



Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: Possible contributing factors

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ABSTRACT

Dopamine's role in inhibitory control is well recognized and its disruption may contribute to behavioral disorders of discontrol such as obesity. However, the mechanism by which impaired dopamine neurotransmission interferes with inhibitory control is poorly understood. We had previously documented a reduction in dopamine D2 receptors in morbidly obese subjects. To assess if the reductions in dopamine D2 receptors were associated with activity in prefrontal brain regions implicated in inhibitory control we assessed the relationship between dopamine D2 receptor availability in striatum with brain glucose metabolism (marker of brain function) in ten morbidly obese subjects (BMI > 40 kg/m²) and compared it to that in twelve non-obese controls. PET was used with [¹¹C]raclopride to assess D2 receptors and with [¹⁸F]FDG to assess regional brain glucose metabolism. In obese subjects striatal D2 receptor availability was lower than controls and was positively correlated with metabolism in dorsolateral prefrontal, medial orbitofrontal, anterior cingulate gyrus and somatosensory cortices. In controls correlations with prefrontal metabolism were not significant but comparisons with those in obese subjects were not significant, which does not permit to ascribe the associations as unique to obesity. The associations between striatal D2 receptors and prefrontal metabolism in obese subjects suggest that decreases in striatal D2 receptors could contribute to overeating via their modulation of striatal prefrontal pathways, which participate in inhibitory control and salience attribution. The association between striatal D2 receptors and metabolism in somatosensory cortices (regions that process palatability) could underlie one of the mechanisms through which dopamine regulates the reinforcing properties of food.

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The increase in obesity and associated metabolic diseases seen over the past decade has raised concern that if not controlled this may become the number one preventable public health threat for the 21st century (Sturm, 2002). Though multiple factors contribute to this rise in obesity the increase in the diversity and access to palatable food cannot be underestimated (Wardle, 2007). Since food availability and variety increases the likelihood of overeating (review Wardle, 2007) the easy access to appealing food requires the frequent need to inhibit the desire to eat it (Berthoud, 2007). The extent to which individuals differ in their ability to inhibit these responses and control how much they eat is likely to modulate

their risk for overeating in our current food rich environments (Berthoud, 2007).

We had shown that in healthy individuals D2 receptor availability in the striatum modulated eating behavioral patterns (Volkow et al., 2003). Specifically the tendency to eat when exposed to negative emotions was negatively correlated with D2 receptor availability (the lower the D2 receptors the higher the likelihood that an individual would eat if emotionally stressed). In addition, in a different study, we showed that morbidly obese subjects (BMI > 40) had lower than normal D2 receptor availability and these reductions were proportional to their BMI (Wang et al., 2001). These findings led us to postulate that low D2 receptor availability could put an individual at risk for overeating. In fact this is consistent with findings showing that blocking D2 receptors (antipsychotic medications) increases food intake and raises the risk for obesity (Allison et al., 1999). However the

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mechanisms by which low D2 receptor availability increases the risk of overeating are poorly understood.

Recently it was shown that in healthy controls polymorphisms in the D2 receptor gene were associated with behavioral measures of inhibitory control (Klein et al., 2007). Specifically, individuals with the gene variant that is associated with lower D2 expression had less inhibitory control than individuals with the gene variant associated with higher D2 receptor expression and these behavioral responses were associated with differences in activation of the cingulate gyrus (CG) and dorsolateral prefrontal cortex (DLPFC), which are brain regions that have been implicated in various components of inhibitory control (Dalley et al., 2004). This led us to reconsider the possibility that the higher risk for overeating in subjects with low D2 receptor availability may also be driven by DA's regulation of DLPFC and medial prefrontal regions, which have been shown to participate in the inhibition of inappropriate behavioral response tendencies (Mesulam, 1985; Le Doux, 1987; Goldstein and Volkow, 2002). Thus we performed secondary analysis on data from subjects that had been previously recruited as part of studies to evaluate changes in D2 receptors (Wang et al., 2001) and of brain glucose metabolism in obesity (Wang et al., 2002) and data from age matched controls. Our working hypothesis was that D2 receptor availability in obese subjects would be associated with disrupted activity in prefrontal regions.

