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TITLE: Inhalational anesthetics decrease central catecholamine activity and improve ischemic outcome.

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Inhalational anesthesia may attenuate ischemic injury by decreasing central sympathetic activity. In this study, brain catecholamines and α_2 -adreno-receptor binding were measured during ischemia in halothane, isoflurane and fentanyl anesthetized rats and correlated with neurologic outcome.

Methods- These experiments were approved by the Michael Reese institutional animal care committee. Male Sprague Dawley rats (350-450g) were used. There were 3 parts to this study. In the first experiment we evaluated the effect of halothane, isoflurane and fentanyl on outcome from incomplete cerebral ischemia. Group 1 (n=10) received 1.1% inspired halothane in room air during ischemia. Group 2 (n=10) received 1.4% inspired isoflurane. Group 3 (n=10) received 25 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ fentanyl iv and 70% N_2O in oxygen. Ischemia was produced by right carotid ligation with hemorrhagic hypotension to 30 mmHg for 30 minutes. Arterial blood gases, pH and skull temperature were maintained at baseline levels. Neurologic outcome was evaluated for 3 days after ischemia using an 18 point scale (0=normal, 18=stroke related death). In part 2, brain α_2 -adreno-receptor binding was measured using H^3 -clonidine in the following groups: 1=unanesthetized, 2=halothane, isoflurane or fentanyl/ N_2O anesthesia alone, 3 = during ischemia with each anesthetic, 4 = 4 hour post-ischemic recovery. In part 3, brain catecholamines and metabolites were measured by HPLC using an electrochemical detector and internal standards under the same conditions.

Results- Following ischemia with halothane and isoflurane, neurologic outcome was improved compared to fentanyl/ N_2O ($P<0.05$). α_2 -adrenoreceptor binding was decreased by inhalation anesthesia (fig 1). A further decrease in binding was seen during ischemia and in the recovery period. Catecholamine turnover was decreased during ischemia with inhalational anesthetics. Isoflurane and halothane treated rats showed less depletion of catecholamines during ischemia and in the recovery period compared to fentanyl/ N_2O .

Discussion- These results indicate that halothane decreases catecholamine activity during ischemia. This suggests that the cerebral protective effect of halothane and isoflurane may be mediated by brain catecholamine mechanisms.

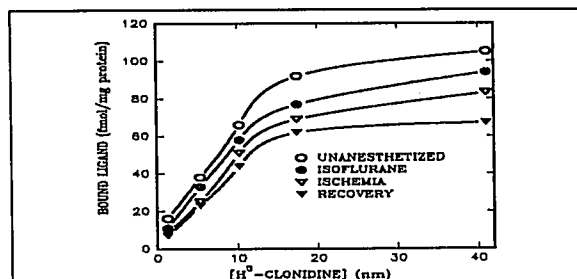


Figure 1. Binding curves in the right (ischemic) hemisphere during isoflurane anesthesia.

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TITLE: Ketamine, an NMDA antagonist, improves outcome from incomplete cerebral ischemia in rats.

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Ketamine and NBQX inhibit NMDA and non-NMDA excitatory receptors respectively. We investigated whether these drugs decrease neuronal injury in a rat model of incomplete cerebral ischemia.

Methods- After institutional animal care committee approval, male Sprague Dawley rats (350-450g) were catheterized during halothane anesthesia. Halothane was withdrawn and a control group (n=10) anesthetized with 25 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ fentanyl iv and 70% $\text{N}_2\text{O}/30\% \text{O}_2$ ventilation. An NBQX treatment group (N=15) was anesthetized with fentanyl/ N_2O and received 30 mg/kg NBQX intraperitoneal 15 minutes before ischemia. A third group (n=10) received 1 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ketamine iv. Unilateral ischemia was produced by right carotid artery ligation with hemorrhagic hypotension to 30 mmHg for 30 minutes. Arterial PaCO_2 and pH were maintained at baseline levels. Skull temperature was maintained at 37°C . Plasma catecholamines and glucose were measured during ischemia. Neurologic outcome was evaluated daily for 3 days after ischemia using an 18 point scale (0=normal, 18=stroke related death).

Results- Total plasma catecholamines (epi+norepi) during ischemia were: control = $2.34\pm1.18 \text{ ng/ml}$ (mean \pm SD), NBQX = $2.20\pm1.04 \text{ ng/ml}$, ketamine = $0.43\pm0.20 \text{ ng/ml}$ ($P<0.05$ vs control). Neurologic outcome was improved with ketamine but not with NBQX compared to control (fig 1).

Discussion- These results show that ketamine but not NBQX improve outcome from incomplete cerebral ischemia in the rat. This suggests that ketamine inhibited NMDA receptors and attenuated sympathetic activation during ischemia. This significantly decreased ischemic injury.

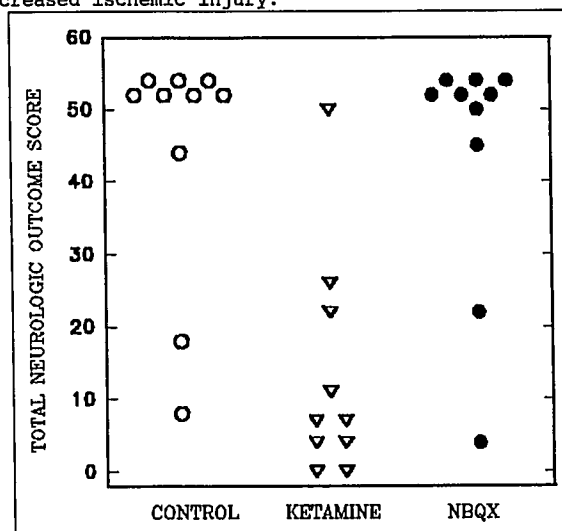


Figure 1. Total 3 day neurologic scores for each rat. Ketamine improved outcome compared to control ($P<0.05$, Kruskal-Wallis test).