TITLE REDUCTION OF HYPOPERFUSION AND PREVENTION OF EEG CHANGES IN TRAUMA PLUS HEMORRHAGIC SHOCK USING A KAPPA OPIATE ANTAGONIST

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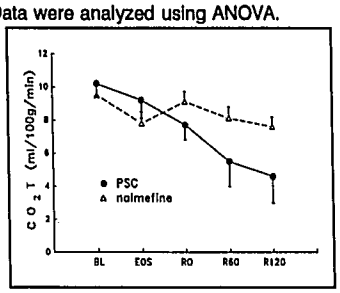
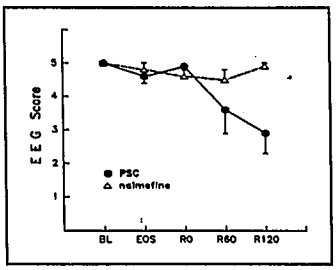
Introduction: Hypotension following traumatic brain injury (TBI) in humans is associated with significantly higher mortality and morbidity than TBI alone[1]. Few data describe the cerebrovascular effects of attempts to reverse hypotension following TBI. Mild hemorrhage and fluid resuscitation after moderate TBI in cats produce significant deceases in CBF, cerebral oxygen transport (CO_2T) and EEG activity[2]. Experimental evidence suggests that opiate antagonists may reduce hypotension and increase CBF after TBI[3]. We determined the effects of a kappa opiate antagonist (nalmefine) on CBF and EEG activity after TBI followed by hemorrhagic hypotension and resuscitation. Cats treated with nalmefine were compared with cats in which systemic blood pressure was supported pharmacologically in order to differentiate cerebral vascular effects from effects related to systemic perfusion pressure.

Methods: Cats were anesthetized with ketamine (25mg/kg), intubated, ventilated with 1.6% isoflurane in N_2O:O_2 (70:30) and prepared for TBI as described[4]. Following surgery, isoflurane concentration was decreased to 0.8% in N_2O. All cats were subjected to moderate TBI (2.2 atms) followed by hemorrhage to 70% of pre-injury blood volume and resuscitation with an equal volume of 10% hetastarch. Cats were then randomized to either a nalmefine group (Group N; 1mg/kg) or to a pressure-supported control group (Group PSC; dopamine infusion) after injury. CBF was determined using radioactive microspheres pre-injury (BL), after hemorrhage (EOS), and 0, 60 and 120 minutes after resuscitation (R0, R60, R120). EEG activity was recorded and scored visually used a scale modified from Prior, et al[5]. CO_2T was calculated as CBF x arterial O_2 content. Data were analyzed using ANOVA.

Results: Mean arterial blood pressures (MAP) did not differ significantly between the two groups. CO_2T and EEG score were significantly lower than baseline at R120 in Group PSC but not in Group N.



Discussion: Dopamine is widely used clinically to support systemic arterial pressure. These data indicate that animals treated with the nalmefine exhibited no significant changes from baseline in CO_2T or in EEG activity after TBI and shock. In contrast, pharmacologic support of MAP was associated with a progressive decline in both CO_2T and EEG score. Since hemorrhagic hypotension after TBI is associated a worse outcome than TBI alone[1], opiate antagonists may reduce the mortality or morbidity of TBI followed by hemorrhagic hypotension.



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A699

TITLE: EFFECT OF SECOBARBITAL AND HALOTHANE ON CHOLINERGIC BINDING TO NEURONAL NICOTINIC RECEPTORS

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The effect of anesthetics on cholinergic binding to postsynaptic nicotinic acetylcholine receptors (nAChR) has been described in detail using receptors purified from *Torpedo* electroplaque (*Torpedo* nAChR)[1,2] However, it is not known whether these drugs have the same effect on the nicotinic receptors present in the mammalian central nervous system (neuronal nAChR). This study examines the effect of secobarbital and halothane on high affinity ^{3}H-ACh binding to these neuronal nAChR.

Binding of ^{3}H-ACh to rat brain nAChR membranes was examined using a filtration binding assay [3]. Briefly, 5% brain homogenates (≈50-60 fmol ACh binding sites/mg protein) were prepared by centrifugation from freshly dissected rat cerebral cotex. These homogenates (200 µl) were incubated with ^{3}H-ACh (10 nM) and secobarbital (10 µM-3.6 mM) or halothane (32 µM-6.8 mM) for 40 min. Reactions were terminated by addition of buffer (4 ml), after which the bound radioligand was separated by filtration. The filters were then washed three times with buffer and counted. All experiments were performed in triplicate at 4°C in TRIS buffer containing atropine to block muscarinic receptors. Binding in the presence of 0.1mM carbachol was defined as nonspecific.

Secobarbital decreased ^{3}H-ACh binding to ≈ 40% of control at 3.6 mM (solubility limit of secobarbital). Analysis of concentration-response data yielded an IC_{50} = 3.0±0.31 mM and n_H =1.0±0.18. Halothane produced a much smaller decrease in binding to ≈ 80.5% of control at 6.8 mM.

These results differ from those obtained from *Torpedo* nAChR in: (1) type of effect (inhibition vs. enhancement)[1]; (2) efficacy (i.e. halothane (2 mM) produced <15% decrease in neuronal vs. >80% increase in *Torpedo* ^{3}H-ACh binding[2]); and (3) slope (n_H ≈1 vs. n_H >1.5 for respective secobarbital-dependent changes in binding[1]). These results suggest that anesthetics may have different mechanism(s) of action on neuronal nAChR than those proposed in studies using other nicotinic receptor subtypes.

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