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PET imaging of dopamine transporter and drug craving during methadone maintenance treatment and after prolonged abstinence in heroin users

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Abstract

It has been documented that methadone maintenance treatment is effective in reducing drug craving and relevant risk behaviors in heroin users. However, it is not understood whether methadone maintenance treatment impairs the dopamine transporter in the striatum. To establish whether chronic opiate use might impair brain dopamine neurons in humans, we assessed dopamine transporter (DAT) uptake function in the striatum (caudate and putamen), and analyzed the correlation between DAT in the striatum and heroin craving and subjective anxiety in former heroin users with prolonged abstinence and in patients receiving methadone maintenance treatment. Binding of [^{11}C]–2β–carbomethoxy–3β–aryltropane ([^{11}C] CFT) as a brain dopamine transporter ligand was measured with positron emission tomography (PET) in eleven former heroin users with prolonged abstinence, ten patients receiving methadone maintenance treatment and ten healthy control subjects. Heroin craving and subjective anxiety in prolonged abstinence and methadone maintenance treatment groups were assessed and the correlations between DAT of striatum and heroin craving or subjective anxiety were determined. In comparison with healthy control subjects, methadone maintenance treatment subjects had lower DAT uptake function in the bilateral caudate and putamen and prolonged abstinence subjects showed significantly lower DAT uptake function in the bilateral caudate. Moreover, in comparison to the prolonged abstinence subjects, the methadone maintenance treatment subjects showed significant decreases of DAT uptake in the bilateral putamen. DAT uptake function in bilateral striatum was not associated with heroin craving in prolonged abstinence or in methadone maintenance treatment subjects; however, DAT uptake function in the bilateral caudate was significantly correlated with subjective anxiety in methadone maintenance treatment subjects. Our findings suggest that chronic opioid use induces long-lasting striatum dopamine neuron impairment, and prolonged withdrawal from opioids can benefit the recovery of impaired dopamine neurons in the brain.
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Keywords: Heroin abuse; Craving; Anxiety; Prolonged withdrawal; Dopamine transporter; Positron emission tomography; Methadone maintenance treatment

1. Introduction

Opioid abuse is a significant global public health problem. Almost 16 million people worldwide are abusers of opioids, of which about 70% (11 million) are abusers of heroin (diacetylmorphine) (UNODC, 2006). Methadone maintenance treatment has been demonstrated to be effective in reducing or eliminating opioid drug use (Dole and Nyswander, 1965; Dole et al., 1966; Strain et al., 1999) and reducing heroin craving (Greenwald, 2002; Leri et al., 2004), and it is the most commonly prescribed opioid agonist therapy for the treatment of heroin dependence.

Methadone hydrochloride is a synthetic mu opioid receptor agonist with pharmacologic and analgesic properties similar to those of morphine. The principal actions of therapeutic value are analgesia or maintenance in opioid dependence. When methadone is administered for treatment of opioid dependence

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for more than three weeks, the therapy transitions from treatment of the acute withdrawal syndrome to methadone maintenance therapy.

Despite its therapeutic effectiveness, relatively little is known about neuronal adaptations in the brains of methadone users. Neuroimaging has rarely been used to examine opioid dependence (Krystal et al., 1995). Using positron emission tomographic (PET) [18F]fluorodeoxyglucose (FDG), it is found that there is significant difference of glucose cerebral metabolism in the anterior cingulate gyrus between the methadone withdrawal and control subjects, which suggest that neurobiological abnormalities can persist in the brain of a chronic opiate user after detoxification from methadone (Galynker et al., 2000). PET using [^{11}C]diprenorphine (Melichar et al., 2005) and [^{18}F]cyclofoxy (Kling et al., 2000) receptor ligands also has been used to examine the methadone dose-opioid receptor occupancy relationship. Though not restricted to examining brain adaptations in patients with methadone maintenance treatment, one study used Single Photon Emission Computed Tomography (SPECT) to examine regional cerebral blood flow in an Austrian sample of opioid-dependent persons who were either actively using heroin or enrolled in either a methadone or morphine agonist therapy program (Pezawas et al., 2002). While not attributable solely to methadone, Pezawas and colleagues (2002) showed a decrease in prefrontal regional cerebral blood flow in chronically opioid-dependent persons relative to drug-free healthy controls. Further, opioid dependent persons demonstrated a left-greater-than-right asymmetry in CBF in comparison to drug-free controls that had a right-greater-than-left asymmetry. The authors speculate that this may be associated with a proclivity toward negative mood states in opioid dependent individuals.

