Reductions in Brain 5-HT$_{1B}$ Receptor Availability in Primarily Cocaine-Dependent Humans

David Matuskey, Zubin Bhagwagar, Beata Planeta, Brian Pittman, Jean-Dominique Gallezot, Jason Chen, Jane Wanyiri, Soheila Najafzadeh, Jim Ropchan, Paul Geha, Yiyun Huang, Marc N. Potenza, Alexander Neumeister, Richard E. Carson, and Robert T. Malison

Background: Preclinical evidence implicates the serotonin receptor 5-hydroxytryptamine 1B (5-HT$_{1B}$) in the effects of cocaine. This study explores 5-HT$_{1B}$ in humans by examining receptor availability in vivo in subjects whose primary addiction is cocaine dependence (CD) using positron emission tomography.

Methods: Study participants included 14 medically healthy subjects with CD (mean age = 41 ± 6 years) who were compared with 14 age-matched healthy control subjects (mean age = 41 ± 8 years) with no past or current history of cocaine or other illicit substance abuse. Participants underwent magnetic resonance imaging followed by positron emission tomography with the highly selective 5-HT$_{1B}$ tracer, [^{11}C]P943, for purposes of quantifying regional binding potential. Voxel-based morphometry and gray matter masking also were employed to control for potential partial volume effects.

Results: The [^{11}C]P943 positron emission tomography imaging data in nine candidate regions (amygdala, anterior cingulate cortex, caudate, frontal cortex, hypothalamus, pallidum, putamen, thalamus, and ventral striatum) showed significant or nearly significant reductions of regional binding potential in subjects with CD in three regions: anterior cingulate (−16%, $p < .01$), hypothalamus (−16%, $p = .03$), and frontal cortex (−7%, $p = .08$). Voxel-based morphometry showed significant gray matter reductions in the frontal cortex of subjects with CD. After gray matter masking, statistically significant reductions in the [^{11}C]P943 regional binding potential were either retained (anterior cingulate, −14%, $p = .01$; hypothalamus, −20%, $p < .01$) or achieved (frontal cortex, −14%, $p < .01$). Whole-brain voxel-wise parameter estimation confirmed these results. Secondary analyses were also significant in some regions for years of cocaine and daily tobacco use.

Conclusions: The reductions found in this study suggest that 5-HT$_{1B}$ receptors may contribute to the etiology or expression of CD and potentially represent a target for medication development.

Key Words: 5-HT$_{1B}$, cocaine, human, serotonin, PET, VBM

Cocaine dependence (CD) is a widespread public health problem in the United States and is associated with considerable personal and fiscal costs to both society and the individual. In 2010, the estimated number of current cocaine users in the United States was 1.5 million (1). Despite the significant number of users and complications from abuse and dependence, there is no medication treatment approved by the U.S. Food and Drug Administration for CD. The identification of novel molecular targets that may modulate the effects of cocaine in humans remains a priority. In the current study, we focused on one such molecular target, the serotonin receptor 5-hydroxytryptamine 1B subtype (5-HT$_{1B}$).

The 5-HT$_{1B}$ receptor is an inhibitory G-protein–coupled metabotropic receptor found primarily as presynaptic autoreceptors on 5-hydroxytryptamine (5-HT) neurons and as heteroreceptors on nonserotoninergic neurons (2). Administration of drugs with agonistic or antagonistic properties at 5-HT$_{1B}$ receptors typically inhibits or enhances, respectively, 5-HT activity in the brain (3). Based on autoradiographic work focusing on subcortical structures, the basal ganglia, hippocampus, substantia nigra, and entorhinal cortex all have significant 5-HT$_{1B}$ binding, but regional differences in receptor-mediated G-protein activation in these areas have been described (4).

Multiple preclinical studies have investigated the role of the 5-HT$_{1B}$ receptor in mediating the neurobiological effects of cocaine, but the nature of its role in drug reward remains unclear because of inconsistencies across studies (5). However, several studies have suggested potentiation of the effects of cocaine by the 5-HT$_{1B}$ receptor (6). This effect is thought to occur via 5-HT$_{1B}$ heteroreceptors that have an inhibitory effect on gamma-aminobutyric acid release in the ventral tegmental area, disinhibiting dopaminergic activity and amplifying drug reward mechanisms. Studies focusing on cocaine administration have similarly shown a reinforcement of stimulant effects via the 5-HT$_{1B}$ receptor (7,8). In contrast, 5-HT$_{1B}$ knockout mice have shown an increased sensitization to cocaine and stimulants that inhibit reinforcement (9), whereas pharmacologic activation has paradoxically shown a reduction in stimulant use with 5-HT$_{1B}$ receptors in the nucleus accumbens (10). More recent studies have focused on potential explanations for seemingly paradoxical effects, implicating variables such as drug dose, brain region, and length of time since last use as potential explanations (11,12). Taken together, the preclinical data indicate that 5-HT$_{1B}$ receptor function in brain reward circuitry contributes to cocaine use and cocaine responsiveness, albeit in a complex and incompletely understood fashion.

In humans, genetic studies have found associations between 5-HT$_{1B}$ receptor polymorphisms and substance abuse, suggesting

From the Departments of Psychiatry (DM, ZB, BPi, JC, JW, PG, MNP, RTM) and Diagnostic Radiology (DM, BPl, J-DG, SN, JR, YH, REC), Yale University, New Haven; Bristol-Myers Squibb (ZB), Wallingford, Connecticut; and Department of Psychiatry (AN), New York University School of Medicine, New York, New York.

Address correspondence to David Matuskey, M.D., Yale School of Medicine, 801 Howard Avenue, New Haven, CT 06520; E-mail: david.matuskey@yale.edu.

