TITLE: PROTEIN-ANESTHETIC INTERACTION: CONFORMATIONAL TRANSITION OF POLYPEPTIDE BY VOLATILE ANESTHETICS

AUTHORS: J.S. Chiou, Ph.D., H. Kamaya, M.D., I. Ueda, M.D.
AFFILIATION: Anesthesia Department, University of Utah, and VA Medical Center, Salt Lake City, UT 84148

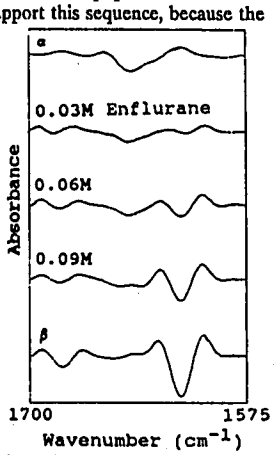
There are at least two schools of thoughts on anesthesia mechanisms: nonspecific interaction with lipid membranes is one, and specific interaction with certain protein is another. It has also been proposed that anesthetics interact both proteins and lipids. In this hypothesis, protein-anesthetic interaction is nonspecific and all protein structures are indiscriminately affected. This idea is supported by the experimental evidence that any enzyme can be inhibited by volatile anesthetics when given at suitable concentrations.

The secondary structure of poly(L-lysine) (PLL) can be formed into α-helix, β-sheet, or random coil by heat treatment or by pH manipulation. Each structure is distinguishable by optical methods, such as circular dichroism, infrared, or Raman spectroscopy.

This study measured the effect of volatile anesthetics on the conformational change of α-helical PLL by infrared spectroscopy. To eliminate the large absorbance of water, PLL (MW 32,000) was dissolved in deuterated water (D_2O). A Perkin-Elmer 1750 FTIR interfaced with a 7300 computer was used to obtain the difference spectra of the amide-I band of 2% (w/v) PLL-D_2O solution.

After addition of anesthetics (chloroform, halothane, and enflurane) to PLL in α-helix conformation, the relative proportions of α-helix, β-sheet, and random-coil structures were calculated from the change in the amide-I band area by a computer routine of the Perkin-Elmer data station. The changes in the absorbance were used to obtain the molar absorptivity of each structure caused by anesthetics. Addition of 0.06 M chloroform, halothane and enflurane increased the β-sheet molar absorptivity 10, 8, and 7%, respectively. The anesthetics partially transformed α-helix to β-sheet. No random-coil conformation was detected.

The α-to-β transition occurs by a change in the hydrogen-bonding between the intramolecular peptide linkage. The present result appears to suggest that the anesthetics broke the peptide bonds by forming competitive hydrogen bonds between anesthetic molecules and the peptide linkage. Then, the intermolecular peptide bonds must disappear. The present data did not support this sequence, because the random-coiled conformation was undetectable. Anesthetics rearranged the peptide bonds to form β-sheet. The β-sheet conformation is stabilized supported by the hydrophobic interaction (bond) among the hydrocarbon side chains of the component amino acids. With PLL, the four methylene groups assemble together to form β-sheet. These hydrophobic contribution of side chains is apparently enhanced by the anesthetic interaction. We propose that anesthetics rearrange the peptide linkage to form β-sheet structure and stabilize the structure by amplifying the hydrophobic force at the peptide-water interface.



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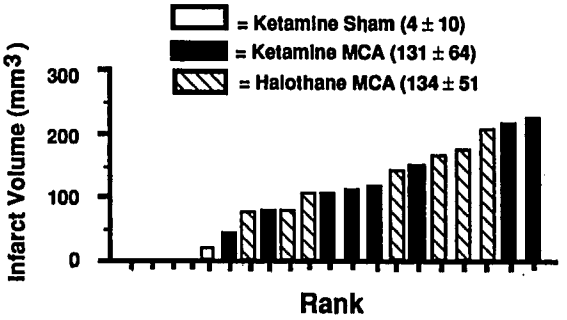
Title: KETAMINE DOES NOT REDUCE INFARCT VOLUME IN RATS UNDERGOING FOCAL CEREBRAL ISCHEMIA

Authors: Warner DS, Ridenour TR, Todd MM, Ramani R, McAllister A
Affiliation: Department of Anesthesia, University of Iowa, College of Medicine, Iowa City Iowa

Ketamine hydrochloride, a potent NMDA antagonist, has been demonstrated *in vitro* to reduce neuronal death associated with hypoxia or neurotransmitter toxicity.[1] *In vivo*, variable effects on rodent outcome from global ischemia have been reported for this agent.[2,3] This experiment was designed to assess the neuroprotective properties of ketamine anesthesia in a rat model of focal cerebral ischemia.

Twenty-three fasted spontaneously hypertensive rats were anesthetized with halothane in N2/O2, intubated and mechanically ventilated (normocarbia and normoxia). Vascular catheters were placed. Via craniectomy, the middle cerebral artery (MCA) was exposed. The animals were then divided into 3 groups as follows. Halothane MCA: halothane anesthesia (0.5-1.0%) during ischemia; Ketamine MCA: halothane discontinued and ketamine anesthesia produced by a 50 mg/kg load and subsequently a 2.5 mg/kg/min i.v. infusion during ischemia; or Ketamine Sham: ketamine anesthesia (as above) but no ischemia. In the ischemia groups, the MCA was reversibly occluded for 2 hrs. A 4d recovery interval was then allowed, whereupon the animals were neurologically evaluated and cerebral infarct volume quantitated with triphenyl tetrazolium chloride staining and computerized planimetry. Parametric data were analyzed by one-way ANOVA. Significance = $p<.05$.

There were no between group differences for MAP, arterial blood gases/pH, pericranial temperature, blood loss, duration of anesthesia or time to awakening. Blood glucose values were greater in the halothane group. Two ketamine MCA rats and one halothane MCA rat died during the post-operative period. Neurologically, both ischemia groups had deficits relative to ketamine shams, although there was no difference between anesthetic groups receiving ischemia. Infarct volumes are given in the Figure: no difference between halothane vs ketamine anesthetized groups occurred($p<.92$). We conclude that in this model, ketamine offers no advantage over halothane anesthesia for protection against focal cerebral ischemia.



1. Rothman SM et al. Neuroscience 21: 673-678, 1987
2. Church J et al. Anesthesiology 69: 702-709, 1988
3. Jensen ML et al. Br J Anaesth 61: 206-210, 1988