Cellular/Molecular

Obesity Is Associated with Decreased μ-Opioid But Unaltered Dopamine D_2 Receptor Availability in the Brain

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Neurochemical pathways involved in pathological overeating and obesity are poorly understood. Although previous studies have shown increased μ-opioid receptor (MOR) and decreased dopamine D_2 receptor (D_2R) availability in addictive disorders, the role that these systems play in human obesity still remains unclear. We studied 13 morbidly obese women [mean body mass index (BMI), 42 kg/m^2] and 14 nonobese age-matched women, and measured brain MOR and D_2R availability using PET with selective radioligands [^{11}C]carfentanil and [^{11}C]raclopride, respectively. We also used quantitative meta-analytic techniques to pool previous evidence on the effects of obesity on altered D_2R availability. Morbidly obese subjects had significantly lower MOR availability than control subjects in brain regions relevant for reward processing, including ventral striatum, insula, and thalamus. Moreover, in these areas, BMI correlated negatively with MOR availability. Striatal MOR availability was also negatively associated with self-reported food addiction and restrained eating patterns. There were no significant differences in D_2R availability between obese and nonobese subjects in any brain region. Meta-analysis confirmed that current evidence for altered D_2R availability in obesity is only modest. Obesity appears to have unique neurobiological underpinnings in the reward circuit, whereby it is more similar to opioid addiction than to other addictive disorders. The opioid system modulates motivation and reward processing, and low μ-opioid availability may promote overeating to compensate decreased hedonic responses in this system. Behavioral and pharmacological strategies for recovering opioidergic function might thus be critical to curb the obesity epidemic.

Key words: **dopamine; obesity; opioids; positron emission tomography; receptors; reward**

Introduction

Obesity is a great challenge to human health worldwide because it is associated with serious medical conditions such as type 2 diabetes, coronary heart disease, and stroke. Food reward is driven by functionally distinct neurochemical mechanisms promoting incentive motivation ("wanting") and hedonic impact ("liking") when food is consumed (Berridge, 2009). Accumulating evidence suggests that obesity is related to altered neurochemistry of the reward circuitry of the brain, making obese individuals prone to overeating (Berridge et al., 2010; Kenny, 2011; Volkow et al., 2013). The dopamine system supports incentive motivation, and dopaminergic reward system dysfunctions are associated with addictive disorders. In the striatum, alcohol and drug dependence are associated with lower dopamine D_2 receptor (D_2R) availability (Volkow et al., 1996, 2001; Martinez et al., 2012). Obese animals with unhealthy eating habits also show downregulation of D_2R (Johnson and Kenny, 2010). However, studies in obese human subjects have provided conflicting results, with some finding lower striatal D_2R availability (Wang et al., 2001; Volkow et al., 2008; de Weijer et al., 2011), and others unaltered striatal D_2R availability (Haltia et al., 2007, 2008; Steele et al., 2010).

Whereas the dopaminergic system is implicated in the desire for eating, the endogenous opioid system is involved in both incentive motivation and hedonic functions, also generating pleasurable sensations when palatable foods are consumed (Berridge et al., 2010). The μ-opioid receptors (MORs) function as a part of complex opioid system, and mediate the effects of endogenous opioids, such as β-endorphins and endomorphins, and various exogenous opioid agonists (Henriksen and Willoch, 2008). Alcohol dependence is associated with increased MOR availability in ventral striatum, possibly be due the upregulation of MORs or a reduction in endogenous opioids (Heinz et al., 2005; Weerts et al., 2011). Moreover, cocaine dependence is linked to increased MOR availability in more extensive neural

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Table 1. Characteristics of the participants

	Obese subjects ($n = 13$)		Nonobese subjects ($n = 14$)		
	Mean	SD	Mean	SD	p value*
Age (years)	39.08	10.74	44.86	12.88	0.22
Weight (kg)	116.82	16.60	61.39	7.19	**<0.001**
Height (cm)	166.27	6.94	164.86	6.32	0.59
BMI (kg/m^2)	41.89	3.88	22.65	2.94	**<0.001**
Fat (%)	50.44	4.06	30.21	10.17	**<0.001**
Subcutaneous fat mass (kg)	17.50	3.53	4.16	1.28	**<0.001**
Visceral fat mass (kg)	3.60	2.18	0.78	0.44	**<0.001**
HbA1c (%)	5.52	0.39	5.60	0.30	0.50
Systolic blood pressure (mmHg)	129.64	12.72	129.54	13.75	0.99
Diastolic blood pressure (mmHg)	83.27	8.81	80.23	8.25	0.40
Amount of alcohol use (drinks/week)	1.50	1.35	2.75	2.09	0.10
Tobacco smokers/nonsmokers (N)	5/13		0/14		**<0.001**
Injected activity of [^{11}C]raclopride (MBq)	243.84	27.83	257.78	18.51	0.14
Injected activity of [^{11}C]carfentanil (MBq)	251.00	10.38	250.14	9.23	0.82

