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Binge eating disorder and morbid obesity are associated with lowered mu-opioid receptor availability in the brain

Juho Joutsa[a,b,c,d,f,*], Henry K. Karlsson[d], Joonas Majuri[c,d], Pirjo Nuutila[d,e], Semi Helin[d], Valtteri Kaasinen[c,d,f], Lauri Nummenmaa[d,g]

[a] Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
[b] Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Boston, MA, USA
[c] Department of Neurology, University of Turku, Turku, Finland
[d] Turku PET Centre, University of Turku, Turku, Finland
[e] Department of Endocrinology, Turku University Hospital, Turku, Finland
[f] Division of Clinical Neurosciences, Turku University Hospital, Turku, Finland
[g] Department of Psychology, University of Turku, Turku, Finland

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ABSTRACT

Both morbid obesity and binge eating disorder (BED) have previously been linked with aberrant brain opioid function. Behaviorally these two conditions are however different suggesting also differences in neurotransmitter function. Here we directly compared mu-opioid receptor (MOR) availability between morbidly obese and BED subjects. Seven BED and nineteen morbidly obese (non-BED) patients, and thirty matched control subjects underwent positron emission tomography (PET) with MOR-specific ligand [^{11}C]carfentanil. Both subjects with morbid obesity and BED had widespread reduction in [^{11}C]carfentanil binding compared to control subjects. However, there was no significant difference in brain MOR binding between subjects with morbid obesity and BED. Thus, our results indicate that there is common brain opioid abnormality in behaviorally different eating disorders involving obesity.

1. Introduction

Obesity and eating disorders are a major public health problem worldwide, and the prevalence of obesity is constantly rising. Despite the economical and academic resources dedicated to obesity research, its neurobiological background still remains poorly understood (Val-Laillet et al., 2015). Recent evidence from human and animals studies however points towards the key contribution of the endogenous opioid system in both food intake and obesity (Nogueiras et al., 2012).

Obesity is a multifactorial condition, resulting from chronic overeating relative to the energy consumption, but obesity may also result from specific eating disorders, such as binge eating disorder (BED) (Val-Laillet et al., 2015). However, most obese individuals do not have BED (Yanovski 1999). Although common (non-BED) obesity and BED are both eating-related problems and involve excessive eating and weight gain, their behavioral underpinnings are clearly different. Common obesity results from long-term increase in food intake relative to energy consumption, whereas BED is characterized by uncontrollable recurrent episodes of eating large amounts of food and feelings of shame, distress or guilt about eating (Kessler et al., 2013). Although the boundary between normal body weight and obesity can be considered somewhat arbitrary, morbid obesity represents a pathological condition with clearly abnormal eating behavior and increased health risks. Comparing morbid obesity and BED provides an opportunity for understanding the neurobiology of different pathological eating behaviors that lead to development of obesity.

Because both morbid obesity and especially BED share behavioral characteristics with substance abuse disorders (SUDs), it has been proposed that obesity might be understood from the viewpoint of addictive disorders (Schulte et al., 2015; Potenza 2014; Ziauddeen et al., 2012). Impaired dopaminergic function and deficits in frontostriatal networks implicated in reward processing and impulse control are the hallmarks of SUDs (Volkow et al., 2011). Although early human neuroimaging studies suggested parallels between dopaminergic dysfunctions in obesity and SUDs (Wang et al., 2001), more recent studies have challenged the view that obesity would be associated with dopamine-deficiency similarly as SUDs, suggesting a crucial role for other neurotransmitters in addition to dopamine (Karlsson et al., 2015a; Haltia et al., 2007; Steele et al., 2010).

Clinical and translational research has indicated that the

* Corresponding author at: MGH/HST/MIT Athinoula A, Martinos Center for Biomedical Imaging, 149 13th street, room 2301, MA 02129, USA.
E-mail addresses: jjoutsa@mgh.harvard.edu, jtjout@utu.fi (J. Joutsa).

