Brain dopamine and obesity

Gene-Jack Wang, Nora D Volkow, Jean Logan, Naomi R Pappas, Christopher T Wong, Wei Zhu, Noelwah Netusil, Joanna S Fowler

Summary

Background The cerebral mechanisms underlying the behaviours that lead to pathological overeating and obesity are poorly understood. Dopamine, a neurotransmitter that modulates rewarding properties of food, is likely to be involved. To test the hypothesis that obese individuals have abnormalities in brain dopamine activity we measured the availability of dopamine D2 receptors in brain.

Methods Brain dopamine D2 receptor availability was measured with positron emission tomography (PET) and [C-11]raclopride (a radioligand for the dopamine D2 receptor). Bmax/Kd (ratio of the distribution volumes in striatum to that in cerebellum minus 1) was used as a measure of dopamine D2 receptor availability. Brain glucose metabolism was also assessed with 2-deoxy-2[18F]fluoro-D-glucose (FDG).

Findings Striatal dopamine D2 receptor availability was significantly lower in the ten obese individuals (2.47 [SD 0.36]) than in controls (2.99 [0.41]; p<0.0075). In the obese individuals body mass index (BMI) correlated negatively with the measures of D2 receptors (r=0.84; p=0.002); the individuals with the lowest D2 values had the largest BMI. By contrast, neither whole brain nor striatal metabolism differed between obese individuals and controls, indicating that striatal reductions in D2 receptors were not due to a systematic reduction in radiotracer delivery.

Interpretation The availability of dopamine D2 receptor was decreased in obese individuals in proportion to their BMI. Dopamine modulates motivation and reward circuits and hence dopamine deficiency in obese individuals may perpetuate pathological eating as a means to compensate for decreased activation of these circuits. Strategies aimed at improving dopamine function may be beneficial in the treatment of obese individuals.

Introduction

The prevalence of obesity is increasing worldwide, which has resulted in a significant increase in morbidity and mortality. Considerable efforts have been devoted to the development of weight-control medications that target neurotransmitters in the brain that regulate food intake.1 Several neurotransmitters (dopamine, GABA, norepinephrine, serotonin) as well as peptides and aminoacids are involved in the regulation of food intake.2 Of particular interest is dopamine since this neurotransmitter seems to regulate food intake3 by modulating food reward via the meso-limbic circuitry of the brain.4 In fact, drugs that block dopamine D2 receptors increase appetite and result in significant weight gain5 whereas drugs that increase brain dopamine concentration are anorexigenc.6 The involvement of dopamine in pathological eating and obesity is poorly understood. Studies in animals have shown that in genetically obese mice (ob/ob), dopamine agonists normalised body weight.8 In human beings, studies have shown a higher prevalence of the Tag I A 1 allele for the dopamine D2 receptors, which is linked with lower amounts of dopamine D2 receptors9 in obese individuals.10 Studies have also shown that genetic variants of the human obesity gene, which predict the body mass index (BMI), interact with the dopamine D2-receptor gene.11 However, the involvement of brain dopamine D2 receptors in obesity has not been directly assessed.

The purpose of this study was to assess if there are differences in brain dopamine D2 receptors in severely obese individuals. The dopamine system was assessed with [C-11]raclopride (radiotracer that binds to dopamine D2 receptors12) with positron emission tomography (PET). In parallel, we also measured regional brain glucose metabolism in these individuals with PET and 2-deoxy-2[18F]fluoro-D-glucose (FDG).13

Methods

Study design

Written informed consent was obtained from each participant after the methodology of the experiment was fully explained. Studies were approved by the Institutional Review Board at Brookhaven National Laboratory.

Obese individuals were selected from a pool of people with a BMI greater than 40 kg/m2 who responded to an advertisement. All were initially screened by telephone and then assessed as outpatients and excluded if they had: (1) current or past psychiatric or neurological disease; (2) head trauma with loss of consciousness for more than 30 min; (3) hypertension, diabetes, or medical conditions that may alter cerebral functioning; (4) used anorexic medications or surgical procedures for weight loss in the past 6 months; (5) used prescription medications in the past 4 weeks; and (6) past or present history of alcohol or substance abuse. Pre-scan urine toxicological tests ensured the absence of psychoactive drug use. All individuals were non-smokers, except one control who was a light smoker. The obese individuals were drug naive and were not on any medication (although three obese individuals took anorexic medication more than 10 years ago as part of a trial [for 1–2 weeks]). Individuals were instructed to discontinue any over-the-counter medication 1 week before the scan.

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PET Imaging

PET scans were done with a CTI-931 (Computer Technologies, Incorporated, Knoxville, USA) tomograph (resolution 6x6x6.5 mm full width half maximum (FWHM), 15 slices). Individuals were scanned with [C-11]raclopride and eight of ten individuals were also scanned with FDG. Procedures for positioning of individuals, scanning protocol, and arterial blood sampling were described previously.\textsuperscript{15,16} Briefly, for [C-11]raclopride, dynamic scans were started immediately after intravenous injection of 4–10 mCi (specific activity >0.25 Ci/μmol at time of injection) for a total of 60 min.\textsuperscript{17} For FDG, a 20 min emission scan was obtained beginning 35 min after injection of 4–5 mCi of FDG. Arterial blood samples were obtained and were used to measure plasma radioactivity and plasma glucose concentration. Metabolic images were computed as described previously.\textsuperscript{18}

