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Decreased dopamine type 2 receptor availability after bariatric surgery: preliminary findings

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Abstract

Background—Diminished dopaminergic neurotransmission contributes to decreased reward and negative eating behaviors in obesity. Bariatric surgery is the most effective therapy for obesity and rapidly reduces hunger and improves satiety through unknown mechanisms. We hypothesized that dopaminergic neurotransmission would be enhanced after Roux-en-Y-Gastric Bypass (RYGB) and Vertical Sleeve Gastrectomy (VSG) surgery and that these changes would influence eating behaviors and contribute to the positive outcomes from bariatric surgery.

Methods—Five females with obesity were studied preoperatively and at ~ 7 weeks after RYGB or VSG surgery. Subjects underwent positron emission tomography (PET) imaging with a dopamine type 2 (DA D2) receptor radioligand whose binding is sensitive to competition with endogenous dopamine. Regions of interest (ROI) relevant to eating behaviors were delineated. Fasting enteroendocrine hormones were quantified at each time point.

Results—Body weight decreased as expected after surgery. DA D2 receptor availability decreased after surgery. Regional decreases (mean ± SEM) were, caudate 10±3%, putamen 9±4%, ventral striatum 8±4%, hypothalamus 9±3%, substantia nigra 10±2%, medial thalamus 8±2%, and amygdala 9±3%. These were accompanied by significant decreases in plasma insulin (62%) and leptin (41%).

Conclusions—The decreases in DA D2 receptor availability after RYGB and VSG most likely reflect increases in extracellular dopamine levels. Enhanced dopaminergic neurotransmission may contribute to improved eating behavior (e.g. reduced hunger and improved satiety) following these bariatric procedures.

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Keywords

dopamine; obesity; bariatric surgery; receptor

1. Introduction

Bariatric surgery is the most effective treatment for obesity. Successful weight loss due to surgery results in substantial improvement in co-morbidities and decreases mortality (Sjostrom et al., 2007). This is in contrast to available medical therapies which have limited effectiveness (Sjostrom et al., 2004). RYGB is the most common weight loss procedure performed in the United States (Santry et al., 2005). RYGB results in 60% loss of excess weight (Buchwald et al., 2009), and the majority of the weight loss is maintained long term (Sjostrom et al., 2007). Much of the success of RYGB is felt to be due to a rapid reduction in food intake that remains below preoperative levels long term (Sjostrom et al., 2004). Morinigo *et al.* reported that at 6 weeks after RYGB, hunger decreases and satiety improves despite ongoing rapid weight loss (Morinigo et al., 2006). The vertical sleeve gastrectomy (VSG) surgical procedure, which results in weight loss and decreased hunger and improved satiety similar to that with RYGB (Karamanakos et al., 2008b), is being performed at increasing rates for advanced obesity (Iannelli et al., 2008). The mechanisms by which these procedures improve hunger and satiety are largely unknown.

Dopaminergic neurotransmission plays a pivotal role in motivating appetitive behaviors and in the reinforcements of food stimuli which drive the desire to eat beyond nutritional requirements (Volkow et al., 2008). Dopamine (DA) underlies the motivation for food intake and rodents mice that do not synthesize DA die of starvation unless DA is restored in the dorsal striatum (Szczycka et al., 2001). Wang *et al.* used PET imaging with a dopamine type D₂/D₃ (DA D₂) receptor radioligand to measure availability of DA D₂ receptors in subjects with extreme obesity (BMI>40 kg/m²). They demonstrated reduction in DA D₂ receptor availability in the striatum (Wang et al., 2001a), similar to what they had seen in numerous studies of drug addiction (Volkow et al., 1999). Various animal models support decreased striatal DA D₂ receptors in obesity (Hamdi et al., 1992; Huang et al., 2006). Reduced striatal DA D₂ receptors in obesity and addiction are felt to cause decreased dopaminergic neurotransmission and sensing of reward, and lead to the compensatory behaviors of increased intake of food or substance of abuse.

We aimed to test the hypothesis that dopaminergic neurotransmission improves in the early months after RYGB and VSG surgery for the treatment of obesity, contributing to higher reward stimuli and improved eating behaviors. Understanding the mechanism of improved appetite after successful bariatric procedures will ultimately support advancement in new therapies for the treatment of obesity.