HbA1c, Glycated hemoglobin A1c.

*Between-groups differences; significant differences in two-sample t test are shown in bold.

areas, such as anterior cingulate and frontal cortex (Gorelick et al., 2005). However, long-term opiate drug use is associated with downregulation in MORs (Koch and Höllt, 2008; Whistler, 2012).

Animal studies suggest that endogenous opioid system has an important role in the control of appetite. MOR agonists increase and opioid antagonists decrease food intake and hedonic pleasures caused by palatable foods (Gosnell and Levine, 2009; Peciña and Smith, 2010). Opioid antagonists also prevent food seeking and binge-like eating (Giuliano et al., 2012; Cambridge et al., 2013). Moreover, stimulation of the MOR in the shell of nucleus accumbens increases the pleasure responses for foods and may also trigger eating behavior (Peciña and Berridge, 2005). The μ-opioid receptor gene *OPRM1* also modulates the intake of fat and possibly the risk for gaining weight in humans (Haghighi et al., 2014). Accordingly, changes in MOR rather than D_2R availability can maintain excessive energy uptake due to altered hedonic processing of food. Here we determined the association between of obesity on the availability of D_2R and MOR using positron emission tomography (PET) in a cross-sectional design. We hypothesized that obesity would be associated with opioid and possibly dopamine neurotransmitter systems, which is reflected in decreased D_2R and MOR availabilities.

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 ethics committee-approved informed consent forms before scans.

Subjects. We recruited 13 morbidly obese women [mean body mass index (BMI), 41.9 kg/m^2; mean age, 39.1 years] for the study (Table 1). The BMI range was 37.1–49.3 kg/m^2. The obese subjects were compared with 14 healthy nonobese female subjects (mean BMI, 22.7 kg/m^2; mean age, 44.9 years) that were age and height matched with the obese subjects (Table 1). Clinical screening included history, physical examination, anthropometric measurements, and laboratory tests. Exclusion criteria involved binge-eating disorders (BEDs); neurological or severe mental disorders; and any kind of opiate drug use, substance abuse, excessive alcohol consumption (>8 U/week), determined by clinical interview, medical history, and blood tests. Subjects also completed questionnaires that measured emotional and reward functioning [Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Inventory (STAI), and behavioral inhibition system (BIS)/behavioral approach system (BAS) scales] as well as food craving and eating behavior [Trait and State Food Cravings Questionnaires (FCQ), Dutch Eating Behavior Questionnaire (DEBQ), Yale Food Addiction Scale (YFAS)]. None of the controls smoked tobacco, but five obese subjects were light smokers (smoking range, 3–15 cigarettes/d). None of the obese subjects had type 2 diabetes or used antidiabetic medications. Of the obese group, five subjects used oral medication for treatment of elevated blood pressure, three for treatment of hypothyreosis, and two for treatment of hypercholesterolemia. Use of antihypertensive and cholesterol-lowering drugs were discontinued before the experiments.

