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General

The role of dopamine in motivation for food in humans: implications for obesity

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Obesity is a major public health problem. The increasing number of obese individuals in the US adds urgency to the efforts to understand the mechanisms underlying pathological overeating. Imaging studies using positron emission tomography implicate the involvement of brain dopamine (DA) in normal and pathological food intake in humans. In normal body weight, fasting subjects, food presentation that could not be consumed was associated with increases in striatal extracellular DA, which provides evidence of an involvement of DA in non-hedonic motivational properties of food intake. In pathologically obese subjects, the authors showed reductions in striatal D2-receptor availability that were inversely associated with the weight of the subject. The involvement of the DA system in reward and reinforcement has led to the hypothesis that low brain DA activity in obese subjects predisposes them to excessive use of food. A better understanding of the role of the DA system in the motivation for food intake will help the development of better therapeutic interventions.

Keywords: dorsal striatum, dopamine (DA) D2 receptors, imaging, reward

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1. Introduction

The prevalence of obesity is increasing throughout the world [1]. Obesity is a major public health problem associated with increased morbidity and mortality, second only to smoking. Contributing factors to obesity include genetics, abnormal eating behaviour, culture, high caloric consumption and lowered energy expenditure (i.e., decreased physical activity) [2-5]. Despite considerable effort towards identifying genetic trait markers for obesity, there is, as yet, no consensus on genetic markers for vulnerability to common obesity [6].

Obesity can result from several possible genetic and environmental interactions [7] some of which may entail a more direct genetic association (i.e., a genetically regulated response to sweet food which is perceived as reinforcing) [8] or, alternatively, an indirect association that makes the individual genetically more susceptible to environmental stressors that will then favour food consumption [9].

It is also likely that there are multiple neurotransmitter systems involved with genetic predisposition and with the reinforcing properties of food (i.e., GABA, dopamine [DA], opiates, 5-HT) and that neuromodulators are also involved (i.e., leptin) [10]. However, there is a large amount of evidence to suggest that DA may be one of the target neurotransmitters linking the genetic and environmental factors that contribute to obesity [11].

2. Biological mechanism underlying obesity: signals that control food intake

Obesity is a complex disease of appetite regulation and energy metabolism that is controlled by many factors. The level of adiposity in most adults tends to remain

constant over long intervals, even though daily energy intake and expenditure may vary considerably over the same intervals. Energy that is expended is precisely matched by energy that is consumed. The regulation of food intake is a balance between excitatory and inhibitory processes. The excitatory processes arise from body needs and a drive for food. The inhibitory processes arise when there is a subjective sensation of fullness after food consumption. Satiety signals generated during individual meals, which include neural and endocrine, and peptides secreted from the gut (i.e., cholecystokinin, ghrelin, amylin) provide information to the brain to inhibit feeding and terminate the meals [12,13]. The satiety signals are conveyed to the brainstem by way of the vagus nerve and other routes [14]. A change of a single satiety signal would only lead to an increase in meal size or a modest increase in meal frequency. However, a small discrepancy between the energy intake and expenditure will lead to gradual weight gain or weight loss [15]. Short-term mis-matches in energy balance are compensated for over long time intervals. The increase in food intake following a period of fasting quickly restores energy reserves and body weight by a highly regulated process that functions to maintain homeostasis [16].

When the body fat content changes, the body releases humoral signals that modify food intake. Major candidates for such signals are leptin (a hormone secreted by adipocytes) and insulin, which are secreted in proportion to body fat content [17,18] and enter the CNS in proportion to their plasma level [19,20]. These adiposity signals stimulate a catabolic pathway [21,22] and inhibit an anabolic pathway [23-25] that originate in the arcuate nucleus. These pathways project to the hypothalamus and make connections with central autonomic pathways that project to the brainstem autonomic centres, which process satiety signals [26]. It seems that the function of leptin is related to long-term regulation of appetite and is linked to the expression of hunger and active food seeking rather than with satiety or short-term inhibition overeating. Leptin modulates the tonic signal derived from metabolism and storage, which are associated with the drive for food consumption. Low leptin and insulin levels during weight loss increase activity of anabolic neural pathways that stimulate eating and inhibit energy expenditure. There is growing evidence that indicates that resistance to leptin (occurring at a postreceptor site) in the CNS is present in most models of rodent obesity [27-30] and is likely to exist in some forms of human obesity [18,31-34].

