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TITLE: ALTERATION OF ALPHA & BETA RECEPTOR BINDING: A POSSIBLE MECHANISM FOR HALOTHANE-EPINEPHRINE "SENSITIZATION."

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Introduction: The mechanism by which halothane "sensitizes" the myocardium to epinephrine induced arrhythmia has long puzzled anesthesiologists. While studies have shown that many factors such as heart rate, blood pressure, pH drugs, etc can raise or lower epinephrine arrhythmogenicity, no study has clearly identified the mechanism of "sensitization." A study by Maze et al (1983), however, suggested the possibility that the process may be mediated in some way by myocardial adrenergic receptors. Unfortunately, the evidence presented in this study was of an indirect nature and not conclusive. It was the purpose of this study, therefore, to examine the role of adrenergic receptors in the sensitization process by directly measuring receptor binding kinetics.

Methods: Myocardial sarcolemma membrane fragments were isolated from adult dog heart tissue. Briefly, the left ventricle was removed, homogenized, and centrifuged at 45,000 xg. The pellet was then re-suspended in 0.6M KCl in order to extract contractile protein, cell debris, etc., and re-centrifuged. Aliquots of sarcolemmal membrane vesicles were then incubated with the alpha-1 receptor ligand ^{3}H-prazosin in order to determine the alpha-1 receptor binding kinetics during 2% halothane. Likewise, aliquots of sarcolemmal membrane were also incubated with the beta receptor ligand ^{125}I-pindolol for similar determinations.

Results/Discussion: As can be seen in Table 1 halothane has a differential effect on receptor binding. Alpha-1-receptor binding is increased in the presence of halothane while beta receptor binding is decreased. How these results may be used to explain the epinephrine "sensitization" process is not clear. However, it is known that enhanced alpha-1 stimulation causes arrhythmia in the nonanesthetized heart by increasing Ca^{++} influx and raising free cytosolic Ca^{++}. Beta receptor stimulation, on the other hand, lowers cytosolic Ca^{++} and, thereby engenders myocardial electrical stability. Our results suggest that halothane may increase epinephrine arrhythmia by enhancing the deleterious effects of alpha-1 binding while at the same time decreasing the beneficial effects from beta receptor binding.

ALPHA and BETA RECEPTOR EQUILIBRIUM BINDING KINETICS

ALPHA - 1	CONTROL	HALOTHANE
HIGH AFFINITY		
K_D(nM)	1.62 ± 0.33	1.94 ± 0.88
Bmax (fmols/mg)	46.50 ± 4.90	89.10 ± 22.60 *
LOW AFFINITY		
K_D(nM)	23.84 ± 7.79	52.15 ± 20.30
Bmax (pmols/mg)	0.95 ± 0.16	2.37 ± 0.60 *
BETA		
K_D(pM)	68.33 ± 9.14	78.98 ± 25.20
Bmax (fmols/mg)	293.2 ± 13.6	219.1 ± 27.2 *

* SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE P<0.05, n = 5
K_D = Binding Affinity Constant; Bmax = Total Number of Binding Sites

References: 1. Anesthesiology 59:1983.

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TITLE: EFFECTS OF VASOPRESSIN ON REGIONAL BLOOD VOLUME IN SUPINE HUMANS

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Introduction: While, in animals, endogenous vasopressin in physiological plasma concentrations, is believed to support arterial blood pressure, there is virtually no knowledge of its action on the low pressure side of the circulation. We determined therefore, whether vasopressin, in plasma concentrations observed during circulatory stress (1), alters the regional distribution of blood in seven healthy supine subjects.

Methods: After injection of radioactively labelled autologous erythrocytes (^{99m}Tc, 5 mCi), regional blood volume was assessed by whole body scintigraphy before (base line) and during arginine vasopressin infusion (bolus injection of 1 ng·kg^{-1} followed by a 14 min infusion of 3 ng·kg^{-1}·min^{-1}). After correction for physical decay, regional counts were evaluated for the thorax, abdomen, liver, intestine, spleen, arms, and legs. Heart rate, mean arterial pressure (electromanometry), calf blood flow (Whitney gauge), hematocrit, vasopressin concentration and renin activity (RIA) in plasma were also measured. Statistics: Wilcoxon-signed-rank test, $p<0.05$. Informed consent and institutional approval were obtained.

Results: Vasopressin infusion increased vasopressin plasma concentration from 4.0 pg·ml^{-1} ±1.4 SD to 91 pg·ml^{-1} ±29. Splenic and intestinal counts decreased significantly by 4.6% ±3.8 and 5.1% ±4.1, respectively. In contrast, liver counts increased by 5.8% ±3.0 ($p=0.02$). Global abdominal and thoracic counts did not change. Radioactivity remained unchanged in the arms and decreased slightly in the legs (-2.1% ±2.5). Heart rate, mean arterial pressure, calf blood flow, hematocrit, and plasma renin activity did not change.

Conclusion: Arginine vasopressin in concentrations observed during hypotensive lower body negative pressure (1) induced substantial blood volume shifts within the splanchnic compartment, but not between the extra- and intrathoracic compartments. Accordingly, vasopressin alters regional blood volume distribution in humans but does not mobilize substantial amounts of blood from the peripheral to the intrathoracic compartment.

References: 1. Am J Physiol. 255: R149-R156, 1988