Anesthetic-dependent pial arteriolar response to ethanol

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Anesthetic agents are often administered in the presence of ethyl alcohol, both in research and in the clinical setting. The authors tested the hypothesis that anesthetic agents may affect cerebrovascular responses to ethanol. A closed cranial window preparation in the rat was used to compare the response of pial arterioles to topically applied ethanol (0.01% to 1% vol/vol) in the presence of α-chloralose/urethane (50 and 600 mg/kg, respectively) or halothane (0.5% to 1%) anesthesia. Heart rate, mean arterial blood pressure, and blood gas levels were maintained stable and within the physiological range throughout each experiment. Ethanol induced significant vasoconstriction in α-chloralose/urethane–anesthetized animals (multivariate analysis of variance (MANOVA), p = 0.039); conversely, ethanol induced significant vasodilation of the pial arterioles in halothane–anesthetized animals (MANOVA, p = 0.017). These responses were significantly different from one another (MANOVA, p = 0.001). Thus, the choice of anesthetic agent alters the cerebrovascular response to ethanol, and care should be taken to ascertain the influence of anesthesia in both research and clinical settings.

Key Words • ethanol • pial arteriole • anesthesia • cerebral blood flow • closed cranial window

The high incidence of elevated blood–alcohol concentrations (BAC) in emergency room patients may require administration of anesthetic drugs in the presence of alcohol. Ethanol itself is an anesthetic agent and the possible influence of this drug on patient response to other anesthetic agents is widely acknowledged. However, relatively few studies have investigated the cerebrovascular response to ethanol as a function of anesthetic agent. Altura and Altura have pointed out that the response of the cerebrovasculature to ethanol is complex, and our understanding of this response has been obscured in some studies because of changes in systemic parameters such as PCO₂ and mean arterial blood pressure (MABP). In other instances the interaction of ethanol and anesthetic agent might also create a diversity of responses.

Very few studies have addressed the issue regarding the interaction between anesthetics and ethanol on the response of the cerebral microcirculation, particularly when MABP and blood gas levels are controlled. However, in both the clinical and research setting, the anesthetic agent and ethanol are coadministered, albeit for different reasons. Thus, it is important to determine if an anesthetic drug has synergistic, antagonistic, or relatively little effect on the response of the cerebrovasculature to ethanol. We used a closed cranial window preparation in the rat to investigate the influence of anesthetic agents on the pial arteriolar response to topically applied ethanol. To our knowledge this is the first report regarding the effect of anesthetic drugs on the response of pial arterioles to ethanol.

Materials and Methods

The animal experimentation was conducted in accordance with institutional guidelines and approved by the University of Washington Animal Care Committee. Adult male Sprague-Dawley rats weighing 350 to 400 g were initially anesthetized with halothane (1.5% to 2.0%). All operative sites were infiltrated with carbocaine hydrochloride (Mepivacaine, 0.5%). The right femoral artery and vein were cannulated for monitoring MABP and intravenous administration of drugs. The rats were tracheostomized, immobilized with intravenous tubocurarine chloride (1 mg/kg), and mechanically ventilated. Following tracheostomy, anesthesia was continued using either halothane (0.5% to 1.0%) or intraperitoneal injection of α-chloralose and urethane (50 and 600 mg/kg, respectively) with concomitant reduction of halothane to 0%. Supplemental doses of α-chloralose/urethane (one-fifth initial dose) were administered as needed. End-tidal CO₂ levels were continuously monitored. Periodically, small (0.2-ml) amounts of arterial blood were sampled anaerobically for the measurement of pH, PaCO₂, and PaO₂, levels. Heart rate, MABP, and blood gas levels remained stable and within the physiological range throughout each experiment. Rectal temperature was maintained at 37°C by a thermostatically regulated heating mat.
The cumulative dose-response of pial arterioles to topically applied ethanol was determined in rats anesthetized with halothane or chloralose/urethane. Four animals were used in each group. Data are presented as the mean ± standard deviation.