Image acquisition and quantification of receptor availability. We measured D_2 receptor availability with the antagonist [^{11}C]raclopride (Farde et al., 1986), and μ-opioid receptor availability with the high-affinity agonist [^{11}C]carfentanil (Frost et al., 1985) using PET on two separate visits. [^{11}C]Raclopride was synthesized using [^{11}C]methyl triflate, where cyclotron-produced [^{11}C]methane was halogenated by gas phase reaction into [^{11}C]methyl iodide (Larsen et al., 1997) and converted on-line into [^{11}C]methyl triflate (Jewett, 1992). The approach used was adapted from the published method (Langer et al., 1999) with the following modifications. The [^{11}C]methane was produced with a CC18/9 cyclotron (Efremov Institute, St. Petersburg, Russia) using 17 MeV protons for $^{14}N(p,\alpha)^{11}C$ nuclear reaction in a N_2-H_2 target gas (10% H_2). [^{11}C]methyl triflate was bubbled into a solution containing acetone (200 μl), *O*-desmethyl precursor (0.4 mg, 1.2 μmol), and NaOH (2.8 μl, 0.5 M) at 0°C. At the HPLC purification step, the mobile-phase composition was adjusted into (32:68) acetonitrile/0.01 M H_3PO_4, and [^{11}C]raclopride peak was cut into a rotary evaporator already containing propylene glycol/ethanol (7:3, 0.4 ml). The evaporation residue was formulated in phosphate buffer (8 ml, 0.1 M) and sterile filtered. A analytical HPLC column (Kinetex XB-C18, Phenomenex; 2.6 μm, 3.00 × 50 mm), acetonitrile in 0.05 M H_3PO_4 (23:77) mobile phase, 1 ml/min flow rate, 3.5 min run time, and detectors in series for UV absorption (214 nm) and radioactivity were used for the determination of identity, radiochemical purity, and mass concentration. [^{11}C]Carfentanil was produced as previously described (Hirvonen et al., 2009), except the mobile phase was changed into CH_3OH/0.1 M NH_4HCO_2 (70:30).

Both radioligands had high radiochemical purity (>99%). Before scanning, a catheter was placed in the subject's left antecubital vein for tracer administration. Head was strapped to the scanner table to prevent head movement. Subjects fasted for 2 h before scanning. A computed tomography (CT) scan was performed to serve as an attenuation map and a reference anatomical image of the brain. The clinical well being of subjects was monitored during the scanning.

We injected 251 ± 24 MBq of [^{11}C]raclopride and 251 ± 10 MBq of [^{11}C]carfentanil in separate scans on separate days. After injection, radioactivity in brain was measured with the GE Healthcare Discovery 690 PET/CT scanner for 51 min, using 13 time frames. MRI was performed with a Philips Gyroscan Intera 1.5 T CV Nova Dual scanner to exclude structural abnormalities and to provide anatomical reference images for the PET scans. High-resolution anatomical images (1 mm^3 voxel size) were acquired using a T1-weighted sequence (TR, 25 ms; TE, 4.6 ms; flip angle, 30°; scan time, 376 s).

All alignment and coregistration steps were performed using SPM8 software (www.fil.ion.ucl.ac.uk/spm/) running on Matlab R2012a (MathWorks). To correct for head motion, dynamic PET images were first realigned frame to frame. The individual T1-weighted MR images were coregistered to the summation images calculated from the realigned frames. Regions of interest (ROIs) for reference regions were drawn manually on MR images using PMOD version 3.4 software (PMOD Technologies). 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 BP_{ND}, which is the ratio of specific to nondisplaceable binding in brain. BP_{ND} was calculated applying the basis function method for each voxel using the simplified reference tissue model with reference tissue time activity curves as input data (Gunn et al., 1997). This outcome measure is not confounded by differences in peripheral distribution or radiotracer metabolism.

The subject-wise parametric BP_{ND} images were normalized to the MNI space using the T1-weighted MR images, and smoothed with a Gaussian kernel of 8 mm FWHM. Subsequently, between-groups, vox-

