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Mu Opioid Receptor Desensitization in Inflammatory Pain

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Due to the epidemic level of opioid overdose deaths in the United States, improving the treatment of chronic pain has become a pressing concern. Opioid treatments such as fentanyl and morphine activate mu opioid receptors (MORs), causing an increase in dopamine release. Long term use of opioids, even as prescribed by a physician, can desensitize the MORs and lead to the appearance of withdrawal symptoms when the receptors are no longer stimulated. Since pain increases endogenous opioid release, we hypothesized that this increase may cause MOR desensitization and the appearance of withdrawal syndrome upon blockade of MORs, as seen in long term opioid use.

Previous Work

In Figure A, reduced dopamine (DA) release in the nucleus accumbens (NAc) was seen in the condition of inflammatory pain when selective MOR agonist DAMGO was administered in the ventral tegmental area (VTA). Furthermore, autoradiography in Figure B showed reduced MOR function in the VTA for animals experiencing pain compared to controls. The circled regions indicate the approximate location of the VTA, while warmer colors (orange and red) signify greater function than cooler colors (light and dark green). These results indicate the importance of MOR function in the VTA necessary for projection to the NAc in DA release and the effect of inflammatory pain on this system.

Hypothesis

To test this hypothesis, we bilaterally inserted cannulae into the VTA, a brain region containing MORs and involved in reward processing, of Sprague-Dawley and Long-Evans rats of both sexes. Figure A: Complete Freund’s Adjuvant (CFA) was used to induce chronic inflammatory pain. Figure C: CTAP, a highly selective MOR antagonist, was injected via cannula to induce withdrawal symptoms. Figure B: Each animal experienced one of three conditions: CFA + CTAP, Saline + CTAP, or CFA + Saline. Wet dog shakes (WDS), a common sign of opioid withdrawal in rats, were measured in five minute periods one, two, three, five, and eight hours after CTAP injection. Why were wet dog shakes used to measure withdrawal syndrome?

• Well established opioid withdrawal symptom in rats
• Functions to easily quantify withdrawal
• Easy to observe – high inter-observer reliability
• Long time course for experiment, different experimenters observed the animals
• Requires no special equipment

Results

A significant increase in WDS was observed for male Sprague-Dawley rats in the CTAP-CFA group compared to each of the other conditions. This increase in WDS may be explained by chronic inflammatory pain causing MOR desensitization in the same manner as long term exposure to opioids does.

Furthermore, pain-induced MOR desensitization may increase the likelihood of developing opioid dependence. As opioids, like morphine and fentanyl, are considered the gold standard for pain treatment, patients may experience the combined risk of exposure to an addictive substance and a dysregulated response to that substance.

More work investigating how pain impacts opioid dependent dopamine release is necessary and may ultimately lead to improved pain treatment and decreased opioid dependence.

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Future Directions

Additional research must be conducted to assess whether chronic pain increases the likelihood of developing opioid dependence. Specifically, self administration experiments provide a useful model for drug use in humans. Animals in pain can be compared to control animals to show the behavioral differences between these groups. To measure motivation, rats are trained to press a lever to receive a food or drug reward. For the condition of pain, a decrease in motivation, often determined by the breakpoint in a progressive ratio schedule, would provide further evidence of decreased DA, as DA is instrumental in motivation and reward. Dose-response exposes the animals to a range of drug doses and plots the number of injections to show which dose was preferred. A positively shifted dose-response curve for animals in pain would support our finding of MOR desensitization, as the most rewarding dose was higher than for controls. In escalation animals are given access to self-administer drugs, in this case opioids, over an extended period. A sharp increase of intake models the development of drug abuse or dependence in humans. If escalation were to occur more quickly for animals in pain, this would indicate an increased risk of developing opioid dependence.

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