Brain dopamine and obesity

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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 D_2 receptors in brain.

Methods Brain dopamine D_2 receptor availability was measured with positron emission tomography (PET) and [C-11]raclopride (a radioligand for the dopamine D_2 receptor). Bmax/Kd (ratio of the distribution volumes in striatum to that in cerebellum minus 1) was used as a measure of dopamine D_2 receptor availability. Brain glucose metabolism was also assessed with 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG).

Findings Striatal dopamine D_2 receptor availability was significantly lower in the ten obese individuals (2·47 [SD 0·36]) than in controls (2·99 [0·41]; $p \leq 0{\cdot}0075$). In the obese individuals body mass index (BMI) correlated negatively with the measures of D_2 receptors (r=0·84; $p \leq 0{\cdot}002$); the individuals with the lowest D_2 values had the largest BMI. By contrast, neither whole brain nor striatal metabolism differed between obese individuals and controls, indicating that striatal reductions in D_2 receptors were not due to a systematic reduction in radiotracer delivery.

Interpretation The availability of dopamine D_2 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.

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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 intake[3] by modulating food reward via the meso-limbic circuitry of the brain.[4] In fact, drugs that block dopamine D_2 receptors increase appetite and result in significant weight gain[5] whereas drugs that increase brain dopamine concentration are anorexigenic.[6–8]

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.[9] In human beings, studies have shown a higher prevalence of the *Taq 1 A* 1 allele for the dopamine D_2 receptors, which is linked with lower amounts of dopamine D_2 receptors[10] in obese individuals.[11] Studies have also shown that genetic variants of the human obesity gene, which predict the body mass index (BMI), interact with the dopamine D_2-receptor gene.[12] However, the involvement of brain dopamine D_2 receptors in obesity has not been directly assessed.

The purpose of this study was to assess if there are differrences in brain dopamine D_2 receptors in severely obese individuals. The dopamine system was assessed with [C-11]raclopride (radiotracer that binds to dopamine D_2 receptors[13]) with positron emission tomography (PET). In parallel, we also measured regional brain glucose metabolism in these individuals with PET and 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG).[14]

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/m^2 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.

PET imaging

PET scans were done with a CTI-931 (Computer Technologies, Incorporated, Knoxville, USA) tomograph (resolution 6×6×6·5 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.[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.[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.[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).[17] 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).[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 D_2 receptor availability, that is the number of receptors that are free to bind to the radiotracer. These measurements are insensitive to changes in body weight.[19]

Brain metabolic images of obese individuals and controls were analysed with regions of interest analysis method. Briefly, regions were selected with a template,[18] of 115 non-overlapping regions which were grouped into 12 composite cortical (frontal, parietal, temporal, and occipital cortices, bilaterally), subcortical (striatum bilaterally, thalamus), and cerebellar regions. Measurement of global brain metabolism was obtained by averaging the values from the pixels located in the brain-tissue component of the brain images as previously described.[18]

Statistical analysis

Differences in the measures of dopamine D_2 receptors (Bmax/Kd) in striatum and of metabolism in the 12 composite brain regions between obese individuals and controls were tested by means of the independent sample *t* test (two-tailed). To correct for multiple comparisons in the metabolic measures incurred by analysing 12 brain regions we set the level of significance at p⩽0·01. A repeated measures ANCOVA (analysis of variance and covariance) with repeated measures on the 12 brain regions was also fitted to further examine the effect of sex and BMI on regional metabolism. The link between the dopamine D_2 receptor measures and the BMI and other possible covariates was explores with the regression methods.

Parameters/regions	Controls	Obese individuals	95% CI
K1			
Cerebellum	0·07 (0·01)	0·06 (0·02)	−0·01–0·03
Striatum	0·12 (0·02)	0·11 (0·02)	−0·01–0·03
Distribution volume			
Cerebellum	0·49 (0·07)	0·48 (0·11)	−0·08–0·10
Striatum	1·98 (0·37)	1·66 (0·35)	−0·02–0·66
Bmax/Kd striatum	2·99 (0·41)	2·47 (0·36)*	0·16–0·88

Data are mean (SD). K1=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/m^2; 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/m^2; 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 K1 (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 D_2 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 D_2 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 differ between the obese group and the controls. For the obese individuals, the best model was the simple linear regression model with BMI as

