Title: ATTENUATION OF EFFECTS OF GLOBAL CEREBRAL ISCHEMIA IN A CANINE MODEL

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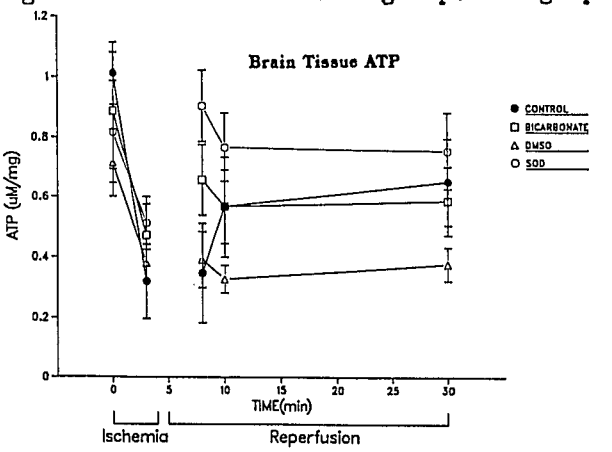
Introduction. Global cerebral ischemia with resulting cellular hypoxia can cause severe neurologic dysfunction. Numerous pharmacologic interventions have been attempted in efforts to ameliorate neurologic damage occuring complete ischemia and also during reperfusion. Though slow calcium blocking agents may show some promise; barbiturates, phenytoin, naloxone, and steroids have no protective effect in this setting. Likewise, deferoxamine, catalase, and superoxide dismutase given intravenously have not been efficacious in attenuating free radical damage occurring during reperfusion of ischemic brain. A part of the problem may be the inability to transport these therapeutic substances directly into the brain. The blood brain barrier may impede the transport of ions and hydrophilic molecules. Circumvention of this obstacle may be achieved by direct infusion of the cerebrospinal pathways with the technique of ventriculocisternal perfusion.

Methods. In this study a technique of ventriculocisternal perfusion was utilized to deliver either: superoxide dismutase (SOD-0.1mg/ml at 2cc/min), dimethylsulfoxide, (DMSO-50mg/ml at 2cc/min), or sodium bicarbonate (1.9 percent at a rate to maintain CSF pH greater than 7.35) to brain during a four minute period of ischemia and 30 min. of reperfusion. 21 caninea were randomly assigned to one of four treatment groups: Controls, Bicarbonate perfusion, DMSO perfusion, SOD perfusion. Brain tissue ATP levels served as our biochemical marker of ischemic effects. Analysis of brain tissue ATP levels were obtained: prior to ischemia, at 3 min of ischemia, and following 4, 10, and 30 min of reperfusion.

Animals were anesthetized with sodium pentobarbital, intubated and mechanically ventilated with room air to maintain normoxia and normocarbia. Core temperature was maintained at 37°. Non-glucose containing physiologic saline solutions were administered IV. Animals were placed in a stereotactic head frame. A generous craniectomy was performed and the dura reflected to expose the cerebral hemispheres. Both lateral ventricles were cannulated stereotactically. Catheters connected to infusion pumps provided a controlled rate of ventriculocisternal perfusion into the lateral ventricles. A catheter inserted into the cisterna magna allowed efflux of perfusate. Global cerebral ischemia was accomplished by electrical fibrillation of myocardium and ventilation was discontinued. After 4 min of ischemia animals were resuscitated. Reperfusion was said to occur when a systolic blood pressure of 100mmHg was obtained. Ventilatory adjustments were made to avoid episodes of hypercapnia or hypoxemia. Brain tissue specimens were analyzed using an enzymatic fluorometric assay.

Results. Brain tissue ATP levels revealed no statistical differences with respect to groups at our mean pre-ischemic value of 0.860± 0.18uM/mg or after 3 min of ischemia with a mean value of 0.420± 0.1uM/mg. After 4 min of reperfusion ATP levels for the SOD group approached 0.91± 0.12uM/mg ATP levels for all other groups remained depressed; Bicarbonate 0.66± 0.12uM/mg, Controls 0.35± 0.16uM/mg, and DMSO 0.33± 0.05 uM/mg. This was found to be significant at $p<0.05$ when the SOD group was compared to Control and DMSO groups. Statistical significance was not found between groups for the remaining time periods;however, upon inspection brain tissue levels of ATP remain higher for the SOD treated group. See graph.




Discussion. This study speaks for a protective effect of SOD on cerebral metabolic energy stores and ATP production during this early period of reperfusion as compared to our Control group and DMSO treated animals. SOD therapy may have more prolonged benefits as ATP levels for this group tend to remain higher by comparison.

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