective action remains unknown (Johnson ES, et al., Br Med J 1985; Shrivastava R, et al., Clin Drug Investig 2006). Migraine is triggered by calcitonin gene-related peptide (CGRP) release from trigeminal neurons (Goadsby PJ & Edvinsson L., Brain 1994). Peptidergic sensory neurons, express a series of transient receptor potential (TRP) channels, including the ankyrin 1 (TRPA1) channel. Recent findings have identified agents either inhaled from the environment or produced endogenously, which are known to trigger migraine or cluster headache attacks, as TRPA1 simulants (Nassini R, et al., Brain 2012; Kunkler PE, et al., Pain 2011). A major constituent of feverfew, parthenolide, may interact with TRPA1 nucleophilic sites (Skalska J, et al., PLoS One 2009), suggesting that feverfew antimigraine effect derives from its ability to target TRPA1.

We found that parthenolide stimulates recombinant (transfected cells) or natively expressed (rat/mouse trigeminal neurons, and urinary bladder sensory nerve terminals) TRPA1, where it, however, behaves as a partial agonist. Furthermore, in rodents, after initial stimulation, parthenolide desensitizes the TRPA1 channel, and renders peptidergic, TRPA1-expressing nerve terminals unresponsive to any stimulus. This effect of parthenolide abrogates nociceptive responses evoked by stimulation of peripheral trigeminal endings.

TRPA1 targeting and neuronal desensitization by parthenolide inhibits CGRP release from trigeminal neurons and CGRP-mediated meningeal vasodilatation, evoked by either TRPA1 agonists or other unspecific stimuli. TRPA1 partial agonism, together with desensitization and nociceptor defunctionalization, ultimately resulting in inhibition of CGRP release within the trigeminovascular system, may contribute to the antimigraine effect of parthenolide.

Goadsby PJ & Edvinsson L. Brain 1994;117: 427-34.
Johnson ES et al., Br Med J (Clin Res Ed) 1985;291: 569-73.
Shrivastava R et al., Clin Drug Investig 2006;26: 287-96.
Nassini R et al., Brain 2012;135: 376-90.
Kunkler PE et al., Pain 2011;152: 38-44.
Skalska J, et al., PLoS One 2009;4: e8115.

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