2. Results

Five females (46±2 years of age) with baseline weight of 118±6kg and body mass index (BMI) of 43±3 kg/m² were studied preoperatively and postoperatively (Table 1). Table 1 details demographic and relevant medical history data. At the postoperative study, the mean weight loss was 14±1 kg, or 12±1% of initial body weight, resulting in significant reduction in BMI to 38±3 kg/m² (both p=0.043). The Beck Depression Inventory-II (BDI) was completed preoperatively and postoperatively with mean scores of 2±1 and 1±1 (p=0.882), respectively. Before and after surgery, binge eating scale (Sjostrom et al.) scores were 11 ± 3 and 3 ± 2 (p=0.109), respectively.

Repeated measures analysis of variance demonstrated no main effects of laterality (left versus right side) or surgery (pre- vs. postoperative) by laterality interaction (all $p \geq 0.152$); therefore, data from right- and left-sided regions were averaged for further analysis within each ROI. Overall DA D2 receptor availability decreased postoperatively for individuals, as shown in Table 2, and for the group, as shown in Table 3. There was a significant decrease in mean binding potential (BP_{ND}) in the substantia nigra (Figure 1) when corrected for multiple comparisons, and reductions were significant in the caudate, hypothalamus, medial thalamus and amygdalae when p-values were not corrected for multiple comparisons (Table 3).

Samples were collected for fasting hormones before each PET scan. Two subjects, one at baseline and another postoperative did not fast for the entire 8 hours before PET scan. Hormone data for these 2 subjects were not included in the analyses, which resulted in decreased statistical power for these tests. We did not appreciate that the shortened fast at these 2 times influenced the imaging results. In the 3 subjects with paired data, insulin levels decreased from 34 ± 7 microU/ml before surgery to 13 ± 1 microU/ml ($p=0.109$) after surgery. Leptin levels also decreased with surgery, from 51 ± 7 ng/ml to 39 ± 11 ng/ml ($p=0.109$). There was no change in total ghrelin levels (637 ± 248 vs. 588 ± 140 pg/ml, $p=1.0$).

3. Discussion

DA D2 receptor availability was decreased at 7 weeks after bariatric surgery in numerous regions relevant for eating behaviors. We interpret the decreased DA D2 receptor availability to represent increased extracellular DA levels competing with the radioligand. The level of decrease in DA D2 receptor availability observed in this study is comparable to other studies where we used pharmacologic agents to increase extracellular DA levels (Riccardi et al., 2006). Wang *et al.* revealed that in human obesity DA D2 receptor availability is decreased (Wang et al., 2001b), which is consistent with preclinical studies showing low levels of DA D2 receptors in rodent models of obesity (Hamdi et al., 1992; Huang et al., 2006). Rodent models of obesity have also provided evidence of decreased DA release (Thanos et al., 2008), though this finding has not been confirmed in human obesity. The alternative interpretation of our data is that DA D2 receptor levels decrease after surgery which would be expected to have a detrimental effect on appetitive behaviors and food intake and be inconsistent with the clinical changes seen after surgery. Improvements in appetitive behaviors following RYGB and VSG surgery are better explained by increases in DA levels which would manifest as decreases in DA receptor availability.

Satiety is improved after RYGB and VSG despite reduced meal size (Morinigo et al., 2006) (Karamanakos et al., 2008b). Our data support increased DA levels in the hypothalamus, a key region in the regulation of appetite, which may be involved in this improvement after surgery. In rodents, DA infusion into the lateral hypothalamic area results in decreased food intake through reduced meal size (Yang et al., 1997) likely by inducing earlier satiety. The hypothalamus receives dopaminergic input that influences eating behavior from the substantia nigra (White, 1986), which is the ROI where we saw the greatest and statistically significant change. Substantia nigra dopamine neuronal activity is also essential for the reward processes of the dorsal striatum (putamen and caudate) (Nakazato, 2005). Using PET imaging, Small *et al.* demonstrated that the level of food induced DA release in the dorsal striatum is positively associated with self-reports of pleasure from food intake (Small et al., 2003). Increased pleasure from food may play a role in how patients readily make immediate and dramatic changes in their eating patterns after surgery.