Several neurotransmitters also play an important role in feeding behaviour and satiation [35,36]. Considerable effort has been devoted to the development of weight control medications that target neurotransmitters in the brain that regulate food intake [10,37,38]. Most of the recent pharmacological efforts have focused on 5-HT, which plays an important role in satiety [39]. The DA system has also been targeted for its role on feeding behaviour. Profound feeding deficiency can be found in pharmacological depletion and genetic disruption of brain DA [40,41]. However, these abnormal feeding behaviours may be confounded with the fact that motor

impairments associated with DA deficiency may also affect feeding behaviour.

3. The involvement of dopamine in food intake

DA release seems to have a site-specific action in food intake regulation. In nucleus accumbens (NAc), DA release has been generally associated with the reinforcing effects of food [42]. 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 meal number and duration of feeding [43].

DA acting locally within the hypothalamus acts as a potent inhibitor of feeding in the perifornical area, ventromedial hypothalamus and arcuate nucleus. DA is a potent inhibitor of hypothalamic neuropeptide Y (NPY, a potent stimulator of food intake) expression and activity and a stimulator of arcuate pro-opiomelanocortin (POMC) expression [44,45]. 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 [46]. It appears that DA is associated with both short-term (individual meals) and long-term (hunger) regulation of food intake [47].

Five subtypes of DA receptors have been identified and categorised into D1- (D1, D3) and D2- (D2, D4 and D5) like subtypes of receptors. Both D1- and D2-like receptors play a significant role in control of feeding behaviour. DA effects on D1 receptors contribute to satiety signals whose main effect is to reduce meal size through a reduction in duration of eating. DA effects on D2 receptors are mainly related to rate of feeding. A mixture of DA agonist, such as apomorphine, suppresses feeding by reducing both feeding duration and the rate of feeding [48].

However, DA agonists also markedly reduce adiposity and the insulin resistance syndrome without influencing food consumption [49-51]. In fact, D2 receptor agonists (e.g., bromocriptine) have been used in humans to treat diabetes [52]. The preclinical data indicates that D2 receptor agonists normalise elevated hypothalamic NPY and body weight gain in hyperglycaemic obese mice [53]. Such treatment increases energy expenditure via increases in protein turnover while reducing lipogenesis. These effects are mediated mainly via influences on the hypothalamus [53,54].

Behavioural studies on animal indicate that D2 receptor antagonists can enhance meal size and duration of feeding [55]. Long-term administration of D2 receptor antagonists increases feeding and body weight in female rats [56]. In humans, patients treated with typical and atypical antipsychotic medications, which block D2 receptors, show significant weight gain [57,58]. Pretreatment of food-deprived rats with D2 receptor antagonists significantly attenuates gut peptides' (i.e., amylin) inhibitory effect on feeding [59]. However, because antipsychotics also affect other neurotransmitter

systems, it is possible that the weight gain they induce is mediated by their effects on DA and other neurotransmitters, peptides and adiposity signals [59-61].

4. The role of mesolimbic dopamine in food intake

Mesolimbic DA is currently hypothesised to regulate food intake by modulating appetitive motivational processes [62-64]. There are also projections from the NAc to the hypothalamus that directly regulate feeding [65]. It is generally believed that the dopaminergic reward pathways of the brain provide one of the drives for eating. However, more recent work has shown that DA systems are necessary for wanting incentives, which is a distinct component of motivation and reinforcement [42,66]. It is one of the natural reinforcing mechanisms that motivates an animal to perform and seek a given behaviour. Artificial rewards such as drugs of abuse (e.g., cocaine, alcohol, nicotine) also release DA [11]. Furthermore, because most of the drugs abused by humans lead to increased DA concentration in NAc this has been suggested as being a common mechanism for reinforcement [67,68].

