

Title: KETAMINE ANALGESIA IN MORPHINE TOLERANT MICE

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**Introduction.** Previous reports suggest that analgesia induced by subanesthetic doses of ketamine (K) involves the opioid receptors in the brain.<sup>1-3</sup> If K produces analgesia through binding to opioid receptors, then it should be less effective as an analgesic in morphine-tolerant animals, just as morphine (M) is. We tested this hypothesis.

**Methods.** Male Swiss-Webster mice (CF1 strain) weighing 22-26 g were implanted, sc, with morphine pellets (MP, 75 mg base) or placebo pellets (PP) under isoflurane anesthesia. Seventy-two hrs later, pellets were removed and the analgesic action of M (1 mg/kg, sc) or K (20, 25 or 30 mg/kg, sc) was measured in the two groups using an acetic acid (HAc) induced abdominal constriction test. Control mice received normal saline (NS). Five min after the injection of drug or NS, 1% HAc in NS (0.01 ml/g) was injected ip. The number of abdominal constrictions (writhes) was counted for each mouse during the interval of 10-15 min after the HAc injection. After assay for analgesia, mice implanted with MP were challenged with naloxone (1 mg/kg, sc) and observed for withdrawal symptoms. The observer was uninformed as to drug pretreatment and treatment. All mice were used only once. Student's t-test for unpaired data was used to analyze results obtained with M; two-way factorial ANOVA was used to analyze data obtained with K, using Newman-Keuls test for post hoc comparisons. Percent analgesia was calculated for both groups according to the formula: 100 times

$$\frac{\# \text{ writhes(saline)} - \# \text{ writhes(ketamine)}}{\# \text{ writhes(saline)}}$$

**Results.** When treated with NS, PP implanted mice writhed  $9.8 \pm 0.9$  (mean  $\pm$  SEM) times, not significantly different from the  $12.2 \pm 0.8$  times seen in the MP implanted group ( $n = 39$  each). M decreased the number of writhes in PP implanted mice to  $4.5 \pm 0.6$  ( $n = 40$ ,  $P < 0.05$ , 54% analgesia), but not in MP implanted mice, which writhed  $10.1 \pm 1.0$  times ( $n = 35$ ). In PP implanted mice, at the doses of 20, 25 and 30 mg/kg, K decreased the number of writhes to  $5.8 \pm 0.8$  ( $n = 40$ ),  $4.2 \pm 0.7$  ( $n = 38$ ) and  $1.3 \pm 0.3$  ( $n = 23$ ), respectively. In MP implanted mice, K at the 20 and 25 mg/kg doses did not significantly decrease the number of writhes,  $10.0 \pm 0.9$  ( $n = 40$ ) and  $9.3 \pm 1.1$  ( $n = 38$ ), respectively. At the dose of 30 mg/kg, K decreased the number of writhes to  $5.2 \pm 0.9$  ( $n = 33$ ). At each dose of K, the number of writhes was significantly increased in MP

implanted mice. Results in mice treated with K are shown in terms of percent analgesia in Figure 1. Withdrawal symptoms, jumping and loss of body weight, were observed upon naloxone challenge in MP implanted mice.

**Discussion.** A state of M tolerance in MP implanted mice is confirmed by the absence of analgesia after M injection, as well as the response to naloxone challenge. The results showed that M tolerance confers cross-tolerance to the analgesic action of subanesthetic doses of K, providing further evidence that K induces analgesia through interaction with opioid receptors.

Supported in part by NIGMS Grant GM26407.

#### References

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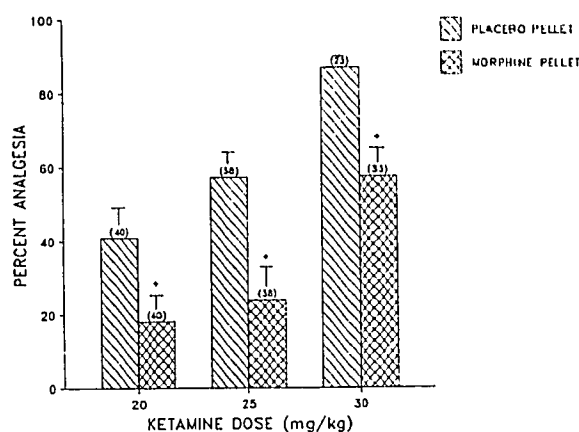


Figure 1. Analgesic effects of K. Vertical bars, SEM. + = Significantly less analgesia in MP compared with corresponding PP implanted mice.