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endogenous opioid system regulates food consumption (Nogueiras et al., 2012; Pecina and Smith 2010). Administration of opioid agonists increase and antagonists decrease food intake in rodents and humans (Pecina and Smith 2010; Nogueiras et al., 2012). Neuroimaging studies in humans have confirmed that obesity and eating disorders are associated with lowered mu-opioid receptor (MOR) availability in the brain (Karlsson et al., 2015a; Bencherif et al., 2005; Burghardt et al., 2015; Majuri et al., 2017a). These findings are in striking contrast to SUDs (apart from opioid addictions) that are in general associated with increased rather than decreased MOR availability and show treatment response to opioid antagonist medication (Gorelick et al., 2005; Heinz et al., 2005; Palpacuer et al., 2015). The affected brain regions in obesity and eating disorders vary from study to study, but there are no studies directly comparing brain MOR availability between these conditions. Characterizing how differences in regional brain opioid function contribute to the behavioral phenotype would be valuable for understanding the pathophysiological mechanisms and development of pharmacological or neuromodulation therapies.

Here we directly compared cerebral MOR availability between two forms of pathological overeating: BED and morbid (non-BED) obesity. We hypothesized that although both conditions are associated with widespread reduction in MOR availability, regional differences in MOR function might explain the differences in behavioral phenotypes.

2. Methods

The study was approved by the Ethics Committee of the Hospital District of South west Finland. Written informed consent was obtained and the study was conducted according to the principles of the Declaration of Helsinki.

2.1. Subjects

The study sample ($n = 56$; see Table 1 for details) consisted of nineteen non-BED morbidly obese and seven BED patients with their control groups ($n = 14$ and $n = 16$, respectively) selected from our earlier studies using the criteria described later in this paragraph (Karlsson et al., 2015a; Karlsson et al., 2015b; Majuri et al., 2017a). MOR binding abnormality in both of the conditions separately have been published earlier (Karlsson et al., 2015a; Karlsson et al., 2015b; Majuri et al., 2017a). BED diagnoses were excluded or confirmed by a structured clinical interview. Exclusion criteria were age below 18 years, poor compliance, current pregnancy or lactation, BMI over 60 kg/m^2 or weight over 170 kg, any clinically significant psychiatric or medical condition (apart from type 2 diabetes not requiring insulin treatment), psychopharmacological medications, contraindication for MRI, substance abuse, and claustrophobia. Alcohol (< 48 h), coffee (< 12 h), and cigarette (< 8 h) consumption was prohibited prior the PET scanning. Mood and reward functions were evaluated using the Beck Depression Inventory (BDI-II), Behavioral inhibition system / behavioral approach system scale (BIS/BAS), Dutch Eating Behavior Questionnaire (DEBQ) and Yale Food Addiction Scale (YFAS).

2.2. Imaging

MOR availability was measured using [^{11}C]carfentanil positron emission tomography (PET). The radioligand production and scanning protocols have been described previously (Karlsson et al., 2015a). Morbidly obese patients with their matched controls were scanned using GE Healthcare Discovery 690 PET/CT scanner (General Electric Medical Systems, Milwaukee, WI) and BED patients with their matched controls using Siemens High Resolution Research Tool scanner (HRRT, Siemens Medical Solutions, Knoxville, TN). Antecubital vein was cannulated prior the scanning for the radioligand administration and the [^{11}C]carfentanil solution was given as a rapid bolus at the beginning of the scan. Patients and controls received similar radiation doses of [^{11}C]carfentanil (two-sample t-tests $P > 0.2$), because the outcome measure the ratio of specific relative to the non-displaceable binding potential (BP_{ND}) is not considered sensitive for injected activity per weight. Injected [^{11}C]carfentanil masses did not differ between patients and controls in either of the scanners (two-sample t-tests $P > 0.4$). The mean (SD) injected [^{11}C]carfentanil radiation dose and mass were 253 (11) MBq and 0.23 (0.20) ug for GE, and 498 (16) MBq and 0.42 (0.28) ug for HRRT (difference between scanners t-test $p = 0.007$ for mass and $p < 0.001$ for radiation dose), respectively. The total scanning time was 51 min from the injection. A strap or thermoplastic mask was used to reduce head motion during the scanning. Structural T1-weighed MR images (1 mm cubic voxels) were acquired to exclude structural brain lesions and to provide an anatomical reference for PET images using Philips Gyroscan Intera 1.5T CV Novo Dual scanner (Philips Healthcare, Cleveland, Ohio, USA) (morbidly obese patients and matched controls) or Philips Ingenuity 3T PET-MRI scanner (BED patients and matched controls).