We also showed decreases in DA D2 receptor availability in the amygdala, a brain region that assigns emotional value to rewarding stimulus, and along with the striatum and the prefrontal cortex plays a crucial role in conditioning (Grimm and See, 2000). The amygdala and ventral striatum, as well as the medial thalamus (and possibly the substantia nigra), are preferentially activated by food cues and food anticipation compared to actual food receipt (Small et al., 2008). The observation that DA increases in numerous regions of the brain that are activated by food cues and anticipation enhance our understanding of how our current environment that is filled with excessive food cues and exposures influences negative eating behaviors in many patients. The increases in DA levels we observed, are likely reflective of increases in tonic DA activity, serving to attenuate the phasic DA increases associated with exposure to condition food cues that result in food craving (Volkow et al., 2002). Taken together, increased DA levels in regions involved in food anticipation may play a role in decreased food cravings after bariatric surgery.

As reported by others (Faraj et al., 2003), we observed that insulin and leptin decrease after bariatric surgery. We postulate that these hormonal changes could also contribute to the changes in dopaminergic signaling after surgery. In preclinical studies, restricted food intake increases striatal DA levels and decreases insulin and leptin (Thanos et al., 2008), and enhances reward related behaviors. Dopaminergic neurons contain insulin and leptin (Figlewicz et al., 2003) receptors, and treatment with insulin and leptin suppresses reward related behaviors (Figlewicz and Benoit, 2009). Insulin increases the activity of the dopamine transporter (Figlewicz and Benoit, 2009), therefore states of high insulin levels (such as obesity) would be expected to lead to decreased extracellular DA levels from enhanced dopamine uptake into the terminal. Reductions in plasma leptin after bariatric surgery could also have contributed to elevated DA levels. Switching obese rodents from a high fat to a low fat diet decreases plasma leptin levels and increases tyrosine hydroxylase (TH, the rate limiting enzyme in dopamine synthesis) mRNA expression in the ventral tegmental area and the substantia nigra (Li et al., 2009). Leptin decreases the firing of dopaminergic neurons (Hommel et al., 2006), presenting another potential mechanism as to how DA levels may increase after bariatric surgery.

It is important to note that our report differs from the only other study reporting DA D2 receptor availability post-RYGB (Steele et al., 2009). Steele *et al.* reported a non-significant increase in DA D2 receptor availability at 6 weeks after RYGB in five females with similar preoperative BMI and weight loss. A few key differences are present between our report and theirs. Steele *et al.* used the DA D2 radioligand [^{11}C] raclopride, while we used [^{18}F] fallypride. The use of the different radioligands is not felt to contribute to the discrepancy in results as the literature reveals similar results with [^{11}C] raclopride (Martinez et al., 2003) and [^{18}F] fallypride (Mark et al., 2004; Riccardi et al., 2006) in comparable ROIs. Our cohort's mean age is 14 years older than Steele *et al.* and this could have influenced the dopaminergic response. Since estrogen and progesterone, which decrease markedly in middle age, have been associated in preclinical studies with DA 2 receptor expression and function it could be possible that age differences contributed to the differences in findings between both studies (Bazzett and Becker, 1994) (Febo et al., 2003).

We feel that a more relevant difference between our cohort and Steele's was that their subjects had considerably higher preoperative BDI scores that decreased notably postoperatively. In contrast our subjects had low baseline BDI scores that did not change after surgery. While the mean BDI scores in Steele *et al.* were in the mild range and not consistent with a clinical diagnosis of depression, it is possible that preclinical depression might have been a confounder. Depression is a state of reduced dopaminergic neurotransmission (Dunlop and Nemeroff, 2007); however, the relationship of DA D2 receptors to depression is unclear. Imaging studies are conflicting and some of the conflict

may arise from the various techniques used (D'Haenen H and Bossuyt, 1994; Hirvonen et al., 2008). Further, regulation of extracellular DA levels may be altered in depression (Meyer et al., 2001) and could influence DA D2 receptor availability. Knowing that depression can improve after bariatric surgery (Bocchieri et al., 2002), we excluded subjects with any concerns for even preclinical disease and given the very low baseline and post-operative depression scores in our cohort, changes in depression are not felt to have affected our outcomes.