Received Apr 11, 2013; revised Sep 30, 2013; accepted Nov 12, 2013.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.11.022

that modified 5-HT_{1B} receptor activity may be a contributing factor to increased susceptibility to addiction (13). To understand better the potential role of 5-HT_{1B} receptors in CD, we employed the newly available 5-HT_{1B} positron emission tomography (PET) radioligand [^{11}C]P943 to image receptor availability in individuals with CD compared with healthy control (HC) subjects.

Animal work has indicated that knocking out 5-HT_{1B} receptors in mice is associated with increased cocaine self-administration (9), and 5-HT_{1B} receptor overexpression in rats is associated with stress-related stimulant responsiveness (14); these data suggest that individuals with CD would show either increases or decreases in 5-HT_{1B} receptors. Given this ambiguity and the unknown effects of cocaine on the 5-HT_{1B} receptor in humans, the current work could provide evidence for a mechanism in humans and future development by showing either an increase in 5-HT_{1B} receptor availability in CD, which would support a model of 5-HT_{1B} sensitization in CD, or a decrease in 5-HT_{1B} receptor availability, which would support a desensitized model of 5-HT_{1B} within reward-related brain regions in chronic CD.

Methods and Materials

Subjects

Study participants included 14 medically healthy, non–treatment seeking subjects with CD (CD subjects) who were compared with previously reported age-matched HC subjects (15,16). All CD and HC scans occurred over 3 years, and the mean scan time between groups was 1 year, 4 months. In the 3 months preceding scans, significant nicotine (with the exception of one subject), alcohol, or illicit substance use was not present in HC subjects. Based on our prior work showing statistically significant effects of age (declining) but not sex or race (17) with [^{11}C]P943 availability, CD subjects and HC subjects were matched as a group for age (41 $\pm$ 6.2 years vs. 41 $\pm$ 7.8 years; $p = .73$) but not sex (4/10 vs. 5/9 for women/men) or race (3/9/1/1 vs. 10/3/0/1 for Caucasian/African-American/Hispanic/other).

Eligibility for the study was confirmed through comprehensive psychiatric histories and clinical semistructured interviews (e.g., Mini-International Neuropsychiatric Interview or Structured Clinical Interview for DSM-IV, Axis I disorders), a physical examination with medical history, routine laboratory studies, pregnancy tests, urine toxicology, and electrocardiograms. Measures of clinical data for secondary analyses included the Hamilton Depression Rating Scale (18), Barratt Impulsiveness Scale (19), State Trait Anxiety Inventory (20), and Childhood Trauma Questionnaire (21).

Criteria for exclusion from the study included evidence of a diagnosis of current or lifetime severe Axis I psychiatric disorder (e.g., schizophrenia or bipolar disorder), current or past serious medical or neurologic illness (including a history of head injury with loss of consciousness), current pregnancy (as documented by pregnancy testing at screening and on the day of the PET study), breastfeeding, and general magnetic resonance imaging (MRI) exclusion criteria. All subjects were medication-free for a minimum of 6 weeks at the time of scanning.

The CD subjects met DSM-IV criteria for CD; were 18–50 years old; used a high-potency, rapid-onset form of cocaine (i.e., smoked or intravenous); reported a history of regular and recent use; and provided objective evidence of current use (i.e., benzoylecgonine positivity) on urine toxicology testing before admission into the study. Clinical characteristics of the CD subjects are presented in Table 1.

The study was performed under protocols approved by the Yale Human Investigation Committee, the Human Subjects Subcommittee of the Veterans Affairs Connecticut Healthcare System, the Yale University Radiation Safety Committee, the Yale–New Haven Hospital Radiation Safety Committee, and the Yale MRI Safety Committee. Subjects were recruited from New Haven and surrounding areas by advertisement and word of mouth referrals. Written informed consent was obtained from all participants after a full explanation of study procedures (including risks and potential benefits).

Radiochemistry

The radioligand [^{11}C]P943 (*R*-1-[4-(2-methoxy-isopropyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)benzyl]-pyrrolidin-2-one) was prepared as previously described by *N*-methylation of the precursor with [^{11}C]methyl triflate, using the PETtrace cyclotron and a TRACERlab FX C automated synthesizer (GE Healthcare, Chalfont St. Giles, United Kingdom) (22). The GE Microlab was employed in some of the preparations as a source of the requisite [^{11}C]methyl iodide.

Table 1. Characteristics of Subjects with Cocaine Dependence

CD Subjects ($N = 14$)	Demographics				
Age (Years)	41 (6)				
Gender (Female/Male)	4/10				
Ethnicity: C, AA, H, Other	3 C/9 AA/1 H/1 other				
Clinical Use Characteristics, Mean (SD)					
Years of cocaine use	21 (7)				
Weekly cocaine use (U.S. dollars)	652 (617)				
Weekly cocaine use (g)	4.6 (4.4)				
Weekly alcohol use (drinks)	16 (13)				
Daily nicotine use (cigarettes)	10 (7)				
Cannabis use in the last week (joints)	3 (7)				
Secondary Measures, Mean Scores (SD)					
State Trait Anxiety Inventory State and Trait subscales	41 (11)		45 (12)		
Barratt Impulsiveness Scale	74 (14)				
Hamilton Rating Scale for Depression	5 (5)				
Childhood Trauma Questionnaire raw scores: EA, PA, SA, EN, PN	11 (4) EA	10 (4) PA	7 (4) SA	13 (4) EN	10 (4) PN

AA, African-American; C, Caucasian; CD, cocaine dependence; EA, emotional abuse; EN, emotional neglect; H, Hispanic; PA, physical abuse; PN, physical neglect; SA, sexual abuse.