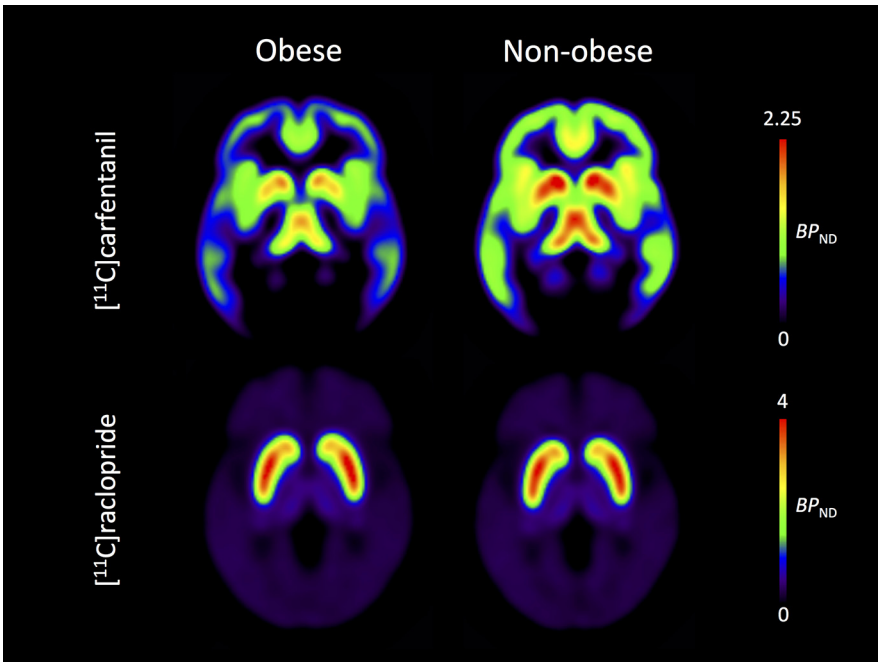

Figure 1. Averaged images of [^{11}C]carfentanil and [^{11}C]raclopride showing lowered MOR availability but unaltered D_2R availability among obese patients.

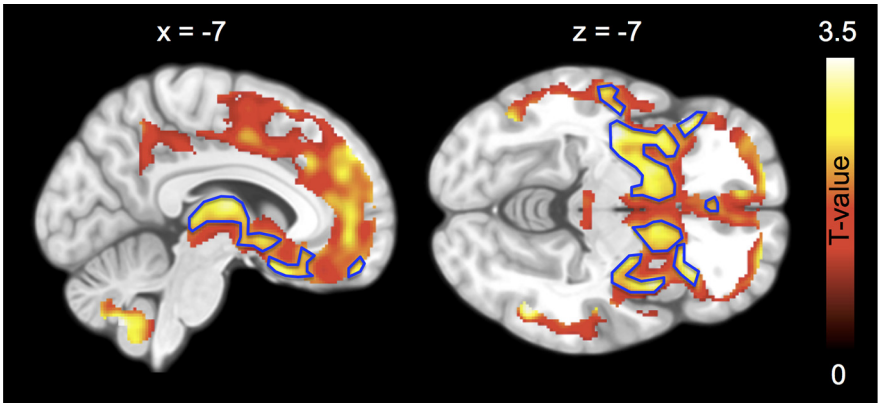

Figure 2. Brain regions showing lowered MOR availability in morbidly obese patients versus healthy control subjects. The data are thresholded at $p < 0.05$, FDR corrected. The blue outline shows regions where the effect is significant at a more stringent statistical threshold ($p < 0.01$, FDR corrected).

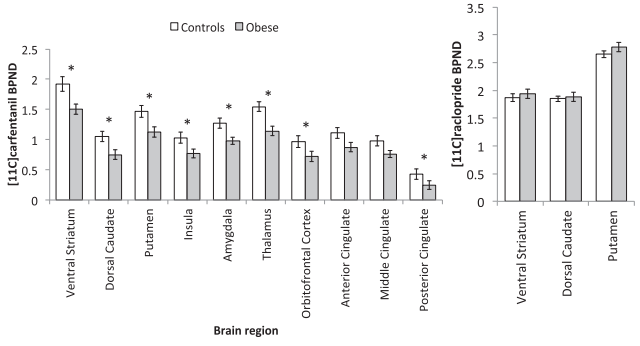

Figure 3. Mean [^{11}C]carfentanil and [^{11}C]raclopride BP_{ND} in regions of interest. Note: MOR data show a main effect of group (obese < lean) with no interaction with ROI. *$p < 0.05$ in complementary contrast test.

elwise differences in D_2R and MOR BP_{ND} were compared using independent samples *t* tests in SPM8. The statistical threshold was set at $p < 0.05$, false discovery rate (FDR) corrected at the cluster level. In a complementary approach, anatomic regions of interest were generated in ventral striatum, dorsal caudate nucleus, putamen, insula, amygdala, thalamus, orbitofrontal cortex, anterior cingulate cortex, medial cingulate cortex, and posterior cingulate cortex using the AAL (Tzourio-Mazoyer et al., 2002) and Anatomy (Eickhoff et al., 2005) toolboxes. These data were analyzed with a 2 (group) × 10 (ROI) mixed ANOVA. Associations among receptor availabilities (i.e., BP_{ND} values in each ROI), BMI, and questionnaire scores were assessed using Pearson correlations.