DA systems are linked to the motivation to seek food. To assess the involvement of DA in the non-hedonic motivation for food intake in human subjects, Volkow *et al.* evaluated changes in extracellular DA in dorsal striatum and in the ventral striatum, where the NAc is located, in response to food stimulation after placebo and after methylphenidate (MP) [69]. Since MP blocks the DA transporters [70], the main mechanism regulating the uptake of DA from the extracellular space, Volkow and collaborators used MP as a strategy to amplify the DA signals from the stimulation. Ten healthy subjects were studied 16 – 20 h after their last meal. During the food stimulation condition, the subjects were allowed to smell, taste, see and talk about food without the pleasure of its consumption. For the neutral stimulation condition, the subjects were asked to describe in as much detail as possible their family genealogy. The food and the neutral stimulations were started 15 min prior to radiotracer injection and were continued for a total of 40 min. Subjects were scanned four times with [¹¹C]raclopride over a 2-day period. The first [¹¹C]raclopride scan on a given day was conducted 60 min after oral placebo; for 1 day, the placebo was followed 45 min later by neutral stimulation and for the other day by food stimulation. The second scan on a given day was conducted 2 h after the first scan and 60 min after oral administration of MP (20 mg); for 1 day the MP was followed 45 min later by neutral stimulation and for the other day by food stimulation. B_{\max}/K_d (the ratio of distribution volumes in striatum to that of distribution volumes in cerebellum) was calculated using Logan plot analysis [71] to estimate DA receptor availability. The responses to food stimulation (with or without MP) were quantified as the difference in B_{\max}/K_d with respect to the placebo with neutral stimulation condition (used as baseline). The difference in the B_{\max}/K_d measures with respect to the baseline condition

represents the relative changes in extracellular DA in striatum. The food stimulation, when given with placebo, increased DA in dorsal striatum but this effect was not significant. However, when the food stimulation was given with MP, the increases in extracellular DA in the dorsal but not in the ventral striatum were significant (Figure 1). Moreover, the magnitude of the DA increases predicted the intensity of the subjective 'desire for food' and for 'hunger'. These results provide evidence that DA in the dorsal striatum is involved with the desire and motivation for food consumption in human subjects.

Though the effects of DA in the NAc are the ones traditionally implicated in motivation for food [72-75], a recent study in DA-deficient knockout mice provided clear evidence of the relevance of the dorsal striatum in the motivation for food consumption. DA-deficient mice will die of starvation a few weeks after birth, but they can be rescued by either providing L-DOPA daily as a systemic injection or by transducing small brain regions with viruses that allow local L-DOPA production, which can then restore local DA neurotransmission [76]. Interestingly, restoration of DA signalling in the dorsal striatum but not in the NAc, sustained feeding of normal lab/chow mix. Restoration of DA signalling in NAc did restore preference for palatable sweet foods but it was insufficient to maintain feeding over long periods. 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 rewarding properties of food that implicates the NAc.

5. The involvement of dopamine in obesity

Genetic studies in humans on the involvement of the DA system in obesity have mainly concentrated on the gene encoding for the D2 receptors. Studies in laboratory animals have shown that in genetically obese mice (*ob/ob*), DA agonists normalised body weight [77]. Human studies have shown a higher prevalence of the *Taq I A* allele for the D2 receptors in obese individuals [78]. Though not replicated by all studies [79], the *Taq I A* allele has been linked with lower levels of D2-receptors [80]. Variants of the human obesity (*ob*) gene and the D2 receptor gene have been examined in relation to obesity. These two polymorphisms together account for ~ 20% of the variance in body mass index (BMI: weight in kilograms divided by the square of height in metres), particularly in younger women [81]. The association of the *Taq I A* allele with reduced number of D2 receptors suggests that the obese individuals with the A1 allele may use food to increase DA stimulation to a more acceptable level [82]. This is consistent with the finding in bulimic patients with frequent binge episodes who are reported to have low DA metabolite concentrations in cerebrospinal fluid [83].