For this study morbidly obese subjects and non-obese subjects had been evaluated with Positron Emission Tomography (PET) in conjunction with [¹¹C]raclopride to measure DA D2 receptors (Volkow et al., 1993a) and with [¹⁸F]FDG to measure brain glucose metabolism (Wang et al., 1992). We hypothesized that DA D2 receptors would be associated with metabolism in prefrontal regions (DLPFC, CG and orbitofrontal cortex).

Method

Subjects

Ten morbidly obese subjects (5 women and 5 men, mean 35.9±10 years of age) with mean body mass (BMI: weight in kilograms divided by the square of height in meters) of 51±5 kg/m² were selected from a pool of obese subjects who responded to an advertisement. Twelve non-obese subjects (6 women and 6 men, mean 33.2±8 years of age) with mean BMI of 25±3 kg/m² were selected for comparison. Participants were screened carefully with a detailed medical history, physical and neurological examination, EKG, routine blood tests, and urine toxicology for psychotropic drugs to ensure they fulfilled inclusion and exclusion criteria. Inclusion criteria were: 1) ability to understand and give informed consent; 2) BMI>40 kg/m² for the obese subjects and BMI<30 kg/m² for the comparison subjects and 3) 20–55 years of age. Exclusion criteria were: (1) current or past psychiatric and/or neurological disease, (2) head trauma with loss of consciousness greater than 30 min, (3) hypertension, diabetes and medical conditions that may alter cerebral functioning, (4) use of anorexic medications or surgical procedures for weight loss in the past 6 months, (5) prescription medication(s) in the past 4 weeks, (6) past or present history of alcohol or drug abuse (including cigarette smoking). Subjects were instructed to discontinue any over-the-counter medication or nutrition supplements 1 week prior to the scan. Pre-scan urine tests

were done to ensure absence of psychoactive drug use. Signed informed consents were obtained from the subjects prior to participation as approved by the Institutional Review Board at Brookhaven National Laboratory.

PET imaging

PET scans were performed with a CTI-931 (Computer Technologies, Incorporated, Knoxville, Tenn.) tomograph (resolution 6×6×6.5 mm FWHM, 15 slices) with [¹¹C]raclopride and [¹⁸F]FDG. Details on procedures for positioning, arterial and venous catheterization, quantification of radio-tracer and transmission and emission scans have been published for [¹¹C]raclopride (Volkow et al., 1993a), and for [¹⁸F]FDG (Wang et al., 1992). Briefly for [¹¹C]raclopride, dynamic scans were started immediately after iv injection of 4–10 mCi (specific activity>0.25 Ci/μmol at time of injection) for a total of 60 min. For [¹⁸F]FDG, one emission scan (20 min) was taken 35 min after an iv injection of 4–6 mCi of [¹⁸F]FDG. The scans were done on the same day; the [¹¹C]raclopride scan was done first and was followed by [¹⁸F]FDG, which was injected 2 h after [¹¹C]raclopride to allow for the decay of ¹¹C (half-life 20 min). During the study subjects were kept lying in the PET camera with their eyes open; the room was dimly lit and noise was kept at a minimum. A nurse remained with the subjects throughout the procedure to ensure that the subject did not fall asleep during the study.

Image and data analysis

Regions of interest (ROI) in the [¹¹C]raclopride images were obtained for striatum (caudate and putamen) and for cerebellum. The ROI were initially selected on an averaged scan (activity from 10–60 min for [¹¹C]raclopride), and were then projected to the dynamic scans as previously described (Volkow et al., 1993a). The time activity curves for [¹¹C]raclopride in striatum, and cerebellum and the time activity curves for unchanged tracer in plasma were used to calculate distribution volumes (DV) using a graphical analysis technique for a reversible system (Logan Plots) (Logan et al., 1990). The parameter Bmax/Kd, obtained as the ratio of the DV in striatum to that in cerebellum (DVstriatum/DVcerebellum) minus 1, was used as a model parameter of DA D2 receptor availability. This parameter is insensitive to changes in cerebral blood flow (Logan et al., 1994).

