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Availability of dopamine transporters in heroin-dependent subjects: A ^{18}F-FECNT PET imaging study

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ABSTRACT

This study was to reconfirm the reduced dopamine transporter (DAT) availability in heroin-dependent subjects and validate the use of 2β-carbomethoxy-3β-(4-chlorophenyl) − 8-(2-fluoroethyl)-nortropane (^{18}F-FECNT) as a PET radiotracer to assess the changes of striatal DAT in drug addicted subjects. Herein, we assessed DAT standardized uptake values (SUV) of ^{18}F-FECNT in the striatum and cerebellum of 20 heroin-dependent subjects and 10 healthy controls and analyzed the correlation between DAT availability and heroin withdrawal symptom scores and anxiety/depression rating scales in heroin-dependent subjects, as well as the relationship between the withdrawal symptoms scores and age. The striatal DAT availability in heroin-dependent subjects was significantly lower (by ~15.7–17.6%) than that in healthy controls. Age was positively related to heroin withdrawal symptom scores. The withdrawal symptom scores in older patients (Age: 49.5 ± 2.5) were significantly higher (by ~20%) than those in younger patients (Age: 30.9 ± 4.8). These results confirm that chronic heroin use induces striatal DAT reduction, suggesting that ^{18}F-FECNT could be used as an alternative PET imaging radioligand for in vivo imaging of DAT in drug addicted subjects. Moreover, older patients might suffer more severe withdrawal symptoms than younger patients, suggesting that older patients with heroin withdrawal could be given more medication.

1. Introduction

Heroin addiction is a complex, multifaceted and relapsing chronic brain disorder. Heroin-related deaths, with overdose as the primary cause, have recently showed an increase (by 39.4% in 2013) in the world, reaching the highest level in a decade (UNODC, 2015). As a result, heroin addiction exerts a heavy burden on the public health system in terms of treatment and care for drug addicts and their health consequences.

Many disease states, including addictive disorders and Parkinson's disease, are linked to abnormalities within the brain's DA system. Degeneration of the DA system is thought to contribute to intense drug craving and addictive behaviors (Di Chiara and Bassareo, 2007). Chronic heroin use leads to a variety of compensatory changes, such as reductions in DA transporters (DAT), DA receptors, and synaptic DA levels (Kish et al., 2001; Liu et al., 2013; Wilson et al., 1996).

The DAT protein is a component of the DA nerve terminal and is involved in the regulation of synaptic DA levels, and its density has been used as a marker for the integrity and number of presynaptic terminals on DA neurons. Recently, noninvasive molecular imaging of the brain DAT with positron emission tomography (PET) or single-photon emission computed tomography (SPECT) has been successfully used to assess the pathophysiology, disease progression and effects of therapy in brain disorders (Chen et al., 2008; Davis et al., 2003).

The majority of previous SPECT imaging studies reported that chronic heroin use induces a significant reduction in striatal DAT availability (Jia et al., 2005; Liu et al., 2013; Shi et al., 2008; Xu et al., 2015; Yeh et al., 2012). However, fewer PET imaging studies have been investigated to study the changes of DAT availability in heroin-dependent subjects because of the significantly lower expense and wider availability of SPECT scans relative to PET. Considering the higher spatial resolution and sensitivity level and more versatile

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modality of PET than SPECT, PET is generally considered to provide a more informative imaging modality for the measurement of the in vivo levels of neurotransmitter transporters and receptors in humans.

Compared with other radionuclides, ^{18}F-radionuclide-labeled PET ligands have the advantages of a long half-life (110 min) that allows longer synthesis times, improved specific activity and reliable equilibration of uptake in the brain. Among the few ^{18}F-labeled radioligands available for DAT imaging, 2β-carbomethoxy-3β-(4-chlorophenyl) − 8-(2-fluoroethyl)-nortropane (^{18}F-FECNT) is highly specific for DAT, with higher peak striatum-to-cerebellum ratios (~9) and more favorable kinetics than others (Davis et al., 2003; Masilamoni et al., 2010; Pavese, 2012). Despite these advantages, ^{18}F-FECNT has only been used for DAT PET imaging in patients with Parkinson's disease, but not in the study of drug abuse (Davis et al., 2003; Masilamoni et al., 2010).

As one part of our previous study series that was previously published (Liu et al., 2013; Xu et al., 2015; Gao et al., 2014; Tu et al., 2015), the purposes of the present study were to test if there is a difference on DAT availability among heroin-dependent subjects and further to validate the use of ^{18}F-FECNT as a PET radiotracer to assess the changes in striatal DAT function in heroin-dependent subjects. Representative images, typical time–activity curves, and target tissue-to-cerebellum ratios for the healthy controls and the heroin-dependent subjects are presented. In addition, the relationships between striatal DAT, withdrawal symptoms and negative moods (anxiety/depression) were investigated.

