Brain Imaging and Behavior (2019) 13:588–593
https://doi.org/10.1007/s11682-018-9878-0

ORIGINAL RESEARCH

Prediction of future weight change with the dopamine transporter

Kyoungjune Pak[1] · Keunyoung Kim[1] · Myung Jun Lee[2] · Jae Meen Lee[3] · Bum Soo Kim[4] · Seong-Jang Kim[4] · In Joo Kim[1]

Published online: 9 May 2018
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Abstract

The brain plays a critical role in controlling and inhibiting pre-potent responses to foods. We investigated the predictive value of dopamine transporter (DAT) availability in the striatum of healthy subjects using ^{123}I-FP-CIT single-photon emission computed tomography (SPECT). In total, 84 participants with available data on their weight for the 60 months after SPECT were included. Specific binding of ^{123}I-FP-CIT to DAT was calculated using region-of-interest analysis, and the putamen-to-caudate nucleus ratio (PCR) was determined. After comparing the weights at 12, 24, 36, 48, and 60 months after SPECT with the baseline weight, we categorized participants into three groups: weight gain (> 5%), stable (−5%–5%), and weight loss (< −5%). PCRs of the weight-loss, stable, and weight-gain groups significantly differed at 36 and 48 months. According to post-hoc analysis, PCRs were lower in the weight gain group at 36 and 48 months compared with at the remaining time points. Overall, our results suggest that PCRs calculated based on DAT availability could be used to predict future weight changes. It is possible that the interactions between the caudate nucleus and the putamen, rather than the individual behavior of each structure, might play an important role in weight regulation. Further studies are needed to investigate the time-dependence of the predictive value of DAT.

Keywords Obesity · Single-photon emission computed tomography · Dopamine plasma membrane transport proteins

Introduction

The prevalence of obesity is increasing globally (Dhanda and Taheri 2017). Obesity is known to be a risk factor for malignancies of the colon (Na and Myung 2012), pancreas (Gukovsky et al. 2013), thyroid (Mijovic et al. 2011), liver (Alzahrani et al. 2014), and uterus (Gu et al. 2013), as well as for cardiovascular disease (Ellulu 2017) and diabetes mellitus (Gross et al. 2017). Therefore, the socioeconomic costs of overweight and obesity have become substantial (Kang et al. 2011).

There are phenomenological similarities between overeating in obesity and excessive drug use in addiction (Kenny 2011). Obesity begins with a loss of balance between energy intake and expenditure over long periods of time (Morton et al. 2014). The brain plays a critical role in this imbalance by controlling and inhibiting pre-potent responses to foods (Morton et al. 2014; Volkow et al. 2008). The

✉ Kyoungjune Pak
ilikechopin@me.com

Keunyoung Kim
buisket@naver.com

Myung Jun Lee
mslayer9@gmail.com

Jae Meen Lee
geosung1@naver.com

Bum Soo Kim
bum8112@gmail.com

Seong-Jang Kim
growthkim@daum.net

In Joo Kim
injkim@pusan.ac.kr

[1] Department of Nuclear Medicine and Biomedical Research Institute, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea

[2] Department of Neurology and Biomedical Research Institute, Pusan National University Hospital, Busan, South Korea

[3] Department of Neurosurgery and Biomedical Research Institute, Pusan National University Hospital, Busan, South Korea

[4] Department of Nuclear Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, South Korea

neurotransmitters dopamine and serotonin are involved in the regulation of food intake and body weight (Ravussin and Bogardus 2000; Lam et al. 2010). Previous studies have investigated the role of ^{123}I-FP-CIT in evaluating the availability of the dopamine transporter (DAT) of the striatum (Booij et al. 2007) and the serotonin transporter (SERT) of the midbrain (Roselli et al. 2010), pons (Koch et al. 2014), thalamus (Koch et al. 2014), and hypothalamus (Borgers et al. 2013), as ^{123}I-FP-CIT shows a higher affinity for DAT followed by SERT (Joutsa et al. 2015).

The role of DAT in obesity is controversial. Previous studies have reported a negative correlation between DAT availability and body mass index (BMI) (Hsieh et al. 2010); however, this correlation was not significant in other studies (Thomsen et al. 2013; Versteeg et al. 2016). Moreover, it remains unclear whether changes in the dopaminergic system of the brain are a cause or a consequence of obesity (Wang et al. 2001).

