Regional \( \mu \)-Opioid Receptor Binding in Insular Cortex Is Decreased in Bulimia Nervosa and Correlates Inversely with Fasting Behavior

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The endogenous opioid system of the brain has been implicated in feeding behavior. Abnormal repeated activation of this system may constitute a neural substrate for the compulsive eating behavior observed in bulimia nervosa. This study examined the binding potential of the brain \( \mu \)-opioid receptor (\( \mu \)-OR) in bulimia nervosa.

**Methods:** Eight women with bulimia nervosa and 8 female controls underwent brain MRI followed by \(^{11}C\)-carfentanil PET. Voxel-based methods were used to assess group differences in \( \mu \)-OR binding between controls and bulimic subjects and to correlate \( \mu \)-OR binding with the frequency of recent self-reported abnormal eating behaviors in bulimic subjects. **Results:** \( \mu \)-OR binding in the left insular cortex was less in bulimic subjects than in controls and correlated negatively with recent fasting behavior. **Conclusion:** Changes in \( \mu \)-OR binding in the insula may be important in the pathogenesis or maintenance of the self-perpetuating behavioral cycle of bulimic subjects because the insula is the primary gustatory cortex and has repeatedly been implicated in the processing of the reward value of food.

**Key Words:** bulimia nervosa; \( \mu \)-opioid receptor; \(^{11}C\)-carfentanil; PET; insula


Bulimia nervosa, characterized by a driven behavioral cycle of restricting, bingeing, and vomiting, shares phenomenologic similarity with the addiction disorders. This similarity suggests involvement of the opioid system in maintenance of the bulimic cycle, and high-dose naltrexone, an opiate blocker, has been used with some success in the treatment of bulimia (1). Consistent with its role in reward-driven behaviors, the endogenous opioid system of the brain modulates palatability and deprivation-induced feeding (2,3). We have previously shown in rats that cyclic food deprivation followed by access to food alters \( \mu \)-opioid receptor (\( \mu \)-OR) binding in limbic regions (4), suggesting that repeated activation of the opioid system by restricting and bingeing may help sustain bulimic behavior. In this study, we compared in vivo opioid function in bulimic subjects and controls and correlated \( \mu \)-OR binding with abnormal eating behaviors in bulimic subjects.

**MATERIALS AND METHODS**

**Subjects**

The study was approved by the Johns Hopkins Institutional Review Board. Eight normal-weight, medication-free female subjects (mean age \( \pm \) SD, 24.4 \( \pm \) 2.8 y; range, 19–29 y) with DSM-IV–defined bulimia nervosa (5) and 8 healthy female controls (mean age, 26.4 \( \pm \) 4.3 y; range, 22–32 y) provided written informed consent to participate. The body mass index, defined as weight (kg) \( \times \) height (m)\(^{-2}\), averaged 21.7 \( \pm \) 1.9 (range, 18.4–23.9) for the bulimic subjects and 23.3 \( \pm \) 2.8 (range, 19.6–27.3) for the controls. Bulimic subjects were screened by a psychiatrist and underwent a full psychiatric evaluation to rule out comorbid psychiatric conditions. The Eating Disorders Examination Questionnaire, or EDE-Q (6), was administered to bulimic subjects to assess the frequency of fasting, bingeing, vomiting, laxative abuse, and excessive exercise behaviors, as well as their concerns about weight, shape, and eating, during the prior month. All controls were screened by psychiatric interview and were determined to have no prior psychiatric history and to be free of psychotropic medications. None of the controls reported fasting or having abnormal eating behaviors in the previous month.

**Imaging Protocol**

The methods for imaging and processing data have been described previously (7). An individually fitted thermoplastic facial mask was used during MRI and PET scans of the brain to restrict motion and allow reproducible positioning. In addition, both controls and bulimic subjects were asked not to eat within 3 h of their scheduled PET scan.

T1-weighted MR images were acquired on a 1.5-T Signa Advantage system (GE Healthcare) using 3-dimensional spoiled gradient-recalled acquisition in the steady state. PET data were acquired in 2-dimensional mode on a 4096 Plus PET scanner (GE Healthcare). A 10-min transmission scan using rotating \(^{68}\)Ge rods was followed by a dynamic 90-min (6 \( \times \) 30 s, 5 \( \times \) 60 s, 5 \( \times \) 120 s,
and $9 \times 480$ s) emission PET scan after intravenous bolus administration of $621.6 \pm 74.0$ MBq (range, 488.4–703.0 MBq) of $^{13}$C-carfentanil with a high specific activity of $116.416.8 \pm 38.572.5$ MBq/µmol (range, 69.275.1–173.567.0 MBq/µmol). Fifteen axial slices (center-to-center interslice separation, 6.5 mm) extending from the inferior temporal gyrus to the high-convexity region were acquired. The transmission scan was used for attenuation correction, and the data were reconstructed using a ramp filter into $128 \times 128$ 2-mm-pixel matrices and were decay corrected. The final resolution, in full width at half maximum, with these parameters was 7 mm in plane.