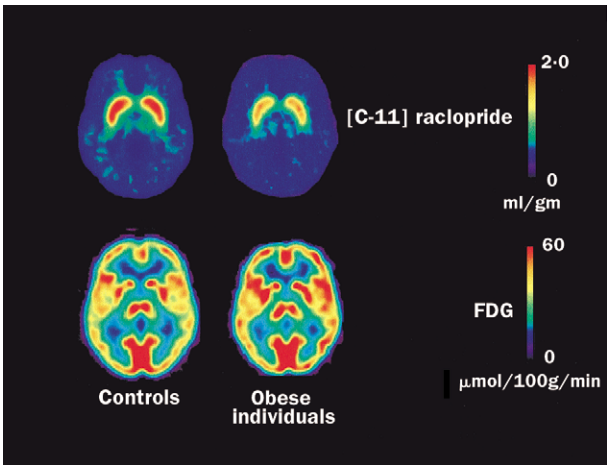

Figure 1: **Group average images of [C-11]raclopride (distribution volume image) and FDG (metabolic image) PET for obese individuals and controls at the level of the basal ganglia**

The images are scaled with respect to the maximum value obtained from the controls and presented by means of the rainbow scale. For [C-11]raclopride, red represents the highest value (2·0) and dark violet represents the lowest value (0 ml/Gm). For FDG, highest value is 60 μmol and lowest value is 0 μmol/100 g/min.

Regions	Controls	Obese	95% CI*
Global value	34·7 (4·1)	37·3 (3·5)	−6·4–1·3
Right frontal cortices	46·2 (6·1)	49·5 (5·0)	−8·9–2·4
Left frontal cortices	46·7 (6·5)	48·4 (4·1)	−7·2–3·9
Right parietal cortices	45·4 (6·5)	48·7 (6·5)	−9·8–3·2
Left parietal cortices	45·9 (7·3)	48·2 (5·7)	−9·0–4·4
Right temporal cortices	44·5 (4·9)	48·6 (5·3)	−9·3–1·0
Left temporal cortices	45·5 (5·3)	48·0 (4·8)	−7·6–2·6
Right occipital cortices	50·2 (7·0)	50·8 (7·1)	−7·7–6·5
Left occipital cortices	52·0 (8·1)	53·8 (8·0)	−9·9–6·2
Right basal ganglia	48·4 (5·8)	50·8 (4·5)	−7·7–2·9
Left basal ganglia	46·8 (6·8)	50·1 (6·0)	−9·8–3·2
Thalamus	49·7 (4·7)	51·9 (5·5)	−7·3–2·9
Cerebellum	38·9 (5·0)	40·8 (4·9)	−6·9 –3·1

Data are mean (SD). *The centre of the CI may be slightly different from the difference of the tabulated mean values due to rounding.

Table 2: **Regional brain metabolic measures (mmol/100 gm/min) in obese individuals and controls**

the sole regressor (two-sided p value=0·002; figure 2). The striatal dopamine D_2 receptor availability had a negative linear link with BMI. The coefficient of determination, which is the square of the usual Pearson product-moment correlation coefficient ($r=-0·84$), was 0·71. For the controls Bmax/Kd was negatively correlated with BMI; however, this link was not significant. In the controls, age was the best predictor of Bmax/Kd (two-sided p value=0·005); the correlation coefficient was r=−0·80, and the coefficient of determination was 0·64. Neither sex or brain metabolism was significantly related to Bmax/Kd. Because age was not significantly associated with Bmax/Kd for the obese individuals and BMI was not significantly associated with Bmax/Kd for the controls, it was not appropriate to model both groups together.

Our analyses also indicate that the whole brain glucose metabolism (100 g per min) did not differ between obese individuals (37·3 [SD 3·5]) and controls (34·8 [4·1] μmol/100 g per min; p=0·2; figure 1). Regional brain metabolism was also not significantly different between these two groups (table 2). The repeated measures ANCOVA showed that neither sex nor BMI was related to metabolism.

