Similarity Between Obesity and Drug Addiction as Assessed by Neurofunctional Imaging

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whatever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.
Summary. Overeating in obese individuals shares similarities with the loss of control and compulsive drug taking behavior observed in drug-addicted subjects. The mechanism of these behaviors is not well understood. Our prior studies with positron emission tomography (PET)
in drug-addicted subjects documented reductions in striatal dopamine (DA) D2 receptors. In pathologically obese subjects, we found reductions in striatal DA D2 receptors similar to that in drug-addicted subjects. Moreover, DA D2 receptor levels were found to have an inverse relationship to the body mass index of the obese subjects. We postulated that decreased levels of DA D2 receptors predisposed subjects to search for reinforcers; in the case of drug-addicted subjects for the drug and in the case of the obese subjects for food as a means to temporarily compensate for a decreased sensitivity of DA D2 regulated reward circuits. Understanding the mechanism in food intake will help to suggest strategies for the treatment of obesity. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <http://www.HaworthPress.com>]

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INTRODUCTION

Obesity is a complex disease of appetite regulation and energy metabolism that is controlled by many factors.\(^1\) It can result from several possible genetic and environmental interactions\(^2\) some of which may entail a more direct genetic association (i.e., a genetically regulated response to sweet food which is perceived as reinforcing)\(^3\) or alternatively an indirect association that makes the individual genetically more susceptible to environmental stressors that will then favor food consumption.\(^4\)

Among the genetic factors, there are neuromodulators (e.g., leptin),\(^5\) and multiple neurotransmitter systems involved with the reinforcing properties of food (i.e., GABA, dopamine, opioids, serotonin). These neurotransmitters also play an important role in feeding behavior and satiation.\(^6\) There is a large amount of evidence to suggest that dopamine (DA) may be one of the neurotransmitters linking the genetic and environmental factors that contribute to obesity.\(^7\) Behavioral studies on rodents indicate that DA D2 receptor antagonists can enhance meal size and duration of feeding.\(^8\) Similarly, long-term administration of DA D2 receptor antagonists increases feeding and body weight in female rats.\(^9\) In clinical studies, patients treated with typical and atypical antipsychotic medications, which block DA D2 receptors, show significant weight gain.\(^10,11\) Dopaminergic agonists (e.g., amphetamine, cocaine, methylphenidate) that increase brain dopamine concentration have anorexigenic effects.\(^12\)
Many obesity researchers focus on how the body’s fuel and fat levels control appetite. But as binge eaters know, habits and desires often override metabolic need, which share some of the characteristics of drug using behavior in drug-addicted subjects. The present article discusses the role of DA in drug abuse and its involvement in the mechanism of obesity.

**BRAIN DA AND ADDICTIVE BEHAVIORS**

The role of DA in addiction (loss of control and compulsive drug intake) is poorly understood. A plethora of studies have reported over the years the role of dopamine and its receptors on alcohol and drug abuse. One example is the role of DA on cocaine addiction, which is considered to be one of the most reinforcing of the abused drugs. Animal studies have shown that the ability of cocaine to block the dopamine transporters appears to be crucial for its reinforcing effects. In humans, the reinforcing effects of cocaine used intravenously or smoked can lead to rapid escalation of drug intake and compulsive drug administration. Animal studies indicate that DA D2 receptor levels mediate reinforcing responses to drugs of abuse. We have shown that overexpression of DA D2 receptors in the nucleus accumbens, which is the brain region associated with the reinforcing effects of drugs of abuse, in animals previously trained to self-administer alcohol resulted in a marked reduction in alcohol intake that returned to baseline levels as the DA D2 receptors decreased to their prior levels.13,14

While the studies on the effects of DA D2 receptor antagonists on the reinforcing effects of psychostimulants in humans have not been as conclusive as those in laboratory animals, they have shown a decrease in the subjective ratings of pleasant sensations and of the craving induced by cocaine.15 The lower efficacy of DA D2 receptor antagonists reported in studies may reflect the fact that the doses used were lower than those used in laboratory animals and resulted in incomplete DA D2 receptor blockade.

