TITLE: Effects of Hypoglycemia and Hypocarbia on Brain pH, ATP Phosphocreatine, and Blood Flow by NMR Spectroscopy.

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Introduction: Hypoglycemia has been shown to alter cerebrovascular responsivity to hypocarbia. The response to hypocarbia during hypoglycemia is characterized by absence of vasoconstriction and flat EEG, despite normal cerebral oxygen and glucose uptake ($CMRO_2$ and CMR glu, respectively). The mechanism of this altered response to hypocarbia is unclear. We sought to elucidate the mechanism of this response by using ^{31}P-NMR spectroscopy.

Methods: Mongrel dogs (9-11 kg) were anesthetized with fentanyl 50 mcg/kg and pentobarbital 10 mg/kg IV, paralyzed with pancuronium 0.2 mg/kg, intubated and mechanically ventilated. Measurements, including arterial and sagittal sinus blood gases and glucose, NMR spectra, EEG, and microsphere injection, were made sequentially at baseline (condition 1), 60 and 90 minutes after 10,000 U. insulin (conditions 2 and 3, respectively) and 10 and 22 minutes after hyperventilation to PCO_2 15 ± 1 torr (conditions 4 and 5). Normoglycemia was then restored by administration of 8cc of 50% glucose (condition 6), followed by resumption of normal ventilation (condition 7). Four dogs were not subjected to either hyperventilation or hypoglycemia (group 1). Seven dogs were subjected to hyperventilation only (group 2). Seven dogs were subjected to hypoglycemia only (group 3). Ten dogs received all interventions (group 4). Data were analyzed by ANOVA and Dunnett's Test.

Results: Insulin lowered blood glucose from 2.8 ± 0.2 mmol/l (mean ± SEM) to 1.1 ± 0.1 mmol/l. $CMRO_2$ and CMR glu did not vary significantly. Cerebral blood flow (CBF) was decreased by hypocarbia in group 2 (36 ± 2 ml/100gm/min) to 23 ± 2 ($P < 0.01$), while CBF did not vary significantly from baseline in any other group. Arterial pH increased from 7.39 ± 0.01 to 7.64 ± 0.02 during hypocarbia but was unaffected by hypoglycemia. Group 4 had significant changes in ATP to 39% of control ($P < 0.01$) and phosphocreatine to 43% of control ($P < 0.01$), as well as an increase in brain pH from 7.13 ± 0.05 to 7.43 ± .09 ($P < 0.01$). There were no significant changes in these parameters in any other group. Isoelectric EEG was seen in five of ten animals during hypoglycemia and hypercarbia; similar changes were not seen during either hypocarbia or hypoglycemia alone.

Discussion: These data suggest that the loss of cerebrovascular hypocarbic responsivity during hypoglycemia and the associated EEG changes are accompanied by decreases in brain phosphocreatine and ATP, and an increase in brain pH. These alterations occur despite maintenance of normal $CMRO_2$ and CMR glu.

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Title: DOSE-RELATED CHANGES IN CBF AND $CMRO_2$ DURING PROPOFOL INFUSIONS IN RABBITS

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Propofol is known to reduce both CBF and $CMRO_2$ (1), but no dose-response information is available. This study was thus undertaken to examine the relationship between blood propofol concentrations and changes in CBF and $CMRO_2$ under conditions where arterial pressures are held constant.

Nine NZW normocarbic, normothermic rabbits anesthetized with morphine (10mg/kg load, 2mg/kg/hr infusion) and 70% N_2O were surgically prepared to allow measurement of forebrain CBF and $CMRO_2$, using a platinum needle electrode and sampling catheter in the confluence of cerebral venous sinuses. CBF was determined using the H_2 clearance technique, and $CMRO_2$ was calculated as AVO2 x CBF. EEG was also recorded. Baseline data was collected, and an infusion of propofol started at a rate of 0.28mg/kg/min. This was increased in increments to a maximum of 1.67mg/kg/min, over a total study period of 3hrs. During this study period, CBF and $CMRO_2$ were determined every 22.5min. At each data point, arterial blood was also obtained for determination of whole blood propofol concentration, using HPLC. Mean arterial pressure was supported using angiotensin.

In spite of angiotensin, MAP decreased slightly, but did not fall below ≈80mmHg. There was a progressive dose-related decrease in CBF, with a minimum CBF ≈ to 65% of baseline at a blood concentration of ≈40μg/ml (at which point the EEG was isoelectric). At higher concentrations, CBF increased reaching baseline values at very high concentrations of propofol (i.e. values 2-3x those required for EEG suppression). $CMRO_2$ fell in parallel with CBF until the EEG was flat, with no further change thereafter. Note that the observed levels of propofol are much higher than seen in humans, but compatible with the levels needed for anesthesia in rabbits (2).

These results indicate a dose-related decrease in CBF and $CMRO_2$ with propofol under conditions were blood pressure is maintained. However, direct drug-related cerebral vasodilation may occur at excessive propofol concentrations.

1) Vandesteene A et al. Anaesthesia (Suppl) 43:42-43, 1988
2) Adam HK et al. Br J Anaesth 52: 743-746, 1980