Pramipexole Reduces Opioid Reward Behavior: Preclinical Evidence Building on Clinical Opioid-Sparing Data

Published clinical data indicate that pramipexole, a dopamine D2/D3 receptor agonist, acts as an opioid sparing agent in a Phase 1 proof-of-concept study of renal colic pain.

Here we show that pramipexole reduces opioid reward related behavior in preclinical self-administration, two-bottle choice, and conditioned place preference assays.

K.L. Brewer[1], S. Clemens[1], A. Subramaniam[1], R. Patton[1], and Malcolm A. Meyn III [2]

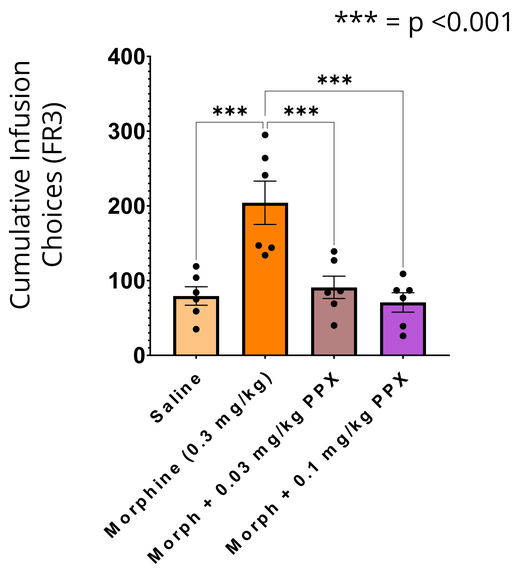
1. Brody School of Medicine, East Carolina University
2. Amalgent Therapeutics, Inc.

Amalgent Therapeutics

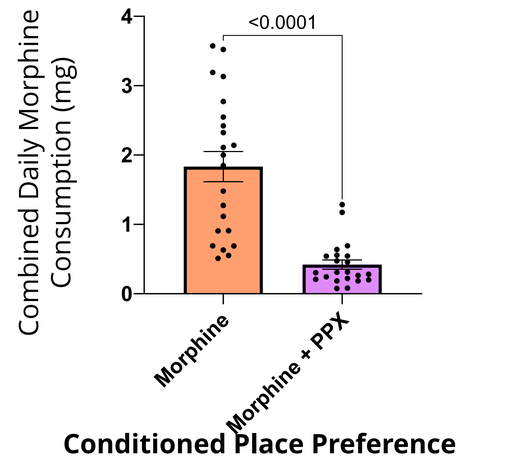
ECU

Results

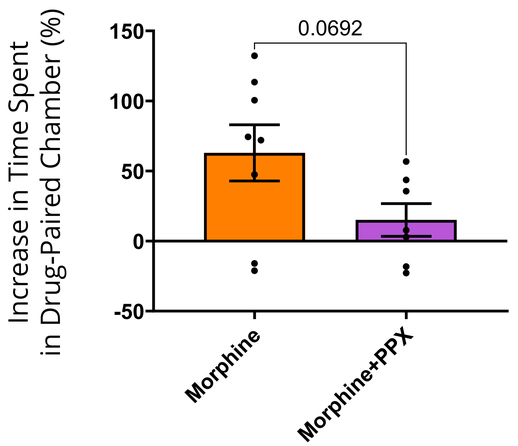
IV Self-Administration Study



Two Bottle Study



Conditioned Place Preference



Introduction

Opioid analgesics are widely used for pain management across acute, perioperative, and chronic settings, but their reinforcing effects contribute to risk of misuse and dependence. This risk is a particular concern in military and veteran populations, where combat related injury and chronic pain conditions can require sustained opioid exposure. Pramipexole, a dopamine D2/D3 receptor agonist, has shown opioid sparing effects in a Phase 1 proof-of-concept study of renal colic pain, suggesting a role for dopaminergic modulation in reducing opioid requirements (PMCID: PMC11476544). Here we evaluate whether pramipexole also reduces opioid reward related behavior in preclinical rodent models, using self-administration, two-bottle choice, and conditioned place preference assays.

Methods

Self-administration: Self-administration was assessed in female rats (n = 6/group) implanted with chronic IV jugular catheters, using a fixed-ratio 3 (FR3) schedule of reinforcement. Rats self-administered saline, morphine (0.3 mg/kg/infusion), or morphine co-formulated with pramipexole at a low (0.03 mg/kg/infusion) or high (0.1 mg/kg/infusion) dose.

Two-bottle choice: Rats were given continuous 24-hour access to two bottles, one containing morphine sulfate (0.05 mg/mL) alone or combined with pramipexole (0.0008 mg/mL), and one containing 2% sucrose vehicle alone, over 21 days. Combined male and female rats were assigned to a morphine plus pramipexole group (n = 20) or a morphine-alone group (n = 12), with daily consumption recorded by personnel blinded to bottle contents.

Conditioned place preference: Conditioned place preference was assessed in sham-operated rats using a three-chambered apparatus. Following baseline testing, rats were conditioned over 7 days with morphine (2 mg/kg, SC) alone or combined with pramipexole (0.1 mg/kg, SC), and place preference was tested 24 hours after the final conditioning session.

Conclusion

Across three independent behavioral assays, pramipexole reduced opioid reward related behavior, most consistently in active drug-seeking and consumption, with a similar trend observed in place preference. These preclinical findings, together with clinical evidence of opioid sparing in renal colic pain, support further development of pramipexole as an adjunct to reduce the reinforcing effects of opioid analgesics.

- Morphine significantly increased active lever pressing relative to saline (p = 0.0067). Co-administration of pramipexole significantly reduced this effect at both the low (p = 0.0091) and high (p = 0.0051) dose.
- In a two-bottle choice assay, pramipexole significantly reduced mean daily morphine consumption in combined male and female rats (p < 0.0001, Mann-Whitney).
- Pramipexole showed a trend toward attenuating morphine-induced CPP (62.9% vs 15.1%, p = 0.069) (PMID:30910641)

This work was supported by NIDA of the National Institutes of Health under award number DA059302 (MM) and the East Carolina University Health and Behavior Research Core (KB).