In this regard, we hypothesized that DAT might play a causative role in the loss of balance between energy intake and expenditure in obesity. Therefore, we employed a longitudinal design with a 60-month follow-up period to investigate the predictive value of DAT availability, measured with ^{123}I-FP-CIT single-photon emission computed tomography (SPECT), based on data from the Parkinson's Progression Markers Initiative (PPMI).

Materials and methods

Participants

Data used in the preparation of this article were obtained from the PPMI database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org (Parkinson Progression Marker 2011). The study population consisted of healthy controls screened with ^{123}I-FP-CIT SPECT. Participants with a follow-up period of at least 60 months were included in this study. The weight of each participant was measured at each visit at 0 (W0), 12 (W12), 24 (W24), 36 (W36), 48 (W48), and 60 (W60) months after ^{123}I-FP-CIT SPECT. Study protocols are shown in Fig. 1. Following the PPMI criteria of healthy participants, males or females aged 30 years or older at screening were included, and participants with a neurological disorder, a first-degree relative with idiopathic Parkinson's disease, a Montreal Cognitive Assessment score of 26 or less, or a condition that precludes safe performance of routine lumbar puncture as well as those taking medications that might interfere with DAT SPECT scans, anticoagulants, or investigational drugs that might preclude safe completion of the lumbar puncture were excluded. Medical history, weight, height, and ^{123}I-FP-CIT SPECT scans were downloaded. The PPMI study was approved by the local Institutional Review Boards of all participating sites (Institute for Neurodegenerative Disorders, University of Pennsylvania; University of California, Los Angeles; Coriell Institute for Medical Research, Clinical Trials Coordination Center, Laboratory of Neurogenetics; National Institute on Aging NIH, Institute for Neurodegenerative Disorders, Clinical Trials Statistical; and Data Management Center, University of Iowa), and written informed consent for imaging data and clinical questionnaires was obtained from each participant at the time of enrollment. All methods were performed in accordance with the relevant guidelines and regulations.

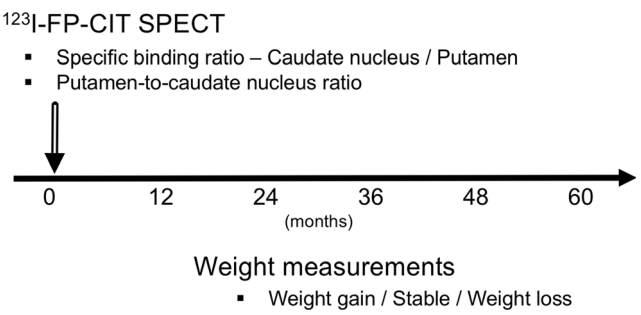

Fig. 1 Study protocol

^{123}?I-FP-CIT SPECT

^{123}I-FP-CIT SPECT was performed on all participants during the screening visit. SPECT scans were acquired 4 ± 0.5 h after injection of 111–185 MBq of ^{123}I-FP-CIT. Participants were pretreated with iodine solution or perchlorate prior to injection to block thyroid uptake. Raw data were acquired into a 128 × 128 matrix each stepping 3 or 4 degrees for the total projections. Raw projection data were reconstructed using iterative ordered subset expectation maximization with HERMES (Hermes Medical Solutions, Stockholm, Sweden). The reconstructed images were transferred to pmod (PMOD Technologies LLC, Zürich, Switzerland) for subsequent processing, including attenuation correction.

Image analysis

Downloaded scans were loaded using pmod v3.6 (PMOD Technologies LLC) with the ^{123}I-FP-CIT template (Garcia-Gomez et al. 2013). Specific binding of ^{123}I-FP-CIT to the DAT was calculated using a region-of-interest analysis. A standard set of volume of interest (VOI) defining the caudate nucleus and putamen based on the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al. 2002) was defined. The cerebellum was chosen as a reference region. The VOI template was applied to measure the specific binding ratios (SBRs) of the caudate nucleus and putamen as follows: SBR = (target − cerebellum)/cerebellum. The putamen-to-caudate nucleus ratio (PCR) was calculated as follows: PCR = SBR of putamen/SBR of caudate nucleus.

