Sex Differences in Striatal Dopamine Release in Healthy Adults

Cynthia A. Munro, Mary E. McCaul, Dean F. Wong, Lynn M. Oswald, Yun Zhou, James Brasic, Hiroto Kuwabara, Anil Kumar, Mohab Alexander, Weiguo Ye, and Gary S. Wand

Background: *Sex differences in addictive disorders have been described. Preclinical studies have implicated the striatal dopamine system in these differences, but human studies have yet to substantiate these findings.*

Methods: *Using positron emission tomography (PET) scans with high-specific-activity [^{11}C] raclopride and a reference tissue approach, we compared baseline striatal dopamine binding potential (BP) and dopamine release in men and women following amphetamine and placebo challenges. Subjective drug effects and plasma cortisol and growth hormone responses were also examined.*

Results: *Although there was no sex difference in baseline BP, men had markedly greater dopamine release than women in the ventral striatum. Secondary analyses indicated that men also had greater dopamine release in three of four additional striatal regions. Paralleling the PET findings, men's ratings of the positive effects of amphetamine were greater than women's. We found no sex difference in neuroendocrine hormone responses.*

Conclusions: *We report for the first time a sex difference in dopamine release in humans. The robust dopamine release in men could account for increased vulnerability to stimulant use disorders and methamphetamine toxicity. Our findings indicate that future studies should control for sex and may have implications for the interpretation of sex differences in other illnesses involving the striatum.*

Key Words: Addiction, amphetamine, binding potential, dopamine release, gender, sex differences, striatum

Men and women differ in their vulnerability to addictive disorders (Brady and Randall 1999; Brecht et al 2004). Sex differences in the prevalence of psychostimulant drug dependence in general, and in methamphetamine use in particular, have been identified (Brady & Randall, 1999; Brecht et al 2004; Substance Abuse and Mental Health Services Administration 2005). Moreover, men compared with women are more susceptible to methamphetamine toxicity (Dluzen et al 2003; Miller et al 1998). Except for N-methyl-D-aspartate antagonists, the amphetamines are the only class of addictive drugs known to be associated with depletion of striatal dopamine (McCann and Ricaurte 2004).

Because the ventral striatum is well recognized as an important site for reward in addictive behaviors, attempts to elucidate the neurobiology of sex differences underlying addiction have focused on gender differences in this region. These investigations have revealed the nucleus accumbens, an area within the ventral striatum, as principally important in the rewarding effects of drugs of addiction (for a review, see Di Chiara et al 2004). In preclinical studies, sex differences in the striatal dopamine system have been observed (Dluzen 2004; Pohjalainen et al 1998). Rodent studies have documented sex differences in the depletion, turnover, and extracellular accumulation of dopamine following methamphetamine administration (Dluzen and Ramirez 1985; Hruska and Silbergeld 1980; Shimizu and Bray 1993; Xiao and Becker 1994; Yu and Wagner 1994).

In addition to addictive disorders, sex differences in the clinical presentation and age of onset of or vulnerability to other neuropsychiatric illnesses that involve the striatum, such as Parkinson's disease (Scott et al 2000), schizophrenia (Aleman et al 2003), Huntington's disease (Tamir et al 1969), obsessive–compulsive disorder (Bogetto et al 1999), and Tourette's syndrome (Kidd et al 1980), have been described. Whether these differences might also be related to striatal dopamine is not known, however.

The purpose of this study was to test the hypothesis that the magnitude of dopamine, subjective, and neuroendocrine responses to amphetamine is greater in men than in women. The hypothesis was studied by measuring striatal binding potential using the D_2/D_3 dopamine (DA) receptor radioligand [^{11}C]raclopride with positron emission tomography (PET). The ventral striatum was the primary volume of interest.

