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The association between heroin expenditure and dopamine transporter availability—A single-photon emission computed tomography study

Shih-Hsien Lin [a,b], Kao Chin Chen [a,b,c], Sheng-Yu Lee [a,b], Nan Tsing Chiu [d], I Hui Lee [a,b], Po See Chen [a,b,c], Tzung Lieh Yeh [a,b], Ru-Band Lu [a,b,e], Chia-Chieh Chen [f], Mei-Hsiu Liao [f], Yen Kuang Yang [a,b,*]

[a] Department of Psychiatry, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[b] Addiction Research Center, National Cheng Kung University, Tainan, Taiwan
[c] Department of Psychiatry, National Cheng Kung University Hospital, Dou-Liou Branch, Yunlin, Taiwan
[d] Department of Nuclear Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[e] Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[f] Institute of Nuclear Energy Research, Atomic Energy Council, Executive Yuan, Taoyuan, Taiwan

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ABSTRACT

One of the consequences of heroin dependency is a huge expenditure on drugs. This underlying economic expense may be a grave burden for heroin users and may lead to criminal behavior, which is a huge cost to society. The neuropsychological mechanism related to heroin purchase remains unclear. Based on recent findings and the established dopamine hypothesis of addiction, we speculated that expenditure on heroin and central dopamine activity may be associated. A total of 21 heroin users were enrolled in this study. The annual expenditure on heroin was assessed, and the availability of the dopamine transporter (DAT) was assessed by single-photon emission computed tomography (SPECT) using [$^{99m}T_C$]TRODAT-1. Parametric and nonparametric correlation analyses indicated that annual expenditure on heroin was significantly and negatively correlated with the availability of striatal DAT. After adjustment for potential confounders, the predictive power of DAT availability was significant. Striatal dopamine function may be associated with opioid purchasing behavior among heroin users, and the cycle of spiraling dysfunction in the dopamine reward system could play a role in this association.

1. Introduction

Heroin is one of the most harmful illicit drugs (Nutt et al., 2010). It not only impairs users' physical and mental health (Darke and Ross, 1997; Callaly et al., 2001; Gyarmathy et al., 2002; Shapatava et al., 2006; Chu et al., 2009), but it also places a huge economic burden on each user and on society (Mark et al., 2001). The large amount of capital allocated for purchasing heroin is one of the consequences of heroin dependency (Healey et al., 1998; Hutchinson et al., 2000; Golub and Johnson, 2004). As in most severe substance use disorders, heroin users spend most of their money on purchasing heroin (Roddy and Greenwald, 2009), which may severely affect their health-related quality of life (Lin et al., 2013). Moreover, the financial need to purchase heroin may compel the heroin user to turn to criminal behavior, which causes a significant social cost to society (Hutchinson et al., 2000). Cumulative evidence has indicated that expenditure on heroin is harmful for users and other individuals (Bretteville-Jensen and Sutton, 1996; Healey et al., 1998; Wall et al., 2000; Mark et al., 2001). Exploration of the possible underlying mechanisms associated with this phenomenon is important.

Heroin purchasing may be a pathological economic behavior per se. At present, little is known about the nature of the pathological economic behaviors related to substance or drug addiction. Meanwhile, it has been found that temporal discounting processes are characteristics of addiction (Kirby et al., 1999). An experimental behavior–economic study indicated that addiction is related to a high temporal discounting rate, which is also predictive of future relapse (Goto et al., 2009). It was also proposed that there could be a neurobiological mechanism associated with this economic behavior (Glimcher and Rustichini, 2004). The central nervous system is associated with economic behaviors that may be related to addiction; for example, a functional

* Corresponding author at: Department of Psychiatry, National Cheng Kung University Hospital, 138 Sheng Li Road, North Dist., Tainan 70403, Taiwan. Tel.: +886 6 2353535x5213; fax: +886 6 2759259.
E-mail address: ykyang@mail.ncku.edu.tw (Y.K. Yang).

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magnetic resonance imaging (fMRI) study found that the economic reward related to addiction may activate several brain areas, such as the anterior lateral and posterior lateral orbitofrontal cortex (OFC) and the striatum, which is one of the sites at which dopamine exerts an effect (Sescousse et al., 2010). Other studies have also reported that activation in the striatum and other brain areas could be related to an abnormal response to monetary reward among substance-dependent individuals (Andrews et al., 2011; Jia et al., 2011; Patel et al., 2013). Meanwhile, diminished frontostriatal activity was found among those with a pathological gambling addiction (Balodis et al., 2012). The findings of these fMRI studies may suggest that the dopaminergic system is associated with risk and pathological economic behaviors. Neuroimaging research has also confirmed that the availability of the dopamine $D_{2/3}$ receptor is associated with pathological gambling behavior (Linnet et al., 2011). Additionally, pathological gambling behavior was also noted to be a side effect of a dopamine agonist among patients with Parkinson's disease (Cilia et al., 2010). The neuropsychological mechanism underlying the economic behavior of purchasing heroin remains to be elucidated.

