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BRAIN RESEARCH

Research report

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%). Conclusion: 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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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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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. (2006) reported that at 6 weeks after RYGB, hunger decreases and satiety improves despite ongoing rapid weight loss. 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 (Szczypka et al., 2001). Wang et al. used PET imaging with a dopamine type D_2/D_3 (DA D2) receptor radioligand to measure availability of DA D2 receptors in subjects with extreme obesity (BMI>40 kg/m^2). They demonstrated reduction in DA D2 receptor availability in the striatum (Wang et al., 2001), 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.

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.

2. Results

Five females (46±2 years of age) with baseline weight of 118±6 kg and body mass index (BMI) of 43±3 kg/m^2 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/m^2 (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 (Fig. 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).

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.