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Review

Obesity, Attention Deficit-Hyperactivity Disorder, and the Dopaminergic Reward System

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A B S T R A C T

The obesity epidemic has focused attention on obesity's health consequences beyond cardio-vascular disease and diabetes. To evaluate the potential consequences of obesity for Attention Deficit-Hyperactivity Disorder (ADHD), we surveyed the literature. Current findings link both obesity and ADHD to the dopamine system and implicate dopamine genes in body weight, eating, and ADHD. Detailed consideration suggests that dopaminergic changes in the prefrontal cortex among individuals with the ADHD subtype Attention Deficit Disorder (ADD) may increase their risk for obesity. Thus, individuals and populations with a high prevalence of hyperdopaminergic genes may experience higher rates of obesity in the presence of abundant food. From an evolutionary perspective, alterations in the dopamine system appear to effect a wide range of behavioral phenotypes. We suggest that recent evolutionary changes in the dopamine receptor genes selected to increase cognitive and behavioral flexibility may now be associated with attention problems and increased food consumption in an obesogenic environment.

***Key words**: ADHD, obesity, dopamine*

Introduction

The obesity epidemic threatens to have far reaching and important implications for human health and welfare across the globe[1]. Concerns about the health impact of the epidemic have focused largely on increased rates of diabetes and heart disease[2,3]. As the epidemic continues, consideration of its impact is starting to expand to other outcomes as well, such as the effects of stigmatization and body dissatisfaction on the psychological well-being of obese individuals and Alzheimer's disease[4–6].

In addition to its association with diabetes and cardiovascular disease, obesity has been associated with increased risk of psychiatric disorders[7,8]. Recent studies have suggested a link between childhood obesity and attention-deficit hyperactivity disorder (ADHD)[9–11]. In addition childhood symptoms of ADHD, attention-deficit subtype (referred to in this paper as Attention Deficient Disorder or ADD) have been related to subsequent obesity in adults[12,13]. Together these findings suggest a possible syndrome linking obesity with ADHD. Thus it is important to explore the implications of obesity for ADHD in greater detail.

In this paper we review the literature suggesting that ADHD, and obesity are related through alterations in the dopaminergic system. Briefly put, we suggest that individuals with ADD, in particular, experience »reward deficiency syndrome«as a result of low tonic dopamine levels in the prefrontal cortex[14]. Thus they may eat as a form of self-medication in order to increase their dopamine levels[15]. Decreased sensitivity to reward would also be associated with over-eating, leading to an increased risk of obesity. Thus chronically low levels of dopamine in the pre-frontal cortex may first be evident as ADD and only subsequently lead to obesity.

From an evolutionary perspective, we argue that while ADHD is unlikely to be selected for ADD may be beneficial in some contexts[16]. Alterations in prefrontal working memory may increase the impact of dopaminergic striatal activity leading to increased saliency of novelty and the increased acquisition of information in an unpredictable environment[17]. In addition, increased dopaminergic striatal activity may lead to an increased importance of food and sex as rewards[18–20]. This could promote repro-

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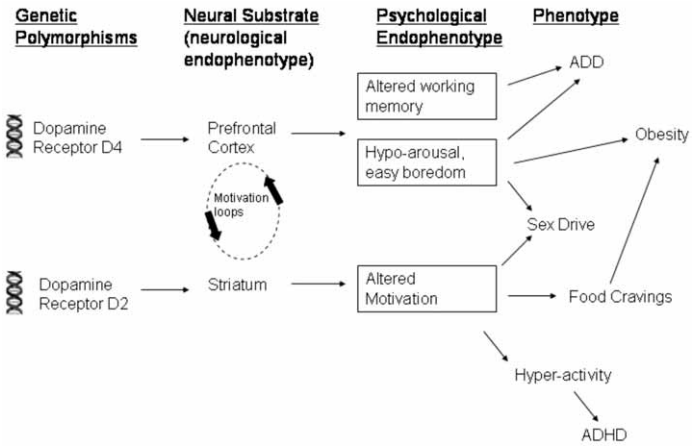

Fig. 1. Postulated model of the dopaminergic roots of Attention Deficit Hyperactivity Disorder (ADHD), Attention Deficit Disorder (ADD) and Obesity. Functional genetic alterations to the Dopamine Receptors D4 and D2 genes have predominant effects in the prefrontal cortex and striatum respectively. The striatum and prefrontal cortex interact via motivation loops with emotional responses in the striatum being relayed to cognitive processing in the prefrontal cortex. Psychological endophenotypes including altered working memory, hypo-arousal, easy boredom and altered motivation influence a variety of distal phenotypes. ADD and ADHD are recognized as having primarily distinct etiologies while both sex drive and obesity are postulated to have dual D2–D4 roots acting through the striatum and the prefrontal cortex respectively.

duction under subsistence conditions. The relative benefits of these traits may vary across populations leading to balanced selection for allelic variants of genes, such as the 7R allele of the DRD4 dopamine receptor associated with hypodopominergic function[21].

