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SHORT COMMUNICATION

The association between availability of serotonin transporters and time to relapse in heroin users — A two-isotope SPECT small sample pilot study

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Abstract

Neuroimaging evidence supporting an association between either dopamine or serotonin and time to relapse of heroin users is limited. In this two-isotope SPECT small sample (N=9) pilot study, the relationship between the availability of serotonin transporter (SERT) and dopamine transporter (DAT) and the relapse of heroin users was investigated. A significant negative association between SERT availability and time to relapse among those who relapsed (N=7) was found.

1. Introduction

It has been suggested that the dopamine system is not only involved in the drug reinforcement process, but also in drug-related behaviors (Volkow et al., 2009). However, direct evidence supporting the effect of dopamine on relapse is scarce (Jia et al., 2005). A lower-level central serotonin

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concentration could also be associated with addiction (Kish et al., 2001). Pharmacological research has indicated that a selective serotonin reuptake inhibitor attenuates the acquisition of opioid use (Magalas et al., 2005), and genetic studies have shown that the short/short serotonin transporter genotype is more frequent in heroin-dependent subjects (Gerra et al., 2004). Moreover, a higher availability of serotonin transporter (SERT) has been found to be associated with a greater alcohol intake in an animal model (Heinz et al., 2003) and among adolescents (Hinckers et al., 2006).

Although the dopaminergic and serotoninergic systems may be associated with addiction behaviors, evidence from neuroimaging is needed (Cosgrove et al., 2010; Yeh et al., 2012). Relapse, which is a very important topic for heroin addiction, may be associated with psychosocial and biological factors (Le Moal and Koob, 2007). To the best of our knowledge, the relationship between the availability of SERT or dopamine transporter (DAT) and time to relapse among heroin users has not yet been investigated. Examination of the neuro-mechanism influencing the time to relapse could be very important, since heroin dependency is often characterized by quick relapse. The aim of this preliminary study was to investigate the association between the availability of DAT and SERT and time to relapse among heroin users after completing the methadone maintenance treatment (MMT).

2. Experimental procedures

Nine patients with opioid dependence (mean age = 38.9 ± 7.9 years; eight males) were recruited from the MMT clinic of National Cheng Kung University Hospital, all of whom fulfilled the DSM-IV-TR criteria for opioid dependence. The patients with opioid dependence were recruited to this study after their methadone use was terminated. The exclusion criteria were: 1) a current diagnosis of mood disorder or other mental disorder; 2) a current diagnosis of alcohol abuse or dependence; 3) any acute or unstable medical condition; 4) any history of head trauma or neurological disease; and 5) current use of medication affecting the central dopamine and serotonin systems. The dosage of methadone in the study site is gradually decreased based on the patients' clinical condition. Physicians had discussions with patients who had decide to discontinue the MMT. Only the patients who were determined to discontinue the MMT and who were approved by their physicians to do so were eligible to join the sample.

Subjects were enrolled from October, 2007 to February, 2010, and had been treated in the MMT program for 430.0 ± 354.11 days. The subjects underwent a monthly laboratory urine morphine test. SPECT using [^{123}I] ADAM for SERT and [^{99m}Tc] TRODAT-1 for DAT was employed to assess the availabilities of midbrain SERT (26.6 ± 21.68 days after discontinuation of the MMT program) and striatal DAT (10.1 ± 14.1 days after discontinuation of the MMT program) upon entry into the study.

The detailed procedure of neuro-imaging was identical to that in our previous study (Yeh et al., 2012).

Before SPECT examination with [^{123}I] ADAM, the thyroid gland was protected with 9 ml of Lugol's solution. For brain SPECT imaging, each participant was intravenously administered with 185 MBq (5 mCi) of [^{123}I] ADAM in a quiet environment about 10 min after insertion of the intravenous lines. We used a triple-headed rotating gamma camera (Siemens Medical Systems, Hoffman Estates, IL, USA) with fan-beam collimators, which yielded an image resolution of approximately 8.5 mm FWHM. A 20% energy window was symmetrically placed at 159 keV. The SPECT images were acquired over a circular 360° rotation of 120 steps, at 50 s/step, in a 128 × 128 × 16 matrix. The images were reconstructed using Butterworth and Ramp filters (cut-off frequency = 0.3 Nyquist; power factor = 7) with attenuation by Chang's method. The reconstructed transverse images were then realigned parallel to the canthomeatal line, and were of a slice thickness of 2.89 mm.

