THE EFFECTS OF VASOACTIVE DRUGS ON HALOTHANE INHIBITION OF CONTRACTIONS OF RAT MESENTERIC LYMPHATICS

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ABSTRACT

The effects of halothane on alpha-adrenergic receptors, beta-adrenergic receptors, and the process of Ca\(^{++}\) dependent contractions on rat mesenteric lymphatics were examined. Halothane depressed the contraction rate of mesenteric lymphatics but did not affect the increase in lymphatic contraction rate caused by noradrenaline (an \(\alpha\)-agonist). The depressant effect of halothane on the contraction rate was also not antagonized by propranolol (a \(\beta\)-blocker), but was partly reversed by CaCl\(_2\). These findings suggest that the depressant effect of halothane on the lymphatic contraction rate derives not from blocking lymphatic alpha-receptors or stimulating lymphatic beta-receptors but rather by halothane inhibition on the process of Ca\(^{++}\) dependent lymphatic contractions.

We earlier reported that halothane produced a decrease in the contraction rate of rat mesenteric lymphatics (1). Others have reported that the lymphatic contraction rate was increased by an alpha-receptor stimulant and decreased by a beta-receptor stimulant or a Ca\(^{++}\) antagonist (2-5). Because the decrease in lymphatic contraction rate following halothane inhalation may result from blockage of lymphatic alpha-receptors or stimulation of lymphatic beta-receptors or alternatively by inhibition of Ca\(^{++}\) dependent lymphatic contractions, we examined the effects of halothane in conjunction with noradrenaline, propranolol, and calcium chloride (CaCl\(_2\)) on mesenteric lymphatic contractions.

MATERIALS AND METHODS

Male Wistar rats, weighing 100-140g, were used. Under halothane-oxygen anesthesia, a tracheostomy was performed and the femoral artery and vein were cannulated for direct arterial pressure recording and intravenous fluid and drug administration, respectively. Halothane anesthesia was then discontinued (after an average duration of 30 minutes) and sodium pentobarbital (20mg/kg) was administered intramuscularly. After administering pancuronium bromide (0.1mg) intravenously, the lungs were artificially ventilated with 100% oxygen. PaCO\(_2\) was maintained at 30-40mmHg. The rats were placed on a microscope stage and the rectal temperature was maintained at 37.0±1.0\(^\circ\)C by a heating pad. The small intestine was exposed and the mesentery was spread on a transparent plastic block. The mesentery was perfused with mammalian Ringer's solution at 37\(^\circ\)C. By using a TV camera attached to a microscope, lymphatic contractions were observed and recorded on a video tape with time markers for later analysis.
Effects of halothane on noradrenalin induced changes in the lymphatic contraction rate

As the mesentery was perfused with Ringer's solution, noradrenalin (30μl) was dripped onto the exposed lymphatic vessels. The concentration of noradrenalin was varied from 100 to 1000ng/ml. The rats received 1.5% halothane in oxygen through a calibrated vaporizer (Halomatic, AIKA Co.) (group-A1). The experiment was started after 20 minutes of halothane inhalation. In the control group, rats received 100% oxygen alone (group-A2). Following a 30 second control period, the lymphatic contraction rate was measured for 30 seconds after noradrenalin administration in both groups.

Effects of propranolol on halothane inhibition of the lymphatic contraction rate

Following a 5-minute control period, 1.5% halothane was administered for 20 minutes. Contractile movements were averaged for 5 minutes during each observation. The averaged values of 0-5, 5-10, 10-15, and 15-20 minutes during halothane inhalation were used for the contraction rates at 5, 10, 15, and 20 minutes, respectively. Propranolol (100μg/ml, 40μl) was dripped onto the lymphatic vessels 30 seconds before the inhalation of halothane, and added at 5, 10, and 15 minutes of halothane inhalation. The contraction rate was determined in the rats receiving propranolol and halothane (group-B1), and in the rats administered halothane alone (group-B2).

