Pain Induced by Repeated Morphine is Reduced by Endocannabinoid Activation

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Introduction

- Opioid-induced hyperalgesia (OIH) is a condition where prolonged use of opioids causes increased sensitivity to various painful and nonpainful stimuli, such as touch and temperature
- OIH occurs via both mu-opioid receptor dependent and independent mechanisms
- Endocannabinoid system interacts with the opioid system in pain regulation and may be a target for reducing OIH symptoms
  - JZL184: MAGL inhibitor. Increases endocannabinoid 2-AG
  - ZCZ011: CB_1 receptor positive allosteric modulator

Hypotheses

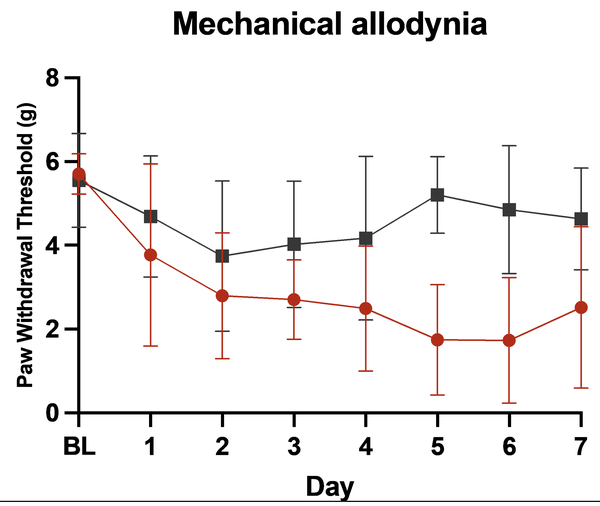
1. Continuous morphine induces mechanical and cold allodynia (OIH), which will be reduced by
2. MAGL inhibitor JZL184
3. CB_1 PAM ZCZ011

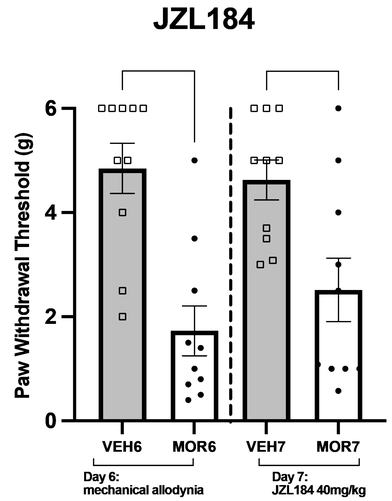
Methods

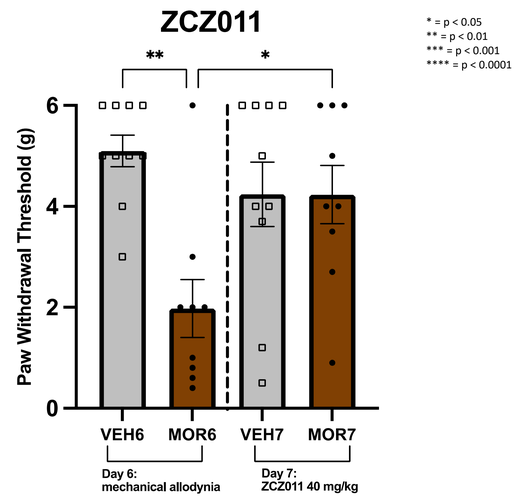
Subjects. Female and male (n=10) C57Bl/6J mice were used for the experiments. Mice were randomly assigned to treatment conditions and balanced for sex. Mice were housed in groups within plastic cages in an AAALAC-accredited facility, with all behavioral testing conducted during the light phase. All experimental procedures received approval from the UConn Animal Care and Use Committee.

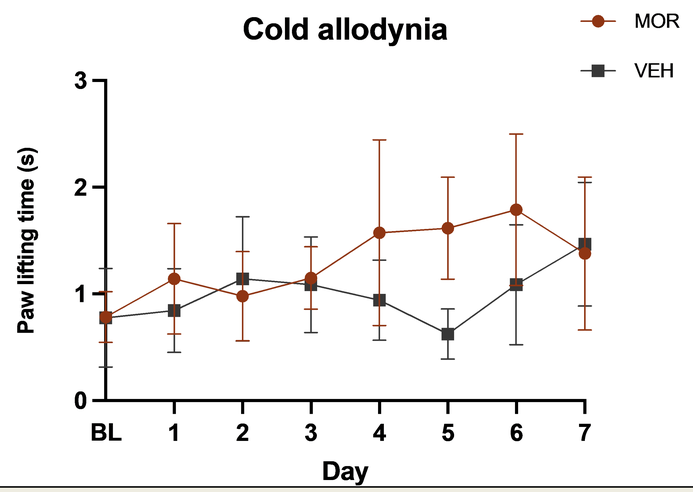
Drugs. Osmotic minipumps were aseptically filled with either morphine (60 mg/ml) or saline vehicle. JZL184 and ZCZ011 were dissolved in a vehicle consisting of 1:1:18 parts of EtOH, Kolliphor EL, and 90% Saline.

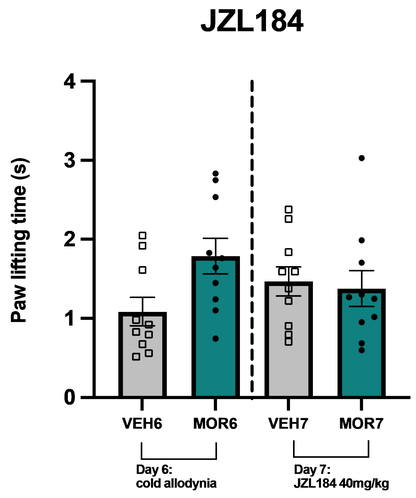
Procedure. Under general anesthesia, mice were implanted with subcutaneous osmotic minipumps (Alzet), which continuously delivered either morphine or saline at a rate of 1.0 µL/hour for 7 days. Mechanical allodynia was assessed using von Frey filaments, and cold allodynia was evaluated using the acetone drop test, measured daily throughout the 7-day observation. On Day 7, mice received JZL184 (40 mg/kg, i.p.) 120 minutes prior to testing, or ZCZ011 (40 mg/kg, i.p.) 75 minutes prior to testing.

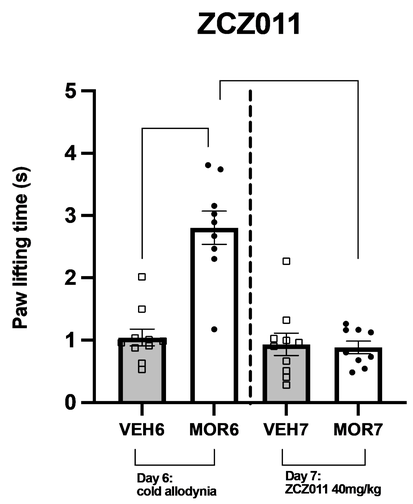












Summary and Conclusion

1. Morphine treatment caused mechanical & cold allodynia in mice
2. MAGL inhibitor JZL184 attenuated morphine-induced mechanical allodynia
3. CB_1 positive allosteric modulator ZCZ011 attenuated both morphine-induced mechanical & cold allodynia

Conclusion: Cannabinoid drugs are effective in reducing opioid-induced hyperalgesia

NIH National Institutes of Health

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