Statistical analysis

Participants were categorized into weight-gain, stable, and weight-loss groups following comparison of weights at 12, 24, 36, 48, and 60 months after ^{123}I-FP-CIT SPECT with baseline weight (W0). Participants were assigned to the weight-gain, stable, or weight-loss group at each time point were following comparison with the baseline weight (W0). Weight change was calculated as follows: weight change (%) = [(W12, W24, W36, W48, or W60) – W0]/W0*100 (%). Participants with a weight change greater than 5% or less than 5% were categorized into the weight-gain (> 5%) and weight-loss (< −5%) groups, respectively, at each time point. Normality was examined using the D'Agostino-Pearson omnibus test. Spearman's correlation was used to measure the relationship among SBR, PCR, and BMI and among SBR, PCR, and weight change. The Mann–Whitney test was used to compare SBRs and PCRs between obese and non-obese participants. The Kruskal–Wallis test was performed to compare SBRs and PCRs among participants in the weight-gain, stable, and weight-loss groups at each time point. When the Kruskal–Wallis test was positive, post hoc analysis was performed to compare subgroups (weight gain vs. others) as previously described (Conover 1999). Logistic regression was used to analyze the predictive value of the PCR for weight gain. Statistical analyses were performed using GraphPad Prism 7 for Mac OS X (GraphPad Software Inc., San Diego, CA, USA) and MedCalc Version 16.8 for Windows (MedCalc Software bvba, Ostend, Belgium).

Results

In total, 84 participants were included in the study (45 male, 39 female). The mean age was 59.9 years, and the mean W0 was 76.3 kg. The absolute values for changes from W0 (mean ± standard deviation) were 3.0 ± 4.7, 3.5 ± 4.5, 4.0 ± 4.9, 4.2 ± 5.1, and 4.4 ± 4.5 kg at 12, 24, 36, 48, and 60 months, respectively, following ^{123}I-FP-CIT SPECT. At 12, 24, 36, 48, and 60 months after ^{123}I-FP-CIT SPECT, 11, 12, 15, 17, and 19 participants lost weight, whereas 9, 16, 17, 19, and 15 participants gained weight, respectively (Table 1).

Correlation of SBR and PCR with obesity

None of the SBRs and PCRs were correlated with the BMIs of the 84 participants. Additionally, the SBRs of the caudate nucleus ($p = 0.9603$), putamen ($p = 0.5540$), and PCR ($p = 0.2790$) did not differ between obese (BMI ≥ 30 kg/m^2, $n = 17$) and non-obese (BMI < 30 kg/m^2, $n = 67$) participants.

Table 1 Participant characteristics

Variable	$n = 84$
Sex (male/female)	45/39
Age (years)	59.9 ± 11.9
Weight (kg), absolute values for changes from W0 (kg)	
W0	76.3 ± 15.6
W12, |W12 – W0|	76.0 ± 16.1, 3.0 ± 4.7
W24, |W24 – W0|	76.2 ± 16.1, 3.5 ± 4.5
W36, |W36 – W0|	76.4 ± 16.1, 4.0 ± 4.9
W48, |W48 – W0|	76.3 ± 15.9, 4.2 ± 5.1
W60, |W60 – W0|	75.8 ± 16.0, 4.4 ± 4.5
Baseline body mass index (kg/m^2)	26.2 ± 4.3

Mean ± standard deviation

Correlation of SBR and PCR with weight change

The SBR of the caudate nucleus exhibited a positive correlation with weight change at 24 ($r = 0.2408$, $p = 0.0274$), 36 ($r = 0.2195$, $p = 0.0449$), and 48 months ($r = 0.2159$, $p = 0.0486$). The PCR exhibited a negative correlation with weight change at 36 ($r = -0.2770$, $p = 0.0108$), 48 ($r = -0.3004$, $p = 0.0055$), and 60 months ($r = -0.2514$, $p = 0.0211$). The SBRs of the caudate nucleus and putamen did not differ among groups at any time point. However, the PCRs using ^{123}I-FP-CIT SPECT of participants in the weight-loss, stable, and weight-gain groups differed significantly at 36 ($p = 0.0449$) and 48 ($p = 0.0367$) months (Fig. 2, Table 2). According to the post hoc analysis, the PCRs were lower in the weight-gain group at both 36 ($p = 0.0143$) and 48 ($p = 0.0354$) months compared with at the remaining time points (Fig. 3). Based on logistic regression, lower PCRs (0.1 unit decrease in PCR) using ^{123}I-FP-CIT SPECT predicted weight gain at 36 months (odds ratio 1.7161, 1.0997–2.6780, $p = 0.0174$).

Discussion

The baseline PCRs of the weight-gain, stable, and weight-loss groups differed at 36 and 48 months following ^{123}I-FP-CIT SPECT. Additionally, the PCRs of participants in the weight-gain group at both 36 and 48 months were lower compared with at the remaining time points. Moreover, the PCR predicted future weight gain 36 months before it happened.