**Statistical Analysis**

Statistical parametric mapping software (SPM99; Wellcome Department of Cognitive Neurology) was used for voxel-based statistical analysis. Data for the 0- to 90-min scan time were spatially normalized to an $^{13}$C-carfentanil template in the Montreal Neurological Institute space, and the transformation matrix was applied to the 34–82 min used for the subsequent analysis. Parametric maps of $\mu$-OR binding (binding potential = [regional/occipital counts] – 1) using the 34- to 82-min spatially normalized data were smoothed using a gaussian kernel of 10 mm in full width at half maximum. A voxel-based t test comparison of control and bulimia nervosa groups was performed after analysis of covariance adjustment for global differences in $\mu$-OR binding. The relationship between $\mu$-OR binding and the frequency of recent (past 28 d) self-reported abnormal eating behaviors in bulimic subjects was also assessed.

Clusters showing differences between groups and correlations with frequency scores for abnormal eating behaviors were retained if the t statistic for all voxels in the cluster met a corrected P value ($P_{corr}$) of $\leq 0.05$ for occurrence in the volume analyzed. These clusters are characterized by their size and their maximum t value or equivalently maximum $z$ value ($z_{max}$) and its $x$, $y$, and $z$ coordinates in the Montreal Neurological Institute space.

**RESULTS**

There were no differences (unpaired t test, $P < 0.05$) in age ($P = 0.35$), body mass index ($P = 0.21$), or whole-brain mean $\mu$-OR binding ($P = 0.41$) between controls and bulimic subjects. In bulimic subjects, an average 17% decrease in $\mu$-OR binding with frequency of fasting behavior in the prior month was found to be significant ($P_{corr} = 0.047$; $z_{max} = 3.78$ at $x = -48$, $y = -14$, $z = 4$). No other regions showed significant group differences in $\mu$-OR binding (Fig. 1).

Within the bulimia nervosa group, an inverse correlation of $\mu$-OR binding with frequency of fasting behavior in the prior month was found in both the left temporoinsular cortex (k = 44; $P_{corr} = 0.042$; $z_{max} = 3.68$ at $x = -52$, $y = -10$, $z = -16$) and the right temporoinsular cortex (k = 174; $P_{corr} = 0.031$; $z_{max} = 4.39$ at $x = 52$, $y = 0$, $z = 6$) (Fig. 2). Among all behavioral and cognitive symptoms assessed by the EDE-Q, frequency of fasting in the prior month was the only one to show a significant statistical relationship with $\mu$-OR binding in the temporoinsular cortex. We defined fasting using question 2 of the EDE-Q: "On how many of the past 28 days have you gone for long periods of time (8 hours or more) without eating anything in order to influence your shape or weight?"

**DISCUSSION**

Bulimia nervosa is characterized by a driven behavioral cycle of restricting, bingeing, and vomiting and by a disturbance in the affective value of food whereby food stimuli acquire excessive salience and induce subjective experiences of increased arousal or anxiety. This emotional response presumably arises from the psychopathologic fear of being or becoming fat that is a hallmark of the disorder. We found that, compared with controls, bulimic individuals showed significantly decreased $\mu$-OR binding in the left insular cortex. Furthermore, the lateral asymmetry noted in the insular region was consistent with findings from previous cerebral blood flow and metabolism studies on subjects with eating disorders (9,10).

The insula is the primary taste cortex, where gustatory sensory information such as taste discrimination (11), and higher cognitive functions such as the anticipation and reward of eating, are processed (9,11–15). Not only has the insular cortex been repeatedly implicated in other reward-driven behaviors, including drug abuse (16) and gambling (17), but it is also the most consistently activated area in anxiety neuroimaging studies (18).

Furthermore, the decrease in $\mu$-OR binding we observed in bulimic subjects was proportional to their recent fasting behavior. That finding is of interest given several publica-
endogenous opioid release by assessing the interval between PET and the last episode of bulimic behavior and by standardizing food intake the day before scanning.

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