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Brief report

Dopamine and serotonin transporter availability in chronic heroin users: A [^{123}I]β-CIT SPECT imaging study

Kelly P. Cosgrove [a,*], Karen Tellez-Jacques [a], Brian Pittman [a], Ismene Petrakis [a], Ronald M. Baldwin [a], Gilles Tamagnan [b], John Seibyl [b], Thomas Kosten [c], Julie K. Staley [a]

[a] Yale University School of Medicine and the VACHS, New Haven, CT, United States
[b] Institute for Neurodegenerative Disorders, New Haven, CT, United States
[c] Baylor College of Medicine, Houston, TX, United States

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ABSTRACT

Dopamine (DA) and serotonin (5-HT) transporter availability in heroin users and healthy controls was measured using [^{123}I]β-CIT and SPECT imaging. Heroin users had statistically similar striatal DA and brainstem and diencephalon 5-HT transporter availability compared with controls. No associations between transporter availability and heroin use characteristics were found.

1. Introduction

A core feature of acute administration of opioid drugs of abuse is their activation of brain dopaminergic neurons and increase in striatal dopamine (DA) release (Di Chiara and Imperato, 1988; Wise et al., 1995). With more chronic administration, compensatory changes begin to occur, such as downregulation of DA receptors, transporters and function (Spampinato et al., 1988; Simantov, 1993; Wang et al., 2008) that may promote continued use of opioid drugs. Lower DA transporter availability has been reported in imaging studies in recently detoxified heroin users (Jia et al., 2005) and former heroin users with prolonged abstinence (Shi et al., 2008) compared with controls. However, a postmortem study found no difference in striatal DA transporter levels between actively using heroin users and controls (Kish et al., 2001).

The effects of heroin on serotonin (5-HT) function are not as well researched. Acute opiate administration enhances 5-HT activity (Spampinato et al., 1985; Desole et al., 1996); however, the effects of prolonged opiate use on 5-HT activity are not clear. In postmortem brain of chronic heroin users, striatal levels of 5-HT were slightly elevated, whereas levels of the serotonin metabolite 5-hydroxyindoleacetic acid were significantly decreased compared with levels in controls (Kish et al., 2001), suggesting 5-HT activity may be reduced after prolonged use.

In this study, we used [^{123}I]β-CIT and single photon emission computed tomography (SPECT) brain imaging to measure DA and 5-HT transporter availability in chronic heroin users and healthy controls. [^{123}I] β-CIT binds with high affinity to the presynaptic striatal DA and brainstem and diencephalon 5-HT transporters (Laruelle et al., 1993) with high test–retest reliability (Seibyl et al., 1996, 1997). We hypothesized lower DA and 5-HT transporter availability in subjects with chronic heroin dependence vs. healthy controls.

2. Methods

2.1. Subjects

Eight heroin-dependent subjects (37.0 ± 9.1 years; age range 23–47; 7 men, 1 woman; 6 Caucasian, 2 Hispanic) and eight healthy controls (38.0 ± 9.4 years; age range 26-54; 6 men, 2 women; 8 Caucasian) provided informed consent to participate in the study. Groups were matched for age and smoking status (2 heroin and 2 control subjects were nonsmokers). Eligibility was determined as follows: no use of psychotropic drugs within 3 months prior to the study, no lifetime use of the designer drug "ecstasy" (MDMA), and no significant psychiatric, neurological, or medical problems as determined by physical and psychiatric examinations. Heroin-dependent subjects met the DSM-III-R diagnostic criteria for heroin dependence, had at least a 1-year history of

* Corresponding author. Yale University School of Medicine and the VACHS, 950 Campbell Avenue/116A6, West Haven, CT 06516, United States. Tel.: +1 203 932 5711x3329; fax: +1 203 937 3897.
E-mail address: kelly.cosgrove@yale.edu (K.P. Cosgrove).

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heroin use (subjects reported intravenous and intranasal use), tested positive for heroin on the day of their intake, and were not dependent on any drug other than heroin or nicotine. Within the group of heroin-dependent subjects, one was diagnosed with alcohol abuse, one was diagnosed with cocaine abuse, and one subject tested positive for methadone. Heroin-dependent subjects were currently using and tested positive for heroin with toxicology on the day of their intake evaluation; however, their last use of heroin relative to their SPECT scan was not recorded. All women had a negative pregnancy test prior to radiotracer injection. Heroin use characteristics, including total number of years of heroin use and quantity used per day, were documented during the initial intake.

2.2. [^{123}I]β-CIT SPECT and Magnetic Resonance Imaging

[^{123}I]β-CIT was synthesized as described previously (Baldwin et al., 1993), with a radiochemical purity of >97%. On day 1 of the SPECT study, subjects were given a Lugol's solution approximately 30 min prior to radiotracer administration, to block thyroid uptake of [^{123}I] iodide. [^{123}I]β-CIT was administered by intravenous bolus injection to subjects with chronic heroin use (213.9 ± 35.6 MBq) and healthy controls (223.9 ± 1.3 MBq). SPECT scans (one 24-min emission scan and one 15-min simultaneous transmission and emission scan) were performed on a Picker PRISM 3000 three-headed camera (Phillips, Cleveland, OH) equipped with a low-energy, ultrahigh resolution fan beam collimator (photopeak window 159 keV ± 10%; matrix 128 × 128) with a standardized sensitivity across the field of view. The axial resolution (full width at half maximum) of the camera was 12.2 mm. Blood samples were obtained before radiotracer injection and 24 h after injection to determine blood measures including plasma [^{123}I]β-CIT and protein binding, expressed as free fraction f_P (Baldwin et al., 1993; Gandelman et al., 1994). Subjects were scanned approximately 24 h after radiotracer injection (Laruelle et al., 1994). Magnetic resonance imaging (MRI) studies were performed on a 1.5 Tesla GE Signa device (TR = 25 ms, TE = 5 ms, number of excitations = 2, matrix = 256 × 256 pixels, and field of view = 24 cm).

