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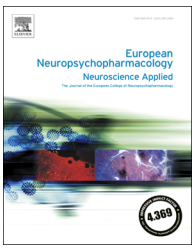

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Striatal dopamine $D_{2/3}$ receptor availability increases after long-term bariatric surgery-induced weight loss

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Abstract
In several studies reduced striatal dopamine $D_{2/3}$ receptor ($D_{2/3}R$) availability was reported in obese subjects compared to lean controls. Whether this is a reversible phenomenon remained uncertain. We previously determined the *short-term* effect of Roux-en-Y gastric bypass surgery (RYGB) on striatal $D_{2/3}R$ availability (using [^{123}I]IBZM SPECT) in 20 morbidly obese women. Striatal $D_{2/3}R$ availability was lower compared to controls at baseline, and remained unaltered after 6 weeks, despite significant weight loss.
To determine whether *long-term* bariatric surgery-induced weight loss normalizes striatal $D_{2/3}R$ binding, we repeated striatal $D_{2/3}R$ binding measurements at least 2 years after RYGB in 14 subjects of the original cohort. In addition, we assessed long-term changes in body composition, eating behavior and fasting plasma levels of leptin, ghrelin, insulin and glucose.
Mean body mass index declined from 46 ± 7 kg/m^2 to 32 ± 6 kg/m^2, which was accompanied by a significant increase in striatal $D_{2/3}R$ availability ($p=0.031$). Striatal $D_{2/3}R$ availability remained significantly reduced compared to the age-matched controls (BMI 22 ± 2 kg/m^2; $p=0.01$). Changes in striatal $D_{2/3}R$ availability did not correlate with changes in body weight/fat, insulin sensitivity, ghrelin or leptin levels. Scores on eating behavior questionnaires improved and

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changes in the General Food Craving Questionnaire-State showed a borderline significant correlation with changes in striatal $D_{2/3}R$ availability.
These findings show that striatal $D_{2/3}R$ availability increases after long-term bariatric-surgery induced weight loss, suggesting that reduced $D_{2/3}R$ availability in obesity is a reversible phenomenon.

1. Introduction

The prevalence of obesity and its health consequences is rising, necessitating fundamental insight into the regulation of energy balance with the aim to improve future treatment modalities (Finucane et al., 2011; Whitlock et al., 2009). Previous studies have implicated the brain dopamine system in the hedonic and motivational aspects of food intake and, similar to findings in addiction, obese subjects exhibited reduced striatal dopamine $D_{2/3}$ receptor ($D_{2/3}R$) availability compared to lean controls in some (de Weijer et al., 2011; van de Giessen et al., 2014; Wang et al., 2001), but not all studies (Eisenstein et al., 2013; Guo et al., 2014; Haltia et al., 2008; Karlsson et al., 2015; Steele et al., 2010). It remains unknown whether lower $D_{2/3}R$ availability reflects a cause or a consequence of obesity (or both). In support of a causal role, it has been hypothesized that overeating in subjects susceptible to obesity constitutes a compensatory response to make up for decreased dopaminergic signaling in the reward circuitry caused by reduced expression of dopamine receptors due to genetic factors (Blum et al., 2000; Stice et al., 2008). In contrast, downregulation of striatal $D_{2/3}R$ occurring *after* the onset of obesity in animal studies suggests changes in the striatal dopaminergic system to be a consequence of a persistent increase in palatable food consumption, positive energy balance and/or fat mass (Johnson and Kenny, 2010; van de Giessen et al., 2012).

To study the reversibility of reduced striatal $D_{2/3}R$ binding in obesity, we previously determined $D_{2/3}R$ availability in 20 morbidly obese women 2 weeks before and 6 weeks after Roux-en-Y gastric bypass surgery (RYGB) using [^{123}I]IBZM single photon emission computed tomography (SPECT). In that study, striatal $D_{2/3}R$ availability was reduced by ~20% compared to lean controls and did not significantly change 6 weeks after surgery, despite significant weight loss (de Weijer et al., 2014). However, reductions in striatal $D_{2/3}R$ availability caused by addiction to drugs of abuse may persist for several months after cessation of drug use, and in one study, self-administration of cocaine caused reductions in striatal $D_{2/3}R$ availability that persisted up to 1 year in some, but not all monkeys (Heinz et al., 2004; Nader et al., 2006; Volkow, 2004). Furthermore, body weight following bariatric surgery only stabilizes after approximately 1 year (Schauer et al., 2000). Therefore, we re-invited the subjects that were included in the study on the short-term effects of RYGB to repeat the striatal $D_{2/3}R$ measurements at least 2 years after RYGB.

Healthier eating behavior was previously reported after bariatric surgery, with reductions in hunger, disinhibition and food craving (Boan et al., 2004; Karlsson et al., 1998; Leahey et al., 2012). As dopamine signaling is known to be involved in drug craving (Wong et al., 2006) and changes in striatal D_2 receptors were linked to the emergence of compulsive feeding behavior in obese rats (Johnson and Kenny, 2010), we hypothesized that changes in food craving after RYGB might correlate with changes in $D_{2/3}R$ availability. To investigate this, we compared the results of eating behavior questionnaires before and after RYGB in these subjects.

Finally, the dopamine system also appears to play a role in glucose control, as e.g. dopamine agonists previously showed insulin-sensitizing effects in obese diabetic subjects (Gibson et al., 2012). Moreover, dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra (SN) express receptors for insulin, leptin and ghrelin (Figlewicz et al., 2003; Zigman et al., 2006) and insulin sensitivity and fasting plasma levels of ghrelin and leptin were previously associated with striatal $D_{2/3}R$ availability (Dunn et al., 2012). Therefore, we additionally studied whether long-term changes in plasma levels of leptin, insulin, glucose and ghrelin and the quantitative insulin sensitivity check index (QUICKI) correlated with changes in striatal $D_{2/3}R$ availability.

2. Experimental procedures

2.1. Subjects

Twenty Caucasian women previously participated in the study on the short-term effects of RYGB on striatal $D_{2/3}R$ availability and insulin sensitivity (de Weijer et al., 2014) (NTR1548) and were therefore eligible for this follow-up study (NTR3684). One subject was excluded due to claustrophobia, one due to pregnancy, one because she had started using anti-dopaminergic drugs (after completion of the short-term study), one did not wish to participate, and two were lost to follow up. Subjects were age-matched to non-obese Caucasian historical controls that participated in a previous study and similarly examined after an overnight fast (van de Giessen et al., 2014). RYGB surgery had been carried out between December 2009 and December 2011 in two hospitals (Rijnstate Hospital, Arnhem and Slotervaart Hospital, Amsterdam, the Netherlands) as described previously (de Weijer et al., 2014). Informed consent was obtained in all subjects and the study was approved by the local medical ethics committee of the Academic Medical Center in Amsterdam.

2.2. Study protocol

After an overnight fast from 22:00 PM the day before, all subjects were admitted for one day to the Metabolic Clinical Research Unit of the AMC. Subjects were weighed and body composition determined using bioelectrical impedance analysis (Maltron BF-906, Rayleigh, UK). Blood samples were drawn after insertion of a catheter into a distal arm vein.