Image preprocessing was performed using Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running in Matlab 2012a (Mathworks Inc., Natick, MA, USA).

Table 1
Demographical data and questionnaire scores.

	MO Controls $n = 14$	Morbidly obese $n = 19$	BED $n = 7$	p-value[1]	BED Controls $n = 16$
Age, [years]	44.9 (12.9)	41.8 (10.3)	49.4 (5.1)	0.07	43.1 (11.4)
Sex, n [f/m]	14/0	19/0	7/0	1.0	8/8
BMI, [kg/m^2]	22.7 (2.9)[2]	40.7 (3.8)	30.9 (6.6)	0.007	24.6 (2.0)[3]
Smoking, n (%)	0 (0%)[2]	6 (32%)	2 (29%)	1.0	6 (38%)
Type 2 diabetes, n (%)	0 (0%)[2]	7 (37%)	0 (0%)	0.13	0 (0%)
BDI-II	4.4 (4.1)	5.1 (5.1)	15.4 (9.6)	0.03	2.8 (3.2)[3]
YFAS	7.9 (5.9)[2]	16.3 (10.1)	42.3 (6.5)	< 0.001	5.3 (3.5)[3]
DEBQ restrained	26.0 (6.2)[2]	33.4 (6.0)	35.3 (3.4)	0.44	24.8 (7.1)[3]
DEBQ emotional	22.1 (6.3)	27.6 (10.9)	50.0 (8.3)	< 0.001	20.1 (4.9)[3]
DEBQ external	25.4 (5.8)	26.3 (6.1)	37.5 (6.3)	0.001	23.6 (5.5)[3]
BIS	16.6 (2.8)[2]	13.9 (2.8)	12.6 (3.2)	0.31	15.8 (2.7)[3]
BAS drive	8.7 (2.6)	10.5 (3.8)	11.9 (2.3)	0.38	12.4 (3.2)
BAS fun seeking	10.6 (2.4)	11.5 (2.8)	11.9 (3.0)	0.77	11.0 (2.9)
BAS reward responsiveness	10.5 (1.8)	10.6 (3.5)	12.4 (1.5)	0.20	12.1 (2.6)

MO Controls = control subjects for morbidly obese subjects. BED Controls = control subjects for BED subjects. BED = binge eating disorder. YFAS = Yale Food Addiction Scale. BDI-II = Beck Depression Inventory. DEBQ = Dutch Eating Behavior Questionnaire. BIS = Behavioral inhibition system. BAS = Behavioral activation system. Mean (SD) values are presented unless otherwise stated. [1]P-values are calculated between morbidly obese and BED patients using t-test or Fisher's exact, as appropriate. [2]Significant difference between MO Controls and morbidly obese patients ($p < 0.05$). [3]Significant difference between BED Controls and BED patients ($p < 0.05$).

First, the individual frames of dynamic PET images were realigned to correct for head motion during the scan. Motion corrected images were then coregistered with the individual T1-weighted MRI and warped to the Montreal Neurological Institute (MNI) space using the structural information of the MRI (Ashburner 2007; Ashburner and Friston 2005). [^{11}C]carfentanil BP_{ND} images were calculated using the simplified reference tissue model with occipital cortex as the reference region (Gunn et al., 1997; Hirvonen et al., 2009). The images were spatially smoothed using 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel to improve the signal-to-noise ratio and to match the resolution of the scanners (4.7 mm for GE and 2.7 mm for HRRT) (van Velden et al. 2009; Bettinardi et al., 2011).

