Neuropharmacology 111 (2016) 314–322

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Adolescent oxycodone self administration alters subsequent oxycodone-induced conditioned place preference and anti-nociceptive effect in C57BL/6J mice in adulthood

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ARTICLE INFO

Article history:
Received 26 May 2016
Received in revised form
11 August 2016
Accepted 6 September 2016
Available online 7 September 2016

Keywords:
Oxycodone
Adolescent
Self administration
Conditioned place preference
Hotplate test

ABSTRACT

Adolescent and young adult abuse of short-acting MOP-r agonists such as oxycodone is a pressing public health issue. Few preclinical studies have examined how adolescent exposure to oxycodone impacts its effects in the transition to adulthood.

Objective: To determine in mice how chronic adolescent oxycodone self-administration (SA) affects subsequent oxycodone-induced conditioned place preference (CPP), locomotor activity, and anti-nociception once mice reach early adulthood.

Methods: Adolescent C57BL/6J male mice (4 weeks old, n = 6–11) and adult mice (10 weeks old, n = 6–10) were surgically implanted with indwelling jugular catheters. Mice then acquired oxycodone self-administration (14 consecutive 2-hr daily sessions; 0.25 mg/kg/infusion) followed by a 14-day drug-free (withdrawal) period in home cage. After the 14-day drug-free period, mice underwent a 10-day oxycodone CPP procedure (0, 1, 3, 10 mg/kg i.p.) or were tested for acute oxycodone-induced anti-nociception in the hot plate assay (3.35, 5, 7.5 mg/kg i.p.).

Results: Mice that self-administered oxycodone during adolescence exhibited greater oxycodone-induced CPP (at the 3 mg/kg dose) than their yoked saline controls and mice that self-administered oxycodone during adulthood. Oxycodone dose-dependently increased locomotor activity, but sensitization developed only to the 3 mg/kg in the mice that underwent oxycodone self-administration as adolescents. Mice that self-administered oxycodone as adolescents decreased in the anti-nociceptive effects of oxycodone in one dose (5 mg/kg), whereas animals that self-administered oxycodone as adults did not show this effect.

Conclusion: Chronic adolescent oxycodone self-administration led to increased oxycodone-induced CPP (primarily 1 and 3 mg/kg, i.p.) and reduced antinociceptive effect of oxycodone (5 mg/kg, i.p.) in adulthood.

1. Introduction

Non-medical use of prescription opioids such as the mu opioid receptor (MOP-r) agonist oxycodone, especially among adolescents and young adults, has increased in recent years and is a major public health concern in the United States (Johnston et al., 2016). Adolescence is a period of heightened sensation seeking, which can include disinhibition and risk-taking behavior (Spear, 2000a, 2000b), potentially due to an imbalance between immaturity of the prefrontal cortex and lack of self-control resulting from developmental changes in the mesocoticolimbic systems (e.g., (Chambers et al., 2003; Yurgelun-Todd, 2007; Crews and Boettiger, 2009). The adolescent brain undergoes programmed re-organizations, remodeling, and maturational refinements corresponding to a variety of molecular changes in different cell types. For example, studies in juvenile rodents have shown that dopamine receptor density increases in the striatum during early adolescence and decreases during later adolescence and early adulthood (Teicher et al., 1991, 2003; Andersen et al., 1997; Teicher et al.,

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http://dx.doi.org/10.1016/j.neuropharm.2016.09.005
0028-3908/

2003); dopaminergic function is known to be involved in the rewarding effects of major drugs of abuse. Prefrontal cortex glutamatergic projections innervating the nucleus accumbens (Brenhouse et al., 2008) and amygdala (Cunningham et al., 2002) increase during adolescence. Since adolescent brains are in a state of developmental flux, they may be more vulnerable to various insults, including drugs of abuse. Adolescent exposure to drugs of abuse, including prescription opioids, may increase the likelihood of neurobiological changes, predisposing the adolescents to be more susceptible to the effects of these drugs, leading to behavioral alterations upon subsequent or continued exposure during the transition to early adulthood.

We have recently developed an animal model of chronic oxycodone self-administration to examine the behavioral and underlying neurobiological consequences of oxycodone exposure in adolescent mice. Our earlier studies found that adolescent mice exhibited differential oxycodone self-administration behavior compared to adult mice (Zhang et al., 2009; Mayer-Blackwell et al., 2014) and differential behavioral response to oxycodone in adolescent versus adult mice (Niikura et al., 2013), as well as differential adaptations in mRNA expression for several genes in the mouse brain (Zhang et al., 2009; Mayer-Blackwell et al., 2014).

