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ORIGINAL ARTICLE

Weight loss after bariatric surgery normalizes brain opioid receptors in morbid obesity

HK Karlsson[1], JJ Tuulari[1], L Tuominen[1,2], J Hirvonen[1,3,4], H Honka[1], R Parkkola[1,4], S Helin[1], P Salminen[5], P Nuutila[1,6] and L Nummenmaa[1,7,8]

Positron emission tomography (PET) studies suggest opioidergic system dysfunction in morbid obesity, while evidence for the role of the dopaminergic system is less consistent. Whether opioid dysfunction represents a state or trait in obesity remains unresolved, but could be assessed in obese subjects undergoing weight loss. Here we measured brain μ-opioid receptor (MOR) and dopamine D_2 receptor (D_2R) availability in 16 morbidly obese women twice—before and 6 months after bariatric surgery—using PET with [^{11}C]carfentanil and [^{11}C]raclopride. Data were compared with those from 14 lean control subjects. Receptor-binding potentials (BP_{ND}) were compared between the groups and between the pre- and postoperative scans among the obese subjects. Brain MOR availability was initially lower among obese subjects, but weight loss (mean = 26.1 kg, s.d. = 7.6 kg) reversed this and resulted in ~ 23% higher MOR availability in the postoperative versus preoperative scan. Changes were observed in areas implicated in reward processing, including ventral striatum, insula, amygdala and thalamus (P's < 0.005). Weight loss did not influence D_2R availability in any brain region. Taken together, the endogenous opioid system plays an important role in the pathophysiology of human obesity. Because bariatric surgery and concomitant weight loss recover downregulated MOR availability, lowered MOR availability is associated with an obese phenotype and may mediate excessive energy uptake. Our results highlight that understanding the opioidergic contribution to overeating is critical for developing new treatments for obesity.

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INTRODUCTION

Obesity is a major public health concern throughout the world. Converging evidence suggests that overeating is associated with altered neurochemistry in the brain circuits controlling reward functions.[1] The dopaminergic system is involved in incentive motivation and reward processing in the brain, and dysfunctions of this system are observed in several addictive disorders, both in preclinical and clinical studies.[2,3] Positron emission tomography (PET) studies show that alcohol and drug dependence is associated with lower dopamine D_2 receptor (D_2R) availability in the striatum,[4–6] reflecting tonic downregulation of the D_2R due to perpetual overstimulation by the drug of abuse. However, PET studies measuring D_2R availability have not shown a consistent pattern of abnormalities in obese versus lean subjects.[7–12]

The endogenous opioid system is also closely involved in reward functions. Human PET studies show that alcohol and cocaine dependence is associated with higher μ-opioid receptor (MOR) availability in the reward circuit,[13–15] although opiate use causes downregulation in MOR.[16,17] Moreover, animal studies suggest that the opioidergic system also plays a significant role in appetite and hedonic liking of foods.[18] We have recently shown that morbidly obese humans have significantly lower MOR availability, but unaltered striatal D_2R availability.[12] Obesity may therefore have unique neurobiological underpinnings, which are not similar to those in addictive disorders in general.

Cross-sectional studies cannot determine whether neuroreceptor alterations are the cause or consequence of obesity. In contrast, longitudinal studies on individuals undergoing weight loss procedures could resolve whether dysfunction of the MOR system reflects a stable vulnerability endophenotype for developing obesity, or whether it is related to the obese phenotype. Bariatric surgery is the most effective method for weight loss in morbid obesity,[19] and is therefore a powerful method for studying the relationship between MOR dysfunction and obesity. Prior imaging studies on the effects of weight loss on D_2R availability after bariatric surgery have shown conflicting results.[10,20,21] Whether weight loss influences brain MOR availability in obesity is unknown.

In this longitudinal study, we investigated whether weight loss caused by bariatric surgery influences brain D_2R and MOR availability. We used *in vivo* PET imaging pre- and postoperatively to quantify D_2R and MOR availability with selective radioligands [^{11}C]raclopride and [^{11}C]carfentanil, respectively. Because MOR systems contribute significantly to appetite control and food hedonics[18] and as patients often report decreased appetite after bariatric surgery,[22,23] we predicted that MOR availability would increase following bariatric surgery.

MATERIALS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the Hospital District of South-Western Finland (SleevePET2, NCT01373892, http://www.clinicaltrials.gov). All participants signed an ethical committee-approved and informed consent form before scans.