6. Use of *in vivo* imaging to study obesity

Very few imaging studies have been conducted in obese subjects. This is partly due to the engineering and mechanical

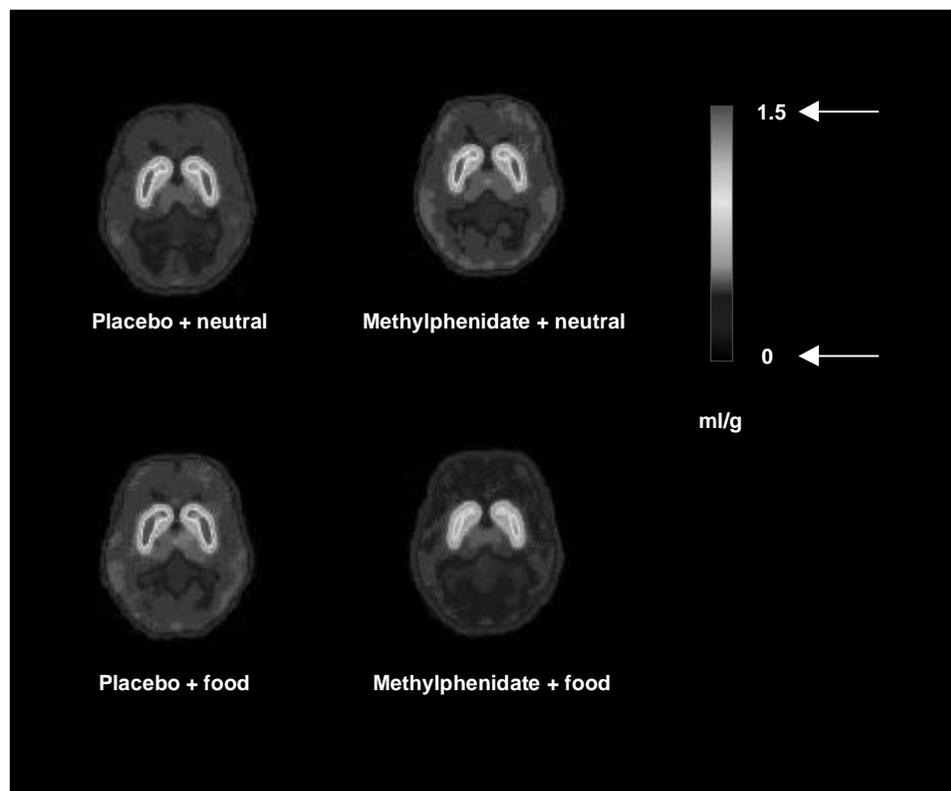


Figure 1. Brain DA response to food stimulation. Group averaged distribution volume images of [¹¹C]raclopride at the level of the striatum for the 10 subjects for the four scanning conditions: neutral stimulation with placebo, food stimulation with placebo, neutral stimulation with MP and food stimulation with MP. The images are scaled with respect to the maximum absolute value obtained on the neutral stimulation with placebo conditions and presented using the rainbow scale where red represents the highest value and dark violet represents the lowest value. Neither the neutral stimuli (with or without 20 mg of oral MP) nor the food stimuli when given with placebo increased brain DA. However, the food stimuli when given with MP did, which is seen as a decrease of [¹¹C]raclopride in the striatum. Reproduced from [69].