Discussion

We have shown that there is a lower dopamine D_2 receptor availability in the striatum of obese individuals than in normal individuals. Moreover, in the obese individuals the D_2 receptor measures were negatively correlated with their BMI. The results lead to an association between low D_2 receptor amounts in obese individuals or a more-severe eating disorder and higher BMI. Low levels of dopamine D_2 receptors have also been reported in individuals addicted to various types of drugs including cocaine,[18] alcohol,[19] and opiates.[20] This would suggest that a reduction in D_2 receptors is associated with addictive behaviour irrespective of whether it is due to food, as in this study, or to addictive drugs as seen in substance abusers. Eating is a highly reinforcing behaviour that not only provides nutrients needed for survival, but that also induce feelings of gratification and pleasure.[21] Feeding increases extracellular dopamine concentration in the nucleus acumbens,[22] which is an effect believed to contribute to the reinforcing effect of euphoria as well as that of drugs of abuse.[23] Thus, one could postulate that the decrements in dopamine D_2 receptors in obese individuals represent a downregulation to compensate for dopamine increases caused by chronic overstimulation from feeding. However, an alternative explanation is that individuals with low numbers of D_2 receptors may be more vulnerable to addictive behaviours including compulsive food intake.[24] In this respect it is noteworthy that obese individuals with a binge-eating disorder are significantly more likely to have a family history of substance abuse than those in the general population.[25] It has been postulated that compulsive disorders such as drug addiction, gambling, and obesity reflect a "reward deficiency syndrome", that is thought to be due, in part, to a reduction in dopamine D_2 receptors.[26] This study provides direct evidence of a deficit in dopamine D_2 receptors in obese individuals. We speculate that in obese individuals decrements in D_2 receptors perpetuate pathological eating as a means to compensate for the decreased activation of reward circuits, which are modulated by dopamine.[27] This study cannot discriminate if the brain changes in obese individuals are a consequence or a cause of the obesity. Further studies that assess D_2 receptors measures before and after successful weight-reduction interventions might help determine if the low levels are due to changes secondary to the individual's large BMI.

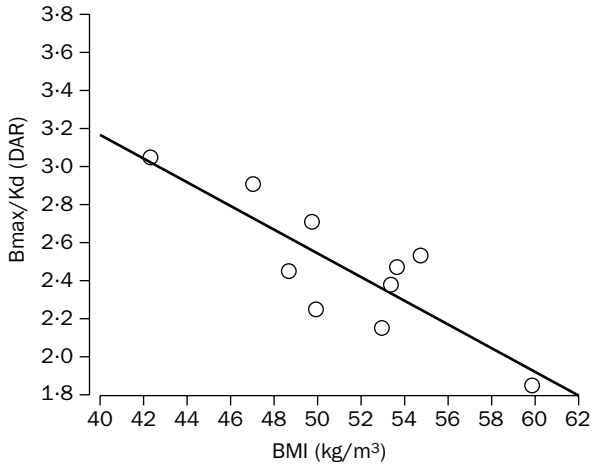

Figure 2: **Linear regression between dopamine receptor availability (Bmax/Kd) and BMI in obese individuals**

Although in this study we have focused on dopamine, it is important to point out that the regulation of body weight is complex and involves other physiological mechanisms and other neurotransmitters.[2] In particular, the brain serotonergic and noradrenergic systems as well as the leptin OB receptor have been important targets in the development of drugs to treat obesity and these and other molecular targets merit investigation in obese individuals.[1] The results from this study have implications for the treatment of obesity since they would suggest that strategies aimed at improving dopamine function might be beneficial in the treatment of obese individuals. In fact psychostimulant drugs (amphetamine,[6] cocaine,[7] and methylphenidate[8]), which increase extracellular dopamine, are anorexigenic[6,8] and this effect is blocked by dopamine receptor antagonists.[6] Unfortunately the therapeutic benefit of these drugs is curtailed by their addictive and psychoactive effects and to our knowledge there are currently no dopaminergic anorexigenic drugs that are not reinforcing. However, strategies to enhance dopaminergic function could involve behavioural interventions such as exercise. In animal models, exercise has been found to increase dopamine release,[28] and to raise D_2 receptors.[29] Further research to identify treatment approaches that enhance the function of the dopamine system as a means to promote long-term maintenance of weight control is warranted.

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 D_2 receptor measures were not due to differences in bioavailability of the radiotracers between these two groups. Inability 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 D_2 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 D_2 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 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 Netusil 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.