Our main study question pertained to MOR availability differences between the obese and BED groups, yet these groups were studied using different PET scanners, known to yield slightly but systematically different BP_{ND} estimates. However, the relationship between regional BP_{ND} estimates is not straightforward. The BP_{ND} differences between scanners could be constant or relative, and also global or regionally specific. To account for this, we used several different measures in the statistical analyses: Original BP_{ND} estimates (BP_{ND}), and relative BP_{ND}s that were normalized to the corresponding control subjects' average regional (BP_{NDrel1}) or to the ratio between control group average whole brain BP_{ND}s (i.e. dataset 2 values were multiplied by the ratio of dataset 1 controls: dataset 2 controls) (BP_{NDrel2}). Relative BP_{ND}s thus reveal proportional BP_{ND} values in relation to the corresponding control groups or average global difference in BP_{ND} between the scanners, thus allowing us to test whether both obesity and BED lead to similar reductions (relative to controls) in MOR availability. ROIs were delineated to the orbitofrontal cortex (OFC, including all orbitofrontal regions of Automated Anatomical Labeling), anterior (ACC), middle (MCC) and posterior cingulate cortex (PCC), amygdala, ventral striatum, dorsal caudate, putamen, thalamus, and insula, as described earlier (Karlsson et al., 2015a). FMRIB Software Library (FSL) MNI152 brain mask was used as the whole brain ROI. ROI values were extracted using Marsbar toolbox (http://marsbar.sourceforge.net/).

2.3. Statistical analyses

Statistical analyses for background variables were performed using SPSS (version 24, IBM Corp, Amonk, NY). Group differences in demographical and ROI data were investigated using Fisher's exact test, *t* test or Mann-Whitney U test, as appropriate. As the primary analyses, regional MOR binding differences between the groups in the two datasets were investigated by testing dataset (2) x group (2) x ROI (10) interaction term in a 3-way multivariate analysis of variance (MANOVA), separately for all 3 outcome measures: BP_{ND}, BP_{NDrel1} and BP_{NDrel2}. If there was no significant interaction, global differences between the groups were subsequently investigated by testing dataset (2) x group (2) interaction. The analyses were repeated by adding gender, smoking, or type 2 diabetes as a covariate to the model. Correlation between BMI and BP_{ND}s were analyzed using Spearman's rank order correlation coefficients in separately in controls and patients. Bonferroni correction was applied to account for multiple comparisons due to 10 ROIs. *P* values < 0.05 were considered significant.

3. Results

Morbidly obese patients had higher BMI but there were no significant differences in age or smoking status compared to patients with BED (Table 1). BED patients had higher scores in BDI-II, YFAS, DEBQ emotional and DEBQ externalizing questionnaires compared to morbidly obese patients (Table 1).

There was no significant BP_{ND} dataset x group x ROI interaction ($F = 0.91$, $p = 0.53$) or dataset *x* group interaction effect ($F = 0.88$, $p = 0.35$) (Figure 1). However, there were significant effects of dataset ($F = 8.19$, $p = 0.006$) and group ($F = 11.5$, $p = 0.001$). Similarly, there

