TITLE: THE CEREBRAL VASOACTIVE EFFECTS OF MK-801, AN EXCITATORY AMINO ACID INHIBITOR

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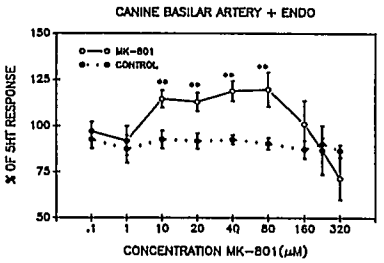
MK-801 (dizocilpine) is a non competitive antagonist of the N-methyl-D-aspartate (NMDA) excitatory amino acid receptor. It has been shown with some consistency to ameliorate the effects of focal cerebral ischemia. However, in global ischemia, the results have been much more variable. Although the beneficial effects of MK-801 are generally believed to reflect a direct cytoprotective effect, this difference between focal and global ischemia could also be due to a vasoactive effect which would improve blood flow in focal ischemia but could not be operant during global ischemia. The aim of this study was to investigate the vasoactive properties of MK-801.
METHODS: Basilar artery rings from adult mongrel dogs (n=13) and guinea pigs (n=16) were carefully disected free from arachnoid and suspended in organ baths of Kreb's buffer at 37°C aerated with 95% O_2-5% CO_2. Each vessel was carefully divided in half, the one half retaining its endothelium while in the other it was removed either mechanically (dog) or chemically (GP). Following equilibration to a steady baseline and after first precontracting the arteries to approximately 40% of maximum with either a receptor mediated agonist (5HT) or a voltage mediated stimulus (KCl), different doses of MK-801 were added in random order. Similar volumes of saline were used as control.
RESULTS: In both species MK-801 produced a dose dependent contraction followed by a relaxation at the highest concentrations. With the endothelium removed, the contraction was greatly attenuated and the dilation enhanced.
DISCUSSION: In the dog and guinea pig, MK-801 has vasoactive effects which are endothelium dependent and are consistent with MK-801 inducing release of an endothelium dependent constricting substance. These vasoactive effects may play a role in the beneficial effects noted with this drug in focal ischemia.



A693

TITLE: HIGH CONCENTRATIONS OF BARBITURATES CAN ENHANCE NEURONAL INJURY IN SUBSTRATE-DEPRIVED CORTICAL CELL CULTURES

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Barbiturates have been studied extensively as possible neuroprotective agents in global and focal ischemia, both in experimental animals and in some clinical trials[1,2,3]. Barbiturates have several actions likely to be beneficial in cerebral ischemia, including inhibition of neuronal excitation with reduction of $CMRO_2$, improved perfusion of compromised areas by vasoconstriction of normal areas, decreased intracranial pressure, and free radical scavenging. However, reports of actual neuroprotective effects have been variable. We examined the effects of barbiturates on cultured cortical neurons, where injury can be readily quantitated and direct cellular effects can be assessed independent of effects on the cerebral circulation. Primary cultures of mouse neocortex containing both neurons and glia were studied[4], and injury was assessed by light microscopy and efflux of the intracellular enzyme lactate dehydrogenase (LDH)[5].

Cultures exposed to glucose deprivation for 6 - 10 hr developed substantial neuronal injury by the next day[6]. Addition of 0.3-0.5mM secobarbital to the medium did not reduce neuronal degeneration; in contrast, neuronal injury was significantly increased. Potentiation of injury was also found with thiopental and methohexital. Even if the period of glucose deprivation was reduced to 4 hr, which produced essentially no neuronal injury, these concentrations of secobarbital induced severe neurotoxicity. Similarly, potentiation of injury was observed with similar concentrations of secobarbital, methohexital and thiopental when combined oxygen and glucose deprivation (30-60 min) was substituted for simple glucose deprivation. On control cultures maintained at normal levels of oxygen and glucose, 24 hr exposure to these 3 drugs also induced neuronal injury, but the concentrations required for toxicity were higher, 0.5 - 2mM.

The concentrations of barbiturates found to induce damage in substrate-deprived cultured neurons overlaps with plasma concentrations reported in anesthesia and barbiturate coma. Further experiments will be needed to define the mechanisms of this damage, but one possibility is the ability of high doses of barbiturates to inhibit phosphofructokinase, mitochondrial respiratory activity and oxidative phosphorylation[2,3]. While observations in cell culture cannot be simply extrapolated to the in vivo setting, present observations raise the possibility that the beneficial actions of barbiturates in brain ischemia may be counterbalanced by some deleterious effects.

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