Neuroscience Letters 581 (2014) 120–124

Contents lists available at ScienceDirect

Neuroscience Letters

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

Reduced responses to heroin-cue-induced craving in the dorsal striatum: Effects of long-term methadone maintenance treatment

Yarong Wang[a,b,1], Hanyue Wang[a,1], Wei Li[a], Jia Zhu[a], Mark S. Gold[b], Dongsheng Zhang[a], Lina Wang[a], Yongbin Li[a], Xuejiao Yan[a], Jiajie Cheng[a], Qiang Li[a,*], Wei Wang[a,*]

[a] Department of Radiology, Tangdu Hospital, the Fourth Military Medical University, 569 Xinsi Road, Baqiao District, Xi'an 710038, China
[b] Department of Psychiatry and Addiction Medicine, University of Florida College of Medicine and McKnight Brain Institute, Gainesville, Florida 32610, USA

HIGHLIGHTS

- The longer MMT, the lower response to heroin craving in caudate of MMT patients.
- Methadone plays its role in MMT by the dorsal striatum.
- The conclusion of this study is novel and significant for designing MMT plan.

ARTICLE INFO

Article history:
Received 19 May 2014
Received in revised form 29 July 2014
Accepted 14 August 2014
Available online 23 August 2014

Keywords:
Methadone maintenance treatment (MMT)
Heroin addiction
Craving, Caudate, Functional magnetic imaging (fMRI)

ABSTRACT

Methadone maintenance treatment (MMT) is safe and effective for heroin addiction, but the neural basis of the length effects of long-term MMT on brain activity during craving in former heroin addicts is unclear. This study explored it by comparing the brain activations of heroin addicts with different length of MMT during pictorial presentation of heroin-related cue. Fifteen male former heroin addicts successfully treated by MMT less than 1 year (Group A), 15 matched patients with 2-3 year MMT (Group B) and 17 healthy controls underwent functional magnetic resonance imaging while heroin-related and neutral stimuli were present to them. Subjective cue-elicited craving was measured with visual analog scale before and after imaging. Then, partial correlation analysis to reveal the relationship between drug-related blood oxygen level dependent (BOLD) signal intensity and heroin or methadone use history. Finally, self-reported craving was not different between Group A and B before and after scanning. Compared with Group A, Group B had a significant reduced brain activity to heroin-related minus neural cues in the bilateral caudate. After controlling for the variable heroin use history, the drug-related BOLD signal intensity in the bilateral caudate was negatively correlated with MMT duration and total methadone consumption. When MMT history was controlled, the drug-related activity intensity in right caudate had a positive correlation with heroin daily dosage. Long-term MMT may improve heroin–craving response by modulating the impaired function in the bilateral dorsal striatum caused by former heroin use.

1. Introduction

Methadone, a long-lasting opioid agonist, exerts its therapeutic effects on heroin addicts by binding to opiate receptors in brain [12]. At present, long-term methadone maintenance treatment (MMT) is the most widely available pharmacotherapy for heroin addiction because of its safety and effectiveness in the prevention or reduction of withdrawal symptoms, drug craving, drug-seeking behavior, etc. [12,22]. Notably, drop off and/or relapse to drug abuse caused by drug-related cue induced craving (DCIC) still exist in MMT [3,4]. It is proposed that altered dopamine neurochemistry and disrupted prefrontal control as well as hyperactive striatal-limbic response during DCIC contribute to the driving force for relapse following abstinence [27].

Three factors are highly associated with DCIC generation, effective dose of methadone [17], medication administration time [13] and MMT duration [24]. The influence of the former two factors upon DCIC has been basically confirmed. But little research has been conducted on the length influence of long-term MMT on the modulation of DCIC [4,10]. By comparing the DCIC of long-term and

* Corresponding authors. Tel./fax: +86 29 84777933.
E-mail addresses: tdqiangqiang@foxmail.com (Q. Li), wangwei_td@163.com (W. Wang).
[1] The two authors contributed to this work equally.

http://dx.doi.org/10.1016/j.neulet.2014.08.026
0304-3940/

short-term MMT patients, Shi proposed that long-term MMT could reduce patients craving severity, but they did not provide neuroanatomical substrates underlying it [26]. Our study, accessing the brain responses to heroin-related stimuli in patients receiving 5–24 months of MMT, found that long-term MMT could not completely block subjective craving and brain reaction, but did not disclose the relationship between treatment length and DCIC level [30]. Considering the critical contribution of DCIC to illicit drug use in MMT patients, this study was to investigate the length effects of long-term MMT on the brain responses to DCIC in former heroin addicts using task-related fMRI.