For semi-quantitative analysis, six consecutive transverse slices on which the midbrain was best visualized were combined to obtain a 17.34-mm-thick slice. The [^{123}I] ADAM SPECT images were acquired in both early (10 min after injection) and late (6 h after injection) phases after IV injection of 185 MBq [^{123}I] ADAM. The early-phase images represent blood–brain barrier transit and mimic cerebral blood flow images, while the late-phase images represent SERT distribution. In this two-step analysis, the late-phase images were co-registered to the early ones. The regions of interest (ROIs) of the midbrain (the specific binding sites where SERT is located) and cerebellum (the non-specific site where SERT is lacking) were then manually drawn over the early images, in which the midbrain and cerebellum were better delineated. In addition, magnetic resonance imaging (MRI) (Signa CV-I, 1.5 Tesla, GE Medical Systems, Milwaukee, WI, USA) was used as a rough guide (non-registered) for defining the midbrain and the cerebellum in the SPECT images. SERT binding sites in the midbrain were drawn manually and normalized to the cerebellum (calculated by (midbrain–cerebellum)/cerebellum or the (Mb–Cb)/Cb ratio) by an experienced nuclear medicine specialist who was blind to the participants' clinical data (Huang et al., 2010; Yang et al., 2007).

For brain imaging, each subject was intravenously administered 740 MBq (20 mCi)-TRODAT-1 (a radio-labeled form of tropan derivative for selective labeling of DAT) in a quiet environment about 10 min after insertion of the intravenous line. The SPECT data were obtained using an energy window of 15% centered on 140 keV (Hwang et al., 2004). Imaging of [^{99m}Tc]-TRODAT-1 was initiated approximately 240 min after injection with [^{99m}Tc]-TRODAT-1, and the SPECT images obtained were similar to those produced by SPECT with [^{123}I] ADAM. The data of six consecutive transverse slices (17.34 mm in thickness) with the most intense striatal activity were summed. ROIs were drawn manually over the left and right striatum and the occipital area using individual MRI scans as a reference (non-registered). In addition, MRI was used as a rough guide (non-registered) to define the striatum and occipital area in the SPECT images, and the ratio of radioactivity [the (St–Oc)/Oc ratio] was derived by dividing the difference between the average activity in the striatum (St) and the average activity in the occipital cortex (Oc) by the average activity in the occipital cortex (Oc) (Hwang et al., 2004). The [^{123}I] ADAM SPECT scan was performed one week after the [^{99m}Tc]-TRODAT-1 SPECT scan for all participants. All patients were scanned for the first time in this study.

The study was terminated in November, 2010. The research protocol was approved by the Ethical Committee for Human Research at National Cheng Kung University, and informed consent was obtained before any procedures were performed. The baseline neuroimage data was also used in our recent cross-sectional study (Yeh et al., 2012), which was conducted for a different purpose without follow-up assessment.

Relapse was defined as: 1) opioid use as confirmed by a urine morphine test (four males; 44% of the total sample); and 2) refusal to provide a urine sample (two males and one female; 33% of the total sample), as, based on our clinical experience, these subjects were highly likely to be reusing morphine. The mean time to relapse was 10.4 months (SD = 8.2). Two males among the nine subjects (22% of total sample) did not experience relapse within 16 and 29 months of the termination of methadone treatment, respectively.

Survival analysis (Cox regressions with time dependent covariate) and nonparametric correlation analysis was conducted. The association between time to relapse with SERT and DAT availability was tested by Spearman correlation. Statistical analyses were conducted using SPSS 17.0. Significance was assumed at the $p < 0.05$ level.