Title: REGIONAL CBF AND $CMRO_2$, CMR_{gl} AND BRAIN METABOLITE LEVELS DURING N_2O OR HALOTHANE: COMPARISON TO THE AWAKE STATE.

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Introduction. N_2O and halothane are commonly utilized anesthetics in experimental animals and are often employed (in artificially ventilated and paralyzed animals) under a variety of physiological and pathophysiological conditions where measurements of CBF, $CMRO_2$, CMR_{gl}, and brain metabolite levels are required. A number of studies have suggested that N_2O (60-70%) can increase CBF, $CMRO_2$ and CMR_{gl}(1,2,3). However, no information regarding N_2O effects on brain tissue metabolite profiles is presently available. Halothane may increase CBF and has been associated with reductions in $CMRO_2$ (4,5) and dose-related reductions in brain high energy phosphate levels and increases in the lactate/pyruvate ratio (L/P) (5). Interpretations of results regarding halothane ($\leq$ 1%) and N_2O effects on all of the above mentioned parameters are complicated by the lack of appropriate controls (i.e. unanesthetized and spontaneously breathing animals) where the influences of immobilization (and sampling) stress are minimized. In the present study we have employed techniques in the awake goat which allowed us to: a) serially obtain rapidly frozen cerebral cortical tissue samples and b) measure $CMRO_2$, CMR_{gl}, and total and local CBF. Thus with each animal utilized as its own control, we studied both N_2O and halothane effects on the above.

Methods. Five female goats (25-35 kg) were used. Two to four determinations of the effects of 60 min. of either N_2O (70% via a mask) or halothane (1% and 3% with paralysis and artificial ventilation) on cerebral metabolite profiles, CBF, $CMRO_2$ and CMR_{gl} were performed on each animal. All animals were surgically prepared 7-8 days prior to use with an acrylic "cranial window" (for tissue sampling), femoral arterial and venous catheters and a sagittal sinus catheter. Two goats were additionally fitted with a left atrial catheter for injection of microspheres for use in local CBF determinations. In the other 3 goats an electromagnetic flow probe was implanted on the internal maxillary artery (following elimination of extracerebral flow) for estimation of total CBF. $CMRO_2$ and CMR_{gl} were calculated via the Fick equation. For awake determination, goats were placed in a stanchion which prevented head movement. Serial tissue samples (50-200 mg) were obtained using a suction freezing apparatus. Freezing time was $<$ 0.5 sec. Up to 6 samples were taken from the cranial window site (2-3 awake). Additional samples (under halothane) were obtained from the opposite hemisphere on the day of sacrifice. Frozen samples were extracted (HCl-methanol, perchloric acid) and metabolites analyzed using fluorometric enzymatic techniques. The metabolites measured were ATP, ADP, AMP, PCr, glucose-6-P, fructose-6-P, lactate, pyruvate, citrate and $\propto$KG. Plasma epinephrine (E) and norepinephrine (NE) were also analyzed throughout. Body temp remained between 39°-40°C in all animals. $Paco_2$ did not vary by more than $\pm$3 mm Hg from control ($\bar{X}$=34.1$\pm$1.3 mm Hg) during N_2O or halothane. Pao_2 was $>$ 80 mm Hg in all animals.

Results. Plasma E and NE were not altered by fixation of the animal's head, nor following brain biopsy, thus suggesting lack of immobilization or sampling stress. No appreciable changes from control in any of the measured metabolites were found when animals were exposed to either N_2O or halothane (1% and 3%). A rather large increase in CBF could be noted during N_2O and was primarily confined to cortical tissue (209%). N_2O was also associated with increases in cortical $CMRO_2$ (157%) and CMR_{gl} (124%). Whole brain analysis showed little or no increase in $CMRO_2$, a similar increase in CMR_{gl} (120%) and a smaller increase in CBF (154%). These N_2O associated changes could not be related to increases in plasma E or NE, which remained constant throughout. Halothane anesthesia increased CBF only at 3%. However, regional flow values indicated much greater increases ($>$200% in most regions) than whole brain flows (140%). This is probably a result of a much smaller fall in MABP at 3% halothane in the microsphere injected animals (-22 mm Hg) as opposed to the animals with flow probes (-55 mm Hg). Both 1% and 3% halothane were associated with similar but marked falls in $CMRO_2$ and CMR_{gl} ($\sim$40% and $\sim$70% of control, respectively).

Discussion. This study represents the first attempts in experimental animals to relate N_2O and halothane effects on CBF and cerebral metabolism and metabolite patterns to non-stressed awake controls. Present results indicate that N_2O can have a profound effect on cortical CBF and can lead to increases in oxygen and glucose consumption as well. These results confirm those of Sakabe et al. (1) in dogs and Ingvar et al. (2) in rats. Results also suggest that even 1% halothane can lead to marked falls in $CMRO_2$ and CMR_{gl}. Although tissue metabolite profiles were not altered by N_2O or halothane, caution must be exercised when interpreting changes in CBF and cerebral metabolism from studies using N_2O or halothane anesthetized animals.

References.

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