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DIFFERENTIAL ANTINOCICEPTIVE EFFECTS OF BUPRENORPHINE AND METHADONE IN THE PRESENCE OF HIV-GP120

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Abstract

BACKGROUND—We showed recently that elevated brain levels of the chemokine stromal cell-derived growth factor-1 α (SDF-1 α /CXCL12, a ligand for the human immunodeficiency virus [HIV] co-receptor CXCR4) diminish the antinociceptive effect of morphine, but failed to influence buprenorphine-induced antinociception.

AIMS—Because the HIV-1 coat protein, glycoprotein 120 (gp120) T-tropic strain, binds to the same receptor as SDF-1 α /CXCL12, the present experiments were designed to investigate the consequence of administering gp120 to rat brain on buprenorphine-induced antinociception in the 54° C hot plate test. For comparative purposes, the effect of gp120 on an equi-antinociceptive dose of methadone was also examined.

METHODS—A sterilized stainless-steel C313G guide cannula was implanted into the periaqueductal grey (PAG), a brain region critical for the processing of pain signals, and a primary site of action of many analgesics. Rats were pretreated with gp120, administered into the PAG.

RESULTS—The subsequent antinociception associated with methadone was diminished whereas buprenorphine-induced antinociception was unaffected. Buprenorphine thus appears to be a more effective analgesic than methadone in the presence of gp120 in the brain, a condition that is associated with HIV-related pain and infection.

Keywords

Buprenorphine; HIV; gp120; antinociception; PAG; chemokine

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. In 2010, the FDA approved a once-weekly buprenorphine transdermal system (Butrans; Purdue Pharma LP) for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period. Compared with morphine and methadone, which behave as mu-opioid full agonists,

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buprenorphine is usually defined as a mu-opioid partial agonist that shows high affinity for, and slow dissociation from, mu-opioid receptors. 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 buprenorphine's lower ceiling effect with regard to respiratory depression. Due to its slow dissociation from mu receptors, and the resulting milder withdrawal syndrome, the risk of development of physical dependence seems to be lower with buprenorphine than with mu full agonists (Walsh et al., 1995; Robinson, 2002; Walsh and Eissenberg, 2003; Pergolizzi et al., 2010).

The entrance of HIV-1 into susceptible cells by fusion of viral and cell plasma membranes is generally initiated by the binding of glycoprotein 120 (gp120) to CD4 on the host cell surface. The resulting conformational change to gp120 allows it to interact with a cellular surface chemokine receptor (co-receptor). The most common types of HIV-1 co-receptors are the CC chemokine receptor 5 (CCR5) and the CXC chemokine receptor 4 (CXCR4) (Berger et al., 1999; Shimizu et al., 2000). Distinct HIV-1 strains show a different infection pattern and also emerge at different stages of disease progression (Berger et al., 1999). M-tropic strain predominates in early asymptomatic stages of infection; moreover, these viruses are responsible for transmission of HIV-1 and its effects are mediated via CCR5 and infected macrophages. However, T-tropic strain appears at later stages of HIV-1 infection, and is associated with accelerated CD4+ T-cell decline and clinical progression towards AIDS (Scarlati et al., 1997).

The PAG region of the brain highly expresses opioid receptors, is involved in pain signal processing, and is a primary site of action for analgesics. CXCR4-immunoreactivity was observed in the mesencephalon, including PAG (Banisadr et al., 2002). Most importantly, co-expression of CXCR4 and mu-opioid receptors has been demonstrated on individual neurons in the PAG (Heinisch et al., 2010).

Recently, we reported that elevated levels of chemokine stromal cell-derived growth factor-1 α (SDF-1 α /CXCL12) in the PAG reduced the antinociceptive effect of morphine (Adler et al., 2005; Chen et al., 2007) yet failed to influence buprenorphine-induced antinociception (Benamar et al., 2011). This finding calls attention to possibly using buprenorphine to treat pain associated with HIV infection. In the present study, we have extended this approach and examined the antinociceptive action of buprenorphine (in comparison with that of methadone) in the presence of gp120 in rat brain.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Ace Animals, Boyertown, PA), weighing 175–200 g, were housed in groups of 3–4 for at least 1 week in an animal room maintained at $22 \pm 1^\circ\text{C}$ and approximately $50 \pm 2\%$ relative humidity. Lighting was on a 12/12-hour light/dark cycle (lights on at 7:00 and off at 19:00). The animals were allowed free access to food and water. All animal use procedures were conducted in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and were approved by Temple University Institutional Animal Care and Use Committee.

2.2. Surgical procedures

Rats were anesthetized with a mixture of ketamine hydrochloride (100–150 mg/kg) and acepromazine maleate (0.2 mg/kg), given i.p. A sterilized stainless steel C313G guide cannula (22 gauge, Plastics One, Roanoke, VA) was implanted into the PAG. The stereotaxic coordinates were as follows: 7.8 mm posterior to bregma, 0.5 mm from midline

and 5 mm ventral to the dura mater (Paxinos and Watson, 1998). The animals were housed individually after surgery.