**USE OF IN VIVO IMAGING TO STUDY DRUG ADDICTION**

Positron Emission Tomography (PET) is a medical imaging technology that uses radioactive positron-emitting atoms (i.e., carbon-11 and fluorine-18) to label and measure the concentration and movement of
positron labeled compounds in living tissue. Positron emitter labeled radiotracers are used to label proteins that are of physiological relevance (i.e., receptors, transporters and enzymes) in the human brain. The measurement of DA D2 receptor using PET and [11C]raclopride has been used to assess neuropsychiatric disorders, substance abuse and aging (reviewed). Since [11C]raclopride is sensitive to endogenous DA concentration and its binding is reproducible, it can also be used to measure relative changes in DA concentration secondary to pharmacological interventions. Methylphenidate is a cocaine-like psychostimulant that increases extracellular DA by blocking DA transporters. Methylphenidate-induced changes in [11C]raclopride striatal binding are interpreted as reflecting changes induced by DA occupancy of D2 receptors secondary to the changes in DA synaptic concentration. The measure has been used as an indication of the responsivity of the DA system to pharmacological challenge. This strategy allowed us to evaluate the relationship between DA changes as assessed by the levels of DA D2 receptors occupancy and subjective perception of pleasure or euphoric “high,” which is associated with rewarding effects of the drug. We found the intensity of the “high” induced by methylphenidate was significantly correlated with the levels of released DA. The subjects who reported the most intense “high” were those who have the greatest increases of DA release. It appears that DA and DA D2 receptors play an important role in the reinforcing response to psychostimulants.

Even though the reinforcing effects of cocaine may involve the initial drug taking behavior, others factors might also contribute to the compulsive drug taking and the loss of control in addicts. Repeated cocaine self-administration often continues (because of acute tolerance to the pleasurable response) and sometimes, despite the presence of an aversive drug reaction. Acute tolerance to cocaine can occur in recreational levels of cocaine consumption. This neurochemical response to cocaine is primarily caused by direct pharmacological effects of the drug rather than by the conditioning to external environmental cues. Chronic administration of cocaine significantly impacts the brain DA system. In fact, our prior [11C]raclopride-PET studies in drug-addicted subjects (cocaine, methamphetamine, alcoholics, and heroin) showed significant DA D2 receptor reductions in striatum (Figure 1). It has been hypothesized that compulsive disorders such as drug addiction, gambling and sex reflect a “Reward Deficiency Syndrome,” that is speculated to be due in part to a reduction in DA D2 receptors.
FIGURE 1. Group average images of $[^{11}C]$raclopride (distribution volume ratio) PET images for 15 methamphetamine users (9 women and 6 men, age range 21-46 years, mean 32 ± 7 years old), their control subjects (6 women and 14 men, age range 21-43 years, mean age 31 ± 7 years old), 10 obese subjects (5 women and 5 men, mean 39 ± 7 years old, age range 26-54) and their control subjects (3 women and 7 men, age range 25-45 years, mean 37.5 ± 5.9 years old) at the level of the striatum. The images are scaled with respect to the maximum absolute value obtained on average image of the control subjects and presented using the gray scale where white represents the highest value and black represents the lowest value. Methamphetamine users and obese subjects have significantly lower measures of striatal dopamine D2 receptor availability than control subjects. Modified from references 24 and 59.
DA release seems to have a site-specific action on the regulation of food intake. In the nucleus accumbens, DA release has been generally associated with the reinforcing effects of food. In the hypothalamus, DA release is associated with the duration of meal consumption, which is a factor in determining feeding pattern. Hence, DA is required to initiate each meal and is associated with the quantity and duration of a meal. DA acting locally within the hypothalamus acts as a potent inhibitor of feeding in the perifornical area, ventromedial hypothalamus, and arcuate nucleus. In addition, DA is a potent inhibitor of hypothalamic neuropeptide Y (NPY, a potent stimulator of food intake) expression and activity and a stimulator of arcuate proopiomelanocortin (POMC) expression. These hypothalamic influences may contribute to DA’s ability to reduce food consumption and hyperphagia. Leptin, insulin, and other peripheral peptides and steroid hormones modulate the synthesis and release of DA. It appears that DA is associated with both short-term (individual meals) and long-term (hunger) regulation of food intake.

DA regulates food intake via the meso-limbic circuitry of the brain apparently by modulating appetitive motivational processes. There are also projections from the nucleus accumbens to the hypothalamus that directly regulate feeding. The dopaminergic reward pathways of the brain are critical for survival since they help influence the fundamental drive for eating. Recent work has shown that DA systems are necessary for wanting incentives, which is a distinct component of motivation and reinforcement. It is one of the natural reinforcing mechanisms that motivates an animal to perform and seek a given behavior. However, unnatural rewards such as drugs of abuse (i.e., cocaine, alcohol, nicotine), also release DA. Furthermore, because most of the drugs abused by humans lead to increased DA concentration in the nucleus accumbens, this has been suggested as being a common mechanism for reinforcement.

Though the effects of DA in the nucleus accumbens are the ones traditionally implicated in motivation for food, a study in DA deficient knockout mice provided clear evidence of the relevance of the dorsal
striatum in the motivation for food consumption. Without intervention, these DA deficient mice die because of lack of food consumption, however, treatment with DA in the dorsal striatum, but not in the nucleus accumbens, restored feeding. Interestingly in these animals rescuing DA in the nucleus accumbens restored the ability of the mice to choose between a palatable and a non-palatable solution but did not prevent them from dying due to inadequate caloric consumption. The latter study points to two separate processes regulating food intake; one to maintain the caloric requirements necessary for survival that implicates the dorsal striatum and another one that relates to the motivation properties of food (palatability) that implicates the nucleus accumbens.