Finally, to weight the existing evidence on striatal D_2R availability in obesity, we conducted a meta-analysis on human PET studies targeting obesity using [^{11}C]raclopride. The meta-analysis includes peer-reviewed studies written in English and published through the end of April 2014. Several search methods were used. The Web of Science, PubMed, and Scopus databases were searched to retrieve documents containing the terms "dopamine," "obesity," "PET," "raclopride," and "receptor," in article title, abstract, or keywords. Articles referred to in articles found by the preceding method were examined. Studies were accepted for the meta-analysis if they met the following criteria: (1) they had compared D_2R availability in obese versus normal-weight subjects using PET; and (2) they used [11C]raclopride as a radiotracer. Effect sizes were estimated using the *r* statistic based on means and variances and the number of participants, or, alternatively, the *F* or *t* test values and degrees of freedom (Rosenthal, 1984; Rosenthal and DiMatteo, 2001). Effect sizes were consistently computed in such a way that positive values reflect lowered D_2R availability in obese individuals. Subsequently, weighted effect sizes were computed and subjected to meta-analysis using unbiased estimates of correlation coefficients and a restricted maximum likelihood estimator, yielding mean and 95% confidence intervals (CIs) for the effect sizes. This model assumes that effect sizes are contingent on study parameters, thus allowing for an estimation of both within- and between-studies variances. Altogether with the present data, the meta-analysis included data from 105 subjects stemming from five independent studies.

Results

Full-volume analysis revealed that morbidly obese patients had significantly lower [^{11}C]carfentanil BP_{ND} values ($p < 0.05$, FDR corrected in the SPM analysis), versus control subjects, throughout the reward circuit, including the ventral striatum, dorsal caudate, thalamus, insula, orbitofrontal cortex, and anterior cingulate cortex (Figs. 1, 2, 3). However, there were no significant differences in [^{11}C]raclopride BP_{ND} values in any brain region. Furthermore, there were no regions with higher [^{11}C]carfentanil or [^{11}C]raclopride BP_{ND} values in obese versus normal-weight individuals. These effects were corroborated in the ROI analysis. For [^{11}C]carfentanil, the ANOVA revealed that BP_{ND} values were lower for obese versus lean subjects ($F_{(1,25)} = 6.17$, $p = 0.02$, $\eta_p^2 = 0.20$) and differed across ROIs ($F_{(1,25)} = 400.42$, $p < 0.001$, $\eta_p^2 =$

0.89), yet no interaction between subject group and ROI was observed ($F = 2.16, p > 0.05$). For [^{11}C]raclopride, there was a main effect of ROI ($F_{(1,25)} = 246.92$, $p < 0.001$, $\eta_p^2 = 0.92$), but there was neither a difference between groups ($F = 1.04$, $p > 0.05$) nor an interaction between group and ROI ($F = 0.52$, $p > 0.05$).

Across the whole sample, BMI correlated negatively with [^{11}C]carfentanil BP_{ND} in ventral striatum, dorsal caudate, putamen, insula, amygdala, thalamus, as well as orbitofrontal cortex ($r_s \leq -0.42$; $p < 0.03$; Fig. 4). No significant correlations between BMI and [^{11}C]raclopride BP_{ND} were observed in any region.

To rule out the possible effect of smoking on receptor availability, we reanalyzed the data excluding the smokers. This analysis yielded results for MOR and D_2R that were similar to those for the whole sample population, confirming that decreased MOR in obese subjects is not due to smoking. We also compared the BP_{ND} values between the obese smokers and obese nonsmokers, and found no significant differences.

