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Acute Rate-Decreasing and Antinociceptive Effects of Morphine and Oxycodone in Male and Female Long-Evans Rats

Background: According to the CDC there were over 69,973 opioid-related deaths in the United States during 2025.[1] One major obstacle to reducing physical and psychological dependence on opioids is the aversive withdrawal syndrome that follows termination of opioid use. Therefore, the purpose of this preclinical experiment was to establish a behavioral model of withdrawal using a naltrexone discrimination procedure to aid in the development of interventions to alleviate withdrawal symptoms. Prior to establishing physical dependence in both male and female rats, however, the effective doses of two opioids (morphine and oxycodone) were determined on food-maintained operant responding (lever pressing) and in a warm-water tail-withdrawal assay.

Methods: Initially, twelve Long-Evans rats (6 male, 6 female) were placed in operant behavioral chambers and trained to make a single lever press to receive a food pellet during 60-minute behavioral sessions. Over successive sessions, the number of lever presses gradually increased until the subjects were making 20 lever presses for each food pellet. When responding under this FR-20 schedule stabilized, test sessions were intermingled twice per week with training sessions to assess the effects of morphine (1-18 mg/kg) and oxycodone (0.32-5.6 mg/kg). During these test sessions, there were four 15-minute components of responding under the FR-20 schedule with a 15-minute blackout before each component to allow for the administration of increasing cumulative doses. At the end of these test sessions the subjects were removed from the chambers and tail-withdrawal latencies were measured in a water bath maintained at either 40°C or 50°C. As controls for these drug administrations and the involvement of the mu opioid receptor, saline injections were also administered during separate test sessions and naltrexone (0.1-3.2 mg/kg) was administered both alone and prior to morphine, respectively. Response rate served as the dependent variable for lever pressing, whereas tail-withdrawal latency served as the dependent measure for antinociception.

Results: Morphine and oxycodone dose-dependently decreased response rate, with female rats more potently affected than male rats. Naltrexone administration produced similar rate-decreasing effects in both sexes when administered alone, but the antagonism of morphine by naltrexone was more complete in males than females. Lastly, morphine was equipotent in increasing tail-withdrawal latency in both male and female rats, but oxycodone was more potent in male rats than female rats.

Conclusions: These findings demonstrate the capacity mu opioid receptor agonists to decrease motivated behavioral responding and produce antinociception in a sex-dependent manner. Further, these findings will allow us to assess how these responses change during both chronic opioid administration and withdrawal.

[1] Opioid Overdose Deaths: National Trends and Variation by Demographics and States | KFF