The rats were secured in a stereotactic frame, and a closed cranial window was mounted over the right parietal cortex using the method of Morii, *et al.* Polyethylene tubes attached to the cranial window allowed perfusion and drainage of artificial cerebrospinal fluid (CSF) over the brain surface and monitoring of intracranial pressure, which was maintained at 3 to 5 mm Hg by adjustment of the fluid level of the outflow tube. The artificial CSF, bubbled in 6% CO$_2$, 10% O$_2$, and balance N$_2$, had the following composition: Na$^+$, 156.5 mEq/L; K$^+$, 2.95 mEq/L; Ca$^{2+}$, 2.5 mEq/L; Mg$^{2+}$, 1.33 mEq/L; HCO$_3^-$, 24.6 mEq/L; dextrose, 66.5 mg/dL; and urea 40.2 mg/dL. After equilibration, the CSF pH was 7.34 to 7.35 and the osmolarity was 298 mOsm/L. The pial circulation was visualized using a Nikon microscope and a halogen lamp with a heat reflection filter and a 546-nm green filter, and vessel diameter was measured with a video micrometer system.

After a stable preparation was obtained, artificial CSF was superfused (0.25 ml/min) through the cranial window for 10 minutes; superfusion was then stopped for 2 to 3 minutes to allow measurement of the pial arteriole diameter. Ethanol in artificial CSF over a concentration range of 0.01% to 1.0% (vol/vol) was then tested in a similar manner. Ethanol did not change the pH of the CSF. At the conclusion of each experiment the reactivity of the pial arterioles to CO$_2$ inhalation was evaluated (CO$_2$ reactivity = 100%/a change of CBF at higher concentrations.1,6,7 How- ever, the response of blood flow in different regions of the brain (rCBF) to ethanol is not uniform.1,6,7,13 However, the response of blood flow in different regions of the brain (rCBF) to ethanol is not uniform.1,6,7

Very few studies have addressed the issue regarding the interaction between anesthetic agents and ethanol on the response of the cerebral microcirculation, particularly in ventilated animals with comparable MABP and blood gas levels. Hadji-Dimo, *et al.*, have investigated the response of the cortical surface CBF to ethanol in cats using the Krypton-85 clearance technique and noted a complex response. A low ethanol dose (55 mg/dL BAC) injected into the vena cava increased cortical blood flow in N$_2$O-anesthetized but not pentobarbital-anesthetized cats.9 In contrast, a higher ethanol dose (135 mg/dL) caused reduced cortical blood flow in both experimental groups.9 Friedman, *et al.*, compared the response of rCBF to intravenous ethanol in awake dogs (0.23% BAC) versus pentobarbital-anesthetized dogs (0.219% BAC) and noted that the reduction in brain blood flow caused by ethanol was obscured by the reduction in rCBF caused by pentobarbital anesthesia.

In the present study we chose to apply ethanol topically, thus avoiding its systemic effects and allowing better control of its concentration at the pial arterioles. If ingest-

**Sources of Supplies and Equipment**

The microscope, with M Plan 10/0.21 and 20/0.35 super long working distance objectives, was obtained from Nikon, Inc., Melville, NY. The video micrometer system was comprised of a Newvicon video camera (Dage-MTI Inc., Michigan City, IN), a NV-8950 video recorder (Panasonic Industrial Co., Secaucus, NJ), and a model 305 video-micrometer (Colorado Video, Inc., Boulder, CO).

**Results**

The response of pial arterioles to topical ethanol application during α-chloralose/urethane versus halothane anesthesia is presented as percentage change from control diameter in Fig. 1. Four animals were used in each group. The control diameter was 33.0 ± 5.4 μm in the α-chloralose/urethane group and 35.3 ± 5.4 μm in the halothane group (difference not significant). Ethanol induced dose-dependent vasoconstriction in the α-chloralose/urethane group (MANOVA, p = 0.039). Conversely, ethanol induced vasodilation in rats anesthetized with halothane (MANOVA, p = 0.017). The response of the arterioles to ethanol was significantly different when the two groups were compared (MANOVA, p = 0.001). Arteriolar CO$_2$ reactivity was 1.4% ± 0.4%/mm Hg for α-chloralose/urethane–anesthetized animals and 1.7% ± 0.1%/mm Hg for halothane-anesthetized animals (difference not significant). There was no significant difference in physiological parameters or blood gas levels in the groups studied. In α-chloralose/urethane– versus halothane-anesthetized animals, pH was 7.43 ± 0.02 versus 7.41 ± 0.02; PaCO$_2$ was 35 ± 1 mm Hg versus 34 ± 1 mm Hg; PaO$_2$ was 118 ± 12 mm Hg versus 126 ± 2 mm Hg; and MABP was 124 ± 2 mm Hg versus 126 ± 2 mm Hg.

