Ventral Striatum Binding of a Dopamine $D_{2/3}$ Receptor Agonist But Not Antagonist Predicts Normal Body Mass Index

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Background: Positron emission tomography research has shown that dopamine $D_{2/3}$ receptor ($D_{2/3}R$) availability is negatively correlated with body mass index (BMI) in obese but not in healthy subjects. However, previous positron emission tomography studies have not looked specifically at the ventral striatum (VS), which plays an important role in motivation and feeding. Furthermore, these studies have only used antagonist radiotracers. Normal-weight rats given free access to high-fat diets demonstrate behavioral sensitization to $D_{2/3}R$ agonists but not to antagonists. Sensitization is associated with increased $D_{2/3}R$ affinity, which affects binding of agonists but not antagonists.

Methods: We examined the association between BMI within the nonobese range (18.6–27.8) and $D_{2/3}R$ availability in the VS with the use of the agonist radiotracer [^{11}C]-(+)-PHNO ($n = 26$) and the antagonist [^{11}C]-raclopride ($n = 35$) in healthy humans.

Results: In the VS, we found a positive correlation between BMI and [^{11}C]-(+)-PHNO binding but no relationship with [^{11}C]-raclopride binding. Secondary analyses revealed no relationship between BMI and binding in the dorsal striatum with either radiotracer.

Conclusions: We propose that in nonobese individuals, higher BMI may be associated with increased D_2R affinity in the VS. This increased affinity may potentiate the incentive salience of food cues and counteract the effects of satiety cues, thereby increasing feeding.

Key Words: Body mass index, dopamine D_2 receptor, food addiction, obesity, PET, ventral striatum

Obesity is one of the leading causes of preventable death, reaching pandemic levels in the United States and affecting 35.7% of adults and 17% of youth (1). A growing perspective conceptualizes overeating as a food addiction. Evidence suggests that striatal dopamine, involved in reward, motivation, and food consumption, is altered in obesity (2). Addiction-like dopaminergic dysfunction, specifically reduced striatal dopamine $D_{2/3}$ receptor ($D_{2/3}R$) availability, has been observed in rat models of obesity (3,4) and in obese humans in vivo (5–8).

A positron emission tomography (PET) study with the use of the antagonist radiotracer [^{11}C]-raclopride found that lower striatal $D_{2/3}R$ availability predicted higher body mass index (BMI) in severely obese individuals but not in nonobese subjects (5). This is contrary to findings in nonobese rats given free access to regular chow, in which lower [^{11}C]-raclopride binding in the ventral striatum (VS) predicted both greater body weight and preference for cocaine (9).

The VS, including the nucleus accumbens, plays an integral role in processing reward cues and motivating behavior to seek rewards such as palatable foods (2). Thus, changes in $D_{2/3}R$ availability in the VS may alter the rewarding properties and consumption of food, affecting body weight. Left VS activation in response to food cues predicts weight gain in healthy females (10) and correlates with dopamine release in response to reward cues (11). These studies suggest that VS activation and $D_{2/3}R$ availability may show changes related to normal BMI.

Previous PET studies of BMI have not specifically examined $D_{2/3}R$ availability in the VS; instead, region of interest (ROI) analyses of the whole striatum (5), the caudate and putamen (6,7), or a voxel-based approach (7) were used. Furthermore, previous PET studies have only used the $D_{2/3}R$ antagonist radiotracer [^{11}C]-raclopride. Normal-weight rats given free access to high-fat diets demonstrate behavioral sensitization to direct and indirect $D_{2/3}R$ agonists but not antagonists (12). This sensitization is also observed in rodent models of drug addiction (13) and is associated with increased D_2R affinity (14–16).

This suggests that, like cocaine and amphetamine, exposure to high-fat foods may increase the affinity for dopamine at D_2Rs. It has been observed in vitro that agonist radiotracers are more sensitive to changes in D_2R affinity than are antagonist radiotracers. Increased D_2R affinity, indexed by increased agonist radiotracer binding, has been found to co-occur with no change and even decreases in total D_2R binding sites given amphetamine sensitization (14). Consequently, differences in BMI within the normal range may be related to differences in VS binding of dopamine agonists but not antagonists.

This study investigated the relationship between healthy BMI and $D_{2/3}R$ availability in the VS in humans, with the use of both the agonist radiotracer [^{11}C]-(+)-PHNO and the antagonist [^{11}C]-raclopride. Understanding the dopaminergic correlates of normal BMI will help elucidate the deficits seen in obesity and may inform current models of food addiction as well as the development of novel prevention and treatment strategies.

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Methods and Materials

Subjects

All participants were right-handed and free of any major medical or psychiatric disorder as determined by clinical interview, the Mini-International Neuropsychiatric Interview, basic laboratory tests, and electrocardiography. Although obesity was not an exclusion criteria, given our exclusion of major medical conditions (such as diabetes or heart disease), we sampled only persons within a normal BMI range (<30). Participants were required to have a negative urine screen for drugs of abuse and/or pregnancy at inclusion and before each PET scan. Participants were also asked to abstain from alcohol or caffeine 3 days before the PET scans. Only data collected from nonsmoking participants was analyzed for this study. The sample analyzed for the current study was collected by our laboratory from various PET studies that were approved by the Research Ethics Board of the Centre for Addictions and Mental Health, Toronto. All participants provided written informed consent.