Both of these studies were limited in sample size. We found recruitment challenging due to the bariatric surgery population's high prevalence of metabolic and psychiatric illness and their frequent use of centrally acting medications (Sears et al., 2008). Another limitation is that we did not directly estimate extracellular DA levels (Riccardi et al., 2007). Techniques to estimate extracellular DA levels do require increased radiation exposure and we chose to take a conservative approach with this initial study. We imaged four RYGB patients and one VSG patient increasing heterogeneity. VSG is growing in popularity and has similar improvement in appetite as RYGB; therefore we felt it was a valuable opportunity to image a patient undergoing this procedure. Interestingly, changes in DA D2 receptor availability were similar after VSG (Table 2, subject 3) as compared to RYGB and the early changes in certain enteroendocrine hormones that influence dopaminergic neurotransmission were similar after both procedures (Peterli et al., 2009) (Karamanakos et al., 2008a). Nonetheless, the two procedures are different and considering our small numbers we are treating our findings as preliminary. Future work with a larger cohort including further comparison of various bariatric procedures is needed.

In summary, we show that after bariatric surgery DA D2 receptor availability decreases in numerous regions of the brain that are relevant to eating behaviors and interpret this as increased DA levels. Increased DA levels would be expected to have a positive influence on reward and may contribute to the improved eating behaviors that occur after RYGB and VSG surgery. Numerous enteroendocrine hormones influence dopaminergic neurotransmission and are altered by bariatric surgery. Future studies are warranted to investigate the role of dopaminergic neurotransmission on the benefits of bariatric surgery and whether the enteroendocrine changes of surgery are essential. Further understanding as to how dopaminergic neurotransmission improves after bariatric surgery will lend to the development of more effective therapies for obesity.

4. Experimental procedures

4.1 Subjects

Protocol approval was obtained from the Vanderbilt University Institutional Review Board and all participants gave written informed consent. Five females (3 right handed, 2 left handed) with preoperative BMI >35 kg/m² were recruited from the Vanderbilt Center for Surgical Weight Loss. Participants had to be approved for either RYGB or VSG surgery. All subjects underwent a history and physical exam by study physician including detailed history of substance exposure. Medical records were reviewed including presurgical psychological interview to examine for any possible psychiatric illness. Evaluation included electrocardiogram and screening laboratories (comprehensive metabolic panel, complete blood count and differential, urinalysis, and urine drug screen). At screening and less than 4 hours before each PET scan, females capable of childbearing underwent serum pregnancy testing. Exclusion criteria included a diagnosis of diabetes mellitus or use of diabetic agents (e.g. metformin, thiazolidiones), significant neurologic, psychiatric, renal, liver, cardiac or pulmonary disease, and current pregnancy. We excluded those with a history of current or prior tobacco use, substance abuse, or heavy alcohol use (7 or more drinks per week for 6 or more months), and also those with current caffeine intake greater than equivalent to 16

ounces of coffee per day. We excluded participants who had used central acting medications (e.g. antidepressants, antipsychotics, neuroleptics, dopaminergic agents, anorexic agents, narcotics) in the last 6 months. Subjects meeting inclusion and exclusion criteria underwent baseline magnetic resonance imaging (MRI) of the brain.

Subjects underwent PET imaging preoperatively and a median of 7 weeks (range 6–11 weeks) after weight loss surgery. The VSG patient had imaging at 11 weeks postoperative when her weight loss was similar to RYGB subjects at 6–8 weeks. The median time between preoperative and postoperative scans was 9 weeks (range 8–23 weeks). On each day of scanning subjects were requested to fast for 8 hours prior to scanning. The day of the scan and 2 days prior participants were restricted to no exercise or alcohol, and no more than equivalent of 8 ounces of coffee daily. On each study day, participants completed the BDI (Beck et al., 1996) and the BES (Gormally et al., 1982).