**Discussion**

The present study is the first to report that the response of pial arterioles to topically applied ethanol is dependent upon the anesthetic agent present. Ethanol caused dose-dependent vasoconstriction in α-chloralose/urethane–anesthetized animals and vasodilation in halothane-anesthetized animals.

The direct response of isolated cerebral blood vessels to ethanol appears to be vasoconstriction.2,8 In human and animal investigations in the absence of anesthetic agents, ethanol appears to cause no effect or only modest increases in cerebral blood flow (CBF) at low concentrations and a reduction of CBF at higher concentrations.1,6,7,13 However, the response of blood flow in different regions of the brain (rCBF) to ethanol is not uniform.1,6,7
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ed, the concentration of ethanol in the CSF parallels that of the blood after an initial lag period. The concentration range of 0.01% to 1.0% (vol/vol) was chosen to span BACs (0.008% to 0.80% wt/vol) associated with altered function in humans. Topical ethanol administration allowed the maintenance of stable physiological parameters, in particular MABP and PCO₂, level, under α-chloralose/urethane or halothane anesthesia while testing varying ethanol concentrations. In the clinical setting, the ethanol and anesthetic agent are both present systemically and their combined effect on rCBF is more complex. It would be difficult to predict the ultimate effect on rCBF resulting from the administration of an anesthetic agent to an intoxicated patient.

Altura, et al., have also described the response of rat pial arterioles to ethanol; however, they used an open cranial window preparation. This preparation may result in altered responsiveness of pial arterioles to vasoactive stimuli because of less optimal control of the PCO₂ of the superfused artificial CSF and therefore may not be directly comparable to our results. With this caveat in mind, it is interesting to compare their experimental results with ours. They found that, in either pentobarbital (25 mg/kg)- or ketamine (80 mg/kg)-anesthetized animals, ethanol caused dose-dependent vasoconstriction in the concentration range of 10 to 500 mg/dL, regardless of the route of administration (topically, intraperitoneally, or intravenously). They also documented a robust vasoconstriction of pial arterioles induced by topically applied ethanol in a concentration range similar to that used in the present study. For instance, at 0.1% (wt/vol, 22 mM) ethanol, Altura, et al., reported a 20.5% reduction in vessel diameter and, at 1.0% (wt/vol) ethanol, a 26.5% reduction in diameter. In comparison, we found that 0.1% (vol/vol, 17 mM) ethanol caused a 4.9% reduction in vessel diameter in α-chloralose/urethane-anesthetized rats and a 5.3% vasodilation in halothane-anesthetized animals. At 1.0% (vol/vol) ethanol we noted a 6.0% vasoconstriction during α-chloralose/urethane anesthesia and a 12% vasodilation during halothane anesthesia.

In general, blood flow in the microvasculature is proportional to the cube of an arteriole’s diameter. For our data at 0.1% ethanol, a diameter reduction of 4.9% (α-chloralose/urethane anesthesia) would cause a 14% reduction in flow through a 33-μm diameter arteriole, whereas a diameter increase of 5.3% (halothane anesthesia) would increase flow 17% in a 35.3-μm diameter arteriole. Thus, an overall flow difference of 31% between the two types of anesthesia would occur at this relatively low ethanol concentration.

We conclude that, in conditions in which PO₂, PCO₂, and MABP are controlled, the type of anesthesia used could significantly influence cerebral pial arteriolar response to ethanol in a range from vasoconstriction to vasodilation. To our knowledge this is the first report to explore the effects of anesthesia on the cerebral pial arteriolar response to ethanol. The dependence of arteriolar response to ethanol upon the type of anesthetic agent present may be of clinical and research importance.

References

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