The antimigraine compound Parthenolide, contained in the feverfew herb, selectively activates and desensitizes the Transient Receptor Potential Ankyrin 1 (TRPA1) channel.

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Parthenolide, the main bioactive component extracted from the leaves of *Tanacetum parthenium*, or feverfew herb, exhibits anti-inflammatory properties and is used for the treatment of migraine and arthritis. However, the mechanism(s) of action of these possible beneficial effects of feverfew is still not unclear. Parthenolide is a sesquiterpene lactone with a α-methylene-γ-lactone ring and an epoxide moiety that can interact with nucleophilic sites of several molecules. The Transient Receptor Potential Ankyrin 1 (TRPA1) channel, co-localized on primary sensory nerves with the "capsaicin receptor" (TRPV1), is activated by a wide variety of noxious and irritant stimuli. These include a series of exogenously or endogenously produced highly reactive molecules that covalently modify cysteine or lysine residues of the protein. We hypothesized that parthenolide, which can trap thiol groups in a irreversible complex, activates and desensitizes TRPA1 channel expressed on primary sensory nerves, producing, through this mechanism, anti-inflammatory and analgesic effects.

By using calcium imaging assay and electrophysiology, we tested whether parthenolide was able to gate human and rodent TRPA1 channel. In addition, its ability to release peptide neurotransmitter from sensory nerve endings was studied. To assess whether parthenolide could cause desensitization we studied the contractile responses evoked by parthenolide in rat urinary bladder, or the irritant response in the eye wiping assay. In all tests selective TRPA1 antagonist or *Trpa1*$^{-/-}$ mice were used.

Both calcium imaging and electrophysiology experiments showed that parthenolide selectively activates, in a concentration-dependent manner, human or mouse recombinant TRPA1 channel, expressed in HEK293 or CHO cells and that evokes TRPA1 mediated calcium end electrophysiological responses in mouse/rat isolated dorsal root ganglion neurons. In addition, we demonstrated that parthenolide elicits sensory neuropeptide release from mouse dorsal spinal cord obtained from wild-type, but not from *Trpa1*$^{-/-}$ mice. Ocular instillation of parthenolide evoked a concentration-dependent acute nociceptive behavior (eye wiping) in wild-type mice, an effect that was absent in *Trpa1*$^{-/-}$ mice. Finally, parthenolide contracted isolated strips of the rat urinary bladder *via* a neurogenic mechanism and TRPA1 activation. Exposure to an elevated parthenolide concentration, caused in eye wiping assay, urinary bladder contraction and neuropeptide release desensitization to parthenolide itself and to the TRPA1 agonist, mustard oil, or the TRPV1 agonist, capsaicin, indicating self- and cross-desensitization.

Taken together, these findings indicate that parthenolide selectively activates TRPA1 channel and following exposure to sufficient concentrations/doses causes channel or sensory nerve

desensitization. The ability of parthenolide to desensitize sensory nerve terminals may be responsible for the anti-inflammatory and analgesic effects of the compound, including the reported antimigraine effect.