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

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ABSTRACT

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 globe1. Concerns about the health impact of the epidemic have focused largely on increased rates of diabetes and heart disease2,3. 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 disease4–6.

In addition, to its association with diabetes and cardiovascular disease, obesity has been associated with increased risk of psychiatric disorders7,8. 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 adults12,13. 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 cortex14. Thus they may eat as a form of self-medication in order to increase their dopamine levels15. 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 prefrontal 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 contexts16. 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 environment17. In addition, increased dopaminergic striatal activity may lead to an increased importance of food and sex as rewards18–20. This could promote repro-
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 hypodopaminergic function.

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, 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, ADHD is thought to reflect loss of inhibitory control of motor activity. 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. 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. 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. 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.

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. 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. 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

Altering 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 Kong29. The DRD2 TaqI A polymorphism is
associated with altered D2 receptor expression levels in
the striatum30. More recently, in sample of over 1000 in-
dividuals, the low activity versions of monoamine oxidase
A (MAOA) and MAOB genes, which determine the avail-
ability of dopamine (and other catecholamines) were
found to be significantly more prevalent in obese individ-
uals34. Together the presence of the low activity version
of both genes results in a five-fold increased risk of obe-
esity, strongly implicating the dopamine system in obesity.

The association between dopamine genes and obesity
is presumably mediated by the role of dopamine in eat-
ing35–37. Dopamine increases in response to presentation
of food, even without consumption35,36. Furthermore, the
degree of dopamine increase in response to food presen-
tation is directly related to subjective reports of hunger
and desire for food36.

As might be expected, the role of dopamine in hunger
and food craving is particularly evident in obese individ-
uals. The availability of D2 dopamine receptors in the
striatum are inversely related to BMI in individuals with
a BMI over 4037. The authors suggest that individual
variation in the D2 dopamine receptor may lead to al-
tered tonic levels of striatal dopaminergic activity. Food,
they suggest acts to stimulate dopamine release thus re-
storing 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 ex-
remely obese individuals who may be genetically distin-
ctive38. However, they can probably be extended to ex-
plain the association of ADD and obesity.

ADD, Dopamine, and Eating

Generally speaking, ADHD reflects the effects of dop-
aminergic conditions in the striatum and prefrontal
cortex27. ADHD has been related to allelic variations as-
associated with altered dopamine levels. These include the
DRD4 gene as well as the DRD2 gene39–42. ADHD has also been linked to higher dopamine transport activi-
ty43,44.

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 thought to be impor-
tant in cognition while dopamine in the striatum is more
directly related to motivation45. Furthermore dopami-
nergic neurons in the prefrontal cortex exhibit a higher
density of D4 dopamine receptors and lower density of
D2 dopamine receptors than those of the striatum46.
Thus, variation in the D4 dopamine receptor may be
more directly related to ADD47. In contrast, variation in
the D2 dopamine receptor may be more directly related
to impulsivity and/or hyperactivity45.

By definition, deficiencies in working memory lead to
the inability to sustain attention on prolonged or de-
manding tasks. Hence individuals with ADD are prone to
switch to other tasks47. This switch in attention may be
associated with a phasic increase in dopamine reinforc-
ing the reward from novelty. In addition, lower tonic
prefrontal dopamine activity is associated with increased
striatal dopamine activity48. Thus, the dopaminergic re-
ward from activities normally associated with the stria-
tum, namely food and sex, will be relatively stronger,
making them more salient as well.

For individuals with ADD food may be particularly sa-
lent. Not only is food readily available in modern devel-
oped 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
levels49. Thus low levels of dopamine in the prefrontal
frontal cortex may be manifested initially as symptoms of ADD,
but also include overeating that eventually leads to obe-
ity 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 dopamine receptor gene (DRD4) are more likely to
have displayed symptoms of ADD in childhood as well as
higher maximal BMI’s as adults10,21. 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 dopa-
iminergic 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 sig-
als, blunts satiety signals and activates the reward
system49. 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 abun-
dant food. In subsistence societies, where food resources
and the opportunity for overeating are limited, increased
food craving or hunger associated with a hypodopami-
nergic 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
ifferences in increasing rates of obesity with moderniza-
tion 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 China50–54. However, we are unaware of any stud-
ies 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\(^5\)\(^7\)\(^8\). 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 detrimental. Thus, the fact the 7R allele of DRD4 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\(^2\(^2\)\(^3\).

We suggest that the 7R allele of DRD4 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\(^5\(^6\)\(^7\). Furthermore, differences in cognitive flexibility have been associated with the 7R allele of the DRD4 gene\(^5\(^8\). 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\(^5\(^9\). 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\(^6\(^0\)\(^6\(^1\).

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\(^6\(^2\)\(^6\(^3\) though see\(^6\(^4\) 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\(^6\(^5\). 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\(^6\(^6\). 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\(^6\(^6\). In fact, attention span increases from the age of 4 to 10\(^7\). This may be related to increased glucose utilization by the brain\(^8\(^7\). 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\(^1\(^8\). 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 findings suggest that those with 7R alleles also have more multi-racial ancestries than those without 7Rs\(^6\(^8\). 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\(^2\(^1\). 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\(^6\(^9\).

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\(^1\(^6\). 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 gene 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 emergence 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\(^2\(^2\)\(^2\)\(^4\).
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 striatal 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 obesogenic environment.

From an evolutionary perspective, alterations in the dopaminergic system thought to date to roughly 50,000 ybp may represent selection on a wide range of behavior, including learning and sociality as well as eating and sex. A less efficient dopaminergic system in the prefrontal cortex may have led 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 causation70,71. 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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PRETILOST, POREMEĆAJ PAŽNJE-HIPERAKTIVNOSTI I DOPAMINERGIČNI OSJEĆAJ UGODE

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