Title: THE EFFECT OF HALOTHANE ON RELEASE OF NOREPINEPHRINE FROM PERIPHERAL VENOUS TISSUE

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Introduction. The purpose of this study was to determine the effects of halothane on the release of norepinephrine (NE) from adrenergic nerve endings in peripheral venous tissue. Clinical observation has shown that halothane causes peripheral vasodilatation (1); in vivo and in vitro studies have documented the relaxing effect of halothane on vascular smooth muscle (1,2,3). The exact cause of the vasodilatation is unknown although it has been suggested to be mediated by inhibition of NE release from adrenergic nerve endings (4). To determine this, the release of endogenous NE evoked by electrical stimulation (ES) of adrenergic nerve endings in isolated strips of dog saphenous veins was studied.

Methods. The experiments were done on strips of saphenous veins removed from 8 dogs (15-25 kg) anesthetized with pentobarbital (30 mg/kg). The veins were cleansed of perivascular tissue, cut into helical strips and mounted for superfusion and isometric tension recording. Veins were superfused with Krebs-Ringer bicarbonate solution at 2 ml/min. The solution was maintained at 37°C and continuously aerated with 95% O_2/5% CO_2. After suspension the veins were allowed to rest for a 45-min period. At the end of this period, cocaine (10^{-5}M) and corticosterone (4.32×10^{-5}M) were added to the superfusate for the remainder of each experiment. In 4 experiments halothane (1.4%) was added to the O_2/CO_2 mixture aerating the Krebs-Ringer superfusate at this time and an additional 30 min was allowed for equilibration prior to ES. ES consisted of rectangular waves (9 V, 2 ms, 2 Hz) delivered continuously for 19 min through two platinum electrodes placed parallel to and in contact with the veins. Following ES the halothane was turned off and after a 30-min rest ES was resumed for an additional 19 min. In 4 other experiments the same protocol was followed except in reverse order (halothane was not added until the end of the first stimulation but then continued until the end of the experiment). Superfusate from each 19-min period of ES was collected in two samples: 0-4 min and 5-19 min. NE was isolated from extracts of vein and superfusate by adsorption of catechols on alumina at pH 8.4 followed by elution with perchloric acid. Catecholamines were separated from catechol acids in the eluate by chromatography on Amberlite CG50. NE was eluted from the resin with boric acid. The NE in the eluate was measured by high performance liquid chromatography (HPLC). For statistical evaluation of the data, Student's t-test for paired observations was used. NE released during the control period was established as 100%; that released during halothane was expressed as a percent of the control value.

Results. Halothane decreased the total release of NE by 17.99 ± 3.12% ($p < .001$). In the initial collection interval (0-4 min) NE release decreased by 25.89 ± 3.76% ($p < .001$) whereas in the second collection interval (5-19 min) NE release decreased by 16.3 ± 3.7% ($p < .01$). The contractile tension also decreased in veins exposed to halothane. The peak tension developed was 23.15 ± 4.36% ($p < .01$) less in the tissues exposed to halothane.

Discussion. Contractions of isolated vein preparations elicited by ES have been demonstrated to be secondary to release of NE; the resulting contractions can be prevented by blocking sympathetic transmission (4). In the present study NE release was elicited by ES. Neuronal reuptake of NE was blocked with cocaine (at a concentration which does not have local anesthetic actions) and uptake of NE by extraneuronal tissues was blocked by corticosterone. Thus in this preparation overflow of NE released by ES approximates true release of NE. The data presented here indicate that halothane inhibits the release of NE evoked by ES. Associated with this decreased NE release is a concomitant decrease in isometric contractile tension. These results are consistent with the theory that the venomotor changes induced by halothane are due, at least in part, to the actions of halothane on NE release.

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