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No association between striatal dopamine transporter binding and body mass index: A multi-center European study in healthy volunteers

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ABSTRACT

Introduction: Dopamine is one among several neurotransmitters that regulate food intake and overeating. Thus, it has been linked to the pathophysiology of obesity and high body mass index (BMI). Striatal dopamine D_2 receptor availability is lower in obesity and there are indications that striatal dopamine transporter (DAT) availability is also decreased. In this study, we tested whether BMI and striatal DAT availability are associated.
Methods: The study included 123 healthy individuals from a large European multi-center database. They had a BMI range of 18.2–41.1 kg/m^2 and were scanned using [^{123}I]FP-CIT SPECT imaging. Scans were analyzed with both region-of-interest and voxel-based analysis to determine the binding potential for DAT availability in the caudate nucleus and putamen. A direct relation between BMI and DAT availability was assessed and groups with high and low BMI were compared for DAT availability.
Results: No association between BMI and striatal DAT availability was found.
Conclusion: The lack of an association between BMI and striatal DAT availability suggests that the regulation of striatal synaptic dopamine levels by DAT plays no or a limited role in the pathophysiology of overweight and obesity.

Introduction

Overweight and obesity are an increasing health problem worldwide and are defined as a body mass index (BMI) of 25–30 and >30 kg/m^2, respectively. Overeating of highly palatable and caloric foods is thought to play a major role in the overweight and obesity epidemic (Davis et al., 2004). There is a large body of evidence that suggests that dopamine is one of the neurotransmitters that is involved in the regulation of food intake and overeating (Ravussin and Bogardus, 2000). Food is able to induce a dopamine release in the nucleus accumbens in animals (Bassareo and Di Chiara, 1999) and in the striatum in humans (Small et al., 2003). The ability of

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food to increase dopamine is thought by some to be crucial for its rewarding and reinforcing effects. Changes in the mesolimbic dopaminergic reward system might therefore result in overeating (Volkow et al., 2011). It has indeed been consistently demonstrated that striatal dopamine D_2 receptor (DRD_2) levels are decreased in obese subjects (de Weijer et al., 2011; Wang et al., 2001) and that BMI correlates negatively with DRD_2 availability (Wang et al., 2001). Functional MRI studies with food-related stimuli also show that the brain activity in the striatal subregions caudate nucleus and putamen is altered in obesity (Rothemund et al., 2007; Stice et al., 2008; Stoeckel et al., 2008) and that this is dependent on DRD_2 genotype (Stice et al., 2008).

Brain synaptic dopamine levels are regulated by the dopamine transporter (DAT), which controls the dopamine level by driving synaptic dopamine back into the pre-synaptic neuron. Influencing brain dopamine levels affects food intake. For example, drugs that increase dopamine levels by inhibiting DAT, such as methylphenidate, have an anorexigenic effect. Animal studies demonstrate that diet-induced obese rodents on a high-fat diet show a significant decrease in DAT density on the cell surface in the striatum (South and Huang, 2008; Speed et al., 2011) or in gene and mRNA expression (Geiger et al., 2008; Vucetic et al., 2012), which is possibly mediated via impairment of a central kinase (Akt) that is involved in insulin signaling (Speed et al., 2011). In healthy humans, a negative correlation between striatal DAT availability and BMI has been reported (Chen et al., 2008). This association was not replicated in a monozygotic twin study, where the lean siblings did not differ in striatal DAT availability from their twin siblings with higher BMI (Koskela et al., 2008). A role for the DAT in obesity and BMI is thus not yet conclusively demonstrated. This knowledge is important, though, for our understanding of the (dys)function of the dopaminergic system in overweight and obesity.

Therefore, the objective of this study is to test for an association between striatal DAT availability and BMI in a large sample of healthy subjects with a large BMI range. Based on the data of the previous animal and human studies, we hypothesize that they are negatively correlated. A European database of [^{123}I]FP-CIT SPECT scans of healthy controls provides a unique opportunity to test this hypothesis.

