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Short communication

HIV-gp120 and physical dependence to buprenorphine

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ABSTRACT

Background: Opioids are among the most effective and commonly used analgesics in clinical practice for severe pain. However, the use of opioid medications is clinically limited by several adverse properties including dependence. While opioid dependence is a complex health condition, the treatment of HIV-infected individuals with opioid dependence presents additional challenges. The goal of this study was to examine the physical dependence to buprenorphine in the context of HIV.
Methods: Young adult male rats (Sprague–Dawley) were pretreated with HIV-1 envelope glycoprotein 120 (gp120) injected into the periaqueductal gray area (PAG) and we examined the impact on physical dependence to opioid.
Results: It was found that the physical dependence to methadone occurred earlier than that to buprenorphine, and that gp120 did not enhance or precipitate the buprenorphine withdrawal.
Conclusion: The results suggest that buprenorphine could be the better therapeutic option to manage opioid dependence in HIV.

1. Introduction

Buprenorphine is a semi-synthetic derivative of thebaine. It has a molecular weight of 467 and its structure is typically opioid with the inclusion of a C-7 side-chain containing a t-butyl group. Comparison of the antinociceptive effects of methadone and buprenorphine shows that 3 mg/kg for methadone is the effective analgesic dose, and 0.3 mg/kg for buprenorphine in rats using the hot-plate test (Bulka et al., 2004). Respiratory depression caused by opioids can be potentially life-threatening but is much less of a problem with buprenorphine than with many other opioids including morphine, hydromorphone, methadone, oxycodone, and transdermal fentanyl (Dahan et al., 2005). This advantage is due to the unique pharmacological characteristics of buprenorphine as a partial mu-agonist. Its ceiling effect, associated with a bell-shaped dose–response (D–R) curve with regard to respiratory depression, means that the risk to induce respiratory arrest does not linearly follow dose-increments of the drug. Although methadone is used as a pharmacotherapy for opioid dependence in HIV-1-infected individuals, its use has been associated with several adverse drug interactions with HIV-1 therapies that can produce either elevated methadone concentrations with toxicity, or decreased methadone levels with withdrawal (Gruber and McCance-Katz, 2010; McCance-Katz, 2005). In contrast, buprenorphine has not been shown to produce significant adverse drug interactions with antiretroviral therapy drugs such as delavirdine, efavirenz, nelfinavir, ritonavir or lopinavir/ritonavir (Gruber and McCance-Katz, 2010; McCance-Katz, 2005). The lack of drug interaction between antiretroviral therapy and buprenorphine is potentially an important advantage of buprenorphine treatment of opioid dependence in HIV-1 infected patients.

Opioid abuse and therapeutic use are frequently associated with HIV infection. With the global HIV prevalence estimated at 35.3 million, approximately 30% of HIV-positive individuals, within developed countries, are intravenous (IV) drug users, and it is the third most frequently reported risk factor for HIV-1 infection in the United States (CDC, 2009). In addition, pain is part of the clinical picture associated with HIV and AIDS. Opioids are among the most effective and commonly used analgesics in clinical practice for severe pain. However, the use of opioid medications is clinically limited by several adverse properties including dependence. Currently, there is no data available examining the physical dependence to buprenorphine in neuroAIDS. Therefore, we determined the physical dependence to these opioids in the context of HIV.

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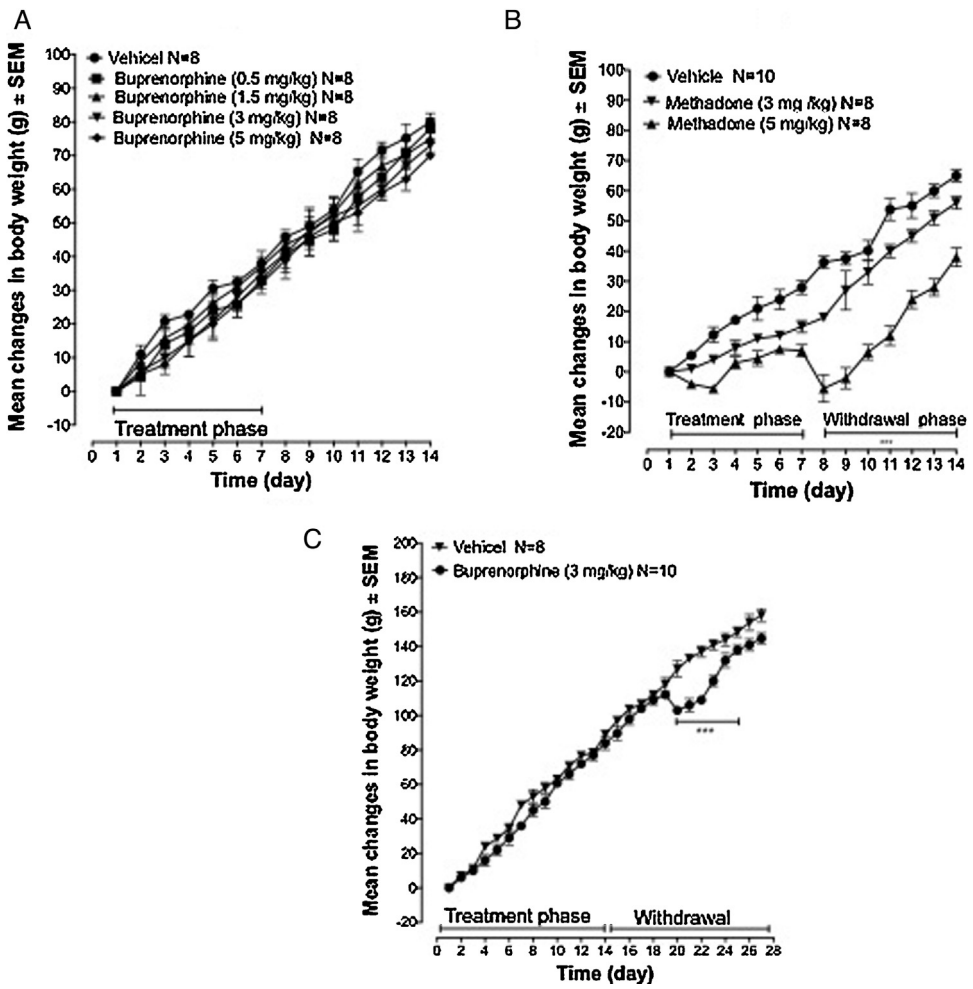