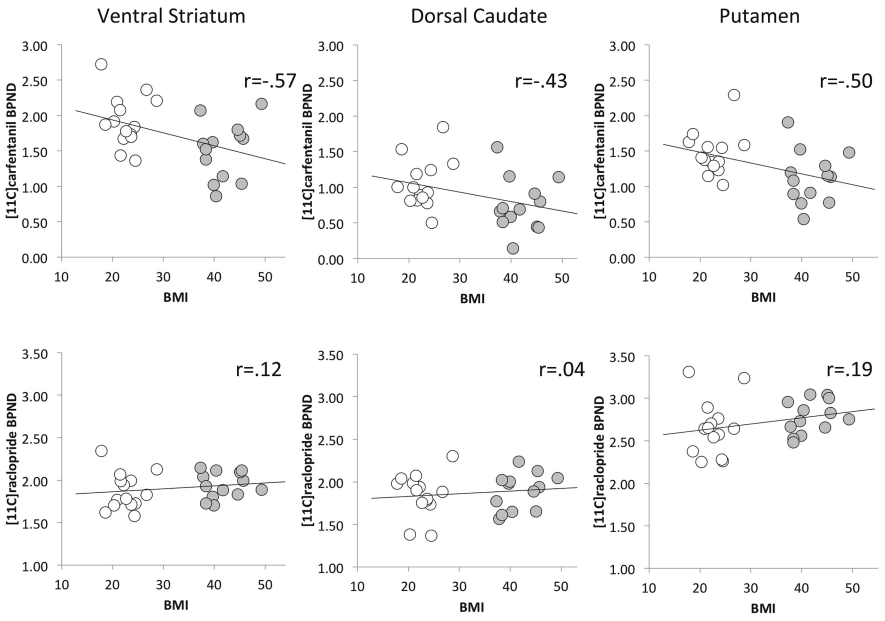

Figure 4. Scatterplots illustrating the relationship between BMI and BP_{ND} in ventral striatum, dorsal caudate, and putamen.

Even though obesity was not associated with D_2R availability per se, we next asked whether MOR and D_2R availabilities would have a joint contribution to an individual's BMI. To this end, we conducted a regression analysis where we predicted BMIs with regional MOR and D_2R availability, running a separate regression model for each striatal ROI. For all tested ROIs, MOR ($p < 0.05$) but neither D_2R availability nor interaction between MOR and D_2R availability ($p > 0.05$) predicted an individual's BMI.

Morbidly obese subjects scored significantly higher on the scales measuring pathological eating (DEBQ restrained and emotional eating) and food addiction (YFAS; Table 2). They also scored significantly lower in the BIS scale measuring behavioral inhibition, but the groups did not differ from each other in depression (BDI-II), trait anxiety (STAI), behavioral activation (BAS), or food craving (FCQ) scores. The STAI scores were negatively associated with MOR availability in anterior cingulate cortex, middle cingulate cortex, and posterior cingulate cortex ($r \leq -0.38$, $p < 0.05$). The DEBQ restrained eating score correlated negatively with MOR availability in ventral striatum, amygdala, and thalamus ($r \leq -0.38$, $p < 0.05$), and YFAS scores were negatively associated with MOR availability in dorsal caudate ($r = -0.39$, $p < 0.05$). However, these analyses were not significant after adjusting for multiple comparisons using the Bonferroni procedure. No significant associations between D_2R availability and questionnaire scores were found. The full volume group differences in MOR availability were in general similar, albeit with slightly weaker effects when each of these factors was included as covariates in the SPM analyses. Including these covariates in the analysis of D_2R availability did not alter the corresponding results.

Finally, the meta-analysis (Fig. 5) confirmed that, even though the overall effect size for BMI on D_2R availability was positive ($r = 0.14$), its 95% CI overlapped with zero (−0.11 to 0.40), suggesting that there was no effect of BMI on D_2R availability. However, moderator analysis using Wald-type test for model coefficients revealed that the effect size had a quadratic relationship between the BMI of the patients studied ($QM(1) = 4.3439$, $p = 0.04$), suggesting that only extreme obesity may lead to lowered D_2R availability ($p > 0.05$).

Table 2. Questionnaire scores

	Obese subjects ($n = 13$)		Nonobese subjects ($n = 14$)		
	Mean	SD	Mean	SD	*p* value*
BDI-II	5.92	5.77	4.36	4.11	0.43
STAI	38.77	9.14	34.07	5.47	0.12
BIS	13.46	3.18	16.64	2.79	**0.01**
BAS					
Drive	9.92	4.27	8.71	2.55	0.39
Fun seeking	11.08	3.09	10.57	2.44	0.64
Reward responsiveness	10.00	3.63	10.50	1.83	0.66
FCQ					
State	30.92	10.32	26.71	6.28	0.22
Trait	104.31	35.34	86.21	25.61	0.14
DEBQ					
Restrained eating	33.54	5.66	26.00	6.18	**0.003**
Emotional eating	31.00	11.31	22.07	6.33	**0.02**
External eating	26.31	6.73	25.36	5.76	0.70
YFAS	18.00	11.00	7.86	5.95	**0.009**

*Between-groups differences; significant differences in two-sample *t* test are shown in bold.

