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ACUTE EFFECTS OF SUBLINGUAL BUPRENORPHINE ON BRAIN RESPONSES TO HEROIN-RELATED CUES IN EARLY-ABSTINENT HEROIN ADDICTS: AN UNCONTROLLED TRIAL

W. MEI,[a,b] J. X. ZHANG[c] AND Z. XIAO[a,b,d]*

[a]*Guangdong Key Lab of Medical Molecular Imaging and Department of Radiology, the First Affiliated Hospital of the Medical College of Shantou University, Shantou, PR China*

[b]*Department of Pharmacology, Medical College of Shantou University, Shantou, PR China*

[c]*Department of Psychology, Chinese University of Hong Kong, Hong Kong, PR China*

[d]*The Second People's Hospital of Shantou, Shantou, PR China*

Abstract—Replacement therapy with buprenorphine is clinically effective in reducing withdrawal and craving for heroin during detoxification but not in decreasing the probability of relapse after detoxification. This study examined the acute effects of buprenorphine on brain responses to heroin-related cues to reveal the neurobiological and therapeutic mechanisms of addiction and relapse. Fifteen heroin addicts at a very early period of abstinence, were studied in two separate periods 10–15 min apart: an early period (5–45 min) and a later period (60–105 min) after sublingual buprenorphine, roughly covering the onset and peak of buprenorphine plasma level. During both periods, fMRI scanning with heroin-related visual stimuli were performed followed by questionnaires. Under effect of buprenorphine, brain responses to heroin-related cues showed decrease in amygdala, hippocampus, ventral tegmental area (VTA) and thalamus but no changes in ventral striatum and orbital-prefrontal-parietal cortices. As an uncontrolled trial, these preliminary results suggest that buprenorphine has specific brain targets in reducing withdrawal and craving during early abstinence, and that ventral striatum and orbital–prefrontal–parietal cortices may be the key targets in developing therapy for drug addiction and relapse.

Key words: heroin, addiction, buprenorphine, relapse, fMRI, replacement therapy.

In the past two decades, the development of new research technology has greatly advanced our understanding of the neurobiological mechanisms and therapeutic strategies for drug addiction. Many chemical medications have been produced, some of which have been widely used in clinical treatment of drug addiction (Kreek et al., 2002), such as methadone and buprenorphine for heroin replacement therapy (O'Brien, 2005), and naltrexone for heroin and alcohol anticraving treatment (Dackis and O'Brien, 2005; O'Brien, 2005). These medications, however, have been found unable to prevent drug relapse following detoxification on a long-term basis (Heidbreder and Hagan, 2005; O'Brien, 2005). For example, naltrexone suppresses euphoria from heroin via its antagonistic effect on opiate receptors, but most heroin addicts would not accept it for long-term therapy (O'Brien, 2005). Methadone and buprenorphine, as opiate agonists, are clinically effective in reducing withdrawal and craving for heroin during detoxification, but it is difficult to use them to reduce the likelihood of relapse after detoxification (O'Brien, 2005). As these results are well-known and seem very robust, it is a crucial research question to understand why methadone or buprenorphine fails to reduce the probability of relapse. Such understanding would help revealing the neurobiological mechanisms of relapse and designing better therapeutic strategies.

One way to address this question is using fMRI to study the dynamic interaction between brain circuitry and neuropsychopharmacological agents. There are so many advantages to the method that it has already formed a field of its own called pharmacological MRI (phMRI) in the past decade (Leslie and James, 2000; Tracey, 2001; Honey and Bullmore, 2004). PhMRI is considered to offer a good way to assess pharmacological effects of medications for addiction therapy such as methadone or buprenorphine, and to understand the neurobiological mechanism of relapse after detoxification (Dackis and O'Brien, 2005).

Recently, Langleben et al. (2008) first employed phMRI to investigate acute effects of methadone on brain responses to heroin-related cues. Heightened responses to heroin-related stimuli were found acutely reduced after methadone administration in insula, amygdala, and hippocampus, but not in orbitofrontal and ventral anterior cingulate cortex. The findings led the authors to conclude that the medial prefrontal cortex and the extended limbic system in methadone maintenance addicts with a history of heroin dependence remain responsive to salient drug cues, suggesting a continued vulnerability to relapse.

With the increasing use of buprenorphine in the treatment of opiate dependence, it is necessary to further study the neuropsychopharmacological mechanism of buprenorphine and to find an objective evaluation of its curative effects. As buprenorphine binds with high affinity to both the μ opiate receptors (as a partial agonist) and the κ

*Correspondence to: Z. Xiao, Guangdong Key Lab of Medical Molecular Imaging and Department of Radiology, the First Affiliated Hospital of the Medical College of Shantou University, #57 Changping Road, Shantou, Guangdong, PR China, 515041. Tel: +86-754-8861-2318; fax: +86-754-8861-2318.
E-mail address: xiaozw@vip.163.com (Z. Xiao).

Abbreviations: BOLD, blood-oxygen-level-dependent; NAc, nucleus accumbens; OFC, orbitofrontal cortex; phMRI, pharmacological MRI; ROI, region of interest; SD, standard deviation; SEM, standard error of estimate; VTA, ventral tegmental area.

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opiate receptors (as an antagonist), it combines the pharmacological benefits of full opiate agonists like methadone and antagonists like naltrexone to block effects of illicit opiates and deter their abuse (Woody et al., 2008). Further, because buprenorphine causes little euphoria and is less likely to be abused, it is much safer than full agonists such as methadone and has a greater degree of treatment ease and compliance than naltrexone (Collins and McAllister, 2007). Previous studies have demonstrated that the effectiveness of buprenorphine for treatment of opiate dependence is comparable to methadone in reducing withdrawal and craving in detoxification (Ling and Wesson, 2003; Oreskovich et al., 2005; Leonardi et al., 2008).

