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.[1-3] 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 (CFI 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 ± 0.9 (mean ± SEM) times, not significantly different from the 12.2 ± 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 ± 0.6 (n = 40, $P < 0.05$, 54% analgesia), but not in MP implanted mice, which writhed 10.1 ± 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 ± 0.8 (n = 40), 4.2 ± 0.7 (n = 38) and 1.3 ± 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 ± 0.9 (n = 40) and 9.3 ± 1.1 (n = 38), respectively. At the dose of 30 mg/kg, K decreased the number of writhes to 5.2 ± 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.

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References

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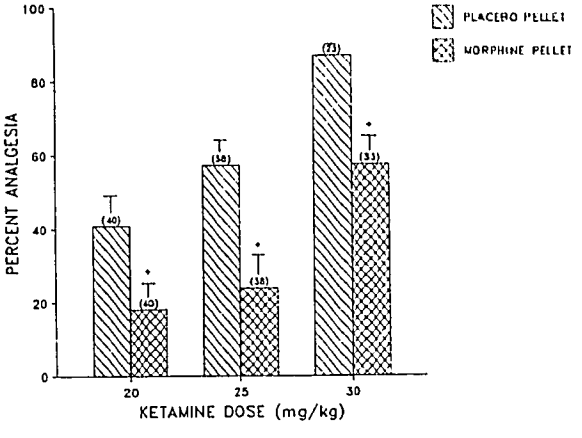

Figure 1. Analgesic effects of K. Vertical bars, SEM. + = Significantly less analgesia in MP compared with corresponding PP implanted mice.