FENTANYL WITH NITROUS OXIDE DOES NOT ALTER CEREBRAL AUTOREGULATION OR BLOOD FLOW COMPARED TO UNANESTHETIZED RATS

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Introduction: It is important to know the effects of anesthetics and other treatments on cerebral autoregulation. However, it is difficult to evaluate autoregulation in the appropriate control model, which is the unanesthetized subject. It is suggested that fentanyl and nitrous oxide (N_2O) provide adequate anesthesia but have little effect on cerebral autoregulation. We have compared regional brain blood flow and autoregulation in unanesthetized rats compared to fentanyl/N_2O anesthesia.

Methods: These experiments were carried out in 24 male Sprague Dawley rats after approval of the Institutional Animal Care Committee. Rats were anesthetized, intubated and ventilated with 2% isoflurane in oxygen for surgery. Catheters were inserted into both femoral arteries and one femoral vein for mean arterial blood pressure measurement (MABP), blood sample withdrawal and drug infusion. A catheter was inserted into the left ventricle via the right carotid artery for radioactive microsphere injection. In group 1 (unanesthetized rats, n=12), catheters were tunneled subcutaneously and exited from a small incision in the back. All incisions were infiltrated with 0.25% bupivacaine and closed. The rats were allowed 2 hours to recover from anesthesia. In group 2 (fentanyl/N_2O, n=12), the isoflurane was replaced by 70 % N_2O in oxygen and the rats were given a bolus of 10 µg/kg fentanyl followed by infusion of 25 µg/kg/h for 30 minutes. Cerebral blood flow (CBF) was measured in cerebral cortex, subcortex, cerebellum and midbrain. MABP was varied by phenylephrine or arfonad infusion combined with hemorrhage. Pressure was maintained for 5 minutes before each CBF measure to obtain steady state values. Arterial blood gases and body temperature were controlled in fentanyl/N_2O anesthetized rats.

Results: Cerebral autoregulation was seen in both unanesthetized and fentanyl/N_2O anesthetized rats over a MABP range of 50-150 mmHg. Autoregulation was present in all tissues measured. The average CBF (mean±SEM) seen in the autoregulatory range was similar between the two treatment groups for each tissue measured (table 1).

	cortex	subcortex	cerebellum	midbrain
	$ml \cdot 100g^{-1} \cdot min^{-1}$			
unanesthetized	149±6	101±6	132±8	108±8
fentanyl /N2O	129±9	91±7	137±8	96±4

Discussion: These results show that fentanyl/N_2O anesthesia has little effect on cerebral autoregulation or regional brain blood flow compared to unanesthetized rats. This supports the use of fentanyl/N_2O to evaluate control CBF and autoregulation in the rat.

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Title: HALOTHANE ATTENUATES BOTH RECEPTOR AND NON RECEPTOR MEDIATED EDRF PRODUCTION IN RAT THORACIC AORTA

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EDRF (endothelium-derived relaxing factor) is a cellular messenger which activates soluble guanylate cyclase and is present in vascular endothelium, respiratory epithelium, macrophages, and brain tissue. A previous report has shown that 2% halothane attenuates EDRF-dependent vasodilation in response to acetylcholine and bradykinin. Whether this was a generalized effect on EDRF production or an inhibition of receptor activation was not determined1. In this study, we tested the hypothesis that halothane inhibits endothelium dependent dilation by interfering with receptor activation on the endothelial cell.

Descending aortic rings from 300g male Sprague-Dawley rats were suspended on Grass force transducers at 2g resting tension in 37oC water jacketed baths containing Krebs solution gassed with 95% O_2/5% CO_2. Following equilibration and the development of active tension with an EC_{50} dose of phenylephrine, the presence of endothelium was confirmed by response to methacholine (>30% relaxation). Following active tension development with phenylephrine, relaxation dose-response curves were obtained to the receptor mediated endothelium dependent dilator methacholine, to the non-receptor mediated endothelium dependent dilator A23187 (a calcium ionophore), and to the endothelium independent dilator sodium nitroprusside. Responses were obtained prior to (control), during (1 and 2 MAC), and following (post HAL control) halothane administration.

Results for 2 MAC halothane are presented in the figures as mean +/- S.E.M. Halothane significantly (*p<.05, **p<.01) attenuated relaxation to both methacholine and A23187, but had no effect on relaxation to sodium nitroprusside. Each point represents 9 rings, 5 animals for methacholine, and 6 rings, 4 animals for A23187. Statistical differences were determined by ANOVA followed by Neuman-Keul's multiple range test.

Because both receptor mediated and non-receptor mediated endothelium dependent relaxation was attenuated while endothelium independent relaxation was not, we conclude that the mechanism of halothane effect on EDRF production is not explained by an inhibition of receptor activation. We have shown that halothane inhibition of EDRF is reversible and occurs distal to receptor activation on the endothelial cell membrane and proximal to the site of guanylate cyclase activation of smooth muscle.

1Anesthesiology 68:31-37, 1988

Supported in part by NIH grant R29 HL-39706.