To assess the correlations between D2 receptor availability and brain glucose metabolism we computed the correlations using Statistical Parametric Mapping (SPM) (Friston et al., 1995). The SPM results were then corroborated with independently drawn regions of interest (ROI); that is, regions obtained using a template that was not guided by the coordinates obtained from the SPM. For the SPM analyses the images of the metabolic measures were spatially normalized using the template provided in the SPM 99 package and subsequently smoothed with a 16 mm isotropic Gaussian kernel. Significance for the correlations was set at $P<0.005$ (uncorrected, 100 voxels) and the statistical maps were overlaid on an MRI structural image.

For the ROI analysis we extracted regions using a template, which we had previously published (Wang et al., 1992). Out of this template we selected the ROIs for medial and lateral orbitofrontal cortex (OFC), anterior cingulate gyrus (CG) and dorsolateral prefrontal cortex (DLPFC) for which we hypothesized “a priori” an association with DA D2 receptors, the ROIs

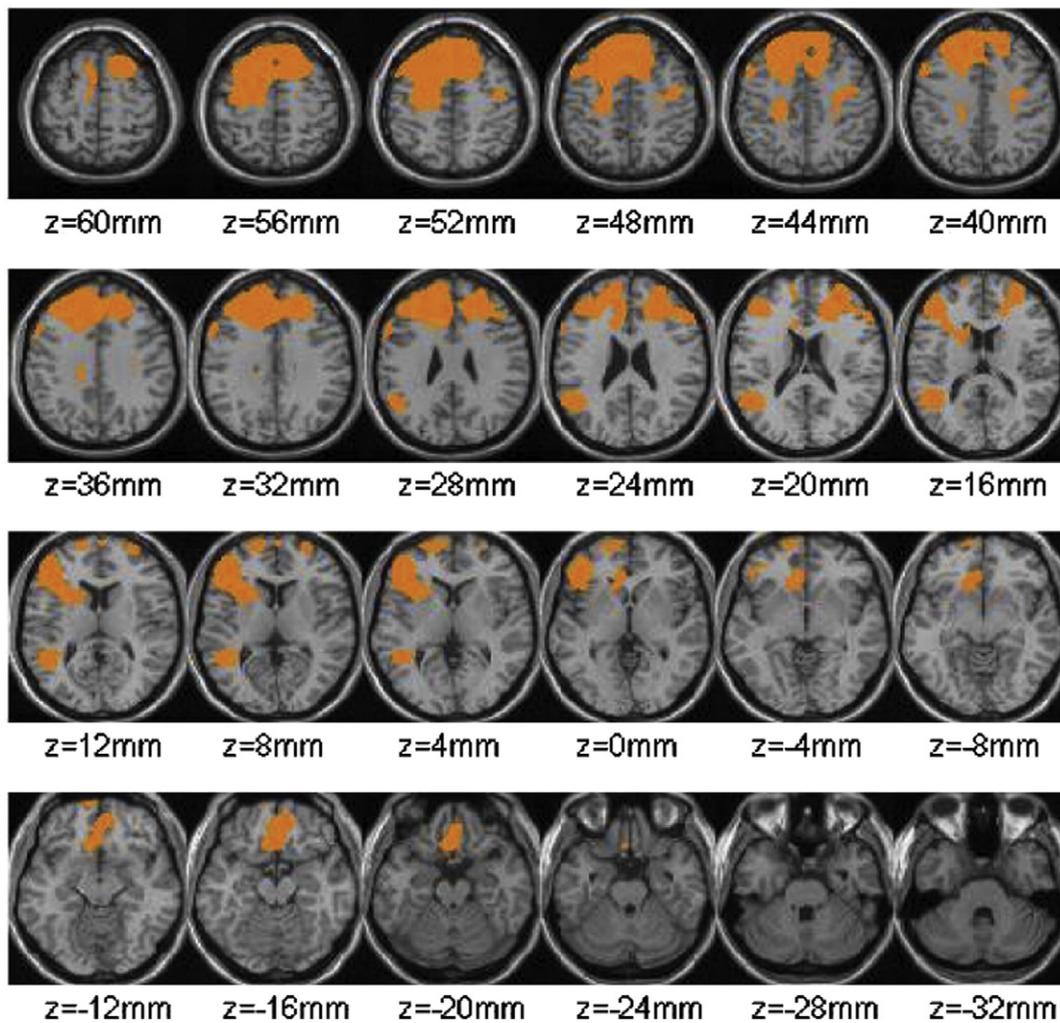


Fig. 1. Brain maps obtained with SPM showing the areas where the correlations between striatal D2 receptor availability and brain glucose metabolism were significant. Significance corresponds to $P < 0.005$, uncorrected, cluster size > 100 voxels.

for caudate and putamen, which were the ROIs where striatal D2 receptors were measured, and the ROIs in parietal (somatosensory cortex and angular gyrus), temporal (superior and inferior temporal gyri and hippocampus), and occipital cortices, thalamus and cerebellum, which were chosen as neutral ROIs.

Pearson product moment correlation analyses were performed between D2 receptor availability in striatum and the regional metabolic measures. Significance level for the correlations between D2 receptors and regional metabolism from the ROI was set at $P < 0.01$ and values of $P < 0.05$ are reported as trends. Differences in the correlations between the groups were tested using an overall test of coincidences for the regressions and significance was set at $P < 0.05$.

