European Journal of Pharmacology 784 (2016) 199–206

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Behavioural pharmacology

Interactions between cannabinoid receptor agonists and mu opioid receptor agonists in rhesus monkeys discriminating fentanyl

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ARTICLE INFO

Article history:
Received 29 February 2016
Received in revised form
10 May 2016
Accepted 11 May 2016
Available online 13 May 2016

Keywords:
Opioid
Cannabinoid
Drug-drug interactions
Drug discrimination
Monkeys

ABSTRACT

Cannabinoid receptor agonists such as delta-9-tetrahydrocannabinol (Δ^9-THC) enhance some (antinociceptive) but not other (positive reinforcing) effects of mu opioid receptor agonists, suggesting that cannabinoids might be combined with opioids to treat pain without increasing, and possibly decreasing, abuse. The degree to which cannabinoids enhance antinociceptive effects of opioids varies across drugs insofar as Δ^9-THC and the synthetic cannabinoid receptor agonist CP55940 increase the potency of some mu opioid receptor agonists (e.g., fentanyl) more than others (e.g., nalbuphine). It is not known whether interactions between cannabinoids and opioids vary similarly for other (abuse-related) effects. This study examined whether Δ^9-THC and CP55940 differentially impact the discriminative stimulus effects of fentanyl and nalbuphine in monkeys (n=4) discriminating 0.01 mg/kg of fentanyl (s.c.) from saline. Fentanyl (0.00178–0.0178 mg/kg) and nalbuphine (0.01–0.32 mg/kg) dose-dependently increased drug-lever responding. Neither Δ^9-THC (0.032–1.0 mg/kg) nor CP55940 (0.0032–0.032 mg/kg) enhanced the discriminative stimulus effects of fentanyl or nalbuphine; however, doses of Δ^9-THC and CP55940 that shifted the nalbuphine dose-effect curve markedly to the right and/or down were less effective or ineffective in shifting the fentanyl dose-effect curve. The mu opioid receptor antagonist naltrexone (0.032 mg/kg) attenuated the discriminative stimulus effects of fentanyl and nalbuphine similarly. These data indicate that the discriminative stimulus effects of nalbuphine are more sensitive to attenuation by cannabinoids than those of fentanyl. That the discriminative stimulus effects of some opioids are more susceptible to modification by drugs from other classes has implications for developing maximally effective therapeutic drug mixtures with reduced abuse liability.

1. Introduction

Pain remains a significant clinical problem (e.g., Institute of Medicine, 2011; Gaskin and Richard, 2012) and although mu opioid receptor agonists are used to treat pain, their utility is limited by unwanted effects (e.g., Benyamin et al., 2008). Drugs can be used in combination to treat pain (e.g., Gilron et al., 2013; Raffa, 2001), to increase effectiveness, or to reduce the doses needed. Opioid agonists have been combined with non-opioid drugs such as nonsteroidal anti-inflammatory drugs to treat pain (e.g., Wideman et al., 1999; Sunshine et al., 1997; Raffa et al., 2010) although currently available mixtures retain many of the adverse effects of opioids alone and contribute to abuse and overdose (e.g., Atluri et al., 2014; Centers for Disease Control and Prevention, 2012; Edlund et al., 2014; Jones et al., 2013).

Cannabinoid receptor agonists such as delta-9-tetrahydrocannabinol (Δ^9-THC) are used to treat pain (e.g., Hosking and Zajicek, 2008; Lynch and Campbell, 2011), although alone their effectiveness is limited (e.g., Kraft, 2012). Cannabinoids augment the analgesic effects of opioids in patients (e.g., Narang et al., 2008) and enhance the antinociceptive effects of opioids in nonhumans (e.g., Cichewicz, 2004; Cox et al., 2007; Li et al., 2008; Welch, 2009; Maguire et al., 2013; Maguire and France, 2014). While cannabinoids increase the potency of opioids for antinociception, the magnitude of enhancement varies among agonists (e.g., Cichewicz, 2004; Maguire and France, 2014), increasing the potency of some agonists (fentanyl) to a greater extent than others (morphine; Maguire and France, 2014). Fentanyl has greater efficacy than morphine (e.g., Saeki and Yaksh, 1993; Gerak et al., 1994; Traynor and Nahorski, 1995; Emmerson et al., 1996; Morgan et al., 1999) suggesting that efficacy impacts cannabinoid enhancement of opioid antinociceptive effects. It is unclear whether interactions between cannabinoids and opioids also vary for other

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http://dx.doi.org/10.1016/j.ejphar.2016.05.018
0014-2999/

measures. Characterizing such differences will aid in evaluating the benefits and risks of opioid/cannabinoid mixtures for treating pain.

Cannabinoids enhance antinociceptive but not some other effects of opioids in rhesus monkeys. In fact, cannabinoids attenuate the discriminative stimulus and positive reinforcing effects of some opioids (e.g., Li et al., 2008, 2012; Maguire et al., 2013; Maguire and France, 2015). That cannabinoids enhance some but not other effects of opioids supports the view that cannabinoids could be combined with opioids to treat pain without increasing adverse effects. It is not known whether interactions between cannabinoids and the discriminative stimulus effects of opioids also depend on the drugs in the mixture. This study examined Δ^9-THC and CP55940 for their ability to modify the discriminative stimulus effects of fentanyl and nalbuphine in monkeys discriminating fentanyl. Δ^9-THC and CP55940 were studied because they attenuate the discriminative stimulus effects of morphine (Li et al., 2008; Maguire et al., 2013). Fentanyl and nalbuphine were studied because they share discriminative stimulus effects with morphine, and because their antinociceptive effects were the most (fentanyl) and the least (nalbuphine) sensitive to enhancement by cannabinoids (Maguire and France, 2014).