Clinical research has demonstrated that increased duration of MMT produces favorable treatment retention and outcomes in heroin addicts. McKenzie reported that those participants who initiated MMT prior to release from incarceration were more likely to enter treatment and had less post-release illicit drug use [20]. Lundgren et al. found that the addicts with more than 1 year MMT were more likely to have stable lives compared with those who dropped out of MMT less than 1 year [16]. Zhang et al. confirmed a positive linear relationship between MMT duration and the illicit drug improvement in MMT patients [32]. These may support the corollary that the longer MMT duration, the lower relapse rate. And some other studies may offer some possible explanations for this. For example, the study on cerebral metabolism in MMT patients with various treatment durations found that longer MMT associated with the smaller range of abnormal cortical activities, suggesting that long-term MMT might protect brain activity [7]. And other studies put forward that MMT might improve retention rate by modulating selective attention capability, reducing drug related attention bias and ameliorating performance of executive functions and visuo-construction in patients [23,28]. Based on these, we hypothesized that the longer the MMT duration was, the lower the brain responded to DCIC in former heroin addicts receiving MMT, or DCIC related brain activity change would has a statistical relationship with MMT history.

2. Materials and methods

2.1. Participants

This study was approved by Institutional Board of the Fourth Military Medical University and conducted in accordance with Declaration of Helsinki. All participants were fully informed about the details of experiment and signed the written consents for their involvement. Thirty male former heroin addicts receiving MMT were recruited from the outpatient of Xi'an Methadone Substitution Treatment Center, in which fifteen heroin addicts who received MMT less than 1 year (Group A) and 15 matched patients with MMT for at least 2 years (Group B). These patients were monitored by caregivers and physicians to confirm their abstinence from illicit drug use during the treatment program. To avoid confounding from poly-drug use, we selected participants who were not dependent on other psychoactive drugs and reported no history of using these drugs, except heroin and nicotine. The urine tests for supervising the illicit drug use of MMT patients were conducted irregularly and before MRI scans. To minimize subject selection bias, Barratt Impulsiveness Scale (BSI-II) was used to access the patients' personality/behavioral construct of impulsiveness during the procedure of enrollment. Moreover, the psychological status of the patients was measured with Becks' Depression Inventory and Hamilton Anxiety Scale (See supplementary materials). The inclusion criteria for MMT patients were: (a) opioid dependence screened by Structural Clinical Interview for DSM-IV (SCID) at first and diagnosed according to the criteria of DSM-IV-TR (American Psychiatric Association, 2002); (b) no less than 24 months of continuous heroin use and 100 milligrams daily dosage; (c) 5 months or longer of MMT.

In addition, 17 male healthy individuals who never used any psychoactive substance except nicotine were matched with the MMT patients in age, education and cigarettes use were enrolled from community control (Group HC). None of these participants was taking prescription drugs that affected central neural system within a week before scanning and had a history of neurological illness. The exclusion criteria for all participants included: (a) history of active neurological and psychiatric disorders besides heroin and nicotine dependence, (b) history of head trauma, medical disorder requiring immediate treatment and contraindications to MRI examination, (c) positive urine test on the day of enrollment. All participants had normal vision and were strongly right–handed as judged by a handedness inventory. Table 1 shows the clinical information of MMT patients and the demographic information of all participants.

2.2. Experiment design and procedure

All participants were required to abstain from smoking, alcohol, tea, caffeine and any other drug or medicine 12 h before the time of MRI scan. All MRI scans were conducted 4 h after the patients took their daily dosage (methadone peak plasma level) to avoid drug withdrawal symptom [31]. An established event-related paradigm was used in this study. Each participant underwent a structural scan and then a functional scan. The functional scan included 48 trials containing 24 heroin-related cues and 24 neutral cues. The heroin-related cues were the images of heroin injection, preparation, and paraphernalia and the neutral cues the images of household objects or chores [30]. All cues were presented in a pseudo-randomized order. Image cues were presented for 2 s with a variable 4–12 s inter-stimulus interval (mean = 8 s), during which a central cross was displayed. The task began with a 10 s dummy scan before the image cues were shown and took 490 s in total. The timing of the cue presentation was synchronized with trigger pulses from the MRI scanner to ensure precise temporal integration of stimulus presentation and fMRI data acquisition. Participants laid supine in the scanner using a foam head holder to reduce motion. Immediately before and after each MRI scan, all the participants were required to assess their subjective heroin craving on a 0–10 visual analog scale (VAS).

2.3. Image acquisition

All MR scans were conducted on a 3.0 T GE Signa Excite HD MRI scanner with an eight-channel head coil. A routine structural scan was performed to exclude gross cerebral pathology. After that session, a BOLD functional imaging data was acquired using T2*-weighted gradient–echo echo planar imaging pulse sequence (GE-EPI, TR = 2000 ms, TE = 30 ms, flip angle = 90°, matrix = 64 ×64, FOV = 256 × 256 mm^2, slice thickness = 4 mm, gap = 0 mm; spatial resolution = 4 × 4 × 4 mm^3; 32 axial slices covering the whole brain). The corresponding high-resolution fast spoiled gradient echo 3D T1-weighted images were also collected for anatomical overlays of the functional data and for spatial normalization of the datasets to a standard atlas (TR = 7.8 ms, TE = 3.0 ms, matrix = 256 × 256, FOV = 256 × 256 mm^2, spatial resolution = 1 × 1 × 1 mm^3).

2.4. Data analysis

The group differences in demographic information, clinical profile measures, subjective craving scores, drug use were analyzed by two-sample *t*-test. A significance threshold was set at $p < 0.05$ for all analyses. Image analysis was performed with SPM8