

THE EFFECTS OF ETHANOL ON SPINAL CORD BLOOD FLOW AND AUTOREGULATION IN RATS

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In this study, we have evaluated the effect of low and high doses of ethanol on plasma ethanol concentration, spinal cord blood flow and autoregulation.

Methods: After approval from the Michael Reese Animal Care Committee, 36 male Sprague Dawley rats (350-450 g) were anesthetized, tracheostomized and ventilated with 1.4% isoflurane inspired. Catheters were inserted into both femoral arteries and veins and the left ventricle via the right carotid artery. Tubocurarine was administered for muscle paralysis. The rats were divided into three groups. Control rats (n=12) were given a saline vehicle injection ip. Group 2 was given 1 mg/kg ethanol ip and group 3 was given 4 mg/kg ethanol ip. Plasma ethanol concentration was measured 30 minutes after ethanol in all rats. Spinal cord blood flow measurements were made using 4 radioactive microsphere species 30-60 minutes after ip ethanol or sham injection. MAP was increased using phenylephrine infusion and decreased using arfonad infusion combined with hemorrhage. MAP was maintained constant for 5 minutes before each spinal cord blood flow measurement. Arterial blood gas tensions and pH were measured before each test. At the end of the study the rat was sacrificed, the spinal cord was removed, dissected into cervical, thoracic and lumbar sections and weighed. Spinal cord

blood flow was determined according to standard techniques. Autoregulation curves for each treatment group were plotted using a least squares fit. Differences in slopes between treatment groups were calculated using analysis of co-variance.

Results: Arterial blood gases remained within physiological limits with no difference between treatment groups over the entire blood pressure range. Plasma ethanol concentrations were 64 ± 7 (mean \pm SE) mg/dl with low dose and 418 ± 11 mg/dl with high dose ethanol. Spinal cord autoregulation was present between a blood pressure range of 60-120 mmHg in sham treated rats. Low dose ethanol did not significantly change the spinal cord autoregulation compared to sham treated animals. However, autoregulation was abolished by high dose ethanol. Within the autoregulatory range, total spinal cord blood flow was 128 ± 8 ml/100g/min in sham treated rats and 118 ± 9 ml/100g/min with low dose ethanol. With high dose ethanol, the average spinal cord blood flow seen in the blood pressure range of 60-120 mmHg was 91 ± 6 mmHg ($p < 0.05$ vs. sham).

Discussion: These results show that low plasma ethanol concentrations produce modest, non-significant changes in spinal cord blood flow and autoregulation. In contrast, high ethanol concentrations decrease spinal cord blood flow and abolish autoregulation. Both the low and high ethanol concentrations are within the range which may be seen clinically. These data suggest that maintenance of blood pressure should be a primary concern to avoid spinal cord ischemia in ethanol intoxicated patients.

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TITLE: INTERACTION BETWEEN OPIATE SUBTYPES AND SEROTONIN IN SUPPRESSING NOXIOUSLY EVOKED ACTIVITY OF WDR NEURONS IN THE SPINAL DORSAL HORN

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Sensory processing within the spinal dorsal horn provides opportunities to develop better spinal and/or epidural analgesia. Several transmitter systems are involved with modulation of noxious afferent input. It has been demonstrated that intrathecally administered opioids and serotonin have antinociceptive effects. This study is part of a series of experiments aimed at determining optimum drug combinations that, at minimal doses, produce maximal depression of noxious activity at the level of the spinal cord. The present study examined interactions between mu and delta opiate subtypes and serotonin.

This protocol was approved by the Yale Animal Care and Use Committee. Noxious activity evoked by radiant heat was recorded from single wide dynamic range (WDR) neurons in decerebrate, spinally transected cats. 1 μ g of DAGO (mu selective opioid agonist) or 30 μ g of DPDPE (delta selective opioid agonist) was combined with 250 μ g of serotonin. Radiant heat stimuli (51°C for 8 sec.) were applied every 3 min. Following baseline determinations drugs were administered spinally and neuronal activity was observed for 30 minutes. At 30 min 0.1 mg of naloxone was administered intravenously.

None of the individual drugs, at the doses used in this study, suppressed activity (Fig 1). Doses had been chosen from previous pilot studies in which

they had been shown to produce no or minimal depression of noxiously evoked activity of spinal WDR neurons. Although the combination of DAGO and serotonin produced no significant suppression of noxiously evoked activity, the combination of DPDPE and serotonin produced significant suppression to $72.8 \pm 8.0\%$ (mean \pm S.E) of control values ($p < 0.05$) (Fig 1). 0.1 mg of intravenously administered naloxone reversed the suppression produced by the DPDPE-serotonin combination.

The perispinal application of some drugs (e.g., local anesthetics, morphine and clonidine) has been shown to be effective for the production of analgesia and devoid of toxic effects on the spinal cord, although adverse side effects have been reported. Toxicity as well as adverse side effects are a concern when administering any "new" substance, even a naturally occurring one, into the perispinal region. Identification of low dose combinations capable of suppressing noxious activity may help to avoid undesired actions while producing adequate analgesia. Our results suggest that combinations of serotonin and delta selective opiates may be more effective in suppressing radiant heat evoked noxious activity than combinations with mu selective opiates.

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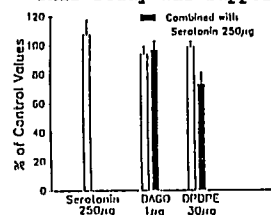


Fig 1. Open bars depict suppressive effect of serotonin, DAGO, or DPDPE alone (n = 5, 6, 6, respectively). Filled bars depict suppressive effect of serotonin combined with DAGO or DPDPE (n = 6 each).