[1]Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland; [2]Department of Psychiatry, University of Turku and Turku University Hospital, Turku, Finland; [3]Medical Imaging Centre of Southwest Finland, Turku, Finland; [4]Department of Radiology, University of Turku and Turku University Hospital, Turku, Finland; [5]Department of Digestive Surgery, University of Turku and Turku University Hospital, Turku, Finland; [6]Department of Endocrinology, Turku University Hospital, Turku, Finland; [7]Department of Neuroscience and Biomedical Engineering, School of Science, Aalto University, Espoo, Finland and [8]Department of Psychology, University of Turku, Turku, Finland. Correspondence: Dr HK Karlsson, Turku PET Centre, University of Turku, Turku University Hospital, Kiinamyllynkatu 4-8, Turku, FIN-20520, Finland.
E-mail: hekrka@utu.fi
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Table 1. Characteristics of the participants

	Non-obese subjects (n = 14)		*Obese subjects before surgery (n = 16)*			*Obese subjects after surgery (n = 16)*		
	M	*s.d.*	*M*	*s.d.*	P-*value*[a]	*M*	*s.d.*	P-*value*[b]
Age (years)	44.86	12.88	42.75	10.19	0.63	43.31	9.90	**0.003**
Weight (kg)	61.39	7.19	111.81	15.20	< **0.001**	85.74	12.75	< **0.001**
Height (cm)	164.86	6.32	165.87	6.21	0.67	166.13	6.13	0.54
BMI (kg/m^2)	22.65	2.94	40.35	3.90	< **0.001**	31.00	3.69	< **0.001**
Percentage of fat (%)	30.21	10.17	49.86	4.04	< **0.001**	42.40	3.60	< **0.001**
Subcutaneous fat mass (kg)	4.10	1.30	16.40	3.50	< **0.001**	10.50	2.90	< **0.001**
Visceral fat mass (kg)	0.80	0.40	3.90	1.80	< **0.001**	2.10	1.11	< **0.001**
GHbA1c (%)	5.61	0.30	5.89	0.79	0.20	5.36	0.46	< **0.001**
HOMA-IR (fraction)	1.30	0.90	4.20	3.17	**0.003**	2.10	1.68	< **0.001**
Amount of alcohol use (units per week)	2.75	2.09	1.33	1.30	0.06	NA	NA	NA
Tobacco smokers/non-smokers (*N*)	0/14		6/10		< **0.001**	3/13		< **0.001**
Injected activity of [^{11}C]raclopride (MBq)	257.78	18.51	245.19	25.50	0.13	256.43	11.36	0.06
Injected activity of [^{11}C]carfentanil (MBq)	250.14	9.23	252.94	11.19	0.46	250.63	15.28	0.57

Abbreviations: BMI, body mass index; NA, data not available. [a]Differences between control subjects and preoperative obese subjects. [b]Differences between pre- and postoperative measurements of the obese subjects. Statistically significant differences are shown in boldface.

Table 2. Questionnaire scores

	Non-obese subjects (n = 14)		*Obese subjects before surgery (n = 16)*			*Obese subjects after surgery (n = 16)*		
	M	*s.d.*	M	*s.d.*	P-*value*[a]	M	*s.d.*	P-*value*[b]
BDI-II (points)	4.36	4.11	5.25	5.40	0.61	3.36	1.50	0.35
STAI (points)	34.07	5.47	38.25	8.19	0.11	36.36	5.15	0.22
FCQ state (points)	26.71	6.28	32.25	9.99	0.08	25.50	6.45	**0.010**
FCQ trait (points)	86.21	25.61	101.81	35.81	0.13	77.36	26.30	**0.006**
DEBQ restrained eating (points)	26.00	6.18	32.38	7.21	**0.014**	33.43	5.08	1.00
DEBQ emotional eating (points)	22.07	6.33	27.63	10.37	0.08	23.21	6.76	**0.042**
DEBQ external eating (points)	25.36	5.76	27.00	5.50	0.43	22.00	3.90	**0.003**
YFAS (points)	7.86	5.95	16.06	10.36	**0.012**	7.64	5.61	**0.010**

Abbreviations: BDI-II, Beck Depression Inventory II; DEBQ, Dutch Eating Behaviour Questionnaire; FCQ, Trait And State Food Cravings Questionnaires; STAI, State-Trait Anxiety Inventory; YFAS, Yale Food Addiction Scale. [a]Differences between control subjects and preoperative obese subjects. [b]Differences between pre- and postoperative measurements of the obese subjects. Statistically significant differences in *t*-tests are shown in boldface.