The mesolimbic dopaminergic system, which is related to the reward system, plays a pivotal role in addictive behaviors (Wise, 1996; Spanagel and Weiss, 1999; Goldstein and Volkow, 2002; Melis et al., 2005; Volkow et al., 2009). The hypo-dopaminergic state produced by long-term drug use may lead to illegal drug-seeking and drug use (Melis et al., 2005). Other neurotransmitters also play roles in this cycle (Koob and Le Moal, 1997; Yeh et al., 2012). As mentioned earlier, hypoactivity of the OFC may be involved in economic behaviors among drug users. It is worthy of note that a study using a novel radioactive tracer also reported a hypodopaminergic state in the anterior cingulate gyrus and the OFC (Volkow et al., 2007). Animal model studies have also confirmed that opioids alter dopaminergic function (Tjon et al., 1994; Xiao et al., 2006). Preliminary research has shown an association between striatal dopamine release and addictive behavior and craving (Di Chiara et al., 1999; Childress and O'Brien, 2000; Grace, 2000; Nader et al., 2006; Volkow et al., 2006; Wong et al., 2006). A low dopaminergic state could be associated with craving for drugs, and using drugs may induce dopamine release, which suppresses the craving (Volkow et al., 2006). The availability of the dopamine transporter (DAT) could be a potential marker for assessing the toxicity and plasticity of dopamine neurons among heroin users. Imaging studies (Jia et al., 2005; Shi et al., 2008; Yeh et al., 2012) and a post-mortem study (Kish et al., 2001) have suggested that a decrease in DAT is associated with heroin use; however, a recent study reported that DAT availability was unrelated to the number of years of heroin use and the quantity used per day (Cosgrove et al., 2010).

Evidence of a relationship between the economic expense of illicit drugs and dopaminergic neuro-function is still scarce. It is worthy of note that experimental studies with the self-administration paradigm suggest that the dopaminergic system may play a role in drug-purchasing behavior. In a positron emission tomography (PET) study with [^{11}C]raclopride, Martinez et al. (2007) demonstrated that patients with cocaine dependency may have a lower level of amphetamine-induced dopamine release (as measured by D_2/D_3 receptor availability), and this effect is also associated with a tendency to choose cocaine over money. However, this effect was not supported in another experiment with a similar paradigm and radiotracer (Martinez et al., 2012).

We speculated that striatal dopamine function could be linked to the economic behavior of illicit drug purchasing. As the dopaminergic system, particularly in the striatum, may play a critical role in relapse, bingeing, and drug-seeking behaviors (Goldstein and Volkow, 2002; Melis et al., 2005), striatal dopamine function may play a role in heroin-purchasing behavior, according to the above-mentioned evidence. It has also been found that morphine targets gamma-aminobutyric acid (GABA)-ergic neurons to increase the firing of dopamine neurons through the activation of μ opioid receptors to reinforce the effect in heroin users (Jalabert et al., 2011). This may indicate that subjects with a lower level of DAT availability need to purchase more heroin to ease their craving. On the other hand, the amount of money spent on heroin is not identical to, but might be associated with, the actual amount of chronic heroin use, which could induce dopamine function impairment and a decrease in DAT availability. These potential mechanisms may induce a cycle of spiraling dysfunction in the brain reward systems (Koob and Le Moal, 1997), and may cause an association between a decrease in the level of DAergic function and compulsive drug purchasing.

Meanwhile, acute drug administration may enhance dopamine release, but prolonged use of a drug may result in downward regulation in dopaminergic activity (Koob and Le Moal, 1997; Volkow et al., 2009). It was found that chronic heroin use may be associated with a lower level of DAT availability, and those who receive methadone treatment have a lower level of DAT availability than those who have been abstinent for a prolonged period (Shi et al., 2008). However, this issue remains controversial. A recent finding reported a similar level of DAT availability between heroin users and controls (Cosgrove et al., 2010), while our study indicated that methadone-free abstinent and low-dose methadone users may have similar levels of DAT availability (Yeh et al., 2012). In the current study, we investigated the relationship between expenditure on heroin and the availability of striatal DAT among heroin users.

2. Methods

2.1. Ethics statement

The research protocol was approved by the Ethical Committee for Human Research at the National Cheng Kung University, and written informed consent was obtained from each subject before any procedures were performed.

2.2. Participants

Twenty-one patients who fulfilled the DSM-IV-TR criteria for opioid dependence were recruited from the methadone maintenance treatment clinic of National Cheng Kung University hospital, 12 of whom were still receiving methadone maintenance treatment during the investigation. The methadone dosage varied in individual patients. Before the imaging study began, the dose of methadone for these patients with opioid dependence had been gradually decreased. Ten patients were abstinent opioid users (confirmed by follow-up urine tests) and had completed their methadone treatment. All patients were intravenous heroin users; 16 had a history of methamphetamine use and had quit it for more than 1 year. All were tobacco smokers. As an effect of methadone on DAT availability cannot be ruled out, we assessed the clinical characteristics of these patients (e.g., dosage of methadone and duration of treatment) and probed their association with DAT availability.

The exclusion criteria were as follows: (1) a current diagnosis of schizophrenia, mood disorder, or other mental disorders; (2) a current diagnosis of alcohol abuse or dependence; (3) any acute or unstable medical condition; (4) a history of head trauma or neurological disease; and (5) current use of medication that affects the central dopamine and serotonin systems (except methadone). All participants were interviewed using the Chinese version of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) by a senior psychiatrist to screen out those who currently had comorbid mental disorders (exclusion criterion 1). Their demographic data are shown in Table 1. To assess the psychological craving regarding opioid use, a 10-item Craving Scale (Lin and Huang, 2004; Yeh et al., 2012) developed based on the instrument of Beck (1993) was administered. A higher total score on the Craving Scale indicated a greater craving tendency.

2.3. Economic cost of heroin

The expenditure on heroin in the past year was assessed using a questionnaire designed to estimate the economic cost of opioid dependency. Five patients were incarcerated in jail within a year. To calculate the annual expenditure on heroin, the