Methods and Materials

Forty-three healthy individuals (28 men, 15 women), aged 18 to 29 years, were recruited for participation by newspaper advertisements and fliers posted in the Baltimore metropolitan area. Under the auspices of the Johns Hopkins School of Medicine Institutional Review Board, all participants provided written informed consent after receiving oral and written descriptions of study procedures and aims. Subject assessment included a medical history and physical examination performed by a physician, blood chemistry profile, complete blood count, liver and renal function tests, electrocardiogram, urinalysis, alcohol breathalyzer test, and urine toxicology screen. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al 1994) was administered by a master's-level interviewer to identify *Diagnosis and Statistical Manual* (4th edition; DSM-IV) Axis I psychiatric diagnoses. Exclusionary criteria included 1) presence of DSM-IV Axis I disorder; 2) treatment in the last 6 months with antidepressants, neuroleptics, sedative hypnotics, glucocorticoids, appetite suppressants, sex hormones, or opiate or dopamine medications; 3) use of any prescription medications

From the Department of Psychiatry and Behavioral Sciences (CAM, MEM, DFW, LMO, GSW), Russell H. Morgan Department of Radiology and Radiological Sciences (DFW, YZ, JB, HK, NK, MA, WY), and Department of Medicine (GSW), The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Address reprint requests to Gary Wand, M.D., Department of Medicine, The Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 863, Baltimore, MD 21205; E-mail: gwand@jhmi.edu.

Received November 30, 2005; revised January 10, 2006; accepted January 13, 2006.

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2006.01.008

within the past 30 days; 4) women currently using a hormonal method of birth control, hormone replacement therapy, currently pregnant or lactating women, women with oligo- or amenorrhea; 5) medical conditions, including history of seizure disorder or closed head trauma; 6) unable to provide clean urine drug screens at intake or during study participation; 7) report of drinking more than 30 alcoholic drinks per month or illicit drug use within the 30 days before participation; and 8) current smoking. Following screening procedures, eligible subjects were scheduled for admission to the Johns Hopkins General Clinical Research Center (GCRC) to complete the study.

Behavioral Measures

Measures of psychiatric symptoms and perceived stress were administered during the initial assessment interview. These assessments included the following: State–Trait Anxiety Inventory (STAI; Spielberger 1983), Beck Depression Inventory (2nd edition; BDI-II; Beck et al 1996), Brief Symptom Inventory (BSI; Deragotis and Melisaratos 1993), Perceived Stress Scale (PSS; Cohen et al 1983), Life Experiences Survey (LES; Sarason et al 1978), and the Combined Hassles and Uplifts Scale (Lazarus and Folkman 1989).

Analog Rating Scales (Bigelow and Walsh, 1998)

At 5 min before each scan and 3, 6, 10, 15, 25, 55, and 85 min during scans, subjects were asked to rate verbally, on a 5-point scale (0 = least, 4 = most), the degree to which they were experiencing each of 10 possible drug effects. Positive effects included "high," "rush," "good effects," "liking," and "desire for drug." Negative effects included "fidgety," "anxious," "dizziness," "dry mouth," and "distrust."

Magnetic Resonance Imaging Assessment and Mask Fitting

Use of magnetic resonance imaging (MRI) allowed coregistration of the emission images so that anatomically accurate volumes of interest (VOIs) could be drawn (see VOI Definition). To minimize head motion during MRI acquisition, each subject was fitted for a thermoplastic mask modeled to his or her face before admission to the General Clinical Research Center (GCRC). The MRIs were acquired with an SPGR (spoiled gradient) sequence (TE = 5, TR = 25, flip angle = 40°, slice thickness = 1.5 mm, image matrix = 256 × 192, field of view = 24 cm) for anatomic identification of brain structures, and a double echo (proton density and T2-weighted, 5-mm-thick slices) sequence, used as a diagnostic scan and to segment extracerebral cerebrospinal fluid.