The rise in the prevalence rates of obesity might not be due to genetic factors alone; instead, the increase may also be a result of environmental changes (Hebebrand et al. 2014). To win the fight against obesity, an understanding of the pathophysiological and neurobehavioral mechanisms underlying these states is needed (Val-Laillet et al. 2015). Previous studies

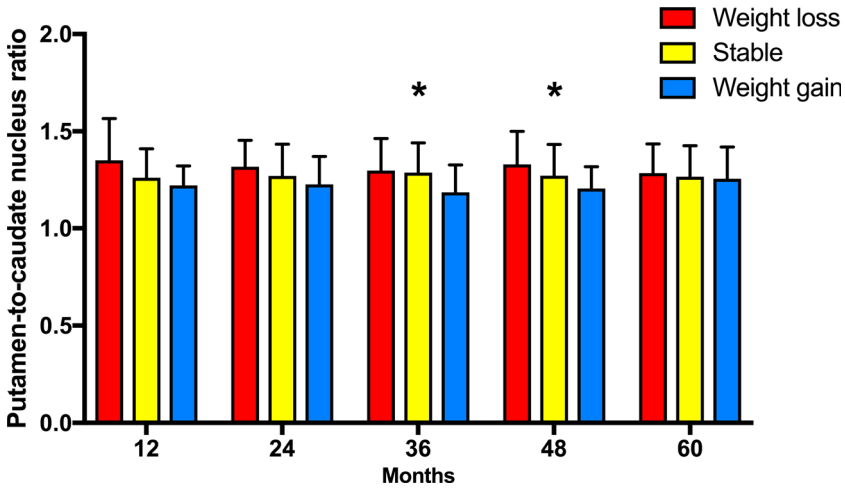

Fig. 2 Comparison of the putamen-to-caudate nucleus ratio of participants in the weight-gain, stable, and weight-loss groups at 12, 24, 36, 48, and 60 months. *$p < 0.05$

have suggested that drug use in addiction and overeating in obesity share common cellular and molecular mechanisms (Kenny 2011). Eating is intrinsically rewarding and reinforcing and activates the reward system in the brain (Volkow et al. 2011). Therefore, neuroimaging studies play an important role in investigating the involvement of neurotransmitters in eating (Volkow et al. 2009). Dopamine plays a pivotal role in reward processing (Kranz et al. 2010). DAT mediates uptake of dopamine into neurons, and various drugs targeting DAT have been identified, including cocaine (Chen and Reith 2000). Unlike the dopamine receptor, the role of DAT in obesity and eating behavior has not received significant attention from researchers. Hsieh et al. (2010) reported a negative correlation between DAT availability and BMI using ^{99m}Tc-TRODAT-1; however, studies using ^{123}I-PE-21 (Thomsen et al. 2013) or ^{123}I-FP-CIT (Versteeg et al. 2016) did not report a significant association. There are several possible explanations for these inconsistencies. First, the radiopharmaceuticals used in each study differed. Second, although BMI is widely used as a criterion for obesity, it is also widely criticized as it is neither an ideal index for the measurement of visceral adipose tissue nor a predictor of cardiovascular disease (Ortega et al. 2016). Although the dopaminergic system is out of balance in obesity (Dierckx et al. 2014), we could not determine the role of DAT in obesity and eating behavior. Michaelides et al. (2012) reported the predictive value of the dopamine receptor using ^{11}C-raclopride positron emission tomography to determine future body weight in rats. Body weights at baseline and 1 and 2 months later were negatively correlated with dopamine receptor availability (Michaelides et al. 2012). Additionally, weight change was positively correlated with the binding ratio of the ventral striatum and not with that of the dorsal striatum in rats with weight gain (Michaelides et al. 2012). However, it is still impossible to determine whether the change in the dopaminergic system of the brain is a cause or a consequence of obesity (Wang et al. 2001). In this regard, we investigated the role of DAT availability using a longitudinal design with a 60-month follow-up period to determine the precursors of obesity.

