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TITLE: PROPOFOL IMPROVES ELECTROPHYSIOLOGICAL RECOVERY AFTER ANOXIA IN THE RAT HIPPOCAMPAL SLICE

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Introduction: Propofol has properties which make it a potential choice anesthetic for use in neurosurgical procedures; however its ability to protect against anoxic neuronal injury has not been demonstrated. An *in vitro* rat hippocampal preparation was used to determine whether propofol could improve recovery of neuronal function after anoxia.

Methods: Hippocampal slices from adult rats were superfused with oxygenated artificial CSF (aCSF) at 37°C. Stimulation of presynaptic pathways elicit a postsynaptic evoked population spike (PS) which was examined in both the CA1 pyramidal cells and dentate granule cells. The clinical formulation of propofol, a fat emulsion vehicle (Intralipid 10%), or propofol without emulsion dissolved in 0.5% dimethyl sulphoxide (DMSO) were added to the aCSF prior to the anoxic interval. Following anoxia the slices were reperfused with oxygenated aCSF. Percent recovery was quantified by dividing the one hour post-anoxic amplitude of the PS by its pre-anoxic amplitude. Significance was determined using ANOVA and t-tests.

Results: Propofol significantly decreased the amplitude of the PS in both the CA1 and dentate regions before anoxia ($p<0.01$). After 30 minutes exposure, propofol reduced the PS by 19% in the CA1 region and by 62% in the dentate gyrus. This decrease is observed over all stimulus intensities tested. When CA1 pyramidal cells are subjected to 4 min. of anoxia the PS is lost and does not recover (4%). Similarly, the fat emulsion has no effect on post-anoxic recovery (6%). When slices are treated with the propofol emulsion (20 ug/ml) 30 min. before, during, and 10 min. after anoxia there is 68% recovery of the response, whereas the propofol/DMSO solution allows 88% recovery of the PS. The efficacy of the propofol emulsion decreased as the anoxic interval was increased to 5 min. After 5 min. anoxia the PS reached 42% of its pre-treated amplitude. When dentate granule cells are subjected to 7 min. of anoxia the PS does not recover(0%). Exposure to the fat emulsion has little effect on post-anoxic recovery (5%). Treating the slices with the propofol emulsion(20ug/ml) results in 70% recovery of the PS. In both the CA1 and dentate regions propofol significantly improved recovery of the response after short periods of anoxia ($p<0.01$). There is no significant difference between mean recovery percentages of the two propofol solutions.

Conclusions: Propofol decreases the PS amplitude in both CA1 pyramidal cells and dentate granule cells. This suggests either depression of excitatory transmission or potentiation of neuronal inhibition. Finally, we have demonstrated that propofol, not the fat emulsion, is able to protect CA1 pyramidal cells and dentate granule cells from short periods of anoxia. Its mechanism of action may be associated with its ability to depress cerebral metabolic activity including decreasing $CMRO_2$. There are several other postulated methods of protection and our current investigation along these lines may yield information as to propofol's specific mechanism of action.

PERCENT RECOVERY OF THE POPULATION SPIKE: CA1 PYRAMIDAL CELLS

4 Minutes Anoxia	mean±SE	n
Untreated	4 ± 4	5
Fat emulsion 0.2% v/v	6 ± 5	5
Propofol 20ug/ml (fat emulsion)	68 ± 12	5
Propofol 20ug/ml (DMSO)	88 ± 4	5

PERCENT RECOVERY OF THE POPULATION SPIKE: DENTATE GYRUS

7 Minutes Anoxia	mean±SE	n
Untreated	0 ± 0	6
Fat emulsion 0.2% v/v	5 ± 4	6
Propofol 20 ug/ml (fat emulsion)	70 ± 17	6

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Title: **Thiopental and Tetrodotoxin have similar effects on sodium levels in the rat hippocampal slice.**

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Thiopental protects against anoxia in the *in vitro* rat hippocampal slice [1] and attenuates the anoxia-induced Na increase and K decrease in hippocampal tissue.[2] Tetrodotoxin (TTX), a Na channel blocker, protects against anoxia in this model.[3] To investigate whether the protective effect of thiopental might be due to its ability to attenuate anoxic depolarization by an interaction with the voltage-dependent Na channels, we examined the effect of 600uM thiopental on veratridine-induced depolarization and the effect of TTX on anoxia-induced Na and K concentration changes in the rat hippocampal slice preparation.

Methods: The slices were prepared as described previously[1] and allowed to recover for two hours in oxygenated artificial CSF (aCSF) at 37°C. Drugs were added under normoxic conditions; veratridine 12.5 uM for 10 min. alone, or preceded by thiopental 600uM for 15 min., no drugs were added to the control slices. In the TTX experiments, 625 nM TTX was added to aCSF 5 min. prior to a 10 min. anoxic insult, which was generated by substituting nitrogen for oxygen. Control slices were either normoxic or made anoxic for 10 min. without a drug pretreatment . After drug exposure and/or anoxia, the slices were immersed in ice-cold isotonic sucrose for 10 min. and dried at 60°C for a week. Dry weights were then obtained and the slices digested with .1N HNO_3. Na and K levels were assayed with a flame photometer. The values reported reflect both intra and extracellular compartment ion levels. Significance was determined with ANOVA and t-test.

Results: Na levels increase by 47% after anoxia without drugs, and by 69% after veratridine during normoxia. Thiopental pretreatment blocks this effect of veratridine; TTX pretreatment blocks the effect of anoxia on Na content. K concentration in the slice decreases by 70% with veratridine and by 41% with anoxia. Thiopental attenuates this effect of veratridine, as does TTX with respect to anoxia, but neither drug blocks K efflux as effectively as Na influx under the same conditions.

Conclusions: We reported previously[2] that thiopental attenuates the anoxic Na increase and K decrease. Current experiments show that TTX, like thiopental, dramatically reduces the anoxic Na increase. Thiopental 600uM also blocks the Na rise due to veratridine-induced depolarization. Thus it appears that thiopental does possess sodium channel blocking properties and since TTX, devoid of other properties, protects against anoxia in our model, it appears as well that the protective properties of thiopental may, at least in part, be due to its sodium channel blocking effects. Despite the strong effect of thiopental on veratridine-induced Na increase, the simultaneous K decrease is only attenuated. Similarly, TTX did not prevent K from decreasing, although it attenuated its fall. Thus the attenuated fall of K may be secondary to thiopental's and TTX's Na channel blocking effect. Increased extracellular K may enhance depolarization and counteract the protective effects of thiopental and TTX against anoxia.

References: 1. Brain Res. 403:136-141, 1987 2. Anesthesiology 73:A685, 1990 3. Neuroscience 33,2: 263-268, 1989

Na and K concentration (uM/g dry weight) (mean ± SEM)

	(A)No drug Normoxia	(B)Veratridine Normoxia	(C)Thiop+Veratridine Normoxia
Na	229 ± 20	388 ± 10*vsA,C	262 ± 11* vs B
K	170 ± 5	51 ± 3*vsA,C	128 ± 3*vsA,B

	(A)No drug Normoxia	(B) No drug Anoxia	(C) TTX Anoxia
Na	208 ± 17	305 ± 16*vsA,C	242 ± 12* vs B
K	160 ± 6	95 ± 3*vsA,C	142 ± 3*vsA,B

*$p<0.01$