Isoflurane, 2-Halogenated Ethanols, and Halogenated Methanes Activate TASK-3 Tandem Pore Potassium Channels Likely Through a Similar Mechanism.

Authors: Joseph F. Cotten, M.D.,Ph.D[1]., Anita Luethy, M.D.[1,2]

[1]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA.
[2]Department of Anesthesia, Kantonsspital Aarau, Aarau, Switzerland.

Background: TASK-3 (KCNK9) tandem pore potassium channel proteins mediate a constitutive potassium conductance activated by several clinically relevant volatile anesthetics (e.g., halothane, isoflurane, sevoflurane, and desflurane); knockout mice lacking the TASK-3 potassium channel are resistant to the hypnotic and immoblizing effects of halothane and isoflurane.

Purpose: To better understand the molecular mechanism by which TASK-3 channels are activated by anesthetics, we studied the functional concentration-response of wild-type TASK-3 potassium channels to isoflurane, to ethanol, and to several halogenated ethanols and methanes. We also studied the concentration-response of M159W TASK-3 to 2,2,2-trichloroethanol; the M159W TASK-3 mutant is known to be resistant to isoflurane activation (1). 2,2,2-trichloroethanol, notably, is an active metabolite of the sedative chloral hydrate; and 2,2,2-tribromoethanol is the active ingredient in Avertin, an injectable veterinary anesthetic.

Methods: Wild-type and M159W TASK-3 function were studied by Ussing chamber voltage clamp analysis during transient expression in Fischer rat thyroid cell monolayers.

Results: 2-halogenated ethanols activate wild-type TASK-3 with the following rank order for efficacy: 2,2,2-tribromo > 2,2,2-trichloro > chloral hydrate > 2,2-dichloro > 2-chloro ≈ 2,2,2-trifluoro > ethanol (Table 1). Similarly, carbon tetrabromide (CBr4) and tetrachloride (CCl4) both activate TASK-3 (with CBr4 > CCl4; Table 1).

Conclusions: Increasing halogention of both ethanol and methane promotes TASK-3 activation, and substitution with a larger and more polarizeable bromine atom, relative to chlorine or fluorine, provides for more potent and more effective TASK-3 activation. Since M159W TASK-3 is resistant to activation by either isoflurane or 2,2,2-trichloroethanol, we speculate these agents share commonalities in their mechanism of activation.

Funding: Massachusetts General Hospital Department of Anesthesia, Critical Care & Pain Medicine; NIH/HL117871; and Kantonsspital Aarau, Aarau, Switzerland (1410.000.062).

Refs: (1) Conway & Cotten, Mol Pharm 2012, 81(3):393-400.

Table 1.

	Activation (% ± 95% conf)	EC50 (mM ± 95% conf)	n-

			value
Carbon tetrabromide (CBr4)	191 (146 to 235)	0.017 (0.008 to 0.04)	4
Carbon tetrachloride (CCl4)	79 (63 to 96)	0.3 (0.2 to 0.5)	3
2,2,2-tribromoethanol	166 (135 to 196)	0.3 (0.2 to 0.4)	6
2,2,2-trichloroethanol	114 (89 to 140)	1 (0.6 to 2)	8
M159W: 2,2,2-trichloroethanol	~4 (unable to fit)	N.D.	3
Chloral hydrate	67 (62 to 72)	7 (6 to 8)	5
2,2,2-trifluoroethanol	-13 (-15 to -11)	0.7 (0.3 to 1.2)	3
2,2-dichloroethanol	24 (12 to 36)	9 (5 to 16)	4
2-chloroethanol	-15 (-18 to -11)	1 (0.4 to 3)	3
Ethanol	-25 (-27 to -23)	1.7 (1.4 to 2)	2
Isoflurane	65 (60 to 70)	0.5 (0.4 to 0.6)	4