An important feature of both psychostimulant and opioid drugs of abuse is their ability to activate brain dopaminergic neurons, as evidenced by increased striatal synaptic concentrations of dopamine (Rouge-Pont et al., 2002; Wise and Rompre, 1989). Chronic dopamine overactivity caused by drug abuse leads to a variety of compensatory changes that could influence the behavior of the drug user. Synaptic dopamine levels are decreased in animals in psychostimulant withdrawal (Ghosh and Grasing, 1999) whereas striatal tissue dopamine levels are reduced in human chronic psychostimulant users (Wilson et al., 1996). These changes could explain the dysphoric motivational state during psychostimulant withdrawal. Both animals and humans (Courtin et al., 2006; Fleckenstein et al., 1999; Kahlig and Galli, 2003; Rothman and Baumann, 2003; Saunders et al., 2000) exposed to psychostimulants also demonstrate altered striatal levels of the dopamine transporter (DAT), a component of the dopamine nerve terminal critically involved in regulation of synaptic dopamine levels.

Chronic exposure to cocaine can alter, by unknown mechanism, levels of striatal DAT independently of any change in number of dopamine neurons (Kahlig and Galli, 2003; Rothman and Baumann, 2003). In rats, DAT concentration in the nucleus accumbens is decreased following chronic morphine administration (Simantov, 1993). However, little attention has been focused on long-term effects of opioid drugs of abuse on the dopamine system in human subjects. In fact, it has been assumed that opioids do not produce “enduring changes” in dopaminergic transmission or cellularity. A post mortem human study of heroin users, however, found no statistically significant change in striatal DAT levels, but had a slight trend for decreased DAT concentration (by 25%) in the nucleus accumbens (Kish et al., 2001). These data suggest that opioid may impair (reversibly or irreversibly) brain dopaminergic function in humans. However, it is at present unknown whether methadone maintenance treatment impairs the DAT in the striatum.

DAT is a protein situated in the presynaptic terminal and participating in the reuptake of dopamine. Thus, the activity of DAT regulates the synaptic content of dopamine, and is the primary indicator of endogenous dopaminergic tone (Dohi et al., 2002). Previous evidence has demonstrated a relationship between cognition and DAT that better memory is associated with greater DAT concentrations in both the caudate and putamen (Mozley et al., 2001). The present study examined whether chronic opioid use impairs brain dopamine neurons in humans. We did this by assessing DAT uptake function in the striatum (caudate and putamen) in former heroin users with prolonged abstinence and in patients receiving methadone maintenance treatment. We further assessed the relationship between striatal DAT uptake function and craving and negative mood (anxiety). To our knowledge, this is the first demonstration of the neuronal adaptations in the brains of patients with methadone maintenance treatment.

2. Methods and materials

2.1. Subjects

Heroin users: Twenty one male and female subjects were selected for inclusion in one of two groups based on their drug use history: (1) opioid-dependent subjects currently receiving methadone maintenance therapy; (2) opioid-dependent subjects who had undergone heroin detoxification and were in prolonged abstinence. For inclusion in the methadone maintenance treatment or prolonged abstinence groups, participants were required to meet Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, American Psychiatric Association, 2002) criteria for opioid dependence in the 3 years prior to the study and to have been free of illicit drug use for the previous 6 months. Both subjects with methadone maintenance treatment and with prolonged abstinence were required to have negative urine toxicology screening tests (excluding methadone in the methadone maintenance treatment group) at the time of study enrollment. Their urine was tested weekly; they were also monitored by police and physician to confirm abstinence from illicit drugs completely during 6 months. The subjects with methadone maintenance treatment were recruited from the methadone maintenance treatment Program of Beijing AnKang Hospital, Beijing City and the subjects with prolonged abstinence were recruited from the Addiction Treatment Center of Beijing AnKang Hospital, Beijing City. In summary, the inclusion criteria were: (1) DSM-IV criteria for heroin dependence; (2) 18–45 years old; (3) continuous intravenous use of heroin for at least 3 years with heroin use of at least one gram daily (estimated cost $50/day); (4) without use with cocaine and other drugs. Exclusion criteria

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