We divide our argument into two parts. In the first part we provide evidence relating ADHD, obesity and dopamine in industrialized societies. Under these conditions, not only has ADHD been associated with obesity, but obesity has been related to variation in various genes associated with dopamine metabolism. Finally, dopamine is directly related to eating, thus providing a behavioral link between ADHD, dopamine and obesity (See Figure 1 for a diagrammatic illustration).

In the second part of the paper we consider how ADHD, dopamine, and obesity might be related in subsistence contexts. An anthropological perspective suggests that individuals with hypodopaminergic reward systems will exhibit obesity only under conditions of plentiful food. From an evolutionary perspective the recent emergence and positive selection for the 7R allele of the DRD4 dopamine receptor suggests that there may be benefits to reduced prefrontal control of striatal impulses associated with important changes in human social environments roughly 50,000 years ago[21–23, but see 24].

Before we begin, it is important to make a distinction between ADD and ADHD. Individuals with ADHD are disorganized, hyperactive, impulsive and socially disruptive[25]. ADHD is thought to reflect loss of inhibitory control of motor activity[26]. In contrast, individuals with ADD are disorganized, sluggish and bored; ADD is thought to reflect poor attention associated with deficits in working memory in the prefrontal cortex[27]. The most compelling findings link obesity with ADD, not ADHD, suggesting that it is a lack of attention and low energy that may be associated with obesity, not hyperactivity

ADHD and Obesity

Recent studies of children provide limited evidence of a connection between ADHD and obesity. A recent German study found higher prevalence of overweight among 97 boys (mean age 10 ± 2 years) diagnosed with ADHD compared to a German reference sample[10]. Perhaps the prevalence would be even higher if not for the fact that many of the drugs used to treat ADHD have side-effects that include weight loss and vomiting[28–30]. In addition, children with ADHD before medication treatment have slightly higher weight and body-mass index (BMI) than the general age and gender matched Centers for Disease Control (CDC) population[28–30,31]. Finally, a chart review of 140 children ages 3 to 18 diagnosed with austism and ADHD, failed to find increased rate of overweight and obesity compared to U.S. reference values[12].

On the other hand, a handful of recent reports indicate a high prevalence of ADD, the inattentive subtype of ADHD not associated with hyperactivity, among obese adults seeking treatment. Among 215 patients receiving treatment for obesity, 27.4% have symptoms of ADD, including 42.6% of those over a BMI of 40, compared to a prevalence of 4.7% in the general population[13]. Another study found that 26.7% of 75 women coming for treatment reported symptoms of ADHD in childhood and adulthood, with a high frequency of inattentive symptoms[14]. While women seeking treatment for obesity represent a select sample, the elevated rates of ADD in the two studies cited above suggest a link between ADD and obesity.

Dopamine, Obesity, and Food

Alterations of the dopaminergic system have also been related to obesity. Obesity is significantly related to the DRD2 TaqI A polymorphism in a sample of Chinese men in Hong Kong[32]. The DRD2 TaqI A polymorphism is associated with altered D2 receptor expression levels in the striatum[33]. More recently, in sample of over 1000 individuals, the low activity versions of monoamine oxidase A (MAOA) and MAOB genes, which determine the availability of dopamine (and other catecholamines) were found to be significantly more prevalent in obese individuals[34]. Together the presence of the low activity version of both genes results in a five-fold increased risk of obesity, strongly implicating the dopamine system in obesity.

The association between dopamine genes and obesity is presumably mediated by the role of dopamine in eating[35–37]. Dopamine increases in response to presentation of food, even without consumption[35,36]. Furthermore, the degree of dopamine increase in response to food presentation is directly related to subjective reports of hunger and desire for food[35].

As might be expected, the role of dopamine in hunger and food craving is particularly evident in obese individuals. The availability of D2 dopamine receptors in the striatum are inversely related to BMI in individuals with a BMI over 40[37]. The authors suggest that individual variation in the D2 dopamine receptor may lead to altered tonic levels of striatal dopaminergic activity. Food, they suggest acts to stimulate dopamine release thus restoring dopamine levels. However, a weaker dopamine response to reward may mean that more food is required to restore dopamine to an adequate level, thus leading to overeating and obesity. These findings are based on extremely obese individuals who may be genetically distinctive[38]. However, they can probably be extended to explain the association of ADD and obesity.

ADD, Dopamine, and Eating

Generally speaking, ADHD reflects the effects of dopaminergic conditions in the striatum and prefrontal cortex[27]. ADHD has been related to allelic variations associated with altered dopamine levels. These include the DRD4 gene as well as the DRD2 gene[39–42]. ADHD has also been linked to higher dopamine transport activity[43,44].