MP: Methylphenidate.

constraints of the scanners, which cannot support weights of > 160 kg. Using a positron emission tomography (PET) scanner bed redesigned to support > 275 kg, Wang *et al.* have shown a significant reduction in D2 receptor availability in obese subjects (Figure 2) [84]. These subjects had BMIs between 42 and 60 (mean $51.2 \pm 4.8 \text{ kg/m}^2$, body weight: 125 – 177 kg). Interestingly, in the obese subjects but not in the controls, the D2 receptors were significantly associated with their BMI ($r = 0.84$, $p \leq 0.002$). The results indicate that the D2 receptors are not involved in modulating body weight *per se*, but rather may regulate compulsion to eat in the pathological eater. Alternatively, in severely obese individuals, DA receptor levels may come under stronger regulatory control by circulating adiposity-signalling factors than in non-obese subjects. This would imply that the role of the D2 receptors is not to enable obesity but if the pertinent genetic or environmental variables that predispose to obesity are present, then it will favour a more severe presentation.

Marked D2 receptor reductions have also been reported in drug addicts, including cocaine abusers [85,86], methampheta-

mine abusers [87], alcoholics [88] and heroin abusers [89]. These addictive states share in common with obesity the inability to restrain from using the reinforcer and its compulsive administration. Thus, D2 receptor decrements are unlikely to be specific for any one of these compulsive behavioural disorders including obesity and may relate to vulnerability for addiction. Wang *et al.* also assessed DA transporter availability in obese subjects and found no changes [90] indicating that the observed effects on D2 receptor levels were mainly postsynaptic.

7. Brain dopamine and addiction

Animal studies indicate that D2 receptor levels mediate reinforcing responses to drugs of abuse. This is evidenced by the decrease in the reinforcing effects of alcohol and morphine in mice lacking D2 receptors (D2 receptor knockout) [91,92] and by the decrease in the reinforcing effects of cocaine in animals given drugs that block D2 receptors [93,94]. While the studies on the effects of D2 receptor antagonists in the reinforcing effects of psychostimulants in humans have not been

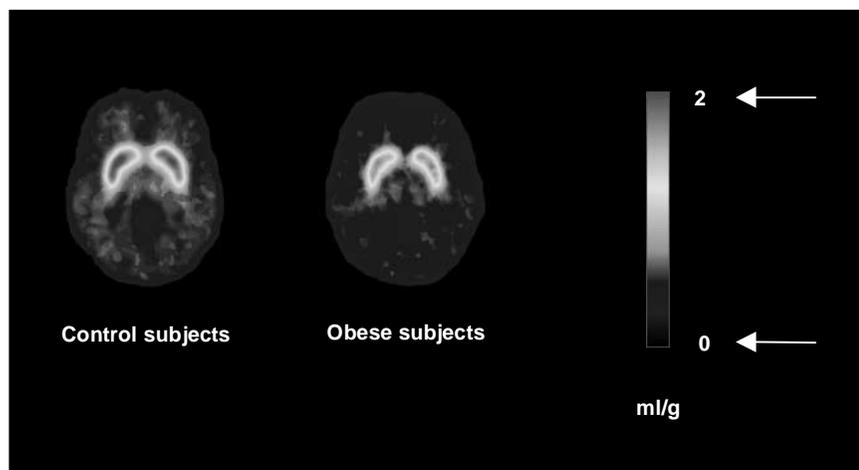


Figure 2. DA receptors. Group average images of [^{11}C]raclopride (distribution volume) PET images for obese and control subjects ($n = 10$ each) at the level of the striatum. The images are scaled with respect to the maximum absolute value obtained on average image of the control subjects and presented using the rainbow scale where red represents the highest value and dark violet represents the lowest value. Obese subjects have significantly lower measures of striatal D2 receptor availability than control subjects. Reproduced from [84].

DA: Dopamine; PET: Positron emission tomography.

