Title: THE ROLE OF LACTIC ACIDOSIS IN NEURONAL TISSUE DAMAGE INFLICTED BY HYPOXIA IN VITRO

Authors: B. M. Rigor, M.D., W.-Q. Dong, M.D., N. H. Brahen, M.D., C. A. West, M.S. and A. Schurr, Ph.D.

Affiliation: Department of Anesthesiology, University of Louisville School of Medicine, Louisville, KY 40292

Introduction. Cerebral lactic acidosis during ischemia has been suggested to be responsible for the damage observed followed ischemic/hypoxic insult. However, measurement of lactic acid levels in ischemic brain tissue showed poor correlation with postischemic recovery of cerebral blood flow and energy metabolism. The hippocampal slice preparation allows the study of neuronal tissue under normoxic and hypoxic conditions in the absence of blood flow and blood-borne factors. This preparation also offers precise control of the extracellular environment including the pH and the concentration of compounds such as glucose and lactate. Using this system it has already been shown that increased glucose levels protect cerebral tissue against hypoxic damage. In the present study the effects of two different concentrations of lactic acid on the outcome of hypoxic insult were evaluated using the hippocampal slice preparation.

Methods. Rat hippocampal slices were prepared as described elsewhere [1]. They were maintained in a linear-flow incubation chamber by perfusion with artificial CSF (ACSF) and a gas atmosphere of 95% O_2/5% CO_2. Temperature was maintained at 34±0.5°C. Evoked population spike (synaptic function) was recorded once/min for the entire duration of the experiment from the CA1 pyramidal cell layer following orthodromic stimulation of the Schaffer collaterals. Hypoxia was produced by changing the gas atmosphere to 95% N_2/5% CO_2 for 10, 12 or 15 min. Control slices were always perfused with normal ACSF. The perfusion fluid for the experimental slices was supplemented with lactic acid (10 or 20 mM) 30 min before exposing the slices to hypoxia. Slices were allowed to recover from the hypoxic insult for 30 min in 95% O_2/5% CO_2 at which time all slices in the chamber were tested for their response to orthodromic stimulation; the presence of a population spike was considered as recovery of synaptic function.

Results. Table I summarizes the outcome of 15, 12 and 10 min hypoxia in 1219 hippocampal slices treated with 0, 10 and 20 mM lactic acid. The longer was the hypoxic episode the lower was the recovery rate of synaptic function both in control and experimental slices. While 10 mM lactic acid appeared to improve the recovery rate of synaptic function, especially following 12 min hypoxia, 20 mM of the metabolite had no detrimental effect on the recovery rate following either 12 or 15 min hypoxia. However, a deleterious effect was noted with the combination of 20 mM lactate and 10 min hypoxia.

Table I. Synaptic function recovery in hippocampal slices following hypoxia in the absence (control) or presence of 10 or 20 mM lactic acid.

Hypoxia (min)	Lactate (mM)	No. of Slices (recovered/total)		% Recovered
15	-	27/163		16.6
	10	15/68	n.s	22.1
	20	11/105	n.s	10.5
12	-	118/166		71.1
	10	76/84	*	90.5
	20	60/98	n.s	61.2
10	-	251/273		91.9
	10	81/87	n.s	93.1
	20	132/175	*	75.4

* Significantly different from control (no lactate) using X^2 test ($P<0.0005$). n.s = Not significant. The pH values for normal ACSF, 10mM lactate-ACSF and 20 mM lactate-ACSF were 7.29±0.07, 6.85±0.05 and 5.52±0.30, respectively.

Conclusion. These results indicate that lactic acidosis plays only a minor role in the neuronal damage inflicted on cerebral tissue by ischemia/hypoxia. If at all, the neuronal tissue appeared to benefit from the presence of moderate levels of lactic acid during the hypoxic insult.

References.

1. Schurr A, Reid KH, Tseng MT, Edmonds HL: The stability of the hippocampal slice preparation: an electrophysiological and ultrastructural analysis. Brain Research 297: 357-362, 1984.