Although the SBR of the caudate nucleus and putamen did not differ among the weight-gain, stable, or weight-loss groups in this study, the PCR between them differed significantly, suggesting that interactions between the caudate nucleus and putamen, and not the individual regions, play an important role in weight regulation. Additionally, differences in the PCRs between the weight-gain group and the other two groups at 36 and 48 months were significant, and the predictive value of the PCR became powerful 36 months before weight gain. Although the caudate nucleus and putamen are anatomically separated by the internal capsule, they are sometimes considered a single functional structure (Ribas et al. 2017). It has been reported that the caudate nucleus is involved in the

Table 2 Comparison of the putamen-to-caudate nucleus ratio among participants in the weight-gain, stable, and weight-loss groups

Variable	Time	Weight loss	Stable	Weight gain	p
Putamen-to-caudate nucleus ratio	12 mo	1.351 ± 0.214	1.261 ± 0.149	1.221 ± 0.100	0.2709
	24 mo	1.318 ± 0.137	1.270 ± 0.164	1.227 ± 0.144	0.2999
	36 mo	1.298 ± 0.165	1.288 ± 0.153	1.185 ± 0.142	0.0449
	48 mo	1.330 ± 0.170	1.272 ± 0.161	1.206 ± 0.112	0.0367
	60 mo	1.284 ± 0.150	1.267 ± 0.160	1.256 ± 0.164	0.6695

Mean ± standard deviation

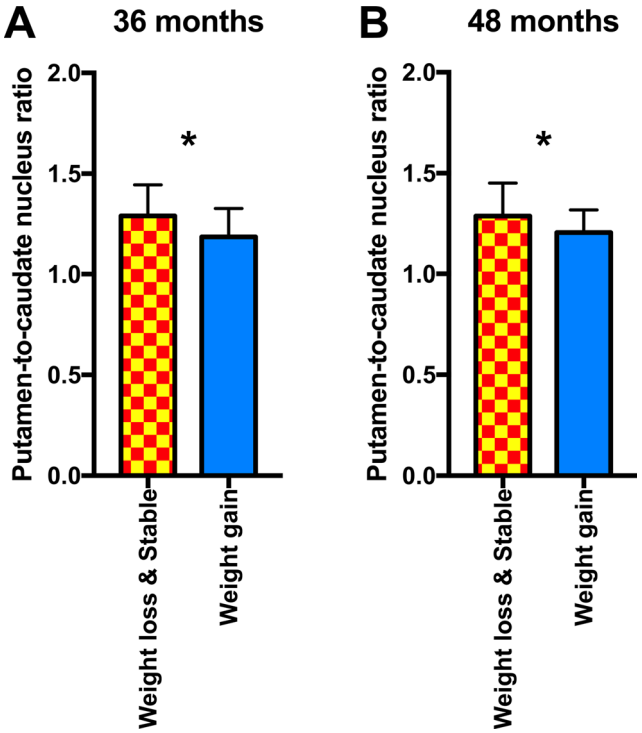

Fig. 3 Post hoc analysis of the putamen-to-caudate nucleus ratio at 36 (**a**) and 48 (**b**) months. *p < 0.05

manifestation or driving of locomotion, whereas the putamen regulates the tonus in contralateral muscles and the responsiveness to a stimulus (Yoshida 1991; Brovelli et al. 2011). However, the differential roles of the caudate nucleus and putamen in obesity, measured by DAT availability, remain unclear.

Further studies are needed to investigate the time-dependence of the difference and the predictive value of the PCR. Moreover, we observed a positive correlation between the SBR of the caudate nucleus and weight change. However, the SBR of the putamen did not exhibit a significant relationship with weight change. Therefore, we can assume that DAT of the caudate nucleus may affect weight change to a greater extent than that of the putamen.

This is the first study to report the predictive value of DAT for weight change in humans. Findings from this study will improve our understanding of the reward mechanisms of food intake and aid in the development of new treatments for obesity as well as eating disorders. However, this study has several limitations. First, as PPMI is not designed to investigate the predictive value of ^{123}I-FP-CIT SPECT for weight change, participants were free to control their own weight. Additionally, ^{123}I-FP-CIT SPECT was performed once, at baseline enrollment, for the normal participants included in PPMI. We could not investigate the change of DAT availability during follow up. Additionally, as the PPMI data were collected from multiple sites, there may have been differences in data acquisition. Further longitudinal studies are needed to investigate changes in DAT availability and subsequent weight changes in participants.

In conclusion, DAT availability and PCR could be used to predict future weight change. Interactions between the caudate nucleus and putamen, rather than the individual behaviors of each structure, might play an important role in weight regulation. Additionally, DAT availability in the caudate nucleus may affect weight change to a greater extent than that in the putamen. Further studies are needed to investigate the time-dependence of the predictive value of DAT.

Acknowledgements PPMI, a public–private partnership, is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including abbVie, Avid, Biogen, Bristol-Myers Squibb, COVANCE, GE Healthcare, Genentech, GlaxoSmithKline, Lundbeck, Lilly, Merck, MesoScaleDiscovery, Pfizer, Piramal, Roche, Sanofi Genzyme, Servier, TEVA, and UCB.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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