THE EFFECTS OF GANGLIONIC BLOCKADE AND CATECHOLAMINES ON NEUROLOGIC OUTCOME IN RATS

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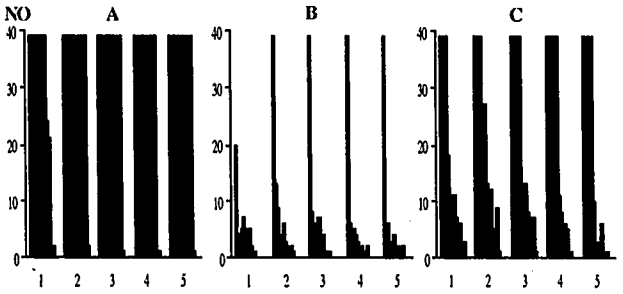
Introduction: The detrimental effects of nitrous oxide (N_2O) on neurologic outcome following ischemia have been attributed to N_2O-induced central metabolic activation. It is unclear whether N_2O-induced sympathetic stimulation may be responsible for increases in brain metabolism. We therefore investigated the effects of N_2O, ganglionic blockade and catecholamines on neurologic outcome after incomplete ischemia in the rat.

Methods: This study was approved by the Institutional Animal Care Committee. Male Sprague-Dawley rats (350-450 g) were anesthetized with isoflurane and 70% N_2O in O_2. Saline filled catheters were inserted into the right femoral artery and both femoral veins and the right subclavian vein. Isoflurane was removed after surgery and the animals were equilibrated for 30 minutes. Ischemia was produced by ligation of the right carotid artery and hemorrhagic hypotension to 35 mmHg for 30 minutes. Rectal temperature, arterial blood gases and pH were maintained constant during the ischemia. Plasma catecholamines and glucose were assayed during the experiment. Group A-animals (n=10) were treated with 70% N_2O in O_2 alone. Hexamethonium (8mg/kg iv) was injected prior to induction of ischemia in group B-rats (n=12). Group C (n=10) received hexamethonium and infusion of epinephrine and norepinephrine (1µg/kg/min of each) during ischemia. Neurologic outcome (NO) was evaluated for 5 days after ischemia using a 39 point performance scale with 0 = normal and 39 = stroke related death.

Results: No differences were obtained for arterial blood gases, pH or post-ischemic blood pressure. Plasma catecholamines were reduced in group B and were not different in group C when compared to group A. Plasma glucose increased in all animals during ischemia with highest values in group 1. Neurologic outcome scores are displayed in figure 1 for all groups over a five day examination period. NO improved in hexamethonium treated groups (B and C) when compared to N_2O alone (A). Additional infusion of catecholamines (C) resulted in an intermediate outcome state ($p<0.05$).

Discussion: The improvement in neurologic outcome following treatment with ganglionic blockade suggests direct involvement of the sympathetic nervous system in the modulation of ischemia. Possible mechanisms are decreases in cerebral blood flow due to sympathetic induced vasoconstriction and neuronal metabolic activation following monoamine release from central stores.



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Title: Increased Alpha-1 Receptor Binding: A Possible Mechanism for Halothane-Epinephrine "Sensitization."

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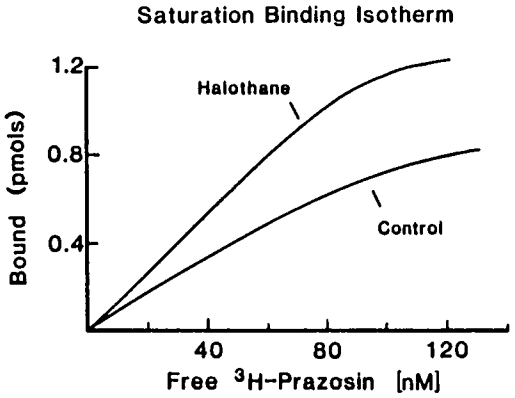
Introduction: The mechanism by which halothane anesthesia "sensitizes" the myocardium to epinephrine induced arrhythmia has long puzzled anesthesiologists. Previous studies have shown that many factors such as heart rate, blood pressure, pH drugs, etc can raise or lower epinephrine arrhythmogenicity, but 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 adrenergic alpha-1 receptors located in the myocardium. 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 as influenced by halothane anesthesia.

Methods: Myocardial sarcolemma membrane fragments were isolated from adult dog heart tissue as described by Jones et al (1979). Briefly, the left ventricle was removed, homogenized, and centrifuged at 45,000 xg for 30 min. The pellet was then re-suspended in 0.6M KCl in order to extract contractile protein, cell debris, etc., and re-sedimented again at 45,000g. The resultant yield of membrane vesicles was approximately 0.4-0.6 mg of protein/g of heart. Aliquots of sarcolemmal membrane vesicles were then incubated with increasing concentrations of alpha-1 receptor ligand ^{3}H-prazosin in order to determine the alpha-1 receptor binding kinetics during 2% halothane.

Results/Discussion: As can be seen in the Figure halothane exposure caused a significant increase in alpha-1 receptor binding compared to non-treated sarcolemma membrane. While 2% halothane did not change receptor affinity, there was an apparent 56% increase in the Bmax i.e., the maximum density of binding sites.

The results of this study suggests that halothane may increase catecholamine arrhythmogenicity by increasing the number of adrenergic receptors or by unmasking available membrane receptors.



Ref. 1) Jones LR, Besch HR, et al: J Biol Chem 254:1979.
2) Maze M, Smith, CM: Anesthesiology 59:1983.

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