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References

1 Bray GA, Tartaglia LA. Medicinal strategies in the treatment of obesity. *Nature* 2000; **404:** 672–77.
2 Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000; **404:** 661–71.
3 Balcioglu A, Wurtman RJ. Effects of phentermine on striatal dopamine and serotonin release in conscious rats: in vivo microdialysis study. *Int J Obes Relat Metab Disord* 1998; **22:** 325–28.
4 Martel P, Fantino M. Mesolimbic dopaminergic system activity as a function of food reward: a microdialysis study. *Pharmacol Biochem Behav* 1996; **53:** 221–26.
5 Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. *Acta Psychiatr Scand* 1999; **100:** 3–16.
6 Towell A, Muscat R, Willner P. Behavioural microanalysis of the role of dopamine in amphetamine anorexia. *Pharmacol Biochem Behav* 1988; **30:** 641–48.
7 Foltin RW, Fischman MW, Nautiyal C. The effects of cocaine on food intake of baboons before, during, and after a period of repeated desipramine. *Pharmacol Biochem Behav* 1990; **36:** 869–74.
8 Wang G-J, Wolkow ND, Wong CT, et al. Behavior and cardiovascular effects of intravenous methylphenidate in normal subjects and cocaine abusers. *Euro Addict Res* 1997; **3:** 49–54.
9 Bina KG, Cincotta AH. Dopaminergic agonists normalize elevated hypothalamic neuropeptide Y and corticotropin-releasing hormone, body weight gain, and hyperglycemia in ob/ob Mice. *Neuroendocrinology* 2000; **71:** 68–78.
10 Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch Gen Psychiatr* 1991; **48:** 648–54.
11 Noble EP, Noble RE, Ritchie T, et al. D2 dopamine receptor gene and obesity. *Int J Eat Disord* 1994; **15:** 205–17.
12 Comings DE, Gade R, MacMurray JP, Muhleman D, Peters WR. Genetic variants of the human obesity (OB) gene: association with body mass index in young women, psychiatric symptoms, and interaction with the dopamine D2 receptor (DRDR) gene. *Mol Psychiatr* 1996; **1:** 325–35.
13 Farde L, Hall H, Ehrin E, Sedvall G. Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. *Science* 1986; **231:** 258–61.
14 Mazziotta JC, Phelps ME. Positron emission tomography studies of the brain. In: Phelps ME, Mazziotta J, Schelbert H, eds. Positron emission tomography and autoradiography. New York: Raven Press, 1986: 493–579.
15 Wang G-J, Volkow ND, Fowler JS, et al. Reproducibility of repeated measures of endogenous dopamine competition with [C-11]raclopride in the human brain. *J Nucl Med* 1999; **40:** 1285–91.
16 Wang G-J, Volkow ND, Wolf AP, Brodie JD, Hitzemann RJ. Intersubjects variability of brain glucose metabolic measurements in young normal males. *J Nucl Med* 1994; **35:** 1457–66.
17 Logan J, Volkow ND, Fowler JS, et al. Effect of blood flow on [^{11}C]raclopride binding in the brain: model simulations and kinetic analysis of PET data. *J Cereb Blood Flow Metab* 1994; **14:** 995–1010.
18 Volkow ND, Fowler JS, Wang G-J, et al. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synpase* 1993; **14:** 169–77.
19 Hietala J, West C, Syvalahti E, et al. Striatal D2 dopamine receptor binding characteristics in vivo in patients with alcohol dependence. *Psychopharmacology (Berl)* 1994; **116:** 285–90.
20 Wang G-J, Volkow ND, Fowler JS, et al. Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. *Neuropsychopharmacology* 1997; **16:** 174–82.
21 Hoebel BG. Brain neurotransmitters in food and drug award. *Am J Clin Nutr* 1985; **42** (suppl 5): S1133–50.
22 Bassareo V, Di Chiara G. Differential responsiveness of dopamine transmission to food-stimuli in nuleus accumbens shell/core compartments. *Neuroscience* 1999; **89:** 637–41.
23 Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature* 1996; **382:** 255–77.
24 Volkow ND, Fowler JS. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cerebral Cortex* 2000; **10:** 318–25.
25 Yanovski SZ, Nelson JE, Dubbert BK, Spitzer RL. Association of binge eating disorder and psychiatric comorbidity in obese subjects. *Am J Psychiatry* 1993; **150:** 1472–79.
26 Blum K, Cull JG, Braverman ER, Comings DE. Reward deficiency syndrome. *American Scientist* 1996; **84:** 132–45.
27 Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev* 1998; **28:** 309–69.
28 Hattori S, Naoi M, Nishino H, et al. Striatal dopamine turnover during treadmill running in the rat: relation to the speed of running. *Brain Res Bull* 1994; **35:** 41–49.
29 MacRae PG, Spirduso WW, Walters TJ, Farrar TP, Wilcox RE. Endurance training effects on striatal D2 dopamine receptor binding and striatal dopamine metabolites in presenescent older rats. *Psychopharmacology (Berl)* 1987; **92:** 236–40.