

## TRPA1 in neuropathic and migraine pain

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Genetic and pharmacological findings indicate that the transient receptor potential ankyrin 1 (TRPA1) channel, expressed by a subpopulation of nociceptors, plays a major role in different models of pain diseases. In particular, TRPA1, a sensor of reactive oxidative, nitrative, and carbonylic species, is activated by an unprecedented series of irritant and pain provoking exogenous and endogenous agents. Notably, TRPA1-expressing primary sensory neurons mediate neurogenic inflammation, and by releasing the pro-inflammatory and vasodilator peptide, calcitonin gene-related peptide (CGRP), seem to contribute to the migraine mechanisms. An indication that TRPA1 plays a major role in neuropathic pain derives from the observation that, in mice, oxaliplatin, paclitaxel, and bortezomib evoked mechanical and cold hypersensitivity, which are abated by TRPA1 antagonists or in TRPA1 deleted mice (Nassini *et al.*, 2011, Materazzi *et al.*, 2012, Trevisan *et al.*, 2013). Given that antioxidant treatment prevented the chemotherapeutic-induced painful neuropathy, the proposal has been advanced that anticancer drugs evoke an oxidative stress burst that, by targeting the TRPA1 channel, induces and maintains pain-like behaviors. Several agents known as triggers of the migraine attack are now recognized as stimulants of the TRPA1 channel. Acrolein, contained in cigarette smoke, or the major volatile component of the *Umbellularia californica* tree (also known the 'headache tree') are able to activate neuronal TRPA1, thereby causing the release of CGRP and the ensuing proinflammatory meningeal vasodilation (Nassini *et al.*, 2012). Accordingly, parthenolide, the major constituent of the analgesic and antimigraine herbal preparation *Tanacetum parthenium*, acts as a partial agonist at the TRPA1 channel, thus limiting the neurogenic inflammation evoked by TRPA1 full agonists (Materazzi *et al.*, 2013). Finally, pyrazolone derivatives, dipyrone and propyphenazone, used worldwide as powerful painkillers, selectively antagonize the TRPA1 channels at relatively low concentrations that are completely inactive as cyclooxygenase inhibitors and fully compatible with those found after analgesic doses in humans (Nassini *et al.*, 2015). In conclusion, we provide evidence that TRPA1 is a major transducer in rodent models of neuropathic pain and that drugs used in humans to treat migraine pain and other types of pain target TRPA1. The current development of TRPA1 antagonists may thus foster new avenues for pain treatment.

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Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation.

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