TITLE: BARBITURATE ATTENUATION OF AGONIST AFFINITY IN CEREBRAL ARTERIES CORRELATES WITH LIPID SOLUBILITY

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There is a correlation between lipid solubility and anesthetic potency of barbiturates. This implies that these drugs have the potential to alter cell membrane properties and the properties of membrane macromolecules. If barbiturates alter vascular function, they would be expected to change the affinity (pKA) of receptors for agonists, since receptors are known to be proteins spanning lipid membranes of cells. Our goal was to determine if the histamine receptor affinity in cerebral arteries is influenced by barbiturates, and to relate this influence to their lipophilicity and anesthetic potency.

Rabbit basilar arteries were isolated and prepared for isometric force measurements in a small vessel myograph containing physiological saline solution (PSS). The buffer was maintained at 37°C and gassed with a 95% O_2, 5% CO_2 mixture and contained cimetidine (1μM) to inhibit H_2-receptor-mediated dilator responses. The arteries were stretched to an optimal tension of 500mg. Three successive dose response curves (DRC) were made by cumulative solutions of histamine. The initial DRC served as control, while the second DRC was made after the tissues were exposed to phenoxybenzamine (PBZ, 20nM, 15 min.), an irreversible alkylating agent known to reduce histamine H_1-receptor number. The third DRC was made after incubation of tissues with a barbiturate (Pentobarbital, Thiopental, and Thiamylal in dosages of 0.1 mM, 0.3 mM and 1 mM for 15 minutes.) The equilibrium dissociation constant (KA) and receptor reserve (RR) were calculated by the method of Furchgott and Burstyn (1967).

KA= Slope-1/intercept RR= -antilog (-log EC_{50}-pKa)

pD_2= -log EC_{50} pKa= -log KA

	Control	Pentobarbital 0.3 mM	Thiopental 0.3 mM	Thiamylal 0.3 mM
KA	6.82±0.15	6.27±0.10	5.59±0.12	5.58±0.10
pD_2	5.84±0.22	4.99±0.11	4.26±0.09	4.21±0.07

Barbiturates decreased the sensitivity (pD_2) of cerebral arteries to histamine. The decrease in sensitivity caused by barbiturates was correlated with a reduction in the affinity of histamine receptors. As there was no change in receptor reserve, we concluded that the change in sensitivity was due primarily to a change in receptor affinity. Thiobarbiturates reduced affinity to a greater extent than did Pentobarbital.

Our findings are consistent with the hypothesis that barbiturates enter the lipid phase of cell membrane to affect membrane functions, including such characteristics of the histamine receptor as affinity and sensitivity.

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TITLE HALOTHANE ALTERS THE VIRUS-SPECIFIC IMMUNE RESPONSE TO INFLUENZA INFECTION IN MICE

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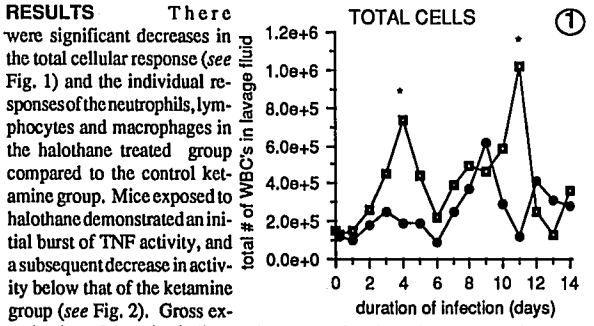
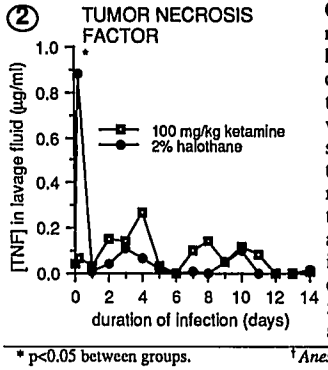
INTRODUCTION Recent evidence suggests that halothane anesthesia ameliorates the pathogenesis of respiratory tract infections in patients undergoing minor surgical procedures. † Although anesthetic agents have been shown to inhibit various components of the immune response there is no direct evidence linking anesthetic induced suppression of the immune system with decreased viral pathogenesis *in vivo*. This study was designed to examine the effect of halothane on the virus specific immune response utilizing the mouse influenza A pneumonitis model.

METHODS This study was approved by the Institutional Animal Review Committee. Two hundred and seventy CD-1 pathogen free mice were randomly divided into two groups. The first group (n=135) was anesthetized with ketamine (100 mg/kg) and inoculated intranasally with 50 µl of influenza type A/PR/8/34 (dose:0.1 LD50/ml). The second group (n=135) was anesthetized with 2% halothane in oxygen for 2 hours prior to virus inoculation. During halothane exposure, anesthetic, oxygen and carbon dioxide concentrations were monitored using an anesthetic circuit evaluator. Temperature was kept constant at 37°C.

The day of viral inoculation was designated as day Ø. Broncho-alveolar lavage (BAL) was performed at 4 hrs post-inoculation and daily thereafter for a period of 14 days. At each time point 9 mice from each group were randomly selected for BAL. The collected lavage fluid was centrifugated and the supernatant analyzed for the monokine tumor necrosis factor (TNF) using the WEHI 164 cytoxicity assay. The cellular pellet was resuspended and differential cellular counts were measured by cytospin.

RESULTS There were significant decreases in the total cellular response (*see* Fig. 1) and the individual responses of the neutrophils, lymphocytes and macrophages in the halothane treated group compared to the control ketamine group. Mice exposed to halothane demonstrated an initial burst of TNF activity, and a subsequent decrease in activity below that of the ketamine group (*see* Fig. 2). Gross examination of the mice indicated that by day 8 of infection the ketamine group appeared much sicker than the halothane group.





CONCLUSIONS The results of this study suggest that halothane anesthesia obtunds the cellular immune response and alters TNF activity in mice infected with influenza A/PR/8/34 virus resulting in an amelioration in the pathogenesis of the infection. Such results are important in evaluating the mechanisms by which volatile anesthetics alter the virus-specific immune response and have implications for the management of infected patients undergoing anesthesia and surgery.

* p<0.05 between groups.

† *Anesthesiology* 67:930-935, 1987.