2.3. Nociceptive test

A 54°C hot plate (Ugo Basile, Varese, Italy) was used, according to the method of Dewey et al. (1970). 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 up to 60 min by using either jumping or hind-paw licking as the nociceptive endpoint while 30 seconds was taken as the cutoff point. The percentage of maximal possible antinociception (%MPA) for each animal at each time point was calculated using the formula: $\%MPA = [(test\ latency - baseline\ latency) / (30 - baseline\ latency)] \times 100$.

2.4. Drugs

Buprenorphine hydrochloride and methadone sulfate 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. Injections

After a 7-day recovery period, rats were allowed to habituate to test chambers for 1 h before testing. A volume of 1 µl of drug or vehicle was delivered over 1 min (manually) and the internal cannula left in place an additional 90 sec to allow diffusion. Immediately thereafter, a dummy cannula (C313DC) was inserted into the cannula guide to prevent any contamination.

2.6. Statistical and histological analyses

All data are reported as means $\pm$ SEM, and variations in %MPA were compared across treatments and time points and analyzed by repeated-measures ANOVA, followed by Bonferroni's test. The data were analyzed by Prism software (Graph-Pad, San Diego, CA). Significance was set at $P < 0.05$.

At the conclusion of experiments, each rat was checked for the correct site of the injection according to our standard histological procedures (Benamar et al., 2004). Only data from animals in which the site of injection was clearly located within the PAG regions were included in the studies.

3. Results

First, we examined the effects of gp120 (10–133 ng) injected directly into the PAG, and hot plate latencies were measured. A dose of 133 ng of gp120 was chosen for further study since doses higher than 133 ng lowered the pain threshold by themselves. After a 60-min baseline interval, saline or gp120 was injected into the PAG. Thirty min later, buprenorphine (0.5 mg/kg) was injected s.c. and produced antinociception in saline-pretreated rats, reaching a peak (~70% MPA) at 30 min (Fig. 1). Pretreatment with gp120 failed to alter the antinociceptive action of buprenorphine (Fig. 1, $P > 0.05$). An equianalgesic dose of methadone (2.5 mg/kg, s.c.) elicited marked antinociception (~70% MPA) at 30 min post-injection (Fig. 2). Gp120 (133 ng) significantly diminished methadone-induced antinociception (Fig. 2, $F_{2,18} = 3.55$; $P < 0.001$). To show that this antagonizing action of gp120 was not due to a nonspecific interaction with hydrophobic regions of functional proteins, their lipid surroundings in the cell membrane, or contamination, heat-inactivated gp120 (90 °C for 30 min) was examined. The administration of this preparation (133 ng) directly into the PAG did not alter methadone-induced antinociception (Fig 2, $P > 0.05$).

4. Discussion

Various pain syndromes have been reported in HIV-1-infected individuals. More than 2 million people die of AIDS every year. Up to 80 percent of these people suffer severe pain. Pain in patients with HIV generally may result from direct effects of HIV on central and/or peripheral nervous systems, opportunistic infections or therapies for HIV (e.g., antiretroviral medications). Gp120 is implicated in the pathogenesis of neurological disorders associated with HIV and is capable of initiating neurotoxic cascades via an interaction with CXCR4 and/or CCR5 chemokine receptors. It can mimic many of the behavioral and physiological dysfunctions that are characteristic of HIV infection, including pain (Milligan et al., 2000). Gp120 has been linked to the genesis of neuropathic pain (Oh et al., 2001) and is capable of producing pain (Milligan et al., 2000).

The key findings from the present study are as follows: gp120 has no marked influence on buprenorphine-induced antinociception, yet antagonizes methadone-induced antinociception, in the rat hot plate test. It appears that buprenorphine is not acting in the same way as methadone when facing the neuroinflammatory conditions imposed by the infusion of gp120 into the brain.

A lack of interaction between buprenorphine and the immune system has been reported previously. For example, administration of buprenorphine (in contrast to morphine) to the PAG of rats elicited no functional changes in splenic natural killer cells, T-lymphocytes or macrophages (Gomez-Flores and Weber, 2000). Additionally, several preclinical studies clearly indicate that buprenorphine does not possess immunosuppressive properties (Gomez-Flores and Weber, 2000; Martucci et al., 2004; Franchi et al., 2007; Sacerdote et al., 2008).

Regardless of the mechanism(s) involved, the fact that buprenorphine is more effective than an equianalgesic dose of methadone in the presence of gp120, a condition that is associated with HIV infection, has great implications and is relevant for public health, particularly HIV-related pain management.

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Fig. 1.

Gp120 fails to alter the antinociception induced by s.c. buprenorphine in the rat hot plate test. Gp120 was given into the PAG 30 min before buprenorphine. % MPA indicates percentage of maximum possible antinociception. Each point represents the mean $\pm$ SEM. Mean responses before injection were as follows: ■ = 7.10 ± 0.14 s; ▼ = 7.10 ± 0.18 s and ● = 6.9 ± 0.20 s.

Fig. 2. Gp120 blocks methadone-induced antinociception. Gp120 was given into the PAG 30 min before methadone. % MPA indicates the percentage of maximum possible antinociception. Each point represents the mean $\pm$ SEM. Mean responses before injection were as follows: ■ = 6.64 ± 0.18 s; ▼ = 6.61 ± 0.13 s and ● = 7.21 ± 0.21 s. *** P < 0.00.