Methods

Subjects

The subjects were healthy volunteers who participated in the ENC-DAT project, i.e. the European database of [^{123}I]FP-CIT (DaTSCAN) SPECT scans of healthy controls (Dickson et al., 2012). This is a collaborative effort by 13 European institutions in 10 European countries. Inclusion criteria were: 1. age between 20 and 90 years, 2. Unified Parkinson's Disease Rating Scale (UDPRS) score of 0 when <60 years or ≤ 5 when ≥ 60 years, 3. Symptom Checklist-90-R (SCL-90-R) score <63 to ensure minimal psychological problems, 4. Beck Depression Inventory (BDI) score <9, 5. no evidence for cognitive impairment as assessed with the Mini-Mental State Examination (MMSE; score ≥ 28), 6. for females negative urine based pregnancy test or hormonal contraceptive method or intra-uterine device (IUD) or postmenopausal state (last menstruation ≥ 12 months, age >60), and 7. negative urine based screening test for drug abuse. Exclusion criteria were: 1. history or evidence of neurological or psychiatric disease, 2. history or evidence of major systemic disease that contraindicates radiopharmaceutical administration and/or interferes with subject's compliance during the study, 3. thyroid disease, 4. aberrant MRI scan, diffuse or confluent white matter hyperintensities in T2-weighted images, corresponding to a white matter lesion (WML), age-related white matter changes (ARWMC) scale score >0 when <60 years or >2 when ≥ 60 years (Wahlund et al., 2001), 5. hypertension that was not controlled with diet or with monotherapy, 6. history of parkinsonism in first-degree relative (sibling, parent, or children), 7. pregnant or lactating female, 8. medication affecting DAT binding or potentially interfering with the dopaminergic system, 9. body temperature >38.5 °C on SPECT scanning day, and 10. contra-indications for MRI examination.

All subjects were seen by a neurologist and received a general physical examination, including weight and height measurement for BMI calculation. The protocol was approved by the Medical Ethical Committees of all participating centers and all subjects provided written informed consent.

SPECT and MRI acquisition

Each subject underwent one SPECT session, prior to which they received thyroid blockade. SPECT scans were performed with the radioligand [^{123}I]FP-CIT (DaTSCAN; GE Healthcare, Eindhoven, the Netherlands), which has a high affinity for the DAT. A total dose of approximately 185 MBq (specific activity >185 MBq/nmol; radiochemical purity $>95\%$) was given as an intravenous bolus. The SPECT cameras that were used were dual- or triple-headed cameras: Amsterdam — E.CAM (Siemens), Ankara — Infinia (GE Healthcare), Copenhagen — Irix (Philips), Genoa — Millennium VG (GE), Leipzig — Symbia (Siemens), Leuven — E.CAM (Siemens), London — Infinia (GE), Munich — Symbia (Siemens), Nice — Prism 3000 (Picker), Southampton — Nucline x-Ring/4HR (Mediso), Stockholm — Trionix (Trionix), Vienna — Irix (Philips), Yvoir — Trionix (Trionix). The main technical data of all the SPECT systems used in this study have been reported by Tossici-Bolt et al. (2011). The scans were acquired at 3 h post-injection, except in Amsterdam, Leipzig, and Yvoir, where they were acquired at 4 h post-injection due to acquisition of another scan at 3 h on a different type of camera, e.g. brain-dedicated system. At both time points the specific-to-nonspecific striatal [^{123}I]FP-CIT binding ratio (SBR) is stable (Booij et al., 1999). Scan parameters were standardized for the participating centers and are shown in Table 2 of Dickson et al. (2012).

For anatomical reference and exclusion of significant structural pathologies (see above), each subject was scanned with MRI (at least 1.5 T) and T1 (SPRG or MPRAGE) and T2 sequences were acquired.

Data analysis

A single core lab reconstructed the SPECT data on a HERMES workstation (Hermes Medical Systems, Stockholm) using iterative reconstruction with 10 iterations and 10 subsets (12 iterations and 8 subsets for 128 project studies), with calculated attenuation correction and scatter correction using the triple-energy window method (Ichihara et al., 1993). Post reconstruction filtering was applied using a Butterworth filter (0.5 cm^{-1}, power 10), and the resultant in-plane matrix size was 128×128 with a pixel size <3 mm.

Region-of-interest analysis

For region-of-interest (ROI) analysis, the SPECT data were transferred to a HERMES workstation and manually co-registered with the T1 MRI scans by using the HERMES MultiModality software according to a previously described procedure (Hesse et al., 2003; Hesse et al., 2009). In a first step, the individual MRI scan was reoriented towards the anterior commissure–posterior commissure line based on a normal standardized MRI. Second, the individual SPECT data were co-registered onto the realigned individual MRI in all three (x, y, z) planes and, third, the atlas-based predefined ROI templates in the normal standardized MRI atlas were adjusted to the individual anatomy. The uptake in each ROI (highest mean count density in adjacent slices comprising the entire brain structure, i.e. the DAT-rich striatal subregions head of the caudate nucleus and the putamen) was determined. The occipital cortex was used as the