TITLE: DIAZEPAM FAILS TO PROTECT BRAIN TISSUE IN HYPOXIC STRESS

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Introduction:

Both barbiturates and hypothermia ameliorate changes in brain tissue metabolites during hypoxic-ischemic stress in the rat and this has been interpreted to represent a protective effect. Reduction of brain oxygen consumption ($CMRO_2$) by both hypothermia and barbiturates may be a major factor in this protection. In hypoxic stress, comparison of equidepressant hypothermic and barbiturate treatment shows hypothermia to be more effective in protecting brain tissue.[1] This may be secondary to cardiovascular depression induced by barbiturates, to increased blood oxygen content in hypothermia, or to other factors. A combination of diazepam and nitrous oxide has been shown to reduce brain oxygen consumption to the same extent as barbiturates with much less cardiovascular depression, therefore we used diazepam/N_2O anesthesia to investigate whether the reduced $CMRO_2$ per se has a protective effect in arterial hypoxia.

Methods:

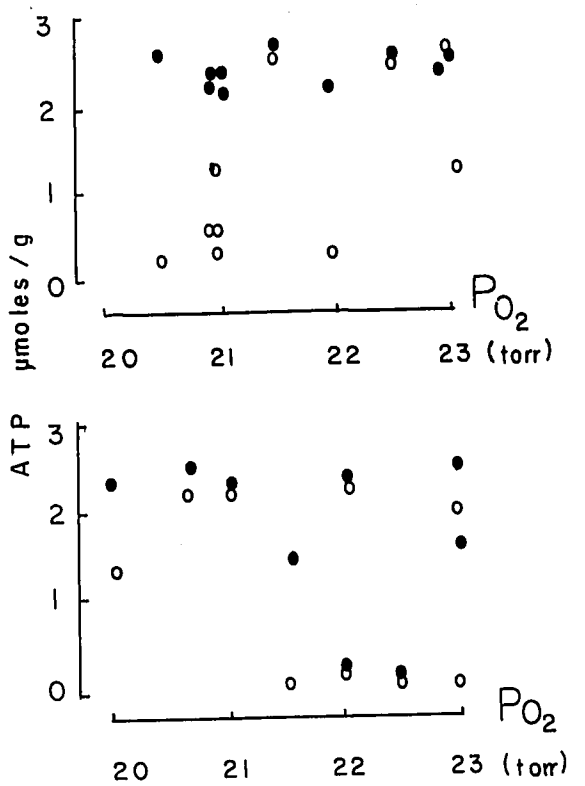
Male Wistar rats were mechanically ventilated with 70% N_2O in O_2 via tracheotomy. Blood pressure and temperature were recorded and arterial blood gases were sampled intermittently. One carotid artery was dissected free. Following stabilization FIO_2 was reduced, and the carotid clamped. Control animals were maintained on 5% O_2, 25% N_2 in N_2O, and the experimental group, in addition, received diazepam 2.25 mg/kg i.v. The brain was frozen in situ with liquid N_2 after 20 min. of hypoxia (PaO_2 21-23 torr) for subsequent analysis of cortical concentrations of ATP, phosphocreatine (PCr) and lactate. Protection was evaluated by the preventive effects of diazepam on the changes in metabolite levels produced.

Results:

There was no difference between the two groups in temperature (37°C), blood pressure (124 torr), PO_2 (21.5 torr) or PCO_2 (30 torr). In the control group 3/10 animals had ATP (figure 1) values close to normoxic levels (2.5 μmoles $.g^{-1}$) on both sides, the rest (7/10) had a pronounced energy failure on the ligated side and normal values on the unligated. The results in the diazepam group were more scattered, 3/9 had preserved ATP concentrations on both sides, 4/9 had very low values in the ligated hemisphere with normal concentrations on the other side, while 2/9 had bilateral energy failure. The concentrations of PCr parallelled the changes in ATP while lactate showed an inverse relationship. This could be expected from pH-dependent creatinekinase equilibrium.

Discussion:

These results indicate that, in the present model, 70% of the control animals had metabolic changes compatible with neuronal damage, while in the diazepam treated group 67% showed the corresponding alterations in the ligated side, but in addition, 22% also had energy failure in the unligated side. These results indicate that the diazepam-induced reduction of $CMRO_2$ does not protect from hypoxic insult.



Figures:

Individual Cerebral Cortical Concentrations of ATP plotted against arterial PO_2. Control group - top figure; Diazepam treated animals - bottom figure. Open circles denote ligated side and closed circles the unligated side.

References:

1. Hagerdal, M., Welsh, F.A., Keykhah, M.M., Perez, E., and Harp, J.R.: Protective effects of combinations of hypothermia and barbiturates in cerebral hypoxia in the rat. Anesthesiology, 49: 165-169, 1978.

2. Carlsson, C., Hagerdal, M., Kaasik, A., Siesjo, B.K.: The effects of diazepam on cerebral blood flow and oxygen consumption in rats and its synergistic interaction with nitrous oxide. Anesthesiology, 45: 319-325, 1976.