A529

TITLE: ISOFLURANE INHIBITS SIGNAL TRANSDUCTION IN CULTURED VASCULAR SMOOTH MUSCLE CELLS (A7r5)

AUTHORS: S. Eskuri, M.D., J.C. Sill, M.D., R. Van Dyke, Ph.D., C. Uhl

AFFILIATION: Department of Anesthesiology, Mayo Foundation, Rochester, MN 55905

Isoflurane decreases vascular resistance in part by a direct action on arteries and arterioles. The mechanism is not understood. Isoflurane was studied for its ability to inhibit inositol phosphate and Ca^{2+} signalling stimulated by the pressor hormone arginine vasopressin (AVP) in cultured A7r5 rat aortic smooth muscle cells.

Changes in intracellular free Ca^{2+} concentration $[Ca^{2+}]_i$ were measured using the indicator Indo-1 and flow cytometry while inositol phosphate levels were determined using ^3H-labeled myo-inositol and column chromatography.

Isoflurane 2.0% resulted in 32% inhibition ($p < 0.001$) of the peak $[Ca^{2+}]_i$ response evoked by AVP 10^{-7}M. Isoflurane 1.25 and 0.5% had less marked effects. In Ca^{2+} free medium isoflurane 1.5% resulted in 53% inhibition ($p < 0.001$) of Ca^{2+} release from intracellular stores but had a minimal effect on subsequent Ca^{2+} influx. Isoflurane 1% and 2% inhibited AVP-induced inositol phosphate formation ($p < 0.05$) (see Figure).

In conclusion, it is tempting to speculate that the vasodepressant effects of isoflurane may be explained in part by an action on cell signalling.

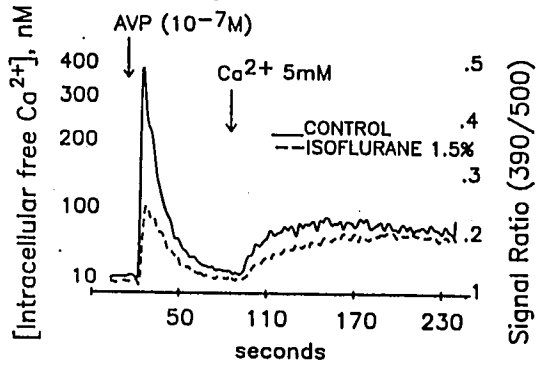

Figure 1. Effects of isoflurane on AVP-induced response in cells suspended in Ca^{2+} free medium. Intracellular Ca^{2+} release (left) and Ca^{2+} influx (right) are shown.

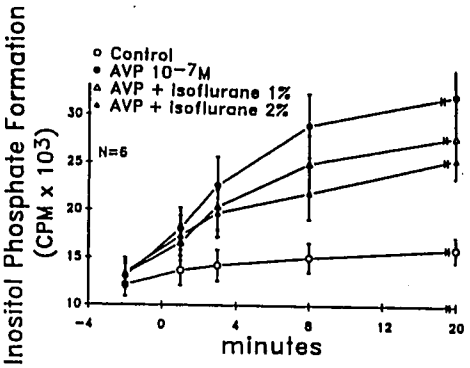

Figure 2. Effects of isoflurane on AVP-induced inositol phosphate formation. Data are expressed as counts per minute (CPM). Control = no agonist.

A530

TITLE: ISOFLURANE INHIBITS ENDOTHELIUM-DEPENDENT RELAXATION AND CYCLIC GMP FORMATION IN RAT AORTA

AUTHORS: K.Nakamura,M.D., Y.Hatano,M.D., H.Toda,M.D., K.Mori,M.D.

AFFILIATION: Dept. of Anesthesia, Kyoto Univ. Hospital, Kyoto, 606, Japan

Vascular endothelium forms EDRF which activates cyclic GMP (cGMP) formation in vascular smooth muscle, resulting in a relaxation of vessels. Anesthetics including halothane (Hal) have been demonstrated to inhibit EDRF-derived relaxation[1]. However, the effect of isoflurane (Iso) on vascular endothelium still remains controversial[2,3]. Therefore, we examined the effects of Hal and Iso on endothelium-dependent relaxation and cGMP formation in rat aorta.

Thoracic aortae were isolated from Wistar rats, and cut into helical strips. They were precontracted with phenylephrine (3×10^{-7}M) and relaxing effects of acetylcholine (ACh, 10^{-8} to 10^{-5}M) or sodium nitroprusside (SNP, 10^{-9} to 10^{-6}M) were tested in the presence or absence of anesthetics. C-GMP contents of aortae were determined by radioimmunoassay.

Hal and Iso (1 to 2 %) significantly attenuated Ach-induced relaxation. By contrast, relaxing effect of SNP, which is mediated by endothelium-independent cGMP formation, was not affected by these anesthetics. C-GMP contents of strips in basal condition or following 1 min exposure to Ach (10^{-5} M) in the presence or absence of Hal (2%) and Iso (2%) are shown in Table; Hal and Iso significantly attenuated Ach-induced increase of cGMP. Furthermore, basal level of cGMP tended to be decreased by Iso. Thus, it is suggested that Iso has inhibitory effects on EDRF formation in basal and Ach-stimulated conditions in rat aorta. The effect of Hal may be less potent than that of Iso.

References 1. Anesthesiology 68:31-37,1988
2. Anesthesiology 67:513-517,1987
3. Anesthesiology 71:126-132,1989

Table

Treatments	cGMP*	Treatments	cGMP*
None	63.5 ± 12.1	None	82.2 ± 11.8
Hal	52.8 ± 7.2	Iso	50.6 ± 11.1
Ach	288.7 ± 64.4	Ach	349.7 ±105.3
Ach,Hal	117.9 ± 27.2★	Ach,ISO	50.0 ± 8.5★

*in pmol/g.wet weight; mean ± SE (n=6, each),
★P<0.05 vs. Ach. (Unpaired Student's T test)