

Wasabi and a Volatile Anesthetic

DECADES ago, nonspecific theories of anesthetic mechanisms yielded more testable hypotheses predicated on anesthetic interactions with specific protein targets. Specific molecular targets have been identified that mediate some individual behavioral effects of intravenous anesthetics. Although many putative targets have been put forth for volatile anesthetic action, no behavior induced by volatile anesthetics has been tied to a specific molecular target. In this issue of ANESTHESIOLOGY, Eilers *et al.*¹ have linked a specific side effect of some volatile anesthetics, pungency, to activation of the transient receptor potential cation channel ankyrin receptor (TRPA1). Pungency is the activation of a nocifensive reflex in the upper airway that is common to the volatile anesthetics, isoflurane and desflurane, but not induced by halothane or sevoflurane. The upper airway is highly innervated by afferent C-fibers that are important in pain transmission and potentially in the airway reflexes induced by isoflurane and desflurane. Many native and exogenous substances known to induce airway sensitivity also play a role in pain sensitivity including bradykinin, nitric oxide, acetylcholine, and Substance P. As such, it is not surprising that TRPA1 activation would play a role in both pungency and pain sensitivity.

In heterologous systems with inducible TRPA1 expression, activation by isoflurane was TRPA1 receptor-dependent, and cell current responses were similar to that induced by the TRPA1 receptor selective agonist, allylisothiocyanate. Dorsal root ganglion neurons from wild-type mice that responded to allylisothiocyanate also responded to desflurane. Neurons from mice genetically altered to lack TRPA1 receptors did not respond to allylisothiocyanate or desflurane. Bradykinin sensitized the TRPA1 channel to subanesthetic desflurane concentrations. TRPA1 receptors are coexpressed with transient receptor potential vanilloid type 1 (TRPV1) channel in primary sensory neurons.² These receptors are activated by native tachykinins and natural irritant substances, such as wasabi and cinnamon. Activation of TRPA1 receptors alone or in combination with TRPV1 receptors may be responsible for some types of inflammatory and pressure-induced nociceptive transmission.² Isoflurane has also been previously shown to directly activate TRPV1 receptors and to sensitize them to heat activation.³ The amount of and consequences due to overlap between volatile anesthetic ac-

tivation of TRPV1 and TRPA1 receptors that occurs in native primary afferent fibers are not known.

All volatile anesthetics are well known to enhance pain at low subanesthetic concentrations.³ The mechanism of that action is not well understood but may involve modulation of nicotinic and noradrenergic systems.^{4,5} In this study, Eilers *et al.* have shown that a small volume of saturated isoflurane and desflurane injected into the hind paw causes hyperalgesia in response to mechanical stimuli. Mice that do not express the TRPA1 receptor do not respond with hyperalgesia, and the halothane injection does not induce hyperalgesia in wild-type mice. The hyperalgesia induced by isoflurane injection can be prevented with TRPA1 antagonists. Taken together, these observations suggest that activation of TRPA1 receptors by isoflurane can cause hyperalgesia. However, it is difficult to know the concentrations that are involved when a saturated solution is directly injected into the hind paw, certainly high but evanescent. Also, what of the hyperalgesia induced by halothane³? Eilers *et al.* assure us that halothane does not activate TRPA1. It is clearly too early to ascribe the hyperalgesic properties of ultra low anesthetic concentrations (0.1 minimum alveolar concentration) to TRPA1 receptor activation.

An increasing number of studies also point to an important role for the transient receptor potential family of receptors in the airway. Because this class of receptors consists of nonselective cation channels capable of regulating intracellular calcium concentrations, they have been associated with a variety of calcium-dependent physiologic processes in the airway including inflammation, cellular proliferation, and smooth muscle contractility. In this issue of Anesthesiology, Eilers *et al.* focus on the role that isoflurane activation of airway TRPA1 receptors may play in bronchoconstriction. TRPA1 receptors have been localized to C-fiber sensory afferents, and these neuronal fibers are known to be abundantly expressed throughout the respiratory tract. Given the wide array of noxious chemical stimuli that serve to activate these receptors, it follows that the irritant effects of pungent volatile anesthetics might involve TRPA1 pathways.

What is not as clear is the association made between airway irritation that elicits a nonadrenergic noncholinergic re-

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sponse (TRPA1 activation) and the subsequent development of bronchoconstriction in humans. This controversy exists, because in humans nonadrenergic, noncholinergic-mediated airway smooth muscle constrictive pathways are thought to be far less prominent than that in guinea pigs.⁶ However, Eilers *et al.* provide convincing evidence for isoflurane-induced TRPA1-mediated airway smooth muscle constriction in an isolated guinea pig airway ring (and these findings are in agreement with other investigators who tested desflurane in a similar animal model⁷)—there remains the possibility that interspecies differences make this effect less important in humans.

Certainly, there is a large body of clinical evidence that suggests that volatile anesthetics (irritant or not) dose dependently attenuate bronchospasm (a common effective clinical therapy in the face of bronchospasm is to increase the inspired concentration of volatile anesthetic). This maneuver seems substantiated by *in vivo* evidence that isoflurane (and other volatile anesthetics) dose dependently bronchodilate and reduce airway resistance.^{8,9} Although isoflurane may indirectly promote nonadrenergic, noncholinergic-mediated airway smooth muscle constriction by neurogenic release of procontractile tachykinin mediators in isolated guinea pig airway rings, it is somewhat surprising that this effect is not counterbalanced by the known attenuation of calcium sensitization in airway smooth muscle by volatile anesthetics.¹⁰

Isoflurane is an upper airway irritant in human patients—the physiologic consequence of which is predominantly a profound cough reflex (not bronchospasm). A common misconception is that airway irritation is synonymous with bronchoconstriction. In fact, airway irritation most commonly activates the cough reflex. However, there is extensive laboratory and clinical evidence that establishes the neural pathways for cough and bronchoconstriction as distinctly different.^{11–13}

Although these controversies remain unsolved, the work of Eilers *et al.* identifies an important family of receptors that is activated by volatile anesthetics and shares functional overlap in both pain and respiratory physiology. The authors may have identified the first behavioral effect caused by volatile anesthetic modulation of a specific ion channel.

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