Results

The measures of striatal D2 receptor availability (B_{max}/K_d) were significantly lower in the obese subjects than in the non-obese controls (2.72 ± 0.5 versus 3.14 ± 0.40 , Student t test = 2.2, $P < 0.05$).

The SPM analysis done on the obese subjects to assess the correlation between D2 receptor availability and regional brain glucose metabolism showed it was significant in 4 clusters that were centered in (1) left and right prefrontal (BA 9),

CG (BA 32) and left lateral orbitofrontal cortices (BA 45); (2) left and right prefrontal (BA 10); (3) ventral cingulate gyrus (BA 25) and medial orbitofrontal cortex (BA 11); and (4) right somatosensory cortex (BA 1, 2 and 3) (Fig. 1, Table 1).

An independent analysis for the correlations between DA D2 receptor availability in striatum and the metabolic measures extracted using ROI corroborated the SPM findings. This analysis showed that the correlations were significant in

Table 1

Brain regions where SPM revealed significant ($P < 0.005$) correlations between striatal D2 receptor availability and glucose metabolism

	Cluster size (voxels)	Coordinates x, y, z	t	P
Left dorsolateral prefrontal	15,121	-20, 36, 32	3.81	0.001
L BA 9				
L BA 45				
Left prefrontal	1095	-44, -52, 18	3.51	0.001
L BA 10				
Medio ventral prefrontal	1138	-10, 26, -4	3.21	0.001
BA 25				
BA 11				
Right somatosensory	383	44, -16, 44	2.91	0.002
BA 1, 2, 3				

Significance for SPM corresponded to $P < 0.005$; cluster size > 100 pixel. Columns show cluster size (number of pixels), location of the center of the cluster with respect to the x, y, z coordinates of the Talairach space, magnitude of the effects (t values) and significance.

Table 2

Correlation coefficients (*r* values) and significance levels (*P* values) for the correlations between the measures of striatal DA D2 receptor availability (Bmax/Kd) and regional brain metabolism in obese subjects and in controls