Subjects

We recruited 16 morbidly obese women (mean ± s.d. BMI 40.4 ± 3.9 kg m^{-2}, BMI range 36.1 – 49.3 kg m^{-2}, mean ± s.d. age 42.8 ± 10.2 years) who were eligible for bariatric surgery (Table 1). Either Roux-en-Y gastric bypass or sleeve gastrectomy was performed as their standard clinical treatment. Fourteen healthy non-obese women, age and height-matched (mean ± s.d. BMI 22.7 ± 2.9 kg m^{-2}, mean ± s.d. age 44.9 ± 12.9 years), served as controls. Sample size was determined by joint *a priori* power analysis based on longitudinal PET studies using [^{11}C]carfentanil,[14,24] which suggested that a sample size of 14+14 would be sufficient for establishing the predicted effects at $P < 0.05$ with actual power exceeding 0.95. Preoperative data for this sample have been reported previously.[12] To increase statistical power in the longitudinal analysis, three additional morbidly obese subjects were included in the sample. Clinical screening included history, physical examination, anthropometric measurements and laboratory tests. Exclusion criteria involved opiate drug use, binge-eating disorders, neurological and mental disorders, substance abuse, excessive alcohol consumption (more than eight units per weeks) determined by clinical interviews, medical history and blood tests. For the obese subjects, screening was performed both pre- and postoperatively and no subjects had to be excluded postoperatively. Depression and anxiety levels were measured using Beck Depression Inventory II and state-Trait Anxiety Inventory (STAI) questionnaires, respectively. Food craving and eating behavior were assessed with the Food Craving Questionnaire, Dutch Eating Behaviour Questionnaire (DEBQ) and the Yale Food Addiction Scale (YFAS) (Table 2). None of the controls smoked tobacco, but six obese subjects were light smokers (3–15 cigarettes per day). Six obese subjects had Type 2 diabetes (T2DM) with oral medication, nine used medication for elevated blood pressure, four for hypercholesterolemia and three for hypothyreosis. Antidiabetic, antihypertensive and cholesterol-lowering drugs were discontinued before the study.

Image acquisition and quantification of receptor availability

We measured MOR availability with [^{11}C]carfentanil[25] and D_2R availability with [^{11}C]raclopride[26] using PET on two separate visits. Preoperative scans were performed before the start of the standard very low-calorie diet. Obese subjects were scanned again with both radiotracers 6 months after the bariatric surgery. Radiotracer production has been described previously.[12] Both radiotracers had high radiochemical purity (>99%). Subjects fasted 2 h before scanning. Before scanning, a catheter was placed in the subject's left antecubital vein for tracer administration and their head was strapped to the scanner table.

Radiotracers were administered as bolus injections. Injected doses were 251 ± 12 MBq for [^{11}C]carfentanil and 253 ± 20 MBq for [^{11}C]raclopride. Radioactivity of both tracers was measured with the GE Healthcare Discovery 690 PET/CT scanner (General Electric Medical Systems, Milwaukee, WI, USA) for 51 min, using 13 time frames. Effective resolution of the PET scanner was 4.7 mm full width at half maximum. Data were corrected for dead-time, decay and CT-based photon attenuation estimate. Dynamic PET-scans were reconstructed using time-of-flight information. Anatomical reference images (1 mm^3 voxel size) were acquired with Philips

Gyroscan Intera 1.5T CV Nova Dual scanner using a T1-weighted sequence (TR 25 ms, TE 4.6 ms, flip angle 30°, scan time 376 s).

Alignment and coregistration were performed using SPM8 software (www.fil.ion.ucl.ac.uk/spm/) running on Matlab R2012a (The Mathworks Inc., Sherborn, MA, USA). To correct for head motion, dynamic PET images were first realigned frame-to-frame. Individual T1-weighted MR images were coregistered to the summed images calculated from the realigned frames. Regions of interest (ROIs) for reference regions were drawn manually on MRI images using PMOD 3.4 software (PMOD Technologies Ltd., Zurich, Switzerland). Occipital cortex was used as the reference region for [^{11}C]carfentanil and cerebellum for [^{11}C]raclopride. Receptor availability was expressed in terms of receptor-binding potentials (BP_{ND}), which is the ratio of specific to non-displacable binding in brain and proportional to receptor density. BP_{ND} was calculated by applying a basis function method for each voxel using the simplified reference tissue model with reference tissue time–activity curves as input data.[27] This model corrects the possible different peripheral distribution of radiotracers when using the same amount of injected activity in both obese and non-obese subjects.

Subject-wise parametric BP_{ND} images were normalized to the Montreal Neurological Institute standard space using the T1-weighted MR images, and smoothed with a Gaussian kernel of 8 mm full width at half maximum. Subsequently, voxel-wise differences in D_2R and MOR availability were compared using SPM8. Preoperative differences between obese and lean subjects were quantified with independent-samples *t*-test and the effects of bariatric surgery in the obese subjects using repeated-measures *t*-test. Statistical threshold was set at $P < 0.05$ with the false discovery rate corrected at cluster level. In a complementary approach, anatomic ROIs were generated in the ventral striatum, dorsal caudate nucleus, putamen, insula, amygdala, thalamus, orbitofrontal cortex, anterior cingulate cortex, medial cingulate cortex and posterior cingulate cortex using the AAL[28] and Anatomy[29] toolboxes. BP_{ND}s were extracted from these ROIs in both pre- (both groups) and postoperative (obese subjects only) scans. Between-groups ROI data were analyzed using a 2 (obese vs lean) × 10 (ROI) mixed ANOVA, and the follow-up data using a 2 (preoperative vs postoperative) × 10 (ROI) fully within-subjects ANOVA. Associations between ROI-wise receptor availabilities, questionnaire scores and biological variables were assessed using Pearson's correlations. Normality assumption was tested with the Kolmogorov–Smirnov test and sphericity assumption was confirmed with Mauchly's test.