To assess the involvement of DA in the dorsal striatum in the non-hedonic motivation for food intake in human subjects, we evaluated changes in extracellular DA in striatum in response to food stimulation (visual, olfactory, and gustatory display of food in food deprived subjects) after placebo and after methylphenidate. In this study, methylphenidate was given as a strategy to amplify DA signals. Neither the neutral stimuli (with or without 20 mg of oral methylphenidate) nor the food stimuli when given with placebo increased DA or increased the desire for food. However, the food stimuli when given with methylphenidate increased both extracellular dopamine and the desire for food. We found that changes in extracellular dopamine in striatum in response to food stimulation were significant in dorsal but not in ventral striatum and were significantly correlated with the increases in self-reports of hunger and desire for food. Such a relationship was not observed for the ventral striatum where the nucleus accumbens is located. Our results showing an effect in the dorsal but not in the ventral striatum is likely to reflect the fact that the food stimulation to the subjects was not rewarding, i.e., in this study subjects were not permitted to consume the food.

THE ROLE OF BRAIN DOPAMINE IN OBESITY

DA plays a role in pathological feeding behavior, since low levels of DA may interfere with the drive and motivation to eat. Binge eating (Bulimia Nervosa), which occurs in about 30% of obese subjects attending weight control programs, is characterized by episodes of eating objectively large amounts of food and with feelings of loss of control. Obese binge eaters consume significantly more calories than obese non-binge eaters when asked to eat as much as they wanted or simply to
eat normally. Obese binge eaters have high relapse rates during weight control programs and experience their disorder for long periods of time. A high prevalence of binge eating disorder (30-80%) was reported among the morbidly obese subjects who have undergone bariatric surgery. The eating disturbances persist (6-26%) in many of the same patients after surgery and are correlated with weight regain. The obese binge eaters lose less excess body weight than obese non-binge eaters after the surgery.

Bulimic nervosa patients have been found to have normal DA metabolite levels. In contrast, high frequency binge eaters have reduced cerebrospinal fluid DA levels. Decreased DA metabolite plasma levels have been found, but they are not associated with symptomatology of binge eating disorder. To this day, it is difficult to determine whether a trait disturbance on the dopaminergic system plays a role in the etiology of binge eating disorder.

There is better evidence for the causal role of DA in obesity. Human studies have shown a higher prevalence of the Taq IA allele for the DA D2 receptors in obese subjects. Though not replicated by all studies, the Taq IA allele has been linked with lower levels of DA D2 receptors. Variants of the human obesity (ob) gene and the DA D2 receptor gene have been examined in relationship to obesity. These two polymorphisms together account for about 20% of the variance in BMI, particularly in younger women. The association of the Taq IA allele with reduced number of DA D2 receptor levels suggests that obese individuals with the A1 allele may use food to increase DA stimulation to a more desirable level. This is consistent with the finding in binge eaters with frequent binge episodes who are reported to have low DA metabolite concentrations in cerebrospinal fluid. These results indicate that low DA brain activity (either due to decreased DA release or to decreased stimulation of postsynaptic DA receptors) may be associated with dysfunctional eating patterns. The DA system has also been targeted for therapy of obesity since DA agonists have anorexigenic effects whereas drugs that block DA D2 receptors increase appetite and result in weight gain.

**USE OF PET IMAGING TECHNOLOGY TO STUDY OBESITY**

Compulsive overeating in obese subjects shares many of the same characteristics as drug addiction. Using a PET scanner with a re-designed bed to support heavy weight, we have shown a significant reduc-
tion in DA D2 receptor availability in obese subjects (Figure 1). These subjects have body mass indexes (BMI: weight in kilograms divided by the square of height in meters) between 42 and 60 (mean 51.2 ± 4.8 kg/m², body weight: 274-416 lb). These subjects do not have current or past psychiatric and/or neurological disease, hypertension, diabetes, and medical conditions that may alter cerebral functioning. Interestingly, in the obese subjects, but not in the controls, the DA D2 receptors were significantly associated with their BMI (Figure 2). It is possible that in obese subjects, DA D2 receptors may play a greater role in regulating eating behavior than in control subjects. The results could also be interpreted to suggest that DA D2 receptors are not involved in modulating body weight per se but rather may regulate compulsiveness in the pathological eaters. This would imply that the role of the DA D2 receptors is not to enable obesity but if the pertinent genetic or environmental variables that predispose to obesity are present, then it will favor a more severe presentation. The obese subjects share in common with drug addicts the inability to refrain from using the reinforcer and its compulsive administration. Thus DA D2 decrements are unlikely to be specific for any one of these compulsive behavioral disorders including obesity and may relate to vulnerability for addictive behaviors.

