# Transient Receptor Potential Ankyrin 1 as a Target for Perioperative Pain Management

PERIOPERATIVE pain remains a clinical challenge. The underlying mechanisms of this pain are incompletely characterized, but likely include both peripheral and central sensitization, driven by inflammation, nerve injury, and ischemia. The current armamentarium for perioperative pain includes opioids, nonsteroidal antiinflammatory drugs, and local anesthetics. Many of the emerging drugs aimed at reducing this pain represent reformulations of tried-and-true mechanisms (*e.g.*, intravenous acetaminophen) but fail to provide clinicians truly new approaches to the issue. Wei *et al.*'s "Transient receptor potential ankyrin 1 ion channel contributes to guarding pain and mechanical hypersensitivity in a rat model of postoperative pain" suggests that TRPA1 antagonists could provide a new mechanism to reduce perioperative pain.[1]

***"Given the multiple pain mechanisms involved in perioperative pain, TRPA1 antagonists present a compelling profile for clinical testing."***

TRPA1 is a nonselective cation channel of the transient receptor potential superfamily. Gain-of-function mutations in humans lead to familial episodic pain syndrome, a disorder characterized by debilitating bouts of pain often triggered by cold, fatigue, or lack of food.[2] It is highly expressed by both sensory nerve endings and their cell bodies residing in the dorsal root, nodose, trigeminal, and jugular ganglia. As such, activation of TRPA1 leads to firing of peripheral nociceptors whose projections terminate in the superficial lamina of the dorsal horn.[3]

The activation mechanism of TRPA1 is unique. More than 10 cysteine residues in the ankyrin domains typify the N-terminus of TRPA1. These cysteine residues are subject to covalent modification by reactive chemicals. The best-characterized activator of TRPA1 is allyl isothiocyanate, commonly known as mustard oil, which underlies the pungency of horseradish and wasabi. As our understanding of the channel increases, an expanding array of activators emerges.[4] These include exogenous chemicals such as formaldehyde and acrolein (a key aldehyde in cigarette smoke), but also drugs such as the volatile anesthetics isoflurane and desflurane, the intravenous anesthetics propofol and etomidate,[5] as well as lidocaine.[6] This ability to activate TRPA1 may account for some of the airway irritation and burning pain upon administration of these compounds. TRPA1 antagonists may prevent pain associated with anesthetic injection as well as desflurane-induced bronchospasm.

In addition to synthetic activators, a variety of endogenously produced chemicals also stimulate TRPA1 currents. These include reactive prostaglandins, products of liposome peroxidation such as 4-hydroxynonenal, and reactive oxygen/nitrogen species.[3,4] Because such molecules are often increased in inflammatory, neuropathic, and ischemic pain states, one could assume that TRPA1 activators are present in the postsurgical milieu.

To test for a potential role of TRPA1 in the Brennan model of incisional pain, Pertovaara *et al.* turned to selective TRPA1 antagonists. Briefly, the group made a 1-cm longitudinal incision in the intraplantar surface of the skin, underlying fascia, and muscle. 24–48 h after surgery they assessed spontaneous pain behaviors, measured by guarding score and mechanical hypersensitivity to calibrated monofilaments. The team found that two structurally unrelated antagonists, Chembridge-5861528 (a close structural analog of HC-030031) and A-967079, attenuated both the duration of guarding behaviors and the mechanical hypersensitivity observed when administered intraperitoneally. This suggests that TRPA1 activity contributes to acute incisional pain. Importantly, the effects of Chembridge-5861528 were observed in the absence of detectable locomotor effects in an open-field test, considered a measure of undesirable sedative side effects.

Because both peripheral and central mechanisms contribute to postsurgical pain, the authors sought to determine the site of action of the TRPA1 antagonists. They found that

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local injection of the antagonists into the ipsilateral, but not contralateral, paw was sufficient to reduce sponataneous pain behaviors, indicating that activation of TRPA1 in peripheral nociceptors likely contributes to this pain. In contrast, intrathecal delivery of the TRPA1 antagonists exerted no significant effect on guarding behaviors, suggesting that spinal TRPA1 does not play a major role in spontaneous pain behaviors.

In addition to its effects on guarding behaviors, systemic delivery of TRPA1 antagonists also reduced pain evoked by mechanical stimulation. However, in contrast to what was observed in guarding pain, both intraplantar and intrathecal administration of TRPA1 antagonists reduced mechanical hypersensitivity after incision, reinforcing the idea that different pain mechanisms contribute to different aspects of incisional pain in the rat. Intrathecal delivery seemed to exert relatively more effect on mechanical allodynia whereas local delivery appeared more effective against mechanical hyperalgesia. Neither systemic nor intraplantar delivery of a TRPA1 antagonist affected mechanical sensitivity in an intact, uninjured paw, indicating some specificity of the TRPA1 mechanism for the injured state.

Although the role of TRPA1 on the distal ends of nociceptors has been the subject of substantial study, the function of TRPA1 in the spinal cord remains underexplored. These results suggest that endogenous activators of TRPA1 are increased in the spinal cord after incision and that activation of TRPA1 contributes to maintenance of mechanical hypersensitivity. These data echo previous findings in inflammatory pain with transient receptor potential vanilloid 1 (TRPV1), a related ion channel with a similar expression pattern. Systemic delivery of a TRPV1 antagonist reduced both thermal hyperalgesia and mechanical allodynia. Although local delivery of the compound was sufficient to reduce the heat hyperalgesia, the effect on mechanical allodynia required central penetration.[7] More recent data suggest that reducing TRPV1 activity also reduced neuropeptide levels and spinal glutamate release.[8] Additional work will be required to determine the mechanism by which TRPA1 is involved in spinal cord pain processing.

The work presented here complements multiple other studies that implicate TRPA1 in pain. Human gain-of-function mutations in TRPA1 lead to a congenital pain disorder termed familial episodic pain syndrome, indicating that TRPA1 overactivity is sufficient to cause pain.[2] TRPA1 antagonists are efficacious in multiple other rodent pain models including those thought to represent inflammatory pain, neuropathic pain, visceral pain, and chemically evoked pain.[3,9] They are also efficacious in multiple rodent models of anesthetic-induced pain.[5,6] Given the multiple pain mechanisms involved in perioperative pain, TRPA1 antagonists present a compelling profile for clinical testing. Because TRPA1 expression appears low outside of sensory neurons, there is significant optimism that selective TRPA1 antagonist will have a good safety profile. Preclinical experiments in rodents suggest that the thermoregulation issues that plagued TRPV1 antagonists may not accompany block of TRPA1.[10] Whether blocking TRPA1 in sensory neurons that innervate the organs such as the lung and intestine will produce undesired side effects such as changes in gastrointestinal mobility or cough reflexes remains to be seen. Results of these tests should be available in the coming years, because two groups have announced that their TRPA1 antagonists have entered phase I clinical trials. It is only with human data that we will be able to truly assess the value of TRPA1 as an analgesic target.

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