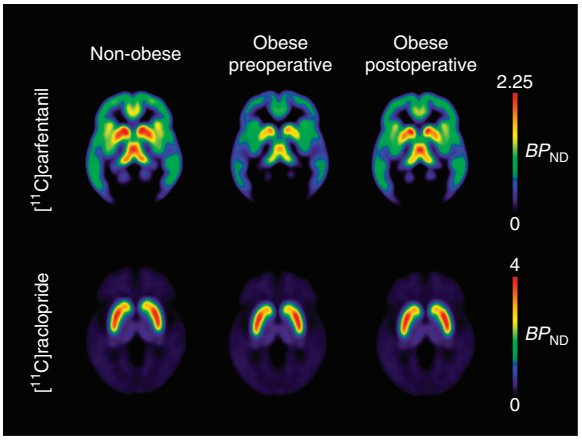

Figure 1. Mean distribution of [^{11}C]carfentanil and [^{11}C]raclopride BP_{ND}.

RESULTS

As reported previously,[12] SPM analysis revealed that MOR availability was preoperatively lower in the morbidly obese in the ventral striatum, dorsal caudate, putamen, insula, amygdala, thalamus, orbitofrontal cortex and posterior cingulate cortex (*P*'s < 0.05; Figure 1). The ROI analysis corroborated these findings (Figure 2). BP_{ND}s were lower in the obese group, $F(1,28) = 6.50$, $P = 0.02$, $\eta_p^2 = 0.18$ and also varied across ROI, $F(1,28) = 467.62$, $P < 0.001$, $\eta_p^2 = 0.94$. The interaction between ROI and group was not significant, $F = 2.19$. Weight loss (mean ± s.d. 26.1 ± 7.6 kg) following the bariatric surgery resulted in an average of 23% higher MOR availability in the postoperative scans. SPM analysis revealed significant increases in MOR availability in several areas implicated in reward processing including ventral striatum, dorsal caudate, insula, amygdala, thalamus, orbitofrontal cortex and anterior cingulate cortex. ROI analysis confirmed that weight loss led to BP_{ND} increase across ROIs, $F(1,15) = 18.72$, $P < 0.001$, $\eta_p^2 = 0.55$ and the mean BP_{ND} varied across ROIs, $F(1,15) = 111.57$, $P < 0.001$, $\eta_p^2 = 0.81$. However, MOR recovery did not vary across ROIs, $F = 1.80$. A postoperative increase in MOR availability was seen in all except one subject (Figure 3). This recovery increased the MOR availability to comparable levels with control subjects, $F(1,28) = 0.41$ and there was no significant difference in MOR availability between postoperative obese subjects and controls in any ROI (*P*'s > 0.05; Figure 2). Weight loss did not influence D_2R