4.2 Surgical Procedure

All surgeries were performed at Vanderbilt University Medical Center. In RYGB a small gastric pouch approximately 30 ml in volume is created by dividing the upper stomach. The small intestine is then divided, and the distal end is brought up and connected to the gastric pouch. The proximal end of the divided small intestine is reattached distally, creating a Roux limb of 100–150 cm, with the length based on the patient's body mass index (Figure 2a). In VSG, a large portion of the stomach is resected, creating a gastric tube by dividing the stomach along a 34 French dilator (Figure 2b).

4.3 Neuroimaging

MRI scans of the brain were completed prior to PET imaging to exclude anatomic pathology and for later co-registration. Thin section T1 weighted images were completed on either a 1.5T (General Electric, 1.2–1.4 mm slice thickness, in plane voxel size of 1×1 mm) or a 3T MRI scanner (Philips Intera Achieva, 1 mm slice thickness, in plane voxel size of 1×1 mm). PET scans with D₂/ D₃ radioligand [¹⁸F] fallypride were performed on a General Electric DTSE scanner with a three-dimensional emission acquisition and a transmission attenuation correction which has a reconstructed resolution of 5 – 6 mm in plane, 3.25 mm axially, and provides 47 planes over a 15 cm axial field of view. Serial PET scans were obtained over 3.5 hours. The first scan sequence (70 minutes) was initiated with bolus injection over 15 seconds of 5.0mCi of [¹⁸F] fallypride (specific activity >2,000 Ci/mmol). The second and third scan sequence started at 85 and 150 minutes lasting 50 and 60 minutes, respectively, with 15 minute breaks between scan sequences.

4.4. Imaging Analysis

The serial PET scans were co-registered to each other and to the thin section T1-weighted MRI scans and were co-registered using a mutual information rigid body algorithm (Maes et al., 1997; Wells et al., 1996). Images were reoriented to the anterior commissure-posterior commissure (ACPC) line. The full reference region method was used to calculate regional DA D₂ receptor BP_{ND} (Lammertsma et al., 1996) with the cerebellum as the reference region.

Regions of interest, including bilateral caudate, putamen, ventral striatum, amygdalae, substantia nigra, and medial thalami were delineated on the MRI scans of the brain and transferred to the co-registered PET scans as our group has prior published (Kessler et al., 2009; Riccardi et al., 2008a). Our group has previously identified the hypothalamus in parametric image analysis (Riccardi et al., 2008b). We selected the hypothalamus as an *a priori* region of interest based on its importance in appetite regulation (Schwartz et al., 2000). The mammillary bodies were excluded due to their limited role on body weight

(Tonkiss and Rawlins, 1992) especially when compared to other hypothalamic areas and to prevent partial voluming from mid brain structures in the vicinity of the interpeduncular fossa including the substantia nigra. The hypothalamus was delineated on the coronal view of the MRI scan encapsulating the ventral portion of the third ventricle (Figure 3a and 3b). The sagittal view was used to establish anatomic borders including the plane of the lamina terminalis and posterior edge of the anterior commissure anteriorly and the mammillary bodies as the posterior border. As proceeding posterior, the orthogonal shape of the hypothalamus was taken into account (Langevin and Iversen, 1980).

4.5. Assays

Fasting blood samples were collected for insulin, leptin, and total ghrelin. A 10 ml sample was collected into tubes containing 10 microliter/ml of serine protease inhibitor pefabloc sc (4-amidinophenyl-methanesulfonyl fluoride, Roche Applied Science, Germany). Plasma insulin concentration were determined by radioimmunoassay (RIA) (Morgan and Lazarow, 1962) with an intra-assay coefficient of variation of 3% (Linco Research, Inc. St. Charles, MO). Leptin (Millipore, St. Charles, MO) and ghrelin concentrations (Linco Research, Inc. St. Charles, Mo) were also determined by RIA. All samples were run in duplicate.