Discussion

Cerebral MOR availability was lowered in morbidly obese patients in brain regions implicated in reward processing, including ventral striatum, orbitofrontal cortex, amygdala, putamen, insula, and anterior cingulate, while D_2R availability remains unaltered. Altered MOR availability was also paralleled with alterations in affect-driven eating, as indicated by elevated self-reported food addiction and restrained eating behavior. Critically, food addiction and restrained eating scores were also associated with MOR availability, suggesting that the lowered MOR availability is directly linked with the tendency to compulsively eat regardless of internal state of hunger or satiety.

Prior work has established that the opioid system is involved in the pathophysiology of addictive disorders by causing altered sensations of pleasure, but it is also involved in hedonic and motivational processing of food (Peciña and Smith, 2010). Opi-

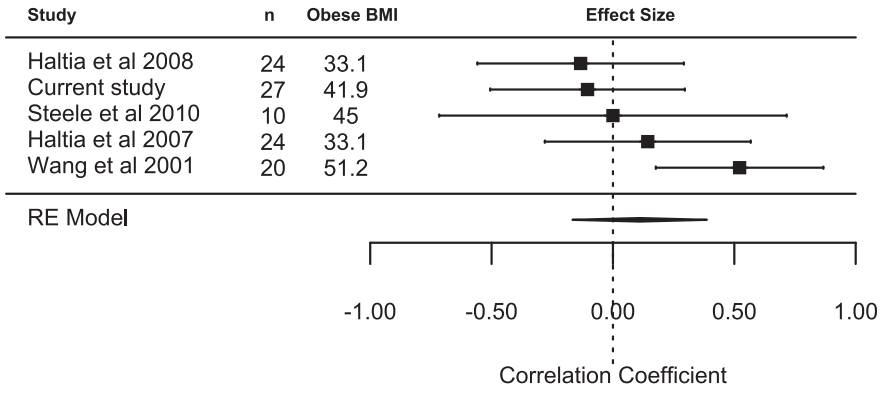

Figure 5. Random-effects analysis for the effects of obesity on D_2R availability in PET studies using [^{11}C]raclopride. RE, Random effects.

oid receptor blockage with opioid antagonists decreases, whereas stimulation with agonists increases, the food intake in both rodents and humans (Glass et al., 1999; Yeomans and Gray, 2002; Giuliano et al., 2012; Ziauddeen et al., 2013). Inverse MOR agonists also reduce the hedonic properties of food and eating in humans (Nathan et al., 2012), and obese humans with BEDs show reduced responses to pictures of high-calorie food in fMRI when using a MOR antagonist, which suggest a strong link with altered MOR functioning and food-related behavior (Cambridge et al., 2013). Opioid peptides and receptors are abundantly expressed in the reinforcement–reward circuit of the human brain (Le Merrer et al., 2009), and in the present study obesity was associated with marked MOR downregulation within this system. Accordingly, altered MOR functioning could underlie obesity and maintain pathological eating behaviors due to altered hedonic processing of palatable foods.

Obesity has been proposed to share neural pathophysiology with addictive disorders (Volkow and Wise, 2005); however, our findings challenge this concept as overly simplistic. Even though the observed downregulation of the MOR system in obesity is in good accordance with that observed in opiate addictions, our results contrast with findings from previous human PET studies measuring MOR and D_2R systems in subjects with other addictive disorders. For example, cocaine addiction is associated with increased rather than decreased MOR availability in frontal, lateral temporal, and anterior cingulate cortices, and the elevated levels are observed also in abstinence (Zubieta et al., 1996; Gorelick et al., 2005). Similarly, patients with alcohol dependency have increased MOR availability in the ventral striatum (Heinz et al., 2005). Thus, different neuromolecular changes appear to underlie obesity on the one hand, and addictive disorders and nonopiate substance abuse on the other.