PET Imaging

The radiosynthesis of [^{11}C]-(+)-PHNO and [^{11}C]-raclopride and the acquisition of PET images have been described in detail elsewhere (17–19). Briefly, images were acquired with the use of a high–resolution, head-dedicated PET camera system (CPS-HRRT; Siemens Molecular Imaging, Munich, Germany), which measures radioactivity in 207 brain slices with a thickness of 1.2 mm each. The in-plane resolution was ~2.8 mm full-width at half-maximum. Transmission scans were acquired with the use of a ^{137}Cs ($T_{1/2}$ = 30.2 years, energy = 662 KeV) single-photon point source to provide attenuation correction, and the emission data were acquired in list mode. The raw data were reconstructed by filtered back-projection. The mean radioactivity dose of [^{11}C]-(+)-PHNO (n = 26) was 8.96 (±1.68) mCi, with a specific activity of 1009.44 (±289.35) mCi/μmoL. The mean radioactivity dose of [^{11}C]-raclopride (n = 35) was 9.22 (±2.49) mCi, with a specific activity of 1133.39 (±433) mCi/μmoL. [^{11}C]-(+)-PHNO scanning data were acquired for 90 min after injection. Once scanning was complete, the data were re-defined into 30 frames (1–15 of 1–min duration and 16–30 of 5–min duration). [^{11}C]-raclopride data were acquired for 60 min and redefined into 28 frames (1–5 of 1-min duration, 6–25 of 2-min duration, and 26–28 of 5-min duration).

Image Analysis

The ROI-based analysis for [^{11}C]-(+)-PHNO and [^{11}C]-raclopride has been described in detail elsewhere (20). Briefly, time-activity curves (TACs) from ROIs were obtained from the dynamic PET images in native space with reference to each subject's coregistered magnetic resonance image (MRI). The coregistration of each subject's MRI to PET space was performed with the use of the normalized mutual information algorithm (21) as implemented in SPM2 (SPM2, The Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm). The TACs were analyzed by means of the Simplified Reference Tissue Method (SRTM) (22), with the cerebellum used as the reference region, to derive a quantitative estimate of binding: binding potential nondisplaceable (BP_{ND}). The basis function implementation of the SRTM (23) was applied to the dynamic PET images to generate parametric voxelwise BP_{ND} maps by means of PMOD (v2.7; PMOD Technologies, Zurich, Switzerland). These images were spatially normalized into Montreal Neurological Institute (MNI) brain space by nearest neighbour interpolation with a voxel size fixed in 2 × 2 × 2 mm^3 by means of SPM2. Regional BP_{ND} estimates were then derived from ROIs defined in MNI space. The ventral striatum and dorsal striatum (dorsal caudate, hereafter caudate; dorsal putamen, hereafter putamen) were defined according with Mawlawi *et al.* (24). The definition was made over the participant's MRI slices oriented in the coronal plane. The VS (inferiorly), caudate, and putamen (superiorly) were defined by a line joining the intersection between the outer edge of the putamen with a vertical line going through the most superior and lateral point of the internal capsule and the center of the portion of the anterior commissure (AC). This line was extended to the internal edge of the caudate. The other boundaries of the VS were visually determined by its dense gray signal and were easily distinguishable from the adjacent structures. The VS was sampled from the anterior boundary of the striatum to the level of the AC coronal plane. The caudate also was sampled from its anterior boundary to the AC coronal plane. Thus, for the VS, the sampled region included the ventral and rostral part of the striatum, with reference to AC having the brain horizontal to the AC-PC line. For the caudate, the sampled region included the dorsal part of the head of the caudate and the anterior third of the body of the caudate. The putamen was sampled from its anterior to posterior boundaries in slices posterior to the AC plane. For [^{11}C]-raclopride scans, BP_{ND} in the substantia nigra ROI was not obtainable because binding in this region falls within noise levels (20).

Statistical Analysis

Statistical analyses were conducted with the use of SPSS (v.12.0; SPSS, Chicago, Illinois) and GraphPad (v.5.0; GraphPad Software, La Jolla California). Pearson product-moment correlation coefficients were calculated to examine the relationship between BMI and BP_{ND} in the ROIs. Normality of variables was determined by means of the D'Agostino-Pearson test. Student t test and Fisher's exact test were used where appropriate. The significance level for all testes was set at $p < .05$ (two-tailed).

Results

Data from 46 healthy volunteers were analyzed, some of which have been reported previously (20,25,26). Twenty-six subjects were scanned with [^{11}C]-(+)-PHNO and 35 subjects were scanned with [^{11}C]-raclopride. A subgroup of these subjects (n = 15) were scanned with both radiotracers in a counterbalanced order, at least 3 hours apart. BMI was calculated as kg/m^2 (Table 1). There was no difference in the time of day at which the [^{11}C]-(+)-PHNO and [^{11}C]-raclopride scans were acquired, neither for the full samples (t_{59} = .16, p = .87) nor for the subsample scanned with both tracers (t_{28} = .97, p = .34). Within the full sample of persons scanned with [^{11}C]-(+)-PHNO, BMI was not related to age (r = .27, p = .18) nor differed by sex (t_{24} = .42, p = .66). Within the full sample of persons scanned with [^{11}C]-raclopride, BMI was not related to age (r = .21, p = .23) nor differed by sex (t_{33} = .21, p = .84).

The BP_{ND} of [^{11}C]-(+)-PHNO in the VS was significantly correlated with BMI (r = .51, p = .008) in the full sample (n = 26) (Figure 1). This corresponded to a large effect size (27), with a shared variance of 26% (r^2 = .26). Neither age (r = .14, p = .50) nor sex (r = .02, p = .92) was related to BP_{ND} in the VS. Given potential hemisphere differences (10,11), we tested for a hemisphere effect. Whereas BMI was correlated with BP_{ND} in the left (r = .40, p = .04) and right (r = .58, p = .002) hemispheres, a dependent-correlations