4.6 Statistical Analysis

Repeated measures analysis of variance ANOVA was used to test, within each ROI (except for the hypothalamus), the within-subjects main effects of surgery (preoperative vs. postoperative) and laterality (left versus right side), and the surgery by laterality interaction effect (which indicated whether responses to bariatric surgery differed in the left and right sides). Non-directional paired tests, either the main effect of surgery from the repeated measures ANOVA or a paired t-test (for hypothalamus data), and nonparametric Wilcoxon signed-rank tests were used to test the effect of bariatric surgery on binding potentials within each ROI. The p-value threshold of 0.007 was used to interpret Bonferroni-corrected comparisons for the 7 ROI. The Wilcoxon signed-rank test was used to test the effect of surgery on pre- and postoperative weight, BMI, psychological scales, and hormone assays. Summary data are reported as the mean $\pm$ standard error of the mean (SEM) and analyses were performed using SPSS (v 17.0, SPSS Inc., IL) statistical software.

Abbreviations

ROI	region of interest
DA	dopamine
DA D2	dopamine type D ₂ / D ₃
RYGB	Roux en Y Gastric Bypass
VSG	Vertical Sleeve Gastrectomy
BDI	Beck Depression Inventory-II
Sjostrom et al.	Binge Eating Scale
BD_{ND}	Binding Potential

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Figure 1.
Axial [^{18}F] fallypride parametric images of BP_{ND} at the level of the substantia nigra (a)
before and (b) 7 weeks after bariatric surgery.

Figure 2.
(a) RYGB procedure and (b) VSG procedure (Reprinted courtesy of Ethicon Endo-Surgery, Inc.)

Figure 3.
Delineating the hypothalamus. (a) Coronal view MRI image and (b) Coronal view PET image.

Table 1

subject Demographics and medical history

Subject	Age	Race	Surgery	Preop BMI	Preop weight (kg)	Postop Weight (kg)	Preop Medical History
1	50	W	RYGB	38	105	92	OA, GERD back pain, HTN
2	42	W	RYGB	42	119	103	OA, HTN, NAFLD Hyperlipidemia, IGT
3	50	AA	VSG	42	118	108	HTN
4	46	W	RYGB	54	139	124	HTN, OSA on CPAP
5	41	W	RYGB	40	107	93	Unremarkable

Preop=preoperative, Postop=postoperative, W=white, AA=African American

Table 2

percent change by region or interest for individuals from preoperative to after bariatric surgery.

Subject	Cau	Put	VS	Hyp	SN	MT	Amy
1	-8.6	-10.2	-8.1	-2.4	-11.6	-4.5	-2.5
2	-13.5	-17.1	-16.8	-13.0	-14.0	-12.4	-13.8
3	-18.7	-16.4	-15.6	-15.8	-13.0	-13.4	-15.2
4	-2.8	2.9	4.6	-4.3	-5.7	-2.9	-4.6
5	-7.2	-6.3	-4.7	-8.3	-6.5	-7.5	-8.8

Cau=Caudate, Put=Putamen, VS= Ventral Striatum, Hyp=hypothalamus, SN= substantia nigra, MT= medial thalamus, Amy=amygdala

Table 3

Regional Binding Potentials (Mean $\pm$ SEM) preoperative and after bariatric surgery for the group, the mean percent decrease after surgery, and significance level by paired t tests and Wilcoxon signed-rank tests in parenthesis.

Region	Preop BP	Postop BP	Percent decrease	Significance level
Caudate	34.88 $\pm$ 1.35	31.30 $\pm$ 1.25	10.14 $\pm$ 2.74	0.023 (0.043)
Putamen	39.77 $\pm$ 1.50	35.89 $\pm$ 1.23	9.39 $\pm$ 3.67	0.069 (0.080)
Ventral Striatum	22.80 $\pm$ 0.77	20.84 $\pm$ 0.32	8.11 $\pm$ 3.90	0.105 (0.080)
Hypothalamus	4.42 $\pm$ 0.13	4.02 $\pm$ 0.12	8.76 $\pm$ 2.52	0.029 (0.043)
Substantia Nigra	2.70 $\pm$ 0.08	2.43 $\pm$ 0.08	10.20 $\pm$ 1.78	0.005 (0.043)
Medial Thalamus	5.00 $\pm$ 0.20	4.58 $\pm$ 0.15	8.17 $\pm$ 2.10	0.023 (0.043)
Amygdala	3.16 $\pm$ 0.17	2.87 $\pm$ 0.14	8.99 $\pm$ 2.52	0.031 (0.043)

Note: The Bonferroni-corrected p-value threshold was 0.007.