**DRUG PREFERENCES AND COMPULSIVE OVEREATING**

One of the challenging questions regarding the neurobiological mechanism(s) underlying these disorders is why some subjects abuse drugs while others do not. We investigated this problem in non-drug abusing individuals in whom we measured DA D2 receptor levels and assessed their response (pleasant or unpleasant) to a challenge dose of the stimulant drug, methylphenidate given intravenously. We found that subjects who reported the methylphenidate as pleasant had lower DA D2 receptor levels. Those who reported methylphenidate as unpleasant had higher DA D2 receptor levels. A replicate study documented that the levels of DA D2 receptors predicted how much subjects liked the effects of methylphenidate. However, vulnerability to drug abuse could not be explained solely on the differences in DA D2 receptor availability since none of these subjects suffered from addiction even though they have very low DA D2 receptor levels. This indicates that while DA D2 receptors may contribute to vulnerability by themselves they are not sufficient to lead to addiction. Further work is neces-
sary to assess if DA D2 receptors also modulate the “liking” responses to food to determine if low DA D2 levels may also be associated with a higher vulnerability for compulsive eating behaviors.

**SENSORY PROCESSING OF THE FOOD AND OBESITY**

What makes obese subjects different from drug addicts? Would obese subjects have an enhanced sensitivity in the brain regions involved with sensory processing of the food? Signals that affect food intake originate from internal sources that directly regulate food intake (i.e., hunger, satiety) and those that regulate emotional responses (i.e., to stress, boredom) as well as from the environmental sources (e.g., food availability, food related cues, alternative reinforcers). Disruption in the sensitivity of the brain to these sources could lead to obesity from excess eating. Irrespective of the source, a particularly relevant variable in the regulation of food intake is the sensory appeal that the food conveys to the subject. Thus, we questioned whether obese subjects

![Graph](https://example.com/graph.png)

**FIGURE 2.** Linear regression between dopamine receptor availability (Bmax/Kd) and body mass index (BMI: kg/m²) in obese and control subjects. Modified from reference 59.
would have an enhanced sensitivity in the brain regions involved in sensory processing of the food associated with eating. We compared brain metabolism of obese subjects with lean control subjects using PET and 2-deoxy-2\[^{18}\text{F}]\text{fluoro-D-glucose (FDG), an analog of glucose, which has been served as an indicator of brain function. This method has been used to assess cerebral dysfunction in neurological and psychiatric disorders.\(^{63}\) The brain metabolic images were analyzed using statistical parameter map (SPM), which showed that obese subjects had significantly greater glucose metabolism in the vicinity of the post-central gyrus in the left and right parietal cortex (Brodmann’s areas 1).\(^{64}\) This area of the parietal cortex is where the somatosensory maps of the mouth, lips, and tongue are located and is an area involved with taste perception (Figure 2).\(^{65}\) The enhanced activation of these parietal regions is consistent with an enhanced sensitivity to food palatability (i.e., consistency, taste) in obese subjects. The enhanced activation in somatic parietal areas for mouth, tongue and lips in obese subjects suggests that enhanced sensitivity in regions involved in the sensory processing of food may make food more rewarding and may be one of the variables contributing to excess food consumption in these obese individuals.

**MODULATION OF SENSORY PROCESSING OF THE FOOD IN OBESE INDIVIDUALS**

Because foods with high palatability tend to have high energy content but are not satiating (fatty foods) in contrast to foods with low energy density that are more satiating but less palatable,\(^{66}\) enhanced sensitivity to food palatability could lead to food over-consumption and obesity. Palatability increases food intake through a positive-feedback reward mechanism that involves the opioid and GABA/benzodiazepine systems.\(^{67,68}\) Thus, interventions that include the use of pharmacological treatments known to decrease palatability (i.e., opioid receptor antagonist)\(^{69}\) in association with behavioral therapies to reduce the likeness of food with high energy content may prove beneficial in reverting the enhanced sensitivity of the somatosensory areas processing food palatability and reducing food intake in obese subjects.

**CONCLUSION**

Though obesity is the product of many interacting variables, there is mounting evidence that the motivation and reward circuits regulated by
DA play a role. Our PET studies show obese individuals have significantly lower DA D2 receptor levels, which is similar to findings from PET studies in drug-addicted subjects. Lower DA D2 receptors in obese individuals would make them less sensitive to reward stimuli, which in turn would make them more vulnerable to food intake as a means to temporarily compensate for this deficit. In addition, obese individuals show an enhanced activity of brain regions that process food palatability, which is likely to increase the rewarding properties of food and could account for the powerful salience that food has in obese individuals. The results from these studies have implications for the treatment of obesity since they would suggest that strategies aimed at improving DA function might be beneficial in the treatment and prevention of obesity.

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