Data

Regions of interest in striatum and cerebellum were drawn directly on an averaged emission image (summation of images obtained between 10 min and 60 min for [C-11]raclopride).\textsuperscript{12} Regions of interest for striatum were obtained bilaterally from the planes where they were best identified (two slices). Right and left cerebellar (two slices) regions were obtained in the two planes 1.0 cm and 1.7 cm above the canthomeatal line. These regions were then projected into the dynamic images to generate time activity curves for striatum and cerebellum. We calculated average values for the striatal and cerebellar regions from the different slices where the regions were obtained. The time-activity curves for tissue concentration along with the time-activity curves for unchanged tracer in plasma were used to calculate the distribution volume (mL/gm) and the blood-to-tissue transport constant (K1) in striatum and cerebellum by means of a graphic analyses technique for reversible systems (Logan Plots).\textsuperscript{17} The measure Bmax/Kd, obtained as the ratio of the distribution volume in striatum to that in cerebellum minus 1, was used to quantify the dopamine D2 receptor availability (Bmax/Kd: 2.47 ± 0.36) in striatum and in cerebellum of controls did not differ from that of obese individuals (table 1). However, obese individuals had significantly lower measures of striatal dopamine D2 receptor availability (Bmax/Kd: 2.47 ± 0.36) than controls (2.99 ± 0.41); difference 0.52 (0.17), p < 0.0075; figure 1). The measure of striatal dopamine D2 receptor availability (Bmax/Kd) had a normal distribution. With this measure as the dependent variable, an intensive model fitting (both linear and non-linear) effort showed that the best regression models differed between the obese group and the controls. For the obese individuals, the best model was the simple linear regression model with BMI as

<table>
<thead>
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<th>Parameters/regions</th>
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<td>Bmax/Kd striatum</td>
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<td>2.47 (0.36)</td>
<td>0.16–0.88</td>
</tr>
</tbody>
</table>

Data are mean (SD). $K_1$ = transfer constant of radiotracer from plasma to tissue. Bmax/Kd = ratio of distribution volume in striatum to cerebellum minus 1. *Controls vs obese individuals p < 0.0075.

Table 1: Average K1 distribution volume (mL/gm), and Bmax/Kd of [C-11]raclopride of obese individuals and controls

Results

Ten severely obese individuals (5 women and five men; mean age 38.9 [SD 7.3] years; age range 26–54 years; BMI range 42–60, mean 51.2 [SD 4.8] kg/m²; body weight 125–177 kg) were selected. The controls were three women and seven men (age range 25–45 years; mean 37.5 [SD 5.9] years; BMI range 21–28, mean 24.7 [SD 2.6] kg/m²; body weight 55–90 kg). The two groups had similar education (obese 14.5 [SD 2.3] years, controls 15 [2.8] years), social, and economic background. The BMI of obese individuals was significantly higher than that of controls (p < 0.0001). The estimates of $K_1$ (transfer constant of radiotracer from plasma to tissue) and of the distribution volume of [C-11]raclopride in striatum and in cerebellum of controls did not differ from that of obese individuals (table 1). However, obese individuals had significantly lower measures of striatal dopamine D2 receptor availability (Bmax/Kd: 2.47 [SD 0.36]) than controls (2.99 [0.41]; difference 0.52 [0.17], p < 0.0075; figure 1).

The measure of striatal dopamine D2 receptor availability (Bmax/Kd) had a normal distribution. With this measure as the dependent variable, an intensive model fitting (both linear and non-linear) effort showed that the best regression models differed between the obese group and the controls. For the obese individuals, the best model was the simple linear regression model with BMI as
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The fact that there were no differences in the K1 (delivery of [C-11]raclopride from plasma to brain) in striatum or in cerebellum between obese individuals and controls, and that there were no differences in striatal cerebellar metabolism, indicates that the differences in D2 receptor measures were not due to differences in bioavailability of the radiotracers between these two groups. The ability to find differences in regional brain glucose metabolism in obese individuals studied at baseline suggests that there are no major differences in regional brain activity during resting conditions in obese individuals when compared with controls. However, studies of regional brain glucose metabolism during stimulation by food or other rewarding stimuli may show abnormalities in regional brain activity in obese individuals.

Although we are interpreting the reduction in Bmax/kd in the obese individuals as evidence of a reduction in dopamine D2 receptors, methodologically we cannot rule out the possibility that the results are due to increase in the concentration of extracellular dopamine, since [11C]raclopride competes with dopamine for binding to the dopamine D2 receptors. However, this is unlikely since the pharmacological evidence indicates that enhanced dopamine activity is associated with reduced food intake.

Contributors
Gene-Jack Wang was the main clinical coordinator, did the PET scanning, and wrote the paper. Nora Volkow designed the study, analysed the PET scan data and wrote the paper. Jean Logan and Christopher Wong analysed the PET scan data and were responsible for data management. Naomi Pappas was responsible for study coordination and recruitment of participants. Noel Netuveli participated in PET scanning. Wei Zhu did the statistical analysis and wrote the paper. Joanna Fowler was the principal investigator of the study, responsible for radiochemistry, and wrote the paper.

Acknowledgments
This work was supported by the US Department of Energy (DE-AC02-86CH10886), National Institute on Drug Abuse (DA 06891-02). We thank David Alexoff, Robert Carciello, investigator of the study, responsible for radiochemistry, and wrote the paper. Nora Volkow designed the study, analysed the PET scan data and were responsible for data management. Naomi Pappas was responsible for study coordination and recruitment of participants. Noel Netuveli participated in PET scanning. Wei Zhu did the statistical analysis and wrote the paper. Joanna Fowler was the principal investigator of the study, responsible for radiochemistry, and wrote the paper.

References