TITLE: DUAL ACTION OF HALOTHANE ON SYMPATHETIC FUNCTION: DECREASE IN NE RELEASE AND CLEARANCE
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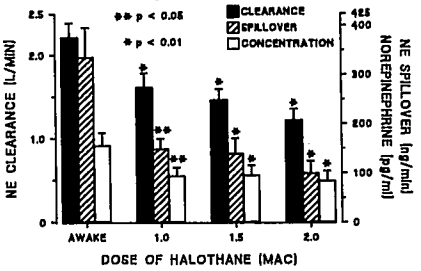
INTRODUCTION: It is well recognized that halothane is a cardiovascular depressant and that plasma norepinephrine (NE) concns are in general decreased. However, plasma NE is not a direct index of in vivo sympathetic activity since it reflects not only NE release from the sympathetic nerve ending but also NE clearance (CL), largely by reuptake. The aim of this study was to define, using isotope dilution techniques (1), the mechanism of halothane's (H) effects on sympathetic function by determining the effect of H on NE clearance and NE spillover (SO), (a measure of NE release).
METHODS: A tracer dose of ^{3}H-NE was infused IV and plasma ^{3}H-NE (dpm/ml) and unlabeled endogenous NE (pg/ml) were determined at steady state. NE CL and NE SO were calculated:

$$SO = \frac{^3\text{H-NE infusion rate (dpm/min)}}{\text{specific activity of plasma NE (dpm/pg)}}$$

$$CL = \frac{^3\text{H-NE infusion rate (dpm/min)}}{\text{plasma } ^3\text{H-NE concentration (dpm/ml)}}$$

6 female dogs trained to lie quietly, were studied awake and during 1.0, 1.5 and 2.0 MAC halothane in each dog. 15μCi of ^{3}H-NE in 0.9% saline with 1 mg/ml ascorbic acid was infused IV over 1 min followed by 0.6μCi/min thereafter for 50 minutes. Arterial blood samples for measurement of ^{3}H-NE and NE were taken prior to, and at 20, 30, 40 and 50 mins during the infusion. NE was measured by HPLC with electrochemical detection and ^{3}H-NE by liquid scintillation counting of the HPLC eluant that coincided with the NE peak. Statistical significance was determined by ANOVA and Student's paired t-test.
RESULTS: 1.0 MAC H decreased ($p<0.05$) plasma NE concn by 35% but no further reduction occurred at higher doses (Fig). H decreased ($p<0.05$) NE spillover by 52% at 1.0 MAC, indicating that H decreased NE release from the sympathetic nerve ending. In addition, H also decreased ($p<0.005$) NE CL in a dose-dependent manner.
DISCUSSION: It has previously been reported that H inhibits stimulation-evoked release of NE from adrenergic nerve endings in vitro. This study has shown that H inhibits NE release in vivo. However, since H decreases NE CL, the extent of inhibition of NE release is underestimated by measures of plasma NE concn alone.
REFERENCE: (1) Hypertension 11: 3-20, 1988.



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TITLE: PROPOFOL DECREASES VOLTAGE ACTIVATED CALCIUM CURRENTS IN RABBIT HEART MYOCYTES
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The effect of propofol on the circulatory system remains controversial.[1] This study examines the effect of propofol on voltage dependent calcium currents (L-type I_{Ca}) in enzyme-dissociated rabbit ventricular cells.

The harvest of rabbit cardiomyocytes was approved by the institutional animal care and use committee. Calcium tolerant ventricular myocytes were obtained by enzymatically perfusing rabbit hearts using a modified Langendorff technique. Individual cells were obtained by trituration in a high potassium storage solution. Calcium currents were measured using the whole cell patch clamp techniques. The internal electrode solution contained CsCl, tetraethylammonium (TEA), and 4-aminopyridine (4-AP) to block potassium currents (I_K). The bathing solution contained 2.5 mM $CaCl_2$, 1mM $MgCl_2$,.110mM NaCl, 4mM KCl, 5mM HEPES buffer, tetrodotoxin to block sodium current (I_{Na}) as well as TEA, 4-AP to block I_K. After a stable seal was obtained the myocytes were held voltage clamped to -35 mV to inactivate I_{Na} then pulsed to +20 mV to activate I_{Ca}. The myocytes then were superfused with isotonic bathing solution containing various concentrations 0-100μM of propofol. More than one concentration was applied to the same cell. Propofol stock solution was made without carrier vehicle. Paired Student's t tests were use to determine significance $p<0.05$.

Propofol decreased the voltage activated calcium current in a dose dependent fashion. The concentration that decreased I_{Ca} by 50% was 10 μM which is within clinical range of 10-30 μM. Propofol's effect on I_{Ca} was reversed by wash off.

Propofol μM	Peak Ca^{++} Current pA	Standard Deviation
0 (control)	103.0	±12.0
5.0 μM	65.4	±15.4
75.0 μM	13.4	± 6.23

Forskolin is known to increase voltage activated calcium currents. Propofol when applied to cells with this enhanced current also decreases I_{Ca}.

The cardiovascular effects of propofol are more pronounced than those that occur after the administration of usual iv. anesthetic agents. Transmembrane Ca^{++} currents are responsible for myocardial automaticity and inotropic state. Understanding propofol's interactions with calcium currents in the heart as well as vascular smooth muscle may explain bradycardia and arterial pressure decreases sometimes seen during propofol administration.

1. Anesthesiology 1990;72:393-396