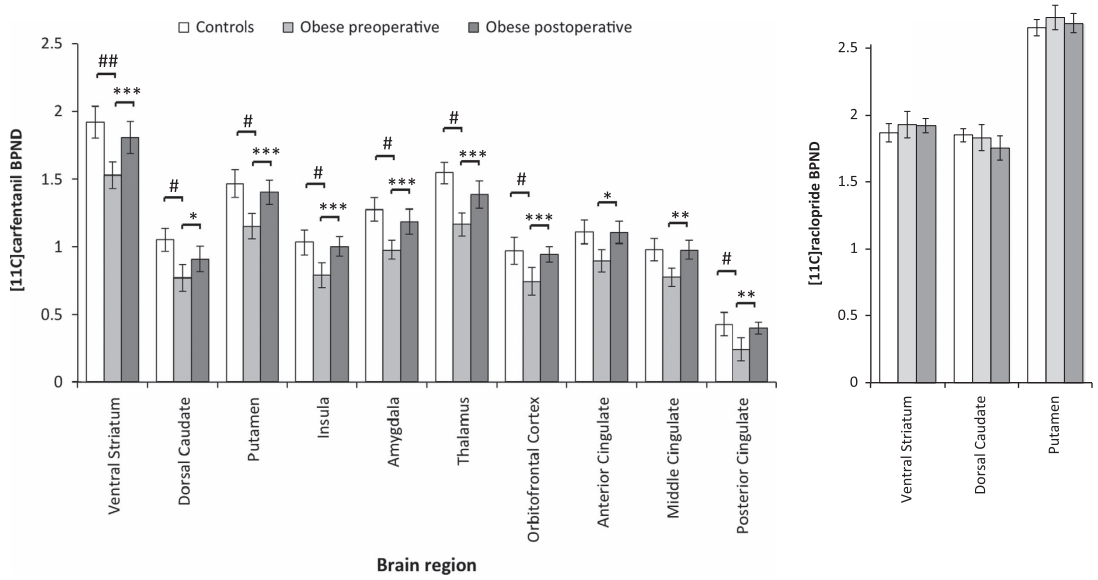

Figure 2. Mean regional MOR and D_2R availabilities. Significant differences between preoperative scans in obese and control subjects: $^{\#}P < 0.05$, $^{\#\#}P < 0.01$. Significant differences between pre- and postoperative scans in obese subjects: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

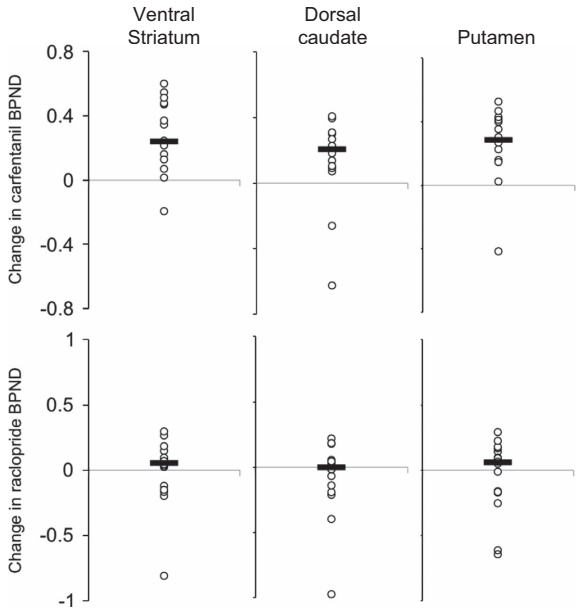

Figure 3. Postoperative changes in striatal MOR and D_2R availability in the obese subjects.

availability in any brain region. However, weight loss was associated with loss of subcutaneous (mean ± s.d. 5.8 ± 2.3 kg) and visceral fat (mean ± s.d. 2.1 ± 1.7 kg). T2DM was remitted in four (67%) subjects.

Preoperatively, BMI correlated negatively with MOR availability in every tested brain region except for anterior cinculate cortex (r's < -0.36, P's < 0.05). MOR availability also correlated negatively with fat percent in ventral striatum, putamen, amygdala and thalamus (r's < -0.43, P's < 0.02), and with subcutaneous and visceral fat mass in ventral striatum, dorsal caudate, putamen, insula, amygdala, thalamus, orbitofrontal cortex and posterior cingulate cortex (r's < -0.39, P's < 0.05). Leptin levels correlated negatively with MOR availability in ventral striatum and thalamus among obese and control subjects (r's < -0.36, P's < 0.05). Postoperatively, MOR availability correlated negatively with BMI in ventral striatum and dorsal caudate (r's < -0.45, P's < 0.05). Other postoperative scores on these variables were not associated with MOR availability in any brain region. Insulin sensitivity and plasma glucose levels did not correlate with MOR availability pre- or postoperatively, and there was no significant difference between MOR availability between obese subjects with or without T2DM. No differences in D_2R availability between obese and non-obese subjects were observed. Moreover, no associations between pre- or postoperative D_2R availability and anthropometric measurements or metabolic variables were found.

Before the surgical procedure, morbidly obese subjects had higher scores in the scales measuring restrained eating (DEBQ) and food addiction (YFAS), P's < 0.05 (Table 2). Obese and control groups did not differ from each other in Beck Depression Inventory II, trait anxiety (STAI), Food Craving Questionnaire scores, or in DEBQ emotional and external eating scales. Postoperatively, obese subjects reported significantly lower scores in food addiction (YFAS), food craving as well as pathological eating patterns (DEBQ emotional and external eating), P's < 0.05. No significant associations between receptor availabilities and questionnaire scores were observed with the exception of STAI scores, which were negatively associated with preoperative MOR availability in all ROIs (r's < -0.31, P's < 0.04); subjects with lower MOR tended to have higher scores for trait anxiety. No correlations between pre- or postoperative D_2R availability and behavioral measures were found.

To rule out the possible effect of smoking on receptor availability pre- and postoperatively, we reanalyzed the data excluding the smokers. This analysis yielded similar results for MOR and D_2R as in the whole sample population, confirming that changes in MOR availabilities among obese subjects are not due to smoking. We also compared the BP_{ND}s between the obese smokers and non-smokers, and found no significant differences in any ROI. In addition, including the use of antidiabetic, antihypertensive and cholesterol-lowering drugs as covariates in the analyses did not change the overall pattern or significance of the results.

