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Title : ATP PROTECTION IN LETHAL HYPOXIA II: CENTRAL INJECTION

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Introduction. We have previously demonstrated that peripherally administered adenosine triphosphate (ATP) (200 mg/kg) significantly increases survival time in mice exposed to a lethal hypoxic atmosphere.[1] Furthermore, we found that adenosine diphosphate (ADP) and adenosine monophosphate (AMP) were also effective; while phosphocreatine (CRP) was not. In this study, we examined the effects of centrally administered ATP in rats exposed to lethal hypoxia.

Methods. Male Sprague Dawley rats (300-350g) were used. Rats were anesthetized with halothane (1.5%) in oxygen; then injected in the right lateral ventricle of the brain by a free hand method described previously.[2] Twenty five microliters of 0.9% saline vehicle with or without 500 micrograms of ATP was injected. Fifteen minutes later (all rats had regained the righting reflex within 10 minutes), rats were individually placed in a 2 liter gas tight flow through chamber. A continuous flow at 7 liters/minute of a mixture of 5% oxygen-95% nitrogen was maintained and monitored with a Beckman OM-11 oxygen analyzer. Body temperature (rectal) was maintained at 37.0 ± 0.5° C. The observation period was arbitrarily truncated at 60 minutes. The interval between the introduction of the hypoxic mixture to the chambers and the last respiratory effort was measured for each animal and defined as the survival time (ST).

Results. In all experiments, the oxygen concentration within the chambers fell to 5.0 ± 0.1% within 90 seconds. In rats injected centrally with saline alone, the mean value of survival time (± standard error of the mean) was 13.72 ± 1.29 minutes (N=11). Within 6-8 minutes, the rats lost the righting reflex; followed by tonic-clonic seizure activity, opistotonous, urination and respiratory arrest. No untreated rat survived beyond 22 minutes. We observed no difference in ST between rats anesthetized with halothane and another series of animals which were not exposed to halothane. Rats injected centrally with ATP survived 48.10 ± 3.94 minutes (N=9), an increase of 250%. (Pairwise analysis of survival times was made via Wilcoxin and median 1 way analysis; statistically significant difference from saline treatment at 0.0001 level via chi square approximation.) ATP injected rats did not lose the righting reflex until shortly before death. Thirty three percent of the ATP treated rats survived the sixty minute hypxoic exposure; no neurologic defects were observed in these survivors.

Discussion. We have demonstrated that pharmacologic doses of ATP centrally administered in rats protects against lethal hypoxia. Similar results with ADP and AMP were obtained (data not presented). This study extends our previous findings that peripherally administered ATP, ADP and AMP significantly increase survival time in mice. Although we cannot exclude a peripheral effect of ATP after systemic administration, the evidence that ATP injected directly into the brain increases survival time, suggests that a direct action within the central nervous system is responsible. While the mechanism by which ATP promotes resistance of the brain to otherwise lethal hypoxic hypoxia remains undefined, it perhaps may be related to the utilization of exogenously supplied ATP for the maintenance of cerebral energy stores. However, it appears unlikely that an energy transfer mechanism accounts for the effectiveness of centrally or peripherally administered AMP. Moreover, CRP was ineffective. In view of this evidence, adenine nucleotide protection may not be directly related to an energy transfer mechanism. Although we have not yet identified the physiological mechanism whereby ATP and other nucleotides exert their protective action against lethal hypoxic hypoxia in the brain, our findings are of considerable potential. Obvious clinical implications may concern the amelioration of brain damage in man after cerebral hypoxic insult due to a variety of causes. Further studies elucidating the biochemical and physiological factors responsible for the protective action observed are necessary.

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References.

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