Effects of CaCl₂ on halothane inhibition of the lymphatic contraction rate

CaCl₂ (1-20mM, 30μl) was dripped onto the lymphatic vessels. Contraction rates were measured in the same manner as in experiment (A) in the rats receiving halothane and oxygen (group-C1) and in the rats receiving oxygen alone (group-C2).

The statistical significance of the data was assessed by Student's t-test.

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Fig. 1. Effects of noradrenalin induced changes in the mesenteric lymphatic contraction rate (n=8). Note that noradrenalin (Norad) (100 and 1000ng/ml) significantly increased the contraction rate both in the oxygen group and the halothane-oxygen group. The difference between the ratios of the increase in the contraction rate of both groups was not significant.

**RESULTS**

Effects of halothane on noradrenalin induced changes in the contraction rate (Fig. 1)

In group-A1, noradrenalin (100 and 1000ng/ml) significantly increased the lymphatic contraction rate from 6.4±1.8 to 9.4±2.2 and from 7.9±1.0 to 12.2±5.0 times/minute, respectively. In group-A2, noradrenalin (100 and 1000ng/ml) significantly increased the contraction rate from 14.0±4.4 to 18.4±5.2 and from 13.4±4.5 to 19.2±4.2 times/minute, respectively. The difference between the ratios of the increase in the contraction rate of group-A1 and group-A2 was not significant.
**Effects of propranolol on halothane inhibition of the contraction rate (Fig. 2)**

In group-B1, propranolol did not alter the lymphatic contraction rate. Following 20 minutes of halothane inhalation, however, the contraction rate significantly decreased from a control value of 16.1±1.9 to 4.2±3.8 times/minute. In group-B2, following 20 minutes of halothane inhalation, the contraction rate significantly decreased from the control value of 13.8±3.9 to 4.1±3.5 times/minute. The difference between the ratios of the decrease in contraction rate of group-B1 and group-B2 was not significant.

**Effects of CaCl$_2$ on halothane inhibition of the contraction rate (Fig. 3)**

In group-C1, CaCl$_2$ (5, 10 and 20mM) significantly increased the contraction rate from 6.2±1.6 to 11.0±3.2, from 5.6±1.6 to 11.6±4.4, and from 7.0±1.8 to 12.2±4.4 times/minute, respectively. In group-C2, CaCl$_2$ (5,10 and 20mM) did not alter the contraction rate.

**DISCUSSION**

**Effects of halothane on noradrenalin (α-agonist) induced changes in the lymphatic contraction rate**

Concerning the effect of halothane on alpha-receptors, Clark (6) noted that the blood vascular response to noradrenalin was depressed by halothane, suggesting that this anesthetic blocked blood vessel alpha-receptors. Moreover, Allen (2) and Tanra (4) described the presence of alpha-receptors in lymphatics. Therefore, it seemed plausible that the decrease in mesenteric lymphatic contraction rate following halothane may relate to an anesthetic blockage of lymphatic alpha-receptors. But, the findings that halothane did not interfere with the facilitating effect of noradrenalin on lymphatic contractile movement, favors that halothane induced inhibition of lymphatic contraction rate is not mediated via anesthetic blockage of lymphatic alpha-receptors.
cardiac contractile force and the heart rate were reduced by halothane inhalation. Bosnjak (9) and Lynch (10) claimed that these phenomena were the result of the inhibitory action of halothane on the influx of Ca$^{++}$ into myocardial cells. Azuma (11) noted that a calcium current through cell membranes produced spike discharges in lymphatic smooth muscles, and McHale (5) observed that a Ca$^{++}$ antagonist reduced the rate of spontaneous contractions of mesenteric lymphatics. Because the depressant effect of halothane on mesenteric lymphatic contraction rate was partially reversed by calcium CaCl$_2$ and was unaffected by the $\alpha$-agonist noradrenalin or the $\beta$-blocker propranolol, it seems reasonable to conclude that the inhibitory effect of halothane on the contraction rate of mesenteric lymphatics is mediated in large part by blocking of the regulatory process of Ca$^{++}$ dependent contractions.

REFERENCES


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