Fig. 1. (A) Body weight changes during buprenorphine treatment (days 1–7) and discontinuation (days 8–14). Rats received either saline or buprenorphine (0.5–3 mg/kg, s.c.). Each point represents the mean ± SEM. *N*, number of animals. (B) Body weight changes during methadone treatment (days 1–7) and discontinuation (days 8–14). Rats received either saline or buprenorphine (3–5 mg/kg, s.c.). Each point represents the mean ± SEM. ***$P < 0.001$. (C) Body weight changes during buprenorphine treatment (days 1–14) and discontinuation (days 14–28). Rats received either saline or buprenorphine (3 mg/kg, s.c.). Each point represents the mean ± SEM. ***$P < 0.001$.

2. Materials and methods

2.1. Animals

All animal procedures were conducted in strict accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee (IACUC). Male Sprague–Dawley rats (250–300 g; Harlan, Indianapolis, IN) were housed two per cage for at least 1 week before surgery and were fed laboratory chow and water *ad libitum* at ambient temperature of 21 ± 0.3 °C, and a 12 h light/12 h dark cycle.

2.2. Surgery procedures

Rats were anesthetized with an intraperitoneal injection of a mixture of ketamine hydrochloride and acepromazine maleate. For cannula implantation, each animal was placed in a stereotaxic instrument. A sterilized stainless steel C313G cannula guide (Plastics One Inc., Roanoke, VA) was implanted into the ventral and ventro-lateral PAG (Palma et al., 2011). The stereotaxic coordinates were as follows: 7.8 mm anterior to bregma, 0.5 mm from midline and 4 mm ventral to the dura mater.

2.3. Microinjection

The animals were habituated to the handling procedure necessary for microinjections during the recovery period. After the recovery period, rats were allowed to habituate to test chambers for 1 h before testing. The rats were gently restrained while the dummy stylets were removed and replaced with a C313I injector cannula (Plastics One Inc., Roanoke). Either vehicle or drug was microinjected into the PAG in a volume of 0.5 μl. The C313I injector cannula was connected by polyethylene tubing to a 10-μl Hamilton syringe. A volume of 0.5 μl of drug or vehicle was delivered at a rate of 0.5 μl/min and the internal cannula left in place an additional 90 s to allow diffusion. Immediately thereafter, a dummy cannula (C313DC) was inserted into the cannula guide to prevent any contamination (Palma et al., 2011).

2.4. Drugs

Buprenorphine and methadone were obtained from the National Institute on Drug Abuse and dissolved in sterile, pyrogen-free saline. HIV-1 envelope glycoprotein gp120 recombinant viral protein was obtained from Advanced Biotechnologies (Columbia, MD).

2.5. Dependence and withdrawal

The development of physical dependence was induced by repeated administrations of opioids. Rats were injected subcutaneously (s.c.) with buprenorphine or methadone at 9:00 a.m. daily. The rats were placed individually into test chambers consisting of boxes (50 cm × 35 cm × 45 cm) and allowed to acclimate for 30 min. Qualitative and/or quantitative evaluation of abstinence consists of measuring a series of withdrawal phenomena (Baldino et al., 1979; Cowan, 1981; Huang et al., 2009) after opioid discontinuation. Examples of behaviors observed are "wet-dog" shakes, teeth chattering, jumping, diarrhea, and flat posture. Simultaneously body weight was monitored.

2.6. Nociceptive test

A 52 °C hot-plate (Ugo Basile, Varese, Italy) was used to measure the nociceptive response. The baseline response latency was obtained for each animal after two conditioning runs. Each rat was retested on the hot-plate at 15 min and thereafter at 15-min intervals by using either jumping or hind-paw licking as the nociceptive endpoint while 30 s was taken as the cutoff point (to avoid any tissue damage).