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Molecular and behavioral mechanisms mediating paclitaxel-induced changes in affect-like behavior in mice

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Abstract

The paclitaxel-pretreated mouse paradigm is a powerful model of pain, depression, and cancer survivors. We show that paclitaxel induces pain and depression-like behaviors in mice. Paclitaxel decreases sucrose preference in a dose-dependent manner, which is antagonized by opioid agonists. These data suggest that paclitaxel-induced changes in affect-like behavior are mediated by opioid receptors.

Role of Kappa Opioid Receptors

1. PAC decreases sucrose preference via KOR.

2. PAC has temporal-, region-, and receptor-selective effects in the brain.

3. PAC induces time- and region-dependent endogenous KOR agonists.

Characterization of Motivation Deficit Behavior

4. PAC is not a KOR agonist.

5. PAC has work-, time-, and sex-dependent effects on operant responding.

Introduction

• No efficacious treatment for paclitaxel-induced depression in cancer survivors.
• PAC-induced depression can last for up to 5 years or longer following cessation of treatment.
• We previously characterized the effects of a clinically relevant duration of PAC on behavior in male C57BL/6J mice over the course of 0-4 months.

Hypothesis: Negative affective state produced by PAC is mediated by kappa opioid receptor signaling in the nucleus accumbens.

Mouse Model of Paclitaxel-Induced Neuropathy

To further characterize the model used by Toma (2017), adult (8-10 wks) C57BL/6J mice received a single intravenous (1:1:1) (ethanol/1% saline/or PAC (Basso, T. Smith, E.M.L. et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced peripheral neuropathy. J Pain. 2008 Mar;9(3):227-37) cohort of vehicle or PAC (uncovered mg/kg); or two sets of four injections of vehicle or paclitaxel (cumulative mg/kg) or paclitaxel, and periodically assessed for depression-like behaviors. Paclitaxel caused significant, time-dependent deficits in sucrose preference and operant responding for palatable sucrose. We observed that PAC administration resulted in a dose-dependent decrease in sucrose preference and operant responding for sucrose, which was not observed in vehicle-treated mice. These data suggest that PAC-induced changes in affect-like behavior are mediated by kappa opioid receptors.

Hypothesis: Negative affective state produced by PAC is mediated by kappa opioid receptor signaling in the nucleus accumbens.

Characterization of Motivation Deficit Behavior

4. PAC is not a KOR agonist.

5. PAC has work-, time-, and sex-dependent effects on operant responding.

Summary & Conclusions

• Mice had temporal-, region-, and receptor-selective changes in their brains.
• PAC is not a KOR agonist, but may activate KOR indirectly via upregulating preexisting opioid receptors.
• Mice show work-, time-, and sex-dependent effects on operant responding for mildly sweetened food pellets.
• Preliminary data suggest that potent, duration, and magnitude of deficit in operant responding may be PAC dose-dependent.
• Future studies will further investigate the effects of KOR modulators on PAC-induced changes in affect-like behavior.

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From ScienceDirect

Cancer survivors experience pain and depression-like behaviors that may persist for years after treatment. We investigated the role of KOR in PAC-induced changes in affect-like behavior in mice using a single or multiple injections of vehicle or PAC. Our data suggest that PAC-induced changes in affect-like behavior are mediated by KOR.

From ScienceDirect

Mice treated with PAC showed decreased sucrose preference and operant responding for sucrose, which was not observed in vehicle-treated mice. These data suggest that PAC-induced changes in affect-like behavior are mediated by KOR.

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