Title: HALOTHANE ANTAGONIZES AIRWAY CONSTRICTION BY ACTING BOTH ON AIRWAY SMOOTH MUSCLE AND PARASYMPATHETIC GANGLION

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Introduction. Halothane (H) antagonizes airway constriction (1,2) but the site of its action is still controversial. On the one hand, in vitro, H at high concentrations has "direct relaxant effects on tracheobronchial smooth muscle" (3), but on the other hand, Shah and Hirshman stated that "block of vagal reflexes was the major action of H responsible for the attenuation of histamine-induced bronchoconstriction" (4). To study the site of action of H, we stimulated isolated canine tracheal smooth muscles at: 1) the muscarinic receptors in the muscular postsynaptic membranes using acetylcholine chloride (ACH), 2) the postganglionic nerve fibers using electrical field stimulation (EFS), 3) the postsynaptic membrane of the intramural parasympathetic ganglia using 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP).

Methods. Six mongrel dogs were anesthetized with pentobarbital, exsanguinated, and their tracheae removed. Trachealis muscle strips were immediately dissected and the epithelium removed. From each dog, six trachealis muscle strips (~18 mg) were suspended in six tissue baths containing a physiologic salt solution (PSS) maintained at 37°C and aerated with 95% O_2-5% CO_2. Tissues were suspended vertically between two platinum electrodes and connected at one end to an isometric force transducer (Gould UC2) and on the other end to a hook at the bottom of the bath. The strips were washed in PSS for 2 hours, during which time they were stretched to their length of maximal active contraction. Then, the contractile force of each strip to 10^{-4} M ACH was determined. This force was defined as the maximal response; all subsequent responses were expressed as a percentage of this force. To stimulate the postsynaptic membrane in the ganglia, DMPP (10^{-6} to 10^{-4} M) was added to the PSS of two tissue baths. Postganglionic nerves were stimulated with EFS (0.25 to 25 Hz, 15 volts) in the presence of hexamethonium (10^{-5} M) and propranolol (10^{-6} M) in two other tissue baths. Muscarinic receptors in the postsynaptic membranes of the smooth muscles were stimulated by ACH (10^{-9} to 10^{-4}) in the presence of tetrodotoxin (10^{-6} M) in the remaining two tissue baths. A dose-response curve for each stimulus was obtained. Thereafter, 3 strips were exposed to H for at least 30 min while the 3 other strips were not. These latter strips served as control to determine the effects of time. H was added to the aerating gas mixture. The H concentration in the PSS was measured at the end of the study by gas chromatography. After 30 min of H exposure, a second set of dose-response curves for the same stimuli (ACH, EFS, DMPP) was obtained for all six tissue baths. Statistical analysis included linear regression, analysis of variance, and paired t test.

Results. During H exposure (mean concentration ± SD = 4.46 ± 1.7 mg% or 0.94 ± 0.28 MAC), the force of contractions induced by ACH, EFS, or DMPP were consistently and significantly ($P<0.05$) reduced from the control (figure). The force of contraction to DMPP was consistently and significantly ($P<0.05$) more reduced than that to ACH or EFS. There was no significant difference between the force of contractions to ACH and EFS.

Discussion. These data demonstrate that in normal canine trachea, 0.94 MAC H depresses the response of the intramural parasympathetic ganglia to DMPP and that it also depresses the response of the trachealis smooth muscle cells to ACH. Therefore, we conclude that H antagonizes airway constriction both by reducing the excitability of intramural ganglia and by acting on the smooth muscle cells somewhere between the muscarinic receptors and the contractile event. Further studies are needed to elucidate the mechanisms of the effect of H on the smooth muscle cell.

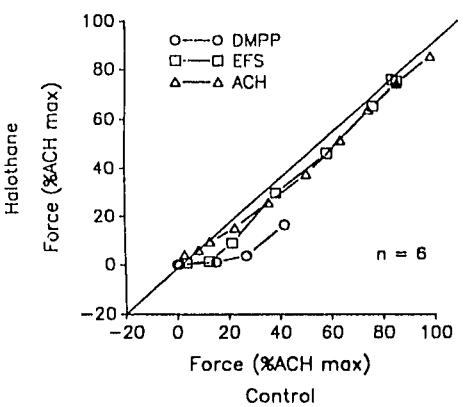

Figure. Mean responses to DMPP, EFS, and ACH (expressed as a percentage of the ACH maximal response) in the absence and in the presence of halothane. Points below the line of identity (solid line) indicate a depressed response in the presence of halothane.

References.
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