2. Methods

2.1. Subjects

Heroin-dependent subjects were recruited from the Drug Rehabilitation Center in Shanghai, China. The inclusion criteria were as follows: (1) age between 18 and 55 years, (2) fulfillment of the DSM-IV criteria for opioid dependence, (3) absence of cocaine and other drug use, (4) positive urine morphine test and (5) the most recent heroin use 8–36 h prior to recruitment. The exclusion criteria were as follows: (1) current or past psychiatric illness other than heroin dependence; (2) neurological signs and/or history of neurological disease (e.g., Parkinson's disease or other movement disorders); (3) history of head trauma; and (4) history of cardiovascular, endocrine, or other serious physical diseases.

Healthy control subjects aged 18–55 years were recruited through newspaper advertisements and flier postings. All healthy subjects were absent of substance abuse, such as heroin, methamphetamine, MDMA, cannabis and/or alcohol. The exclusion criteria were the same as for the heroin-dependent subjects.

Written informed consent was obtained from each subject. The study was approved by Ethical Committee for Human Research at the Shanghai Mental Health Center (No. 2009-15) in Shanghai, China.

2.2. Study design

Prior to PET imaging, all heroin-dependent subjects completed a detoxification protocol for 10 days and a washout period of at least 5 days. After the above 15–18 days of detoxification, PET imaging with ^{18}F-FECNT was performed. All heroin-dependent subjects agreed to comply with the rehabilitation center's strict regulations regarding the discontinuation of illicit drug use. The patients lived and conducted all their daily activities at the center, and they received all necessary supplies from the center's supply store. If the patients had to leave the facility, they were accompanied by physicians or staff members. Any items that were sent to the facility by the patient's families or friends were inspected by the staff to ensure that no illicit drugs were brought in to the facility. Physical examinations were performed, and blood and urine chemistries were analyzed before imaging was performed.

2.3. PET imaging

^{18}F-FECNT was synthesized as described previously and was injected intravenously for each subject at a dose of 370 MB (10 mCi) (Voll et al., 2005). Patients were imaged with the Siemens Biograph True 64 PET/CT (4.2 × 4.2 × 4.2 mm Full Width Half Maximum, 64 slices), which consists of a gadolinium oxyorthosilicate (GSO) full-ring PET scanner with 1.5 mm spatial resolution and a 16-slice helical CT scanner. Dynamic imaging sessions were initiated immediately for 70 min after the injection of radiotracer to obtain the time-activity curves of ^{18}F-FECNT binding in different areas of the human brain. The heroin-dependent subjects and healthy controls were scanned in the 3D mode for 70 min using 21 frames of increasing duration (10 × 30 s, 5 × 1 min, 5 × 10 min, 1 × 20 min). Static imaging sessions were started after a 60 min uptake period, followed by a static PET scan with a 30 min acquisition time to determine significant differences of uptake values collected in each regions-of-interest (ROI) between heroin-dependent subjects and healthy controls. A CT scan (380 mAs, 120 kV, FOV 300 mm, 0.5 s rotation time, pitch of 0.8, collimation 16 × 1.5 mm, slice thickness and increment 1.5 mm, bed height 140.0 cm) was performed before injection of the radiotracer for attenuation correction of the emission data. To reduce head motion during the PET scan, each subject wore a custom-made thermoplastic face mask while in the scanner. PET images were reconstructed by using an iterative algorithm (TrueX, 21 subsets, 6 iterations, matrix size 336 × 336, zoom 2.0). The images were interpreted at a workstation equipped with fusion software (syngo, Siemens Co.) that enables the display of CT, PET, and PET-CT images. The mean 3D standardized uptake values (SUV) [radioactivity concentration (Bq/ml tissue)]/[injected dose (Bq)/body weight (g)] were measured as an index of tissue accumulation of ^{18}F-FECNT. For dynamic acquisition data, regions of interest (ROIs) including the bilateral caudate and putamen were manually drawn on the late images using the SUV threshold method, and the cerebellum was drawn manually in a sphere (volume = 1.0 cm^3). Then, the regions were overlaid on all images to obtain the mean SUV using Hermes software (version 4.14, HERMES Medical Solutions AB). The mean SUV of each subject was recorded to obtain time-activity curves. For the static acquisition data, because the striatum are the only brain regions visibly labeled by ^{18}F-FECNT in the late-phase summed images, the ROIs including the bilateral striatum were drawn manually using the SUV threshold method, and the reference region of the cerebellum was drawn manually in a sphere (volume = 0.5 cm^3) using Mirada software (version XD 3.6, Mirada Medical Ltd). The specific striatal ^{18}F-FECNT uptake was calculated as the following ratio: (SUV in bilateral striatum – SUV in cerebellum)/SUV in cerebellum.

2.4. Neuropsychological evaluation

In heroin users, the modified subjective opioid withdrawal scale (SOWS), a 19-item symptom checklist, was used to measure the severity of heroin withdrawal symptoms (Loimer et al., 1991). The subjective depression and anxiety scores were assessed with the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960) and the Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959) prior to the PET imaging session. The correlation between the DAT levels in the bilateral striatum and SOWS, HAMD or HAMA scores was determined.

2.5. Statistical analysis

Means ± SD and proportions were calculated for the characteristics by groups. The differences in population characteristics among the different groups were compared via the *t*-test for continuous variables or via the chi-square test for categorical variables. Pearson's correlation coefficient was used to compare the correlations between DAT binding and the rating scale scores. The *t*-test was used to compare the