DISCUSSION

Weight loss following bariatric surgery normalized the initially downregulated opioid receptor availability in the brain reward circuit in morbid obesity independently of insulin sensitivity and T2DM. Magnitude (mean increase 23%) as well as effect size for weight loss on MOR availability was substantial ($\eta_p^2 = 0.55$), suggesting that body weight changes play a major role in cerebral MOR availability. However, effects of obesity and weight loss on the dopaminergic system were absent. The MOR system promotes hedonic aspects of feeding,[18] and this can make obese individuals susceptible to overeating in order to gain the desired hedonic response from food consumption, which may further promote pathological eating. We propose that at the initial stages of weight gain, excessive eating may cause perpetual overstimulation of the MOR system, leading to subsequent MOR downregulation. Similar downregulation occurs in the dopaminergic system during prolonged cocaine and amphetamine use.[2,3] Accordingly, overeating may lead to a vicious circle, where eating-induced downregulation of MOR causes overeating in order to get the desired hedonic response, which in turn further suppresses the endogenous opioid system. However, bariatric surgery-induced weight loss and decreased food intake may reverse this process. The presently established link between the MOR system and obesity may thus make adherence to low-calorie diet challenging.

Nevertheless, the link between the receptor systems and overeating can be more complex than what clinical imaging studies suggest. Recent experimental animal work suggests that blunted hedonic responses due to reduced dopamine signaling lead to significantly less *ad libitum* caloric intake and eliminates motivation to work for food.[30] Experimental human studies however show opposite results, with experimentally reduced dopamine function resulting in significantly lower post-meal hunger rating without altering actual food intake.[31] Consequently, more animal and human studies are needed to establish whether lowered MOR (or D_2R) availability is directly linked with blunted hedonic responses following palatable food consumption and subsequent overeating.

Unlike the MOR system, the D_2R system was not altered in the obese state, and we did not observe any changes in D_2R availability after weight loss, even with statistically more lenient thresholds ($P < 0.05$ uncorrected for multiple comparisons). Corroborative evidence also stems from a study showing no change in D_2R availabilities after the bariatric surgery,[21] even though increased[10] and decreased[20] D_2R availability after a short (6–7 weeks) follow-up period have also been reported. Altogether these data indicate that the contribution of the dopaminergic system in human obesity is far more complex than has been previously thought. Even though the dopaminergic system—at least as measured with PET—seems insensitive to weight gain and loss, previous studies clearly implicate the role of this system in feeding and obesity. Feeding elevates dopamine release especially in the dorsal striatum,[32] and there is recent evidence that obese subjects have reduced dopamine release following glucose intake in ventral striatum.[33] In addition, animal studies indicate that the deficits of dopamine signaling and low availability of dopamine receptors in the striatum are associated with weight gain.[34] In fact,

it is likely that the interactions between D_2R and MOR systems are important in human obesity, and these interactions may be crucial when modulating the rewarding properties of food.[35–37]

Altogether our data show that drawing parallels between obesity and drug additions in general may be overly simplistic. For example, cocaine addiction is associated with higher rather than lower MOR availability, and the MOR levels remain elevated in abstinence.[14,38] Similarly, patients with alcohol dependency have elevated MOR availability in the ventral striatum, and the availability remains elevated in abstinence.[13] Our data from the MOR availability, nevertheless, parallel those observed in opiate dependence. Heroin-dependent subjects show reduction in MOR availability on buprenorphine treatment measured with [^{11}C] carfentanil, while MOR availability recovers after detoxification.[24] Similarly, one study using [^{11}C]diprenorphine found increased availability after early opioid abstinence.[39] On the basis of our studies, the neurobiological basis of obesity is more similar to opiate addictions than other addictive disorders, yet the exact mechanism underlying this similarity remains unclear. Our results thus suggest that the MOR system is a convincing target for pharmacological treatments of obesity. Accordingly, combination therapy with opioid antagonist naltrexone and atypical antidepressant bupropion has proven effective for treating obesity.[40]

This study has certain limitations. First, our outcome measure (BP_{ND}) does not distinguish between receptor density, affinity and the amount of endogenous neurotransmitter occupancy. Because we included only female subjects, the results may not be generalizable to male subjects. Also, we used only a D_2R antagonist [^{11}C]raclopride, and D_2R agonist ligands could be more sensitive for revealing between-group differences, especially among the obese subjects with lower BMI, as shown earlier.[41] In addition, some patients may start gaining weight later than 6 months from the bariatric surgery,[42] suggesting that longer follow-up studies are needed. Finally, our study shows that bariatric surgery-induced weight loss leads to increased MOR availability, we cannot fully differentiate the combined effects of weight loss and altered gastrointestinal functions following surgery. Furthermore, the actual mechanisms behind the increased MOR availability are unknown. Altered neuroreceptor availability may be due to the changes in gut hormones but also due to reduced intake of palatable foods. Further studies are thus needed to elucidate the sole effect of weight loss due to altered energy intake on MOR availability by comparing the effects of weight loss by surgery versus dieting.

