TITLE: MK 801 MARKEDLY REDUCES THIOPENTAL AND HALOTHANE REQUIREMENTS IN RATS

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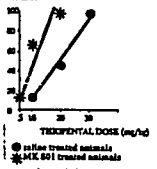
The potency of some anesthetics can be increased by prior administration of compounds like MK 801, which selectively blocks the excitatory aminoacid receptors of the N-methyl-D-aspartate (NMDA) subtype.[1,2] However, the effects of MK 801 on the anesthetic requirements for barbiturates and halogenated anesthetics have not been investigated yet in rats. This study was thus designed to assess the influence of MK 801 on thiopental requirements used for anesthesia induction and on halothane requirements in rats.

Thirty six male rats were randomly allocated to receive a 0.5 ml intraperitoneal (i.p.) injection of either saline (n = 18) or a 2 mg/kg dose of MK 801 dissolved in saline (n = 18) respectively. The rats were given 30 min later a second i.p. injection (1 ml) which consisted of a 10 mg/kg (n = 6), 20 mg/kg (n = 6) or 30 mg/kg (n = 6) thiopental dose in saline treated animals and of a 5 mg/kg (n = 6), 10 mg/kg (n = 6), or 20 mg/kg (n = 6) thiopental dose in MK 801-treated animals respectively. Loss of righting reflex (LRR) defined as the inability for the animal to right itself within 15 sec. after being placed on a side position was assessed by a "blinded" observer.

In addition, 10 animals were mechanically ventilated with halothane in 100% oxygen and ventilation adjusted to maintain normocarbia. Rectal temperature was servocontrolled to 37°C. MAC for halothane (MACh, defined as the end-tidal halothane value which prevented the motor response to a 60 sec noxious tail clamp in 50% of the rats) was determined before and 30 min after a 2 mg/kg MK 801 i.p. dose using a standard up and down tail clamp technique. Statistical significance ($p<0.05$) was assessed by the Chi-square test, analysis of covariance and Wilcoxon's paired test.

The dose-response curve of thiopental requirements for LRR was significantly shifted to the left in MK 801-treated animals (figure), $p<0.05$). In addition, MACh was markedly decreased following MK 801 administration (0.45±0.07 vol%, mean±SD versus 1.02±0.15, $p<0.01$).

Figure



These data indicate that MK 801 reduces markedly both thiopental and halothane requirements in rats. It can be speculated that compounds altering the excitatory amino-acid neurotransmission might have potential to be developed as anesthetic agents.

References

1. Neuropharmacology 28:677-681, 1989
2. Soc Neurosci Abstr 224:17, 1989

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TITLE: **ATP DOES NOT CORRELATE WITH RECOVERY AFTER ANOXIA AND THIOPENTAL IN THE RAT HIPPOCAMPUS.**

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Introduction: We used the in vitro hippocampus as a model system to examine whether CA 1 pyramidal cells (one of the most sensitive cell types in the brain) are protected against anoxic damage by thiopental. A commonly proposed mechanism of thiopental's protective action against anoxic damage is by maintaining cellular ATP levels. Therefore we examined the effect of thiopental on ATP levels during anoxia.

Methods: Hippocampal slices from adult rats were superfused with oxygenated artificial CSF (aCSF) at 37°C. The postsynaptic evoked population spike was recorded from the CA 1 pyramidal cells after stimulation of a presynaptic pathway. The slices were subjected to anoxia and then reperfused with oxygenated aCSF. The percent recovery of the response was calculated as the size of the response 60 min after anoxia divided by its preanoxic amplitude. For ATP measurements slices were frozen in liquid nitrogen and analyzed for ATP. Significance was determined using ANOVA and t-tests ($p < .05$).

Results: When the CA 1 pyramidal cells are subjected to 3.5 min. of anoxia the postanoxic population spike recovers to only 10 % of its preanoxic amplitude. If slices are treated with thiopental (600 uM) 15 min before,during and 10 min after anoxia there is 67 % recovery of the response. Thus thiopental significantly improved recovery of the response after anoxia. A lower concentration of thiopental (250 uM) also showed significant protection (24 %), however there was a clear dose related effect. The lowest dose of thiopental tested (100 uM) did not show significant protection.

Thiopental (600 uM) significantly increased the fall in ATP levels in the CA 1 region during 3.5 min of anoxia. After 5 min of anoxia there was no significant difference between treated and untreated slices. Only after 10 min of anoxia did thiopental show a slight preservation of ATP during anoxia.

Conclusions: Neurons in the rat hippocampal slice recover better from short periods of anoxia if they are treated with high concentrations of thiopental. This recovery does not correlate with ATP levels during anoxia. Thiopental (600 uM) protected against 3.5 min of anoxia yet the ATP levels during 3.5 min of anoxia were worse with thiopental. It is possible that in intact animals thiopental does maintain ATP levels and this is a component of its protection in vivo. However our study indicates that thiopental has an additional protective effect directly on the neurons independent of ATP preservation.

PERCENT RECOVERY WITH THIOPENTAL X ± sem (n)

0 uM	100 uM	250 uM	600 uM
10±4 (8)	17±6 (8)	24±2 (6)	67±10 (6)

ATP (nM/mg dry weight) n > 22 for each group

Anoxic time	0 m	3.5 m	5 m	10m
Untreated	3.7±.14	2.3±.11	1.4±.14	.5±.03
Thiopental 600uM	3.4±.19	1.6±.07	1.2±.04	.7±.04