PET Procedures and Data Acquisition

Subjects were admitted to the GCRC in-patient unit the day before the PET procedures. They were instructed not to ingest any alcohol, drugs, or over-the-counter medications for 48 hour before admission. Laboratory studies at admission included a urine toxicology screen, alcohol breathalyzer test, hematocrit, electrolyte panel, and urine pregnancy screen for women. A calorie-controlled, caffeine-free breakfast was provided to subjects before the PET procedures. Beginning at 8:30 AM, subjects underwent two consecutive 90-min PET scans with [^{11}C] raclopride. This radioligand is a benzamide antagonist at D2 and D3 receptors, previously shown to be sensitive to stimulant-induced changes in brain dopamine concentration (Endres et al 1997; Volkow et al 1994). At the beginning of each scan, a high-specific-activity intravenous bolus injection of approximately 18 mCi [^{11}C] raclopride was administered. The first scan was preceded at −5 min by an intravenous injection of saline; the second scan was preceded at −5 min by .3 mg/kg amphetamine, each delivered over 3 min. The amphetamine free base used in this study was 73.4% of the amphetamine sulfate. The .3 mg/kg of amphetamine sulfate given to each subject is .22 mg/kg amphetamine free base as a bolus over 3 min, starting 5 min before radiotracer injection of bolus [^{11}C] raclopride. The scanning image protocol consisted of up to 30 scan acquisitions in three-dimensional (3D) mode, starting from a 15-sec duration and increasing to 6 min in length over a 90-min period. All images were acquired on the 3D GE Advance whole body PET scanner and were preceded by a 10-min attenuation scan employing a rotating germanium-68 source. Subjects were under continuous cardiovascular monitoring during the scans. They were permitted to arise briefly after the first scan and were repositioned on the scanner table for the second. Subjects were escorted back to the GCRC following the scans. Before discharge, they were evaluated by a physician.

Volumes of Interest Definition

Volumes of interest (VOIs) were defined using interactive segmentation software on spoiled gradient (SPGR) MRI volumes for the caudate nucleus and the putamen bilaterally to obtain regional BP values. The software program allowed for the selection of upper and lower MRI intensity thresholds to delineate striatal structures from surrounding structures and required minimal hand drawing. The ventral striatum (VS) was automatically defined on the SPGR MRI volume, reoriented so the plane containing the midline separating the left and right halves of the brain is orthogonal to the horizontal plane containing the points representing the anterior commissure and the posterior commissure (anterior commissure–posterior commissure plane). On each coronal slice, the portion of the striatal volumes of interest ventral to the line crossing the ventral corner of the lateral ventricle and perpendicular to the bisector of the internal capsule defined the VS (Baumann et al 1999). The MRI volumes were spatially aligned to the PET volumes (averaged volumes across frames taken between 30 and 90 min after tracer-injection) using information theory (Collignon et al 1995) and implemented in SPM2b software (Friston 2002; see http://www.fil.ion.ucl.ac.uk/spm/). The same transformation parameters were applied to transfer VOIs from MRI space to PET space. The cut-off level of VOIs in PET spaces was set at .5; the value of VOI voxels in the MRI spaces was set to 1, and that of remaining voxels was set to 0.

Modeling of PET Outcome Measures

The binding potential (BP) = Bmax/Kd was used to measure [^{11}C]raclopride D2-like receptor-specific binding (Wong 2002). The BP used in this work is based on a simplified reference tissue model (SRTM), which is based on the BP defined as k3/k4 or $(DV\_total - DV\_f + n.(BP = f2B'max/Kd$, where *f2* is the free fraction of tracer in brain tissue, *B'max* is the available receptor density for tracer binding in *nM*, and *Kd* is the equilibrium dissociation constant in NM; see Gunn et al 2001). The cerebellum was the reference tissue used to estimate BP (Lammertsma and Hume 1996). Because the cerebellum is nearly devoid of D2 and D3 receptors, specific binding of [^{11}C]raclopride is thought to be negligible in the cerebellum. A linear regression with spatial constraint algorithm was used to fit SRTM model to measured voxel kinetics, and parametric BP images were generated (Zhou et al 2003). The VOIs defined on MRI images were transferred to BP images to obtain VOI BP values. The percent change in BP from baseline was used to estimate dopamine release as ((BPplacebo-BPamphetamine)/BPplacebo) × 100, with lower BP values