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Title: THE ROLE OF POTASSIUM CHANNELS ON HALOTHANE VASODILATION IN CORONARY VASCULAR SMOOTH MUSCLE

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Potassium channels are important for regulating resting potential, resting tone, and repolarization in vascular smooth muscle (VSM) and other cells. The various K^+-channels are controlled physiologically, *e.g.*, by intracellular $[ATP]_i$ (K_{ATP}-channels[1]) or $[Ca^{2+}]_i$ (K_{Ca}-channels[2]). The opening of VSM K^+-channels results in cell hyperpolarization and vasodilation. Drugs that open K_{ATP}-channels (*e.g.*, diazoxide) are used clinically as vasodilators. Because halothane increases membrane K^+ conductance in certain neurons,[3] we tested the *hypothesis* that halothane causes vasodilation by opening K^+-channels in VSM.

Methods: Epicardial left coronary artery ring segments from fresh pig hearts were suspended after removing the endothelium in Krebs-Hensleit buffer (pH=7.4, 37°C) at the optimal point on the length-tension curve. Developed isometric tension was measured after repeated exposures to $PGF_{2}\alpha$ (PGF, 3 μM) in the presence or absence of halothane (2.5×MAC) following pretreatment with one of the following K^+-channel blockers: glyburide (0.1 μM), tetraethylammonium (TEA, 2 mM), or vehicle. A randomized protocol and appropriate simultaneous time controls were used. Blockade of K_{ATP}-channels was documented in glyburide rings by the loss of relaxation with cromakalim (1 μM), and blockade of K_{Ca}-channels by TEA was indicated by appearance of spontaneous rhythmicity. Halothane was monitored by Raman spectrometry and gas chromatography. Data are percent of the control PGF developed tension (after K^+-blocker) with each ring its own control. Sixty-three rings from $n=23$ hearts were studied, and analyzed by ANOVA with $\alpha=0.05$; values are mean ± SEM.

Results: (See figure). In the absence of halothane, neither K^+-channel blocker altered the developed tension responses to PGF ($P=0.78$). Halothane significantly attenuated the PGF-induced tension in all 3 groups ($P<0.001$). Thus, in vehicle-treated arteries, halothane (2.5×MAC) reduced PGF-generated tension responses from 92±3 to 62±3 percent of control. The magnitude of halothane-induced relaxation was similar among the vehicle, glyburide, and TEA groups ($P>0.42$).

Conclusions: The mechanisms of coronary vasodilation by halogenated anesthetics are poorly understood, yet the studies of Franks and Lieb[3] implicate K^+-channels in the neural mechanism of anesthesia. Our data show that the selective blockade of K_{ATP}-channels with glyburide[1] and the less-selective blockade of K_{Ca}-channels with TEA[2] did not alter the vasodilator action of halothane. To have supported our hypothesis, we would have expected a K^+-channel blocker to reduce the magnitude of halothane-induced relaxation. These data refute the hypothesis that halothane vasodilates coronary VSM by opening K^+-channels, and suggest that the cellular mechanism of halothane in VSM differs from its action in neurons. Supported by NIH and the Dept. of Anesthesia.

References: 1. Edwards G, Weston AH: Pharmacol Ther 48:237,1990; 2. Langton PD, Nelson MT, Huang Y, Standen NB: Am J Physiol 260:H927-34,1991; 3. Franks NP, Lieb WR: Nature 333:662-4,1988

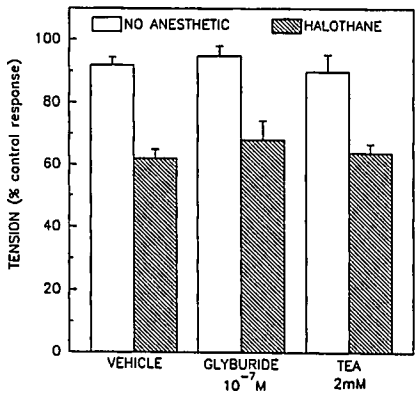

Figure. Developed isometric tension in porcine coronary arteries exposed to $PGF_{2}\alpha$. Halothane attenuates agonist-induced tension similarly in the presence or absence of K^+-channel blockers glyburide and TEA (P=ns).

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TITLE: ISOFLURANE AND HALOTHANE INHIBIT VASCULAR CELL SIGNALLING INDEPENDENT OF G-PROTEINS

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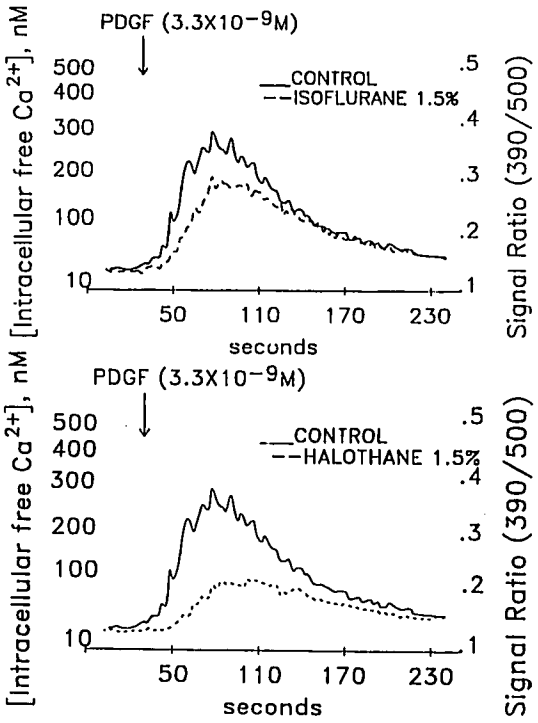
Isoflurane and halothane may attenuate the vascular effects of pressor hormones by inhibiting cell signalling. Receptor linked GTP binding proteins (G-proteins) are considered to be possible targets. In the current experiments, isoflurane and halothane were investigated for their ability to inhibit Ca^{2+} signalling evoked by platelet derived growth factor (PDGF). This agonist, on binding to its receptor, causes receptor monomes to dimerize and autophosphorylate each other, leading to an increase in latent tyrosine kinase activity, enabling ligand activated increases in cytosolic Ca^{2+} concentration $[Ca^{2+}]_i$ to be investigated via pathways that are not dependent upon G-proteins.

Changes in $[Ca^{2+}]_i$ in rat aortic smooth muscle (A7r5) and bovine endothelial cells (GMO) lines were measured using Indo-1 and flow cytometry during stimulation with PDGF (3.3×10^{-9}M).

The $[Ca^{2+}]_i$ responses were inhibited by both isoflurane 1.5% and halothane 1.5%. In vascular smooth muscle cells isoflurane inhibited the response by 31% ($n=11$, $p < 0.0001$) and halothane inhibited it by 44% ($n=11$, $p < 0.0001$). Similar results were seen in endothelial cells.

In conclusion, the results suggest that isoflurane and halothane do not act solely at G-proteins but may also inhibit agonist induced $[Ca^{2+}]_i$ responses at more distal sites in the signal transduction pathway.



Effects of isoflurane (above) and halothane (below) on increases in $[Ca^{2+}]_i$ stimulation by platelet derived growth factor (PDGF) in cultured A7r5 vascular smooth muscle cells. The indo-1 loaded cells were imaged using flow cytometry. Results from typical individual experiments are shown.

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