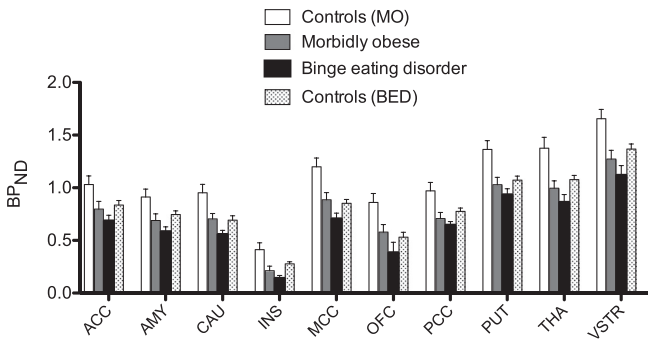

Fig. 1. Regional [^{11}C]carfentanil binding potentials (BP_{ND}) in morbid obese and BED patients and their corresponding control subjects.
Mean (SEM) values are presented. ACC = anterior cingulate cortex, AMY = amygdala, CAU = dorsal caudate, INS = insular cortex, MCC = middle cingulate cortex, OFC = orbitofrontal cortex, PCC = posterior cingulate cortex, PUT = putamen, THA = thalamus, VSTR = ventral striatum.

was no dataset *x* group *x* ROI interaction effect in BP_{NDrel1} ($F = 0.71$, $p = 0.70$) or BP_{NDrel2} ($F = 0.97$, $p = 0.47$), or dataset *x* group interaction effect in BP_{NDrel1} ($F = 0.18$, $p = 0.67$) or BP_{NDrel2} ($F = 0.11$, $p = 0.74$). Group effect remained significant with BP_{NDrel1} ($F = 13.1$, $p = 0.001$) and BP_{NDrel2} ($F = 13.6$, $p = 0.001$). These results did not change when adding gender, smoking or type 2 diabetes as a covariate to the models.

Regional BP_{ND}s did not correlate with BMI in controls or patients (all p-values > 0.05). In BED patients, BAS drive scores correlated negatively with BP_{ND} in ACC ($r = -0.95$, $p = 0.001$), OFC ($r = -0.95$, $p = 0.001$) and ventral striatum ($r = -0.91$, $p = 0.0045$) when correcting for multiple comparisons with 10 ROIs (level of significance $p < 0.005$). There were no significant correlation between any of the ROI BP_{ND}s and other questionnaire scores in BED patients. In morbidly obese patients, there were no significant correlations between questionnaire scores and regional BP_{ND}s.

4. Discussion

Our main finding was that both morbid obesity and BED are associated with widespread reduction in brain MOR availability without regional differences between the two conditions. These data suggest that MOR system dysfunction may be a shared pathophysiological feature in conditions involving overeating: Excess food intake in both conditions may lead to tonic MOR downregulation. Similarities between these two conditions have also been observed previously with resting-state functional magnetic resonance imaging showing widespread cortico-striatal and cortico-thalamic connectivity abnormalities (Baek et al., 2016).

Decreased MOR availability was observed in both morbid obesity (mean BMI = 41) and BED (mean BMI = 31) indicating that excessive weight gain is not required for triggering alterations in the MOR system in disorders involving overeating. This is supported by an earlier study showing also decreased MOR availability in non-obese (mean BMI = 23) patients with bulimia nervosa (Bencherif et al., 2005). Because MOR availability is not dependent of BMI in healthy subjects in the non-obese range (Karjalainen et al., 2016), these data imply that specifically increased food intake, and not necessarily mere weight gain, triggers MOR downregulation. This is in agreement with the recent findings that the brain opioid response to food intake is independent from experienced pleasure (Tuulari et al., 2017). In bulimia nervosa, MOR binding abnormality is restricted only to the left insular cortex (Bencherif et al., 2005), contrasting the widespread MOR downregulation in morbid obesity and BED (Karlsson et al., 2015a; Majuri et al., 2017a). However, the reduced opioid function in both MO and BED was consistent across all analyzed brain regions (see Fig. 1),

indicating a general abnormality in the brain opioid function in these conditions.

Our morbidly obese patients were more overweight compared to BED, but there was no correlation between BMI and MOR availability within either group. This view is supported by the fact that bariatric surgery and concomitant weight loss restores MOR function in morbidly obese patients, even when the patients were still significantly overweight after the surgery (Karlsson et al., 2015b). Thus, abnormalities in the MOR system seem to be reversible, encouraging for treatment efforts targeting the opioid system (Karlsson et al., 2015b).