	Obese subjects (n=10)		Non-obese controls (n=12)	
	D2R right ROI	D2R left ROI	D2R right ROI	D2R left ROI
<i>Frontal</i>				
DLPFC	0.84 0.003	0.86 0.002	0.47 NS	0.48 NS
CG	0.77 0.01		0.57 NS	
Medial OFC	0.76 0.01		0.42 NS	
Lateral OFC	0.26 NS	0.47 NS	0.37 NS	0.64 0.03
<i>Parietal</i>				
Postcentral	0.79 0.007	0.77 0.009	0.41 NS	0.71 0.01
Angular	0.68 0.03	0.54 NS	0.55 NS	0.64 0.03
<i>Temporal</i>				
GTS	0.35 NS	0.34 NS	0.44 NS	0.22 NS
GTI	0.29 NS	0.24 NS	0.46 NS	0.25 NS
Occipital	0.50 NS	0.29 NS	0.38 NS	0.44 NS
Caudate	0.04 NS	0.66 0.05	0.12 NS	0.49 NS
Putamen	0.02 NS	0.52 NS	0.42 NS	0.34 NS
Thalamus	0.08 NS	0.07 NS	0.07 NS	0.15 NS
Cerebellum	0.30 NS	0.42 NS	0.02 NS	0.01 NS

The metabolic values correspond to the regions of interest (ROI) extracted independently of the SPM results. NS=non significant. Comparisons of the correlations between obese and control subjects were not significant.

the left and right DLPFC (corresponding to BA 9 and 10), anterior CG (corresponding to BA 32 and 25) and the medial orbitofrontal cortex (medial BA 11). It also corroborated a significant correlation with the right somatosensory cortex (postcentral parietal cortex) (Table 2, Fig. 2).

In addition the analysis using the ROI also showed significant correlations with the left somatosensory cortex and showed a trend in right angular gyrus and right caudate (Table 2, Fig. 2). The correlations with the other cortical (occipital, temporal and lateral orbitofrontal cortex), subcortical (thalamus, striatum) and cerebellar regions were not significant.

In contrast, in the controls the ROI analysis revealed that the only significant correlation between D2 receptor avail-

ability and metabolism was in the left postcentral gyrus. There was a trend for a correlation in right lateral orbitofrontal cortex and in right angular gyrus.

Discussion

Here we show that in morbidly obese subjects DA D2 receptor availability was associated with metabolic activity in prefrontal regions (DLPFC, medial orbitofrontal cortex and anterior CG). These regions have all been implicated in regulating food consumption and in the hyperphagia of obese individuals (Tataranni et al., 1999, Tataranni and DelParigi, 2003). We also show a significant correlation with metabolism in somatosensory cortex (postcentral cortices) that was significant both in obese and in non-obese controls (left regions only). Whereas we had hypothesized the correlations with the prefrontal regions the association with the somatosensory cortex was an unexpected finding.

Association between D2 receptors and prefrontal metabolism

The significant association between D2 receptors availability and metabolism in prefrontal regions is consistent with our prior findings in drug-addicted subjects (cocaine, methamphetamine and alcohol) in whom we showed that the reductions in D2 receptors were associated with decreased metabolism in prefrontal cortical regions (Volkow et al., 1993b; Volkow et al., 2001; Volkow et al., 2007). Similarly in individuals at high familial risk for alcoholism we documented an association between D2 receptor availability and prefrontal metabolism (Volkow et al., 2006). Both obesity and addiction share in common the inability to restrain the behavior despite awareness of its negative effects. Inasmuch as prefrontal regions are implicated in various components of inhibitory control (Dalley et al., 2004) we postulate that the low D2 receptor availability in the striatum of obese subjects (Wang et al., 2001) and in rodent models of obesity (Hamdi et al., 1992; Huang et al., 2006; Thanos et al., 2008) may