Our outcome measure, BP_{ND}, does not distinguish between receptor density and affinity. Therefore, our finding of lower [^{11}C]carfentanil BP_{ND} values may reflect either a decreased number of receptor proteins or a lowered affinity to bind this radioligand agonist. Downregulation of the receptor protein itself may be caused by long-term overstimulation by endogenous agonists, as a homeostatic mechanism common to various G-protein-coupled receptors. A lower number or a reduced affinity of receptors will result in diminished overall net stimulation of the MOR system after pleasurable stimuli, such as eating, for a given amount of endogenous opioids released. We thus propose that perpetual amplification of the sensory pleasure of eating in the MOR system (Berridge, 2009) may lead to subsequent downregulation of the MOR. Alternatively, lower MOR density could be a predisposing trait factor, making subjects vulnerable to becoming obese. Whatever the cause, this downregulation may render these individuals susceptible to overeating to gain the desired hedonic response and maintain pathological eating behaviors.

In contrast with our hypothesis, we did not observe lowered D_2R availability in the obese subjects. Similarly, when predicting BMIs with regional D_2R and MOR availabilities, only MOR availability was established as a significant predictor. Of the five existing studies on D_2R availability in obese versus lean individuals using [^{11}C]raclopride, only one (Wang et al., 2001) has unambiguously found lowered striatal D_2R availability in obese patients. All the remaining studies (Haltia et al., 2007, 2008; Steele et al., 2010; and the present study) failed to observe any differences between obese and lean subjects in regional analyses in striatum. Consistent with this, our meta-analysis failed to establish a strong association between striatal D_2R availability and BMI, resulting in a modest ($r = 0.14$) negative effect size whose 95% CI included zero. Nevertheless, the strongest effect of BMI on D_2R availability was found in a study (Wang et al., 2001) where the mean BMI among obese subjects was >50 kg/m^2 (compared with 42 kg/m^2 in our study), which suggests extremely pathological eating habits and metabolically more severe disease. This was confirmed in a moderator analysis, which revealed that BMI had a quadratic relationship with lowered D_2R availability. In sum, the PET data seem to suggest that lowered D_2R availability in obesity may be an exception restricted to the most morbidly obese individuals, rather than a general pathophysiological feature.

However, it must be noted that previous human brain-imaging studies support the role of D_2R function in food intake (Guo et al., 2014). Feeding is associated with elevated dopamine release, especially in dorsal striatum (Small et al., 2003; Volkow et al., 2011), and animal studies show that deficits in dopamine signaling and low availability of dopamine receptors in the striatum is associated with weight gain (Geiger et al., 2009; Michaelides et al., 2012). Animal studies also suggest that diet-induced obesity and the resulting blunted dopamine signaling may lead to compensatory eating to normalize dopamine activity (Tellez et al., 2013). Furthermore, The D_2R TaqI A1 allele is also associated with obesity (Carpenter et al., 2013), and it moderates blunted striatal responses to food (Stice et al., 2008). The endogenous opioid system interacts with the dopaminergic system via GABAergic neurons. GABAergic neurons inhibit the dopaminergic system, but MORs prevent this inhibition and may cause elevated dopamine release (Yeomans and Gray, 2002; Volkow and Wise, 2005). This is in line with the fact that MOR agonists increase and MOR antagonists reduce food intake in rodents and humans (Glass et al., 1999; Yeomans and Gray, 2002; Giuliano et al., 2012; Ziauddeen et al., 2013). It is thus possible that interactions between opioid and dopamine systems could be a critical factor underlying the pathophysiology of obesity, even though mere changes in D_2R availability in obesity cannot be consistently observed with PET.

Limitations

Because the present study involved only female subjects, we cannot rule out sex effects. Furthermore, we did not control for the cycle phase in the current study, but the phase of the menstrual

cycle was distributed evenly (data not shown). Even though our sample was sizeable, it is possible that more pronounced differences associated with the obese phenotype could be established in larger studies. Finally, it must be borne in mind that the present cross-sectional study cannot reveal whether obesity causes MOR downregulation or vice versa.

Conclusions

Morbid obesity is associated with decreased MOR availability in the brain, while D_2R availability remains unaltered. We propose that the endogenous opioid system is a key component underlying human obesity, whereas the function of the dopaminergic system is less profound. The neurochemical changes associated with obesity are partially distinct from those observed in patients with addictive disorders and substance abuse. Future longitudinal studies should examine whether decreased MOR function is a trait phenomenon reflecting a vulnerability to develop obesity by overeating, or a direct and possibly recoverable consequence of obesity on the brain.

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