Behaviorally, BED patients are more prone for risky choices and impulsive decisions along with impaired impulse control when compared to non-BED obese individuals and normal-weight controls (Kessler et al., 2016). Psychiatric comorbidity is also more common in BED compared to non-BED obesity (Kessler et al., 2016). In the present study, BED patients showed higher scores in emotional and external eating behavior, and food addiction than patients with morbid obesity. However, none of these measures were associated with cerebral MOR availability and there were no brain regions with more severe MOR impairment in BED compared to morbidly obese patients, suggesting that these characteristics are mediated by other neurotransmitter systems. Indeed, BED has been associated with abnormalities in dopaminergic and serotonergic function, which could also contribute to the behavioral differences compared to non-BED obesity (Kuikka et al., 2001; Majuri et al., 2017b; Majuri et al., 2017a). Interestingly, BAS drive score correlated negatively with MOR availability in BED, but not in morbidly obese, patients indicating that the brain opioid function in these brain regions may play a role in their eating behavior.

Obesity and BED share many common clinical features with SUDs (Schulte et al., 2015; Potenza 2014; Ziauddeen et al., 2012) and the same applies to other non-substance addictions. However, pathological gambling (PG), which has been considered as the prototype of behavioral addictions, is associated with increased rather than decreased brain dopamine function in contrast to SUDs (Joutsa et al., 2012; Clark et al., 2012; Linnet et al., 2010; Boileau et al., 2014). Also non-substance addictions seem to differ from one another, as opioid and dopamine function in PG and BED are strikingly different (Majuri et al., 2017a). Furthermore, although PG is not associated with changes in baseline MOR binding, MOR system abnormalities are demonstrated by blunted amphetamine-induced opioid response (Mick et al., 2016). In addition, SUDs may generally be associated with increased brain MOR binding although the data is not consistent (Gorelick et al., 2005; Heinz et al., 2005; Palpacuer et al., 2015; Hermann et al., 2017). Our results demonstrate similarities in the neurobiology of different obese phenotypes, but future studies investigating other neurotransmitter systems are required to define how alike obesity and BED truly are.

Some limitations should be considered when interpreting the present results. As the data were collected using two different scanners with different spatial resolutions, [^{11}C] carfentanil BP_{ND}s may not be directly comparable between morbidly obese and BED patients. Therefore, the effect of the scanner was addressed by smoothing and normalizing the data with samples of matched controls making direct comparison possible. However, it should be noted that as the control groups for morbidly obese and BED patients were not identical, we cannot exclude the possibility that some differences might be masked by the characteristics of the control groups. It is however very unlikely that the similar widespread general MOR binding reduction would be driven by any differences between the control group characteristics. In addition, although total of 56 subjects were scanned, the sample size in each patient group (especially BED with $n = 7$) remained relatively small possibly masking subtler group differences. Finally, morbidly obese and BED patients in the present study were all females and it is not known if the findings also generalize to male patients.

We conclude that both morbid obesity and BED are associated with lowered cerebral MOR availability. Thus, MOR downregulation may be a general neurobiological mechanism associated with disorders involving excessive food intake. Future studies are required to establish the neurobiological underpinnings of different phenotypes of eating disorders.

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Contributors

J.J., H.K., J.M., V.K., S.H. and L.N. collected the data. J.J. and L.N. analyzed the data and wrote the first draft of the manuscript. All authors interpreted the data, critically revised the manuscript and accepted the final manuscript.

Conflicts of interest

Dr. Joutsa reports travel grants from Abbvie and Orion, a research grant from the Orion Research Foundation. Dr. Kaasinen reports a consultancy for Abbvie and honoraria/travel grants from Medtronic, Abbvie, Orion-Pharma and GE Healthcare. Other authors declare no conflicts of interest.

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