The distinction between prefrontal cortex and striatal aspects of the dopaminergic system may be crucial for understanding the relationship between DRD4, ADD and obesity. Prefrontal dopamine is though to be important in cognition while dopamine in the striatum is more directly related to motivation[45]. Furthermore dopaminergic neurons in the prefrontal cortex exhibit a higher density of D4 dopamine receptors and lower density of D2 dopamine receptors than those of the striatum[46]. Thus, variation in the D4 dopamine receptor may be more directly related to ADD[47]. In contrast, variation in the D2 dopamine receptor may be more directly related to impulsivity and/or hyperactivity[27].

By definition, deficiencies in working memory lead to the inability to sustain attention on prolonged or demanding tasks. Hence individuals with ADD are prone to switch to other tasks[27]. This switch in attention may be associated with a phasic increase in dopamine reinforcing the reward from novelty. In addition, lower tonic prefrontal dopamine activity is associated with increased striatal dopamine activity[48]. Thus, the dopaminergic reward from activities normally associated with the striatum, namely food and sex, will be relatively stronger making them more salient as well

For individuals with ADD food may be particularly salient. Not only is food readily available in modern developed countries, but it provides a predictable reward. Thus ADD may be associated with overeating through 3 potential mechanisms; 1) poor planning associated with deficient inhibitory control; 2) aversion to delay which may lead to increased consumption of highly palatable fast food; 3) self-medication in an attempt to reduce the lack of satisfaction that comes with low tonic dopamine levels[16]. Thus low levels of dopamine in the prefrontal cortex may be manifested initially as symptoms of ADD, but also include overeating that eventually leads to obesity in some individuals.

Recent findings among women with seasonal affective disorder (SAD) provide support for the argument above. In a sample of women with SAD those with the 7R allele of the DRD4 dopamine receptor are more likely to have displayed symptoms of ADD in childhood as well as higher maximal BMI's as adults[19,20]. Women with SAD are susceptible to binge eating making overeating the obvious connection between ADD and elevated BMI.

Anthropological Perspective

The studies cited above suggest a role for the dopaminergic system in over eating and obesity in clinical populations. However, such an argument can easily be extended to the larger population as well. Palatable food (i.e. food high in sugar and fat) up-regulates hunger signals, blunts satiety signals and activates the reward system[49]. Thus the abundance of calorically dense food in our current environment increases the probability that normal individuals will seek food as a reward and overeat as well.

The role of low dopamine in linking ADD and obesity postulated here depends on readily available and abundant food. In subsistence societies, where food resources and the opportunity for overeating are limited, increased food craving or hunger associated with a hypodopaminergic system would be less likely to lead to hyperphagia and weight gain. However, as populations modernize and food becomes more abundant, the role of appetite may come to play a more prominent role. Thus population differences in increasing rates of obesity with modernization may reflect variation in allelic frequency of the DRD4 and DRD2 dopamine genes, among other factors.

The role of dopamine genes in ADHD has been studied in a variety of cultures, including Taiwan, Chile , Korea and China[41,50–54]. However, we are unaware of any studies of dopamine genes and obesity in non-industrialized populations.

Evolutionary Perspective

Current evolutionary arguments suggest that ADHD is unlikely to be selectively advantageous, because of its detrimental long term effects on educational attainment and employment in our society[17,55]. Similar effects on learning may have been evident during human evolution as well. However, to the extent that ADD does not lead to the same level of socially disruptive behavior it may not be as nearly detrimental. Thus, the fact the 7R allele of the DRD4 dopamine receptor is thought to have been under positive selection since its emergence approximately 40,000–50,000 ybp suggests that despite their obvious costs, reduced prefrontal dopamine levels may have been beneficial under some social conditions[22].

We suggest that the 7R allele of the DRD4 dopamine receptor was under positive selection to the extent that reduced prefrontal cortical control of cognition and behavior allowed for increased flexibility in a dynamic social environment. Reduced prefrontal control of striatal dopaminergic reward signals may increase the salience of novelty and disinhibit behavior associated with rewards such as food and sex. In children these changes might have lead to more flexible learning, while among adults they would be associated with increased attention to the opportunity of food and sex.

Increased cognitive flexibility is associated with positive emotions and dopamine is thought to play a role[56, 57]. Furthermore, differences in cognitive flexibility have been associated with the 7R allele of the DRD4 gene[58]. Thus while reduced tonic levels of dopamine in the prefrontal cortex associated with ADD may be associated with a decrease in sustained attention, shifting attention to a novel stimulus may result in a phasic release of dopamine and increase positive feeling[59]. Among children, the association of positive feeling together with the stimulation of novelty would promote faster acquisition of new information, especially under unpredictable conditions. Faster response times among those with ADHD and 7R alleles compared to those with ADHD but no 7R alleles may also aid in rapidly acquiring and implementing new information[60,61].