CONCLUSIONS

Weight loss recovers dysfunction of the MOR system highlighting that the endogenous opioid system may be a key feature of the obese phenotype. The link between obesity and brain opioids established here suggests that future psychological and pharmacological interventions targeting this system could be an effective way for treatment of obesity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

HKK acquired and analyzed PET data and wrote the manuscript, JJT acquired PET data and wrote the manuscript, LT analyzed PET data and wrote the manuscript, JH designed the experiments and wrote the manuscript, HH acquired PET data and edited the manuscript, RP screened MRI data, SH produced the radiotracers and edited the manuscript, PS recruited the study subjects, PN designed the experiments and wrote the manuscript, LN designed the experiments, supervised data analysis and wrote the manuscript.

REFERENCES

1 Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev* 2013; **14**: 2–18.
2 Baik JH. Dopamine signaling in reward-related behaviors. *Front Neural Circuits* 2013; **7**: 152.
3 Ikemoto S, Bonci A. Neurocircuitry of drug reward. *Neuropharmacology* 2014; **76 (Pt B)**: 329–341.
4 Volkow ND, Wang GJ, Fowler JS, Logan J, Hitzemann R, Ding YS *et al.* Decreases in dopamine receptors but not in dopamine transporters in alcoholics. *Alcohol Clin Exp Res* 1996; **20**: 1594–1598.
5 Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M *et al.* Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psychiatry* 2001; **158**: 2015–2021.
6 Martinez D, Saccone PA, Liu F, Slifstein M, Orlowska D, Grassetti A *et al.* Deficits in dopamine D(2) receptors and presynaptic dopamine in heroin dependence: commonalities and differences with other types of addiction. *Biol Psychiatry* 2012; **71**: 192–198.
7 Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W *et al.* Brain dopamine and obesity. *Lancet* 2001; **357**: 354–357.
8 de Weijer BA, van de Giessen E, van Amelsvoort TA, Boot E, Braak B, Janssen IM *et al.* Lower striatal dopamine D2/3 receptor availability in obese compared with non-obese subjects. *EJNMMI Res* 2011; **1**: 37.
9 Haltia LT, Rinne JO, Merisaari H, Maguire RP, Savontaus E, Helin S *et al.* Effects of intravenous glucose on dopaminergic function in the human brain in vivo. *Synapse* 2007; **61**: 748–756.
10 Steele KE, Prokopowicz GP, Schweitzer MA, Magunsuon TH, Lidor AO, Kuwabawa H *et al.* Alterations of central dopamine receptors before and after gastric bypass surgery. *Obes Surg* 2010; **20**: 369–374.
11 Eisenstein SA, Antenor-Dorsey JA, Gredysa DM, Koller JM, Bihun EC, Ranck SA *et al.* A comparison of D2 receptor specific binding in obese and normal-weight individuals using PET with (N-[(11)C]methyl)benperidol. *Synapse* 2013; **67**: 748–756.
12 Karlsson HK, Tuominen L, Tuulari JJ, Hirvonen J, Parkkola R, Helin S *et al.* Obesity is associated with decreased mu-opioid but unaltered dopamine D2 receptor availability in the brain. *J Neurosci* 2015; **35**: 3959–3965.
13 Heinz A, Reimold M, Wrase J, Hermann D, Croissant B, Mundle G *et al.* Correlation of stable elevations in striatal mu-opioid receptor availability in detoxified alcoholic patients with alcohol craving: a positron emission tomography study using carbon 11-labeled carfentanil. *Arch Gen Psychiatry* 2005; **62**: 57–64.
14 Gorelick DA, Kim YK, Bencherif B, Boyd SJ, Nelson R, Copersino M *et al.* Imaging brain mu-opioid receptors in abstinent cocaine users: time course and relation to cocaine craving. *Biol Psychiatry* 2005; **57**: 1573–1582.
15 Weerts EM, Wand GS, Kuwabara H, Munro CA, Dannals RF, Hilton J *et al.* Positron emission tomography imaging of mu- and delta-opioid receptor binding in alcohol-dependent and healthy control subjects. *Alcohol Clin Exp Res* 2011; **35**: 2162–2173.
16 Whistler JL. Examining the role of mu opioid receptor endocytosis in the beneficial and side-effects of prolonged opioid use: from a symposium on new concepts in mu-opioid pharmacology. *Drug Alcohol Depend* 2012; **121**: 189–204.
17 Koch T, Hollt V. Role of receptor internalization in opioid tolerance and dependence. *Pharmacol Ther* 2008; **117**: 199–206.
18 Gosnell BA, Levine AS. Reward systems and food intake: role of opioids. *Int J Obes (Lond)* 2009; **33**: S54–S58.
19 Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G *et al.* Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ* 2013; **347**: f5934.
20 Dunn JP, Cowan RL, Volkow ND, Feurer ID, Li R, Williams DB *et al.* Decreased dopamine type 2 receptor availability after bariatric surgery: preliminary findings. *Brain Res* 2010; **1350**: 123–130.
21 de Weijer BA, van de Giessen E, Janssen I, Berends FJ, van de Laar A, Ackermans MT *et al.* Striatal dopamine receptor binding in morbidly obese women before and after gastric bypass surgery and its relationship with insulin sensitivity. *Diabetologia* 2014; **57**: 1078–1080.