We hypothesized that exposure to oxycodone during adolescence would result in characteristic adaptations to the effects of oxycodone in reward- and non-reward related endpoints, once these animals reach adulthood. To test this hypothesis, the current study examined whether chronic adolescent oxycodone self-administration affects oxycodone-induced conditioned place preference (CPP) and the anti-nociceptive property of oxycodone during adulthood in a mouse model. Specifically, mice that had self-administered oxycodone during adolescence underwent either an oxycodone-induced CPP procedure or were tested for thermal antinociception following 14 days withdrawal from 14 consecutive daily oxycodone self-administration sessions. CPP and antinociception testing thus occurred after these mice had entered young adulthood. These animals were compared to those undergoing similar procedures, but which self-administered oxycodone in young adulthood.

2. Materials and methods

2.1. Subjects

Male adolescent and adult (4 or 10 week old on arrival) C57BL/6J mice (Jackson Laboratory, Bar Harbor, ME) were housed in groups of five with free access to food and water in a light-(12:12 h light/dark cycle, lights on at 7:00 p.m.) and temperature-(25 °C) controlled room. Animal care and experimental procedures were conducted according to the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources Commission on Life Sciences 1996). The experimental protocols used were approved by the Institutional Animal Care and Use Committee of The Rockefeller University. The time line of self-administration and later CPP or hot plate test studies and the ages of mice are shown in Table 1.

2.2. Self-administration of oxycodone

2.2.1. Catheter implantation

Following acclimation for 7 days, the mice were anesthetized with a combination of xylazine (8.0 mg/kg i.p.) and ketamine (80 mg/kg i.p.). After shaving and application of a 70% alcohol and iodine preparatory solution, incisions were made in the mid-scapular region and anteromedial to the foreleg. A catheter approximately 6 cm in length (ID: 0.31 mm, OD: 0.64 mm; Helix Medical, Inc. CA) was passed subcutaneously from the dorsal to the ventral incision. After exposure of the right jugular vein, a 22-gauge needle was inserted, to guide the catheter into the jugular vein. Once the catheter was inside the vein, the needle was removed and the catheter was inserted to the level of a silicone ball marker, 1.1 cm from the end. The catheter was tied to the vein with surgical silk. Physiological saline then was flushed through the catheter to avoid clotting, and the catheter then capped with a stopper. Antibiotic ointment was applied to the catheter exit incisions on the animal's back and foreleg. Mice were group housed after the surgery and were allowed 7 days of recovery before being placed in operant test chambers for the self-administration procedure (Zhang et al., 2009; Mayer-Blackwell et al., 2014).

2.2.2. Intravenous self-administration chamber

The self-administration chamber (ENV-307W: 21.6 cm × 17.8 cm × 12.7 cm; Med Associates, St. Albans, VT) was located inside a sound attenuating chamber (Med Associates). The front, back and top were constructed of 5.6 mm polycarbonate. Each chamber contained a wall with two small holes (0.9 cm diameter, 4.2 cm apart, 1.5 cm from the floor of the chamber). One hole was defined as active, the other was inactive. When the photocell in the active hole was triggered by a nose-poke, the infusion pump (Med Associates) delivered an infusion of 20 μl/3 s from a 5 ml syringe connected by a swivel via Tygon tubing. The infusion pump and syringe were located outside the chamber. During infusion, a cue light above the active hole was illuminated. Each injection was followed by a 20-sec "time-out" period during which poking responses were recorded but had no programmed consequences. All responses at the inactive hole were also recorded. Mice were tested during the dark phase of the diurnal cycle (all experiments were performed between 8:00 a.m. and 2:00 p.m.).

2.2.3. Oxycodone self-administration

A 2-hr self-administration session was conducted once a day. Each day, mice were weighed and the catheter flushed with heparinized saline (0.01 ml of 30 IU/ml solution) to maintain patency. During each of the 14 self-administration sessions, mice in the oxycodone (Sigma, St. Louis, MO) groups received an infusion of oxycodone (0.25 mg/kg/infusion) under an FR1 schedule following each active hole nose poke. During all sessions, mice in the yoked control groups received a saline infusion (20 μl/inf) when the oxycodone mouse self-administered oxycodone.

At the end of the self-administration experiment, only data from mice that passed a catheter patency test [defined as loss of muscle tone within a few seconds after i.v. administration of 30 μl of ketamine (5 mg/ml; Fort Dodge, IA)] were included in the analysis of self-administration data. Of a total 346 mice that started the study,

Table 1
Age and experimental procedure.

	On arrival	Surgery	14-day SA	Withdrawal	CPP or Hotplate test	
Adolescent postnatal day	28	35	42–56	57–70	71–80	71
Adult postnatal day	70	77	78–91	92–105	106–115	106