Reduction of prefrontal dopamine levels may have been associated with changes in social behavior as well. The 7R allele has been associated with disorganized infant attachment[62,63 though see 64] suggesting a reduced ability of infants to experience adequate comfort from their mothers. Furthermore, the 7R allele has been associated with lower self-reported rates of altruism toward both kin and non-kin[65]. Thus, it comes as little surprise that the 7R allele has been associated with elevated rates of childhood dysphoria, and ADD among women with SAD[16]. Not only may these individuals be less likely to find normal activities rewarding, but they also may be less likely to elicit help from parents for dealing with the frustration that comes with a diminished sensation of reward.

Decreased familial attachment and interest in kin might act to speed up the acquisition of new knowledge during childhood. During the juvenile period kids become increasingly less dependent on their parents and spend much more time with their peers[66]. In fact, attention span increases from the age of 4 to 10[27]. This may be related to increased glucose utilization by the brain[67]. Poorer attachment may speed the shift of attention away from parents and towards one's peers In general, this would bias the acquisition of information away from traditional sources and towards novel stimuli or people.

As adults such individuals might be expected to show higher levels of novelty-seeking. Thus, our argument is consistent with the hypothesis that distribution of the 7R allele worldwide reflects selection for novelty seeking[18]. Novelty seeking among adults would increase the pull factors for migration by increasing exploratory behavior and enhancing the attraction to more exotic mates. In support of this, recent finding suggest that those with 7R alleles also have more multi-racial ancestries than those without 7Rs[68]. Weaker parental attachment, a history of dysphoria and less interest in promoting the welfare of kin might also increase the push factors for migration.

Our argument can also incorporate the suggestion that selection for the 7R allele reflects the impact of social non-compliance on male-male reproductive strategies [21]. For males, reduction in prefrontal control of the dopaminergic reward system may increase the salience of both sex and novelty as rewards, while at the same time decreasing the propensity for kin altruism. Such individuals may be pre-disposed to put their energy into seeking additional sexual partners and away from investment in current kin, including offspring. Recent findings suggest that variation of the DRD4 gene is associated with sexual desire, function and arousal[69].

Our argument may also help to elaborate the suggestion that increased binge eating and reduced activity levels associated with the 7R allele were selected to promote seasonal accumulation of energy and optimal reproductive timing in a seasonal environment[16]. The impact of seasonality on binging may be specific to women with seasonal mood changes. However, increased binge eating when food was available in fluctuating tropical environments may have lead to increased weight gain and increase the probability of conception among women with the 7R allele.

We suggest that alterations in the function of the prefrontal cortex, associated with the 7R allele of the DRD4 dopamine receptor may have been compensated for by an increased role for striatal based reward which increased the saliency of novelty, as well as the importance of food and sex as rewards. Together these changes would have lead to increased variability in cognition and behavior and promoted reproduction. Thus, the emer-

gence of the 7R allele of the DRD4 dopamine receptor at about 50,000 ybp may be associated with an increase in cultural innovation, migration and population expansion thought to occur about this time[22–24].

Summary

Work linking ADHD, obesity, and dopamine is still in its infancy. However, current findings suggest that alterations in the dopamine reward system may underlie overeating in much the same way as pathological gambling, addiction and ADHD. Changes in the control of striatum dopamine activity associated with low dopamine in the prefrontal cortex may increase the salience of novelty and disinhibit appetites for food and sex. In addition, reduced reward sensitivity may lead to a failure to quit eating when calorically satiated. Together these factors may increase the risk of obesity in individuals with ADD. Thus, low dopamine appears to represent a vulnerability to developing obesity, a factor that may have gained prominence in our current obeseogenic environment.

From an evolutionary perspective, alterations in the dopaminergic system thought to date to roughly 50,000 ypb may represent selection on a wide range of behavior, including learning and sociality as well as eating and sex. A less efficient dopamine system in the prefrontal cortex may have lead to greater salience of novelty in learning and social interaction. Furthermore disinhibition of food and sex impulses may have promoted reproduction. However, even this preliminary consideration suggests the possibility of many subtle changes in the dopaminergic system in response to environmental conditions. More careful work is needed to distinguish the outcome of dopaminergic alterations in the prefrontal cortex and striatum and their relationship with specific dopaminergic genes. Such studies would benefit from the use of endophenotypes (underlying behavioral traits) to elucidate the actual webs of causation[70,71]. Perhaps impulsivity, behavioral inhibition, low motivation, and/or dopamine metabolism patterns will prove to be valuable endophenotypes for understanding obesity and psychopathology.

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