22 Morinigo R, Moize V, Musri M, Lacy AM, Navarro S, Marin JL *et al.* Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab* 2006; **91**: 1735–1740.
23 Karamanakos SN, Vagenas K, Kalfarentzos F, Alexandrides TK. Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-YY levels after Roux-en-Y gastric bypass and sleeve gastrectomy: a prospective, double blind study. *Ann Surg* 2008; **247**: 401–407.
24 Zubieta J, Greenwald MK, Lombardi U, Woods JH, Kilbourn MR, Jewett DM *et al.* Buprenorphine-induced changes in mu-opioid receptor availability in male heroin-dependent volunteers: a preliminary study. *Neuropsychopharmacology* 2000; **23**: 326–334.
25 Frost JJ, Wagner HN Jr, Dannals RF, Ravert HT, Links JM, Wilson AA *et al.* Imaging opiate receptors in the human brain by positron tomography. *J Comput Assist Tomogr* 1985; **9**: 231–236.
26 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**: 258–261.
27 Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *NeuroImage* 1997; **6**: 279–287.
28 Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 2002; **15**: 273–289.
29 Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K *et al.* A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage* 2005; **25**: 1325–1335.
30 Tellez LA, Medina S, Han WF, Ferreira JG, Licona-Limon P, Ren XY *et al.* A gut lipid messenger links excess dietary fat to dopamine deficiency. *Science* 2013; **341**: 800–802.
31 Hardman CA, Herbert VM, Brunstrom JM, Munafo MR, Rogers PJ. Dopamine and food reward: effects of acute tyrosine/phenylalanine depletion on appetite. *Physiol Behav* 2012; **105**: 1202–1207.
32 Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *NeuroImage* 2003; **19**: 1709–1715.
33 Wang GJ, Tomasi D, Convit A, Logan J, Wong CT, Shumay E *et al.* BMI modulates calorie-dependent dopamine changes in accumbens from glucose intake. *PLoS One* 2014; **9**: e101585.
34 Michaelides M, Thanos PK, Kim R, Cho J, Ananth M, Wang GJ *et al.* PET imaging predicts future body weight and cocaine preference. *NeuroImage* 2012; **59**: 1508–1513.
35 Volkow ND, Wise RA. How can drug addiction help us understand obesity? *Nat Neurosci* 2005; **8**: 555–560.
36 Yeomans MR, Gray RW. Opioid peptides and the control of human ingestive behaviour. *Neurosci Biobehav Rev* 2002; **26**: 713–728.
37 Tuominen L, Tuulari JJ, Karlsson HK, Hirvonen J, Helin S, Salminen P *et al.* Aberrant mesolimbic dopamine-opiate interaction in obesity. *NeuroImage* 2015; **122**: 80–86.
38 Zubieta JK, Gorelick DA, Stauffer R, Ravert HT, Dannals RF, Frost JJ. Increased mu opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving. *Nat Med* 1996; **2**: 1225–1229.
39 Williams TM, Daglish MR, Lingford-Hughes A, Taylor LG, Hammers A, Brooks DJ *et al.* Brain opioid receptor binding in early abstinence from opioid dependence: positron emission tomography study. *Br J Psychiatry* 2007; **191**: 63–69.
40 Billes SK, Sinnayah P, Cowley MA. Naltrexone/bupropion for obesity: An investigational combination pharmacotherapy for weight loss. *Pharmacol Res* 2014; **84c**: 1–11.
41 Caravaggio F, Raitsin S, Gerretsen P, Nakajima S, Wilson A, Graff-Guerrero A. Ventral striatum binding of a dopamine d2/3 receptor agonist but not antagonist predicts normal body mass index. *Biol Psychiatry* 2015; **77**: 196–202.
42 Cooper TC, Simmons EB, Webb K, Burns JL, Kushner RF. Trends in weight regain following Roux-en-Y gastric bypass (RYGB) bariatric surgery. *Obes Surg* 2015; **25**: 1474–1481.