In the present study, we used phMRI to examine acute effects of sublingual buprenorphine on brain responses to heroin-related cues at a very early period of heroin abstinence. Such preliminary data would identify brain regions in which neural responses to heroin-related cues are affected by buprenorphine as its therapeutic targets. Meanwhile, the unaffected brain regions may help to understand its limited therapeutic effects on addiction. Additionally, comparison between the effects of buprenorphine and methadone observed in the literature should help to reveal commonalities and differences in their brain mechanisms in addiction therapy and to provide further evidence for the application of phMRI in therapeutic research on drug addiction.

EXPERIMENTAL PROCEDURES

Participants

Fifteen active heroin users (mean age=33.5 years, SD=7.9, one female) all meeting DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria for current (at least prior 6 months) dependence on heroin participated in this study. All had normal vision and were strongly right-handed. They were native inpatients from a detoxification clinic in the local city (Shantou, PR China). Heroin was the primary drug of choice for all participants (six by sniffing or smoking, nine by injecting). Participants' average heroin use history was 4.5 years (SD=4.4) with a mean dose of 2.5 g (SD=2.4) per day. For all participants, the length of prior-study abstinence was longer than 12 h (mean=50 h, SD=24), a period inducing moderate heroin craving, based on interviews with addict participants in a previous study (Xiao et al., 2006). Their participation in this study was from 12 to 36 h after they entered the detoxification clinic. All participants were current tobacco users (mean=28 cigarettes per day, SD=12) and only one reported habitual alcohol use. There was no other drug abuse for them. None had any neurological or psychiatric disorders other than substance dependence.

Observing the Declaration of Helsinki, written informed consent was obtained from each participant following a research protocol approved by the Human Subjects Review Committee of the Medical College of Shantou University. All participant were clearly informed that they were free to participate and to terminate throughout the study without incurring any punishment.

Buprenorphine

Sublingual tablets of buprenorphine (2.0 mg per tablet, Qinghai Pharmaceutical Factory, Qinghai, PR China) were used in this study and were provided by the detoxification clinic. Experimentally and empirically, concentration of buprenorphine in blood peaks around 1–1.5 h following sublingual administration (Mendelson et al., 1999; Strain et al., 2004; Chawarski et al., 2005; Ciraulo et al., 2006), with a plasma half-life of about 3 h (Gutstein and Akil, 2006).

Design and procedure

The time of study was held constant for all participants at 13:00 to 15:00 PM. Their participation in this study was either prior to their receiving any clinical treatment or more than 8 h after receiving their first single dose buprenorphine (2.0 or 4.0 mg) in the detoxification clinic. Following a sublingual administration of buprenorphine (2.0 or 4.0 mg), participants were scanned in two periods, an early period from 5 to 45 min, and a late period from 60 to 105 min, each for about 35–40 min long. The two periods were selected to capture the onset and peak, respectively, of sublingual buprenorphine plasma levels (Mendelson et al., 1999; Strain et al., 2004; Chawarski et al., 2005; Ciraulo et al., 2006). Pharmacologically and therapeutically, the effect of buprenorphine in the late period should be greater than in the early period.

In between the two scans, participants were removed from the scanner and took a short break (10–15 min), during which they completed a questionnaire. They completed the same questionnaire again after the second scan was ended. Other than buprenorphine, no use of tea, caffeine, cigarette, alcohol, and other drug and medicine was allowed 8 h prior to the study and during the study.

Within each scan period, each participant underwent three functional runs and two structural runs, with a 2–3 min interval between two neighboring runs. In each run, there were three blocks presenting heroin-related images and three blocks presenting neural images, in alternative order and separated by a 26 s fixation as the resting baseline. In each block, four images were presented, each for 5 s with zero inter-stimulus interval, followed by a 4 s interval during which participants were instructed to press a button once to indicate they were attentive in passively viewing the images. The total length for each run was 5 min 38 s.

The heroin-related stimuli were taken from our previous study (Xiao et al., 2006) consisting of 24 heroin-related images of heroin drugs, drug injection, smoking or preparation scenes, and 24 graphically and contextually matched neutral images of flowers, toys, furniture, everyday activities (e.g., reading or playing sport), or street scenes. Stimuli were presented using the Inquisit software package (Psychology Software Tools, Pittsburgh, PA, USA).

The early and late scans involved the same design, each using half of the stimulus set (Langleben et al., 2008). The stimulus images were balanced across subjects, and the order of the heroin-related and the neutral blocks was balanced across runs and subjects.

Subjective heroin craving was assessed on a 10-point (0 to 9) scale (Langleben et al., 2008; 0 for least craving and 9 for strongest craving) before and after buprenorphine administration, and after both the early and the late scans. After each scan, participants also evaluated their response to the images they just saw by completing retrospective self-report measures consisting of 10 questions adapted from Garavan et al. (2000).

Image acquisition

Participants lay supine inside the scanner and wore goggles specially designed for MR environment. They were told to keep their head still inside the scanner.

All MR imaging was conducted at the Medical College of Shantou University on a 1.5 T Philips MR scanner with a standard headcoil. Twenty axial slices covering the whole brain were acquired with a T2*-weighted gradient-echo echo planar imaging pulse sequence (GE-EPI, TR=2000 ms, TE=45 ms, flip angle=90 degrees, matrix=64×64, FOV=230×230 mm^2, slice thickness=6 mm, gap=0 mm) for blood-oxygen-level-dependent (BOLD) functional imaging. This sequence delivered a voxel res-