2. Materials and methods

2.1. Subjects

Four adult female rhesus monkeys (AM, CI, HA, MA; *Macaca mulatta*) were previously trained to discriminate morphine from saline and participated in earlier studies (e.g., Li et al., 2008, 2011; Maguire et al., 2013). Body weight (range: 5–9 kg) was maintained via post-session feeding of chow (Harlan Teklad, High Protein Monkey Diet, Madison, WI, USA), fresh fruit, and peanuts; water was continuously available in the home cage. Subjects were housed individually in a colony room maintained under a 14/10-h light/dark cycle (lights on at 0600 h) in an AAALAC accredited facility. Monkeys used in these studies were maintained in accordance with the Institutional Animal Care and Use Committee of The University of Texas Health Science Center at San Antonio, and the 2011 Guide for the Care and Use of Laboratory Animals (8th edition; Institute of Laboratory Animals Resources on Life Sciences, National Research Council, National Academy of Sciences).

2.2. Apparatus

Monkeys were seated in primate chairs (Model R001, Primate Products, Miami, FL, USA) and positioned in sound-attenuating operant conditioning chambers. Each chamber contained a custom-made response panel with two horizontally aligned response levers located 32 cm apart. Lights that could be illuminated red were located above each lever. Feet were placed in shoes containing brass electrodes to which a brief (250 ms, 3 mA) electric stimulus could be delivered from a remote current generator (H13-15, Coulbourn Instruments, Allentown, PA, USA). Extraneous sounds were masked by white noise and an exhaust fan provided ventilation. Experimental events were arranged and data were collected by an interface (Med Associates, Inc., Georgia, VT, USA) connected to a PC computer operating with Med-PC IV software (Med Associates).

2.3. Behavioral procedure

Monkeys were previously trained to discriminate morphine from saline (Li et al., 2008); however, one monkey (MA) developed a reaction to morphine injections and the training stimulus for all monkeys was changed to fentanyl (0.01 mg/kg). This dose of fentanyl was chosen because it produced high levels of morphine-appropriate responding in all monkeys and maintained reliable discrimination performance during training. Sessions comprised 2–8 cycles, with each cycle consisting of a 10-min timeout period followed by a 5-min response period. During the timeout all lights were off and responding had no programmed consequence; injections occurred during the first min of each timeout. The beginning of the response period was signaled by illumination of both side key lights red. When the red lights were on, a brief electric stimulus was scheduled to be delivered every 15 s. Ten consecutive responses on the correct lever turned off the red lights and suspended the schedule of stimulus presentation for a 30-s timeout (reinforcer). After the timeout, the red lights were turned on and the stimulus presentation schedule was restarted. Response periods ended after 10 reinforcer presentations, 4 electric stimulus presentations, or after 5 min elapsed, whichever occurred first.

For training, levers were designated as correct and incorrect for each cycle based on the injection given during the first min of the cycle. For monkeys CI and HA, the left lever was correct following saline injections (saline lever) and the right lever was correct following injections of 0.01 mg/kg of fentanyl (drug lever); for monkeys AM and MA, the contingencies were reversed. Responses on the incorrect lever reset the response requirement on the correct lever and were counted but otherwise had no programmed consequence. During saline training sessions, saline or sham injections were administered prior to 2–6 cycles, and no drug was administered. During fentanyl training sessions, 0.01 mg/kg of fentanyl was administered at the beginning of one cycle that was preceded by 0–5 saline or sham training cycles; the number of saline or sham cycles preceding the fentanyl training cycle varied quasi-randomly across sessions.

Test sessions occurred when the following criteria were satisfied for at least two consecutive sessions, consisting of at least one fentanyl training session and at least one saline training session: (1) at least 80% of responses in all cycles were on the correct (injection-appropriate) lever; and (2) fewer than 10 responses were on the incorrect lever prior to the first reinforcer presentation. Test sessions were identical to training sessions except that completion of 10 consecutive responses on either lever was reinforced.

Dose-effect curves for fentanyl and nalbuphine were determined under test conditions using a cumulative dosing method. Saline or naltrexone (see below) was administered during the first cycle of the session and increasing doses of drug were administered across successive cycles in 0.25-log unit increments until at least 80% of responses in a cycle were on the drug lever or when 8 cycles were completed, whichever occurred first. Based on previous studies (Li et al., 2008; Maguire et al., 2013), Δ^9-THC and CP55940 were administered 60 min prior to the start of the first cycle when tested in combination with fentanyl or nalbuphine. Naltrexone was administered at the beginning of the first cycle instead of saline. In all monkeys, 0.01 mg/kg of CP55940, 0.32 mg/kg of Δ^9-THC, and 0.032 mg/kg of naltrexone were tested in combination with both fentanyl and nalbuphine. Tests with additional doses of each cannabinoid were selected individually for each monkey in order to assess differential sensitivity to cannabinoids between opioids. Tests were conducted in an irregular order across subjects, and tests with cannabinoids were separated by at least 6 days.

2.4. Data analyses

For each cycle, the number of responses on the drug lever was divided by the total number of responses on either lever and