Title: HYPERGLYCEMIA DECREASES NEURONAL ISCHEMIC CHANGES AFTER MIDDLE CEREBRAL ARTERY OCCLUSION IN THE CAT

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Introduction. In models of global cerebral ischemia, hyperglycemia increases both morphologic brain damage and neurologic deficit.[1] Interventions which affect outcome after global ischemia may have different effects in focal ischemia. Therefore, we examined the effect of hyperglycemia on pathologic outcome after focal cerebral ischemia in the cat.

Methods. Twenty cats weighing 2-4 kg were anesthetized with ketamine 10 mg/kg IV, intubated, and mechanically ventilated to maintain $PaCO_2$ between 36-40 mm Hg. Anesthesia was maintained with halothane (0.85% end-tidal) in oxygen. Rectal temperature was maintained at 36.5 - 38.0° C. Femoral artery and vein were cannulated by cutdown. Mean arterial pressure (MAP) was maintained greater than 80 mm Hg by saline boluses as necessary; MAP never exceeded 120 mm Hg. Cats were randomized to glucose or control groups. The glucose group received fluid consisting of 50% dextrose in 0.45% NaCl; the control group fluid was 0.45% NaCl. Both groups received an infusion of 8 ml over 5 minutes followed by 8 ml/hr. Approximately 45 minutes after the start of fluid infusion, the left middle cerebral artery (MCA) was clipped via the transorbital approach. Plasma glucose levels were measured at the time of MCA clipping and 3 and 6 hours later. A cannula was then inserted into the aortic root via sternotomy, the descending aorta was clamped, the right atrium was opened and the animal was perfused with saline followed by 10% buffered formalin. The brain was removed, fixed, sectioned, and stained with hematoxylin and eosin. Neuronal ischemia was determined by microscopic examination of a coronal section through the optic chiasm. Neuronal ischemic changes were graded from 0 to 3.[2] Grade 2 and 3 regions were considered to show severe and probably irreversible ischemia and the area of severe neuronal ischemia (grades 2 or 3) was expressed as a percentage of total left hemisphere cortex area. Values are expressed as mean ± SEM and compared with t - tests.

Results. There were no significant differences between the two groups with respect to the volume of saline administered or the MAP at 0, 3 and 6 hours after MCA clipping. Plasma glucose levels in the control group were 209 ± 28, 193 ± 16 and 185 ± 12 mg/dl, at 0, 3 and 6 hours after MCA clipping; corresponding values in the glucose group were 561 ± 36, 632 ± 67 and 668 ± 73. The area of severe neuronal ischemia was 28.4 ± 5.0% in the control group and 12.4 ± 1.6% in the glucose group ($P < 0.01$). The area of severe neuronal ischemia was inversely correlated with glucose level at the time of clipping, both in the control group ($r = -0.803$, $P < 0.01$), and in both groups combined ($r = -0.692$, $P < 0.01$).

Discussion. In this model of focal cerebral ischemia, hyperglycemia was associated with significantly less morphologic brain damage. This result may be due to the beneficial effect of increased substrate availability. A study using a rat hippocampal slice preparation showed that elevated perfusate glucose levels facilitated the recovery of synaptic function following hypoxic insults.[3] Lactic acid accumulation, which has been suggested as being responsible for the adverse effect of hyperglycemia in global cerebral ischemia,[1] may not affect ultimate neuronal outcome in focal cerebral ischemia without reperfusion or its effects may be outweighed by beneficial effects of hyperglycemia. Further studies are in progress to confirm the results of the present study and to elucidate the mechanisms whereby hyperglycemia may exert a protective effect in focal cerebral ischemia.

References

1. Lanier WL, Stangland KJ, Scheithauer BW, Milde JH, Michenfelder JD: The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: examination of a model. Anesthesiology 66:39-48, 1987.
2. Little JR: Modification of acute focal ischemia by treatment with mannitol. Stroke 9:4-9, 1978.
3. Schurr A, West CA, Reid KH, Tseng MT, Rigor BM: Hyperglycemia improves recovery from cerebral hypoxia: an in vitro study. Anesthesiology 65: A314, 1986.

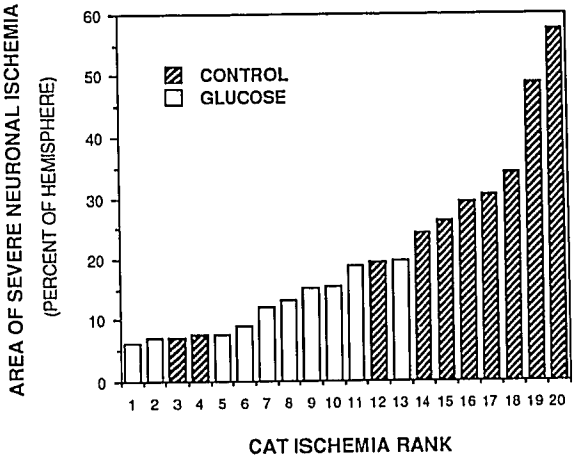

Figure 1. Percent hemisphere demonstrating severe neuronal ischemic changes and area ranks according to IV fluid group. Ischemia ranks were significantly worse in the control group at the $P < 0.01$ level by the Mann-Whitney rank sum test.