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 [95,96]. The lower efficacy of D2 receptor antagonists reported in the human studies may reflect the fact that the doses used were lower than those used in laboratory animals and are likely to have resulted in incomplete D2 receptor blockade.

8. Brain dopamine receptors and drug preferences

Compulsive overeating shares many of the same characteristics as drug addiction. Animal studies have indicated parallels between feeding and drug-seeking behaviour [97]. One of the challenging questions in the neurobiological mechanism(s) underlying these disorders is why some subjects abuse drugs and others do not, which pertains to the question of why some individuals lose control over food intake while others do not. Volkow *et al.* investigated this issue in drug-naive, normal individuals by measuring their D2 receptor levels and by assessing their response (pleasant or unpleasant) to a challenge dose of the stimulant drug, 0.5 mg/kg MP *i.v.* They found that normal subjects who reported MP as pleasant had lower D2 receptor levels than those that reported MP as aversive [98]. However, none of the subjects had a history of drug addiction, even though some of the subjects that reported MP's effects as pleasant had D2 levels equivalent to those the authors had reported in drug-addicted subjects. They interpret this to indicate that while D2 receptors may be relevant for vulnerability to drug addiction, they are not sufficient. Studies to assess if low levels of D2 receptors affect the responses to food in non-obese subjects are required to determine if low D2 levels may also affect the liking responses to food stimulation.

9. Modulation of brain dopamine and obesity

The results from these studies have implications for the treatment of obesity since they suggest that strategies aimed at improving DA function might be beneficial in the treatment of obesity. In fact, psychostimulant drugs (amphetamine [99], cocaine [100] and MP [101]), which increase extracellular DA, are anorexigenic and this effect is blocked by DA receptor antagonists [99]. Unfortunately, the therapeutic benefit of these drugs is precluded by their addictive and psychoactive effects and, to the authors' knowledge, there are currently no dopaminergic anorexigenic drugs that are not reinforcing. However, strategies to enhance dopaminergic function could involve behavioural interventions such as exercise.

Even though obese individuals have either normal or high absolute levels of energy expenditure [102-104], studies of physical activity in obesity have found that physical activity decreases as percentage of excess body weight increases [105]. DA is a critically important transmitter in the central mediation of reinforcement, directly involved in motor control in the striatum and is key to the mechanism underlying increased and maintained efficiency of physical activity. *In vivo* microdialysis studies in laboratory animals have shown that the release of DA is influenced by exercise [106-109]. Endurance exercise training can also alter the number of D2-binding sites and the metabolism of DA in young adult animals [110].

10. Conclusion

This review provides evidence that links pathological overeating and obesity with abnormal DA activity. It is shown that rewarding as well as motivational properties of food are mediated in part by its effects on DA. The

pathological overeating behaviour of some obese subjects shares many of the characteristics seen with drug consumption in drug-addicted subjects; namely the lack of control and compulsive consumatory behaviour, which are known to involve the DA system. Brain imaging studies from Wang, Volkow and Fowlers' laboratory document lower D2 receptor levels in obese than in normal body weight subjects. DA modulates motivation and reward circuits and, hence, DA deficiency in obese subjects may perpetuate pathological eating as a means to compensate for the decreased activation of reward circuits. Further studies to evaluate the interaction between DA and other neurotransmitters and neuromodulators known to be involved in eating behaviours, may help identify better treatments for obesity.

11. Expert opinion

Obesity poses a serious health hazard and its treatment is often ineffective. A more detailed understanding of the

pathogenesis of obesity may ultimately guide treatment of affected individuals. More is now known about the cause of obesity than ever before. The cloning of the obesity gene, *ob*, is a major breakthrough promoting the understanding of obesity as a complex disease involved with appetite control and energy metabolism. 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. Understanding the involvement of DA in food intake will help in the treatment of obesity. Further research to identify treatment approaches that enhance the function of the dopaminergic system as a means to promote long-term maintenance of weight control is warranted.

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