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TITLE: HYPERCAPNIC CEREBRAL BLOOD FLOW REACTIVITY IS BLUNTED BY HYPOGLYCEMIA IN PIGLETS

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Introduction: The effects of hypoglycemia on normal control of cerebrovascular responses to physiologic stimuli have not been previously studied. In adult rats cerebral blood flow (CBF) reactivity to changes in $CO_2$ remains intact despite of hypoglycemia to the point of isoelectric electroencephalogram (EEG)[1]. We tested the hypothesis that severe insulin induced hypoglycemia would result in impaired CBF reactivity to altered $CO_2$.

Methods: One to two week old piglets (2.5-3.5 kg) were taken from the sow the morning of surgery. They were anesthetized with pentobarbital (65 mg/kg, IP and 10-12 mg/kg/hr, IV infusion), mechanically hyperventilated via tracheostomy to maintain $PaCO_2$ 24-26 mmHg. Prior to the experimental protocol $CO_2$ was added to inspired gases to maintain $PaCO_2$ approximately 40 mmHg. Oxygen was administered to maintain $PaO_2$ 100-200 mmHg. Blood pressure (MABP) was monitored via an axillary artery and fluids and drugs were administered via a femoral vein. Intracranial pressure (ICP) was monitored with a catheter in the lateral ventricle. Brain temperature was maintained at 38.0±0.5°C with a heat lamp. CBF (microspheres), cerebral oxygen consumption ($CMRO_2$=CBFX[arterial-sagittal sinus $O_2$ content]), and cerebrovascular resistance (CVR=[MABP-ICP]/CBF) were determined at a $PaCO_2$ of approximately 25, 40 and 65 mmHg before and after hypoglycemia. CBF reactivity was measured as the change in CVR between 25 and 40 and between 40 and 65 mmHg (DELTA CVR/DELTA $CO_2$). After obtaining normoglycemic measurements each piglet was given 200 U/kg regular pork insulin and CBF reactivity to $CO_2$ was again measured at either 60 (n=5) or 120 minutes (n=5) following insulin injection. EEG and blood glucose were measured at 15 min intervals following insulin injection. MABP was maintained at normoglycemic values by partially occluding the descending aorta with a balloon catheter.

Results: Prior to insulin injection there was no difference between groups for blood glucose, or reactivity to $CO_2$, in brainstem or cerebrum. Blood glucose decreased from 58±5 to 13±3 mg/dl at 1 hr and 6±2 at 2 hrs. Blood flow was increased at 1 (e.g. cerebrum 40±5 to 127±20 ml/min/100g) and 2 hrs (e.g. cerebrum 36±9 to 128±20 ml/min/100g) following hypoglycemia. At 1 hr, 3 of 5 piglets and at 2 hr 4 of 5 piglets had an isoelectric EEG. In piglets with isoelectric EEG (n=7) blood glucose was 7±0.9 mg/dl (vs 25±5 mg/dl), hypercapnic reactivity to cerebrum was ablated and hypocapnic reactivity was attenuated (0.05±0.01 to 0.01±0.003 mmHg/ml/min/100g). In piglets with isoelectric EEG we found no decrease in $CMRO_2$ (2.8±0.2 to 3.9±0.4 ml/min/100g, n=7).

Discussion: Our data suggest that CBF increases in response to hypoglycemia but reactivity to $CO_2$ is attenuated. The mechanism for attenuation appears to be linked to altered electrical activity even though oxygen consumption is maintained.

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1. Nilsson B, et al, *Acta Physiol Scand* 111:455, 1981.

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ROLE OF ADENOSINE IN CBF INCREASES DURING HYPOGLYCEMIA VS HYPOXIA IN THE RAT.

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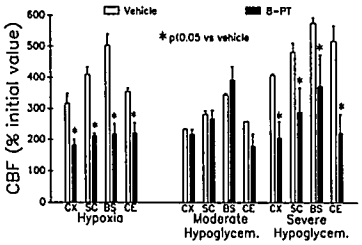
Previous work has shown that a substantial attenuation of the cerebral hyperemia accompanying hypoxia (HX) could be produced in the presence of the adenosine (ADO) receptor antagonist theophylline (1,2). This indicated a significant role for endogenous ADO release in the hypoxic CBF response. Acute hypoglycemia (HG) (plasma glucose <2.5 mM) is also associated with increases in CBF. A significant portion of the CBF response appears to be mediated via ß-adrenergic stimulation (3). However, there is preliminary evidence indicating an increase in cerebral ADO levels during HG (4), suggesting a role for ADO in the CBF increase. In the present study, we used the ADO-receptor antagonist 8-phenyltheophylline (8-PT) to evaluate whether ADO-related mechanisms contribute in any way to the CBF increase during HG. 8-PT is superior to theophylline, with respect to ADO-receptor antagonist potency and inability to affect phosphodiesterase. As a basis for comparison, CBF responses to HX were measured in the presence and absence of 8-PT. Following Animal Care Committee approval, male SD rats were surgically prepared using 0.8% halothane/70% $N_2O$ anesthesia and studied with the animals maintained on 70% $N_2O$/30% $O_2$ and fentanyl (25 mg/kg/h), paralysis and artificial ventilation. Regional CBF (rCBF) was measured in the following structures using radiolabeled microspheres : cortex (CX), subcortex (SC), brainstem (BS) and cerebellum (CE). One µl 8-PT (10 µg/kg) or saline vehicle was administered intracerebroventricularly (icv) via a 26g needle in the right lateral ventricle. For HX evaluations (n=8), rCBF was measured during normoxia (prior to and 10 min following icv saline or 8-PT) and at 10 min hypoxia ($PaO_2$=30-35 mmHg). No significant effect of icv 8-PT or vehicle on rCBF was seen under normal conditions. For HG studies (n=8), rCBF was measured immediately preceding HG induction via i.v. insulin and rCBF evaluated when plasma glucose (G) reached ~1.5mM. With G maintained at this level, 8-PT was introduced and rCBF measured after 15 min (moderate HG). G was then permitted to fall to ~1mM (severe HG), taking ~15 min, and rCBF was again measured. Arterial pressure (100-120 mmHg) and $PaCO_2$ (35-40 mmHg) remained relatively constant in all experiments. The results for HX and HG studies are summarized in the figure below. During HX, 8-PT produced a profound attenuation of the CBF response in all regions studied ($p<0.05$). In comparison, during HG, icv 8-PT resulted in an attenuated rCBF response only in severe HG, with the all regions showing statistically significant changes ($p<0.05$ vs vehicle-injected rats). Previous studies have demonstrated that the relative role of ADO in the cerebral hyperemic response to HX decreases with increasing hypoxic severity (1,2). On the other hand, in the CBF increases associated with HG, ADO appears to have a significant influence only when G falls to values near 1 mM (coma threshold) and lower. This contention is supported by measurements of brain ADO levels obtained in a preliminary study (4).

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