2.3. Image analysis

SPECT data were reconstructed and attenuation corrected as previously described (Staley et al., 2001). MRIs were coregistered to the SPECT images to provide an anatomical guide for placement of the regions-of-interest using Medx (version 3.4) software (Medical Numerics, Inc., MD). [^{123}I]β-CIT labels DA transporter availability in the striatum and 5-HT transporter availability in the diencephalon and brainstem. The ROIs were: right and left striatum (average of caudate and putamen), diencephalon, brainstem, and right and left cerebellum. Regional brain activities are reported as the average value of right and left hemispheres. The primary outcome measure for regional brain uptake is the binding potential (BP_{ND},) which is proportional to the receptor concentration ($Bmax/K_D$) at equilibrium. BP_{ND} is defined as the ratio of specific to nonspecific binding with the cerebellum as the reference region. The cerebellum has no detectable levels of DA transporters and very low levels of 5-HT transporters (Laruelle et al., 1988; Backstrom et al., 1989; Laruelle and Maloteaux, 1989) that are not measured reliably in vivo (Laruelle et al., 1993). BP_P (ratio of specific binding to total plasma parent) was also evaluated as an outcome measure, but because results were similar between BP_{ND} and BP_P, only BP_{ND} results are described.

2.4. Statistical analysis

DA availability and 5-HT transporter availability were analyzed independently. Striatal DA transporter availability was compared between chronic heroin users and controls using independent *t*-tests. A linear mixed model was used to compare diencephalon and brainstem 5-HT transporter availability (within-subjects factor) between groups (between-subjects factor). The best fitting variance–covariance structure was determined by information criteria. Confidence intervals on the difference between the means were also calculated. Potential associations between brain and heroin use characteristics including total number of years of heroin use and quantity used per day were assessed using correlation analysis. Analyses were performed using SAS, version 9.1 (Cary, NC). Due to the preliminary nature of this report, all significance levels are uncorrected at the $p \leq 0.05$ level.

3. Results

Chronic heroin users had been using heroin for 8.3 ± 8.6 years (mean ± SD; range 1–24 years). They reported using 11.6 ± 5.3 bags of heroin per day (range 6–18 bags/day). There were no differences between groups in blood measures, e.g., total plasma parent or free fraction. There was no significant difference in striatal DA transporter availability between chronic heroin users (7.4 ± 0.90) and controls (6.7 ± 1.15) [$t = -1.33$, $df = 14$, $p = 0.20$, 95% CI_{diff} −1.80, 0.42] (Figs. 1 and 2). There was no significant difference in diencephalon ($t = 2.02$, $df = 14$, $p = 0.06$, 95% CI −0.03, 0.85) or brainstem ($t = 1.33$, $df = 14$, $p = 0.21$, 95% CI −0.17, 0.71) 5-HT transporter availability between chronic heroin users compared with controls (Figs. 1 and 2). There were no significant associations between DA or 5-HT transporter availability and heroin use characteristics including total number of years of heroin use and quantity used per day.

4. Discussion

In this preliminary study, we report statistically similar DA and a trend for lower 5-HT transporter availability in chronic heroin users compared with healthy controls. We did not find associations between DA or 5-HT transporter availability and chronicity of heroin use or amount of heroin used per day in this small sample.

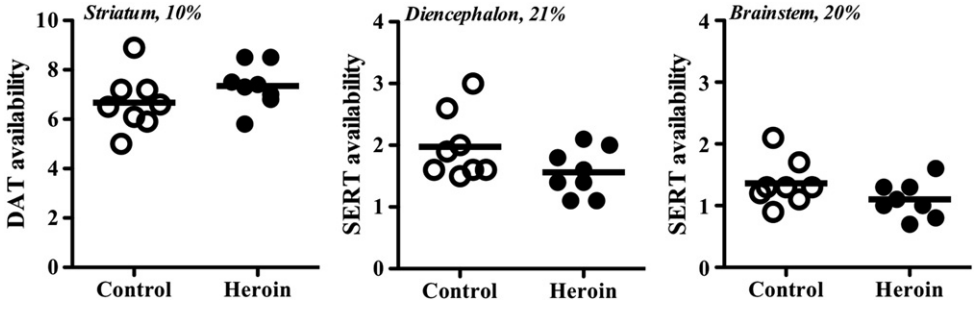

Fig. 1. Striatal DA transporter availability (BP_{ND}) (left panel), and diencephalon (middle panel) and brainstem (right panel) 5-HT transporter availability (BP_{ND}) in control subjects (open circles) and chronic heroin users (filled circles). The percent difference reflects the difference between heroin users and controls in each brain region.