Title: THE CEREBRAL AND SYSTEMIC EFFECTS OF THE EXCITATORY AMINO ACID RECEPTOR ANTAGONIST MK-801 IN DOGS: MODIFICATION BY PRIOR COMPLETE CEREBRAL ISCHEMIA

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Introduction. The dibenzocycloheptenimine drug, MK-801, is a potent, orally active anticonvulsant that possesses anxiolytic and central sympathomimetic properties.[1] The drug is also a potent and selective noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor,[2] a property it shares with the dissociative anesthetics phencyclidine (PCP) and ketamine. MK-801 is lipid soluble, crosses the blood-brain barrier and results in sparing of selectively vulnerable hippocampal neurons following cerebral ischemia in animals.[2] The present study examined the effects of MK-801 on cerebral blood flow (CBF) and metabolic rate ($CMRO_2$) in dogs. In addition, the influence of prior cerebral ischemia on these effects was studied.

Methods. Twelve mongrel dogs were initially anesthetized with halothane in N_2O/O_2. Animals were then paralyzed and mechanically ventilated. CBF was measured by direct cannulation of the sagittal sinus and $CMRO_2$ was calculated as the product of CBF and the arterial to sagittal sinus O_2 content difference.[3] Inhalational anesthetic agents were discontinued after total spinal anesthesia was achieved with 1% tetracaine. After control measurements, the first six dogs (Group I) received MK-801 150 $\mu g \cdot kg^{-1}$ i.v. bolus, followed by a 90 min infusion at 75 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Samples for plasma drug levels were taken at 5, 60 and 90 min. Cerebral spinal fluid (CSF) samples for measurement of drug levels were withdrawn from the cisterna magna at 90 min. At the conclusion of the study, brain biopsies were obtained for measurement of cerebral ATP, ADP, AMP, lactate, pyruvate, phosphocreatine and glucose levels. Six additional dogs (Group II) were prepared as described above. In addition, catheters were placed into the lumbar subarachnoid space and cisterna magna for infusion of normal saline. The systolic blood pressure (SBP) was decreased with trimethaphan and 37°C normal saline was then infused into the subarachnoid space to raise the intracranial pressure (ICP) 20 mmHg above SBP for 11 min. An isoelectric electroencephalogram (EEG) was achieved within seconds of the subarachnoid infusion. The ICP was decreased to zero by opening the subarachnoid catheters to air and the mean arterial pressure (MAP) was increased to > 60 mmHg 1 min post ischemia (PI) using norepinephrine. MK-801 was administered as described above at 60 min PI and CBF, $CMRO_2$, and systemic physiological variables were measured for 60 min. Statistical comparisons between drug treatment and control variables were made using ANOVA for repeated measures with Dunnett's test. Cerebral metabolite levels were compared with historic control[4] using Student's unpaired t test.

Results. Plasma MK-801 levels were maintained at > 25 $ng \cdot ml^{-1}$ in both groups of dogs. The 90 min CSF MK-801 level was 13.2 ± 0.8 $ng \cdot ml^{-1}$. Five minutes after the initial dose of MK-801, Group I dogs experienced an average 63% increase in heart rate (HR) and 10% decrease in MAP that persisted for the duration of the drug infusion. Five minutes after the MK-801 bolus, CBF in normoxic dogs increased by an average of 84% and remained elevated. In parallel with the increase in CBF, ICP more than doubled from the control value of 5 mmHg ($p < 0.01$). Shortly after initial drug administration, the EEG of all Group I dogs showed periodic bursts of 100-200 μV delta waves and polyspikes on a background of low ampitude beta activity. No significant change in $CMRO_2$ was observed in Group I following drug administration. Of the cerebral metabolites measured, only the glucose differed significantly ($p < 0.05$) with a 30% decrease from historic control. No significant changes in CBF, $CMRO_2$ or systemic physiological variables were observed in Group II animals, nor were epileptiform EEG changes observed.

Discussion. The dose of MK-801 used in this study resulted in blood levels comparable to those in animal studies demonstrating neuronal sparing. The CSF level of the drug was half the plasma level, quantifying the extent to which the drug crosses the blood-brain barrier. The absence of a significant drug effect on systemic or cerebral physiological variables in postischemic dogs suggested that the effects of MK-801 on HR and MAP in normoxic dogs were centrally mediated and that complete cerebral ischemia resulted in abolition of these responses. The marked elevation in hemispheric CBF with no change in $CMRO_2$, the observed EEG changes, and the systemic physiological effects of MK-801 were similar to reported effects of ketamine and PCP.[5]

References.

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