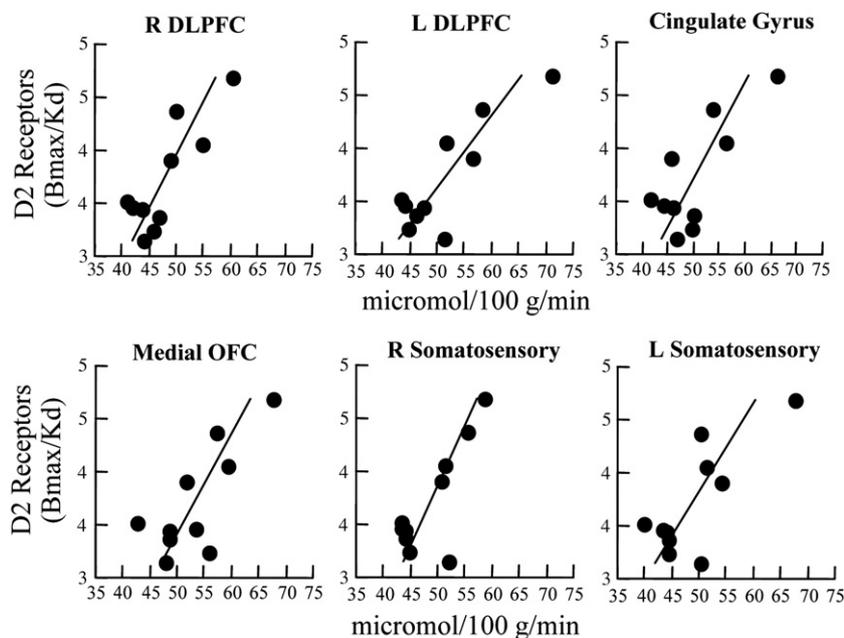


Fig. 2. Regression slopes between DA D2 receptor availability (Bmax/Kd) and regional glucose metabolism ($\mu\text{mol}/100 \text{ g}/\text{min}$) in prefrontal regions and in somatosensory cortex. The values for these correlations are shown in Table 2.

contribute to obesity in part via DA's modulation of prefrontal regions that participate in inhibitory control.

The findings also suggest that dopaminergic regulation of prefrontal regions as it relates to the risk for obesity may be mediated through D2 receptors. This is consistent with genetic studies, which have specifically implicated the D2 receptor gene (TAQ-IA polymorphism), as one that is involved in vulnerability to obesity (Fang et al., 2005; Pohjalainen et al., 1998; Bowirrat and Oscar-Berman, 2005). Moreover, the TAQ-IA polymorphism, which appears to result in lower D2 receptor levels in brain (striatum) (Ritchie and Noble, 2003; Pohjalainen et al., 1998; Jonsson et al., 1999) was recently found to be associated with decreased ability to inhibit behaviors that result in negative consequences and with impaired activation of prefrontal regions (Klein et al., 2007). Similarly preclinical studies have shown that animals with low D2 receptor levels are more impulsive than their littermates with high D2 receptor levels (Dalley et al., 2007). Thus the findings from our study provide further evidence that the association of D2 receptors with inhibitory control and with impulsivity is mediated in part by their modulation of prefrontal regions. In this respect it is interesting to note that brain morphological studies have reported reduced gray matter volumes in prefrontal cortex in obese subjects when compared to lean individuals (Pannacciulli et al., 2006).

The association between D2 receptors and the DLPFC is particularly interesting since this region was recently implicated in endogenous inhibition of intentional action (Brass and Haggard, 2007). The evidence that neuronal activity precedes an individual's conscious awareness of intention by 200–500 ms (Libet et al., 1983), has led some to question the concept of “free will” behind intentional actions and to propose that control reflects the ability to inhibit actions we do not want. Indeed, it was suggested that this veto power or “free won't” may be the way we exert “free will” (Mirabella, 2007). In the case of obesity one could postulate that exposure to food or food conditioned cues will result in the non-volitional activation of neuronal systems involved in procuring and eating the food and that the control reflects the ability to inhibit these intentional actions to want to eat the food. One can conceive how improper function of DLPFC, which enables inhibition of actions that result in negative outcomes, such as eating when we are not hungry because we do not want to gain weight, could result in overeating. Imaging findings showing greater decreases in activation of the DLPFC after a meal in obese subjects than in lean individuals support this hypothesis (Le et al., 2006).

The association between D2 receptor availability and medial orbitofrontal cortex (OFC) and anterior CG is consistent with their involvement in appetite regulation (Pliquet et al., 2006). There are several ways that one can propose by which disrupted dopaminergic activation of the OFC and the CG could increase the risk for overeating. The medial OFC is involved with salience attribution including the value of food (Rolls and McCabe, 2007; Grabenhorst et al., 2007; Tremblay and Schultz, 1999) and thus its activation secondary to food-induced DA stimulation could result in an intense motivation to consume food with a concomitant inability to inhibit it. Moreover, because disruption in the activity of the OFC results in impairment in the reversal of learned associations when a reinforcer is devalued (Gallagher et al., 1999) this could result in continued eating when the value of food is devalued by satiety and could explain why damage of the OFC is associated with compulsive behaviors including overeating (Butter et al.,

1963, Johnson, 1971). Also the OFC participates in learning stimulus-reinforcement associations and conditioning (Schoenbaum et al., 1998, Hugdahl et al., 1995) and could therefore participate in conditioned-cue elicited feeding (Weingarten, 1983). This is relevant because food-induced conditioned responses very likely contribute to overeating irrespective of hunger signals (Ogden and Wardle, 1990).

The dorsal CG (BA 32) is implicated in inhibitory control in situations that demand monitoring of activity and thus its disrupted activity along with that of DLPFC with which it interacts (Gehring and Knight 2000) is likely to further impair the ability of the obese individual to inhibit the tendency to overeat. The ventral CG (BA 25) is implicated in mediating the emotional responses to salient stimuli (rewarding as well as aversive) (Elliott et al., 2000) and imaging studies have shown that BA 25 is activated by natural and drug rewards (Breiter et al., 1997, Francis et al., 1999; Berns et al., 2001). Thus the negative association between D2 receptors and the tendency to eat when exposed to negative emotions we previously reported in healthy controls (Volkow et al., 2003) could be mediated by modulation of BA 25.

The association between metabolic activity in prefrontal regions and D2 receptors could reflect projections to the prefrontal cortex from ventral and dorsal striatum (Ray and Price, 1993), which are regions implicated in the reinforcing and motivational effects of food (Koob and Bloom, 1988) and/or from the ventral tegmental area (VTA) and substantia nigra (SN), which are the main DA projections to striatum (Oades and Halliday, 1987). However, the prefrontal cortex also sends projections to the striatum so the association could reflect the prefrontal regulation of DA striatal activity (Murase et al., 1993).

In non-obese controls the correlations between D2 receptor and prefrontal metabolism were not significant. In prior findings we had shown significant correlation between D2 receptor and prefrontal metabolism in addicted subjects with low D2 receptor availability but not in controls (Volkow et al., 2007). However, comparison of the correlations between the obese and the control groups were not significant, which suggests that it is unlikely that the association between D2 receptors and prefrontal metabolism is unique to obesity (or to addiction as per Volkow et al., 2007). It is more likely that the stronger correlations seen in the obese individuals reflect the greater range of striatal D2 receptor measures in obese (Bmax/Kd range 2.1–3.7) than in control subjects (Bmax/Kd range 2.7–3.8).

In interpreting these findings it is also important to consider that [¹¹C]raclopride is a radiotracer whose binding to D2 receptors is sensitive to endogenous DA (Volkow et al., 1994) and thus the reductions of D2 receptor availability in obese subjects could reflect low receptor levels or increases in DA release. Preclinical studies in animal models of obesity have documented reduction in the concentration of D2 receptors (Thanos et al., 2008), which suggests that the reductions in obese subjects reflect decreases in D2 receptor levels.

Correlation between D2R and somatosensory cortex

We had not “a priori” hypothesized an association between D2 receptors and metabolism in somatosensory cortex. When compared with the frontal or temporal regions there is relatively little that is known about the influence of DA in the parietal cortex. In the human brain the concentration of D2 receptors and D2 mRNA in parietal cortex while much

lower than in subcortical regions is equivalent to that reported in frontal cortex (Suhara et al., 1999; Mukherjee et al., 2002; Hurd et al., 2001). Though there is limited literature on the role of the somatosensory cortex in food intake and obesity. Imaging studies reported activation of the somatosensory cortex in normal weight subjects with exposure to visual images of low caloric foods (Killgore et al., 2003) and with satiety (Tataranni et al., 1999), and we had shown higher than normal baseline metabolism in the somatosensory cortex in obese subjects (Wang et al., 2002). Also a recent study reported that in obese individuals with leptin deficiency administration of leptin normalized their body weight and reduced brain activation in parietal cortex while viewing food-related stimuli (Baicy et al., 2007). The functional connectivity between the striatum and the somatosensory cortex was recently corroborated for the human brain by a meta-analysis study on 126 functional imaging studies, which documented co-activation of the somatosensory cortex with that of the dorsal striatum (Postuma and Dagher, 2006). However, from the correlations in our study we cannot ascertain the direction of the association; so we cannot determine if the association with D2 receptors reflects DA's modulation of the somatosensory cortex and/or the influence of the somatosensory cortex on striatal D2 receptor availability. Indeed there is ample evidence that the somatosensory cortex influences brain DA activity including striatal DA release (Huttunen et al., 2003; Rossini et al., 1995; Chen et al., 2007). There is also evidence that DA modulates the somatosensory cortex in the human brain (Kuo et al., 2007). Inasmuch as DA stimulation signals saliency and facilitates conditioning (Zink et al., 2003; Kelley, 2004), DA's modulation of the somatosensory cortex's response to food is likely to play a role in the formation of conditioned association between food and food-related environmental cues and in the enhanced reinforcing value of food that occurs in obesity (Epstein et al., 2007).

Study limitations

A limitation for this study is that we did not obtain neuropsychological measures and thus we cannot assess if the activity in prefrontal regions is associated with behavioral measures of cognitive control in these obese subjects. Though neuropsychological studies on obesity are limited and the findings are confounded by the medical complications of obesity (i.e. diabetes and hypertension), there is evidence that in obese subjects inhibitory control may be disrupted. Specifically, when compared with normal weight individuals, obese subjects make less advantageous choices, which is a finding consistent with impaired inhibitory control and with prefrontal dysfunction (Pignatti et al., 2006). Moreover rates of attention deficit hyperactivity disorder (ADHD), which involves disruption in impulsivity, are elevated in obese individuals (Altfas, 2002). Similarly impulsivity has been linked with high BMI in some populations (Fassino et al., 2003) and in healthy controls BMI has also been associated with performance in tasks of executive function that mediate impulsivity (Gunstad et al., 2007).

Also while in this paper we focus on the role that the prefrontal cortex has on inhibitory control and impulsivity we recognize that the prefrontal cortex is involved with a wide range of cognitive operations many of which are not disrupted in obese subjects (Kuo et al., 2006; Wolf et al., 2007). It is possible that the functions of the prefrontal cortex that

contribute to obesity are the ones sensitive to DA modulation via striatal prefrontal pathways (Robbins, 2007; Zgaljardic et al., 2006).

Neither the dysregulation of prefrontal activity nor the impairment of executive function is specific for obesity. Indeed abnormalities in prefrontal metabolism and impairment in executive function have been documented in a wide range of disorders including those with dopaminergic involvement such as drug addiction, schizophrenia, Parkinson's disease and ADHD (Volkow et al., 1993b; Gur et al., 2000; Robbins, 2007; Zgaljardic et al., 2006).

Another limitation was that the limited spatial resolution of the PET [¹¹C]raclopride method did not allow us to measure D2 receptor availability in small brain regions that are important in mediating food associated behaviors such as the hypothalamus.

Finally correlations do not imply causal associations and further studies are required to evaluate the consequences of disrupted DA brain activity in prefrontal function in obese subjects.

Summary

This study shows a significant association in obese subjects between D2 receptors in striatum and the activity in DLPF, medial OFC and CG (brain regions implicated in inhibitory control, salience attribution and emotional reactivity and their disruption can result in impulsive and compulsive behaviors), which suggests that this may be one of the mechanisms by which low D2 receptors in obesity could contribute to overeating and obesity. In addition we also document a significant association between D2 receptors and metabolism in somatosensory cortex that could modulate the reinforcing properties of food (Epstein et al., 2007) and that merits further investigation.

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