

# Addictive Genes and the Relationship to Obesity and Inflammation

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Received: 13 December 2010 / Accepted: 29 March 2011 / Published online: 19 April 2011  
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**Abstract** There is increasing evidence that the same brain reward circuits involved in perpetuating drug abuse are involved in the hedonic urges and food cravings observed clinically in overweight and obese subjects. A polymorphism of the D2 dopamine receptor which renders it less sensitive to dopamine stimulation has been proposed to promote self-stimulatory behavior such as consuming alcohol, abusing drugs, or binging on foods. It is important to determine how this polymorphism may interact with other well-known candidate genes for obesity including polymorphisms of the leptin receptor gene and the opiomelanocortin gene. Leptin is a proinflammatory cytokine as well as a long-term signal maintaining body fat. Upper-body obesity stimulates systemic inflammation through the action of multiple cytokines including leptin throughout many organs including the brain. The association of numerous diseases including diabetes mellitus, heart disease, as well as depression with chronic low-grade inflammation due to abdominal obesity has raised the possibility that obesity-associated inflammation affecting the brain may promote addictive behaviors leading to a self-perpetuating cycle that may affect not only foods but addictions to drugs, alcohol, and gambling. This new area of interdisciplinary research holds the promise of developing new approaches to treating drug abuse and obesity.

**Keywords** Food addiction · Genetics · Dopamine · Obesity · Drug abuse · Inflammation

## Introduction

Addiction is an acquired, chronic relapsing disorder that begins with some experimentation and pleasurable responses and, for subgroups of individuals, is followed by preoccupation, escalation, tolerance, denial, and a series of medical, psychological, and social consequences that relate directly to the continued addictive behaviors. Discoveries over the last 20 years have clearly defined a relationship between obesity and systemic inflammation. The association of numerous diseases including diabetes mellitus, heart disease, common forms of cancer, as well as depression and Alzheimer's disease with chronic low-grade systemic inflammation due to abdominal obesity has raised the possibility that obesity-associated inflammation affecting the brain may promote addictive behaviors leading to a self-perpetuating cycle that may affect not only foods but addictions to drugs, alcohol, and gambling.

A key element of chronic addictions is continued addictive behavior in the face of clear knowledge of the expected consequences. Many obese individuals identify specific foods that promote continued consumption in the face of the known consequences of obesity. Yet they feel powerless to control these urges. While for many individuals, these are simply bad habits that can be changed; there is increasing evidence suggesting that genes implicated in other addictive behaviors may also be associated with food addiction, most commonly to sweet and fat foods. Specific associations of genetic polymorphisms of the dopamine, opiomelanocortin, and leptin receptor have been hypothesized to increase the risk of food addiction. Exercise and regular physical activity can entrain some of the same reward pathways and its efficacy in maintaining body weight after weight loss may be due to the activation of neural pathways involved in the initiation of overeating. Insights into the

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genetics of addictive behaviors associated with obesity may both lead to improved therapies of obesity and at same time may provide insights into adjunctive therapies useful in treating drug addiction, alcoholism, and other addictions.

### Food Urges, Addiction, and Eating Behavior

Humans eat even when they are not physically hungry as psychological, environmental, and hedonic influences affect food urges. The peripheral and central pathways which regulate food intake are geared toward the storage of calories when food is eaten in excess of metabolic needs, leading to obesity in situations of high fat and sugar food availability coupled with sedentary lifestyles.

Dopamine increases the motivation for food intake in animals and humans as demonstrated by imaging studies carried out using food images [1]. It has also been demonstrated that obese individuals have reduced levels of dopamine D2 receptors and that these are inversely related to body weight [2]. Presentation of desirable foods increases metabolism in the orbitofrontal cortex (OFC), the area of the brain that programs chewing and salivation, in proportion to the subjective perception of hunger and the desire to eat [3]. Obese subjects studied with functional magnetic resonance imaging (fMRI), which detects changes in blood flow, had evidence of activated striatum and OFC as well as the insula while viewing pictures of high-caloric food [4]. Wang and co-workers used positron emission tomography imaging which detects uptake of 2-deoxy-2 [ $^{18}\text{F}$ ]fluoro-D-glucose ( $^{18}\text{FDG}$ ) to assess the ability of men and women to inhibit the activation of brain metabolism following presentation of images of favorite foods. In men food stimulation with inhibition significantly decreased activation in amygdala, hippocampus, insula, orbitofrontal cortex, and striatum, but this did not occur in women [5]. The regions studied are integral to emotional regulation, conditioning, and motivation of food intake and in men suppressed activation of the orbitofrontal cortex with inhibition was associated with decreased self-reports of hunger. These observations suggest that hormonal mechanisms may underlie a gender difference in the ability to suppress hunger, and may contribute to the greater incidence of obesity in women compared to men.

The repeated stimulation of DA (dopamine) reward pathways has been proposed by Volkow to trigger adaptations in other neurotransmitters and in brain reward circuitry that may lead to increases in compulsive behaviors affecting both food and drug intake [6]. Moreover, exposure to drugs that elicit dependence alters gene expression profiles throughout the reward circuitry of the brain [7]. Drugs of abuse induce repeated profound

dopamine stimulation which, with chronic use, may induce changes in neuronal plasticity resulting in increased emotional reactions to drugs and reduced ability to inhibit drug consumption leading to compulsive chronic drug abuse [6]. Sugar-induced dependence in rats has been shown to promote increased consumption of ethanol, suggesting that food-related dependence may influence drug addiction [8]. As reviewed above, repeated exposure to favorite foods, especially those that are calorie dense due to excess sugar and fat could lead to binge eating disorder, and poor inhibitory control of food intake [9]. The increased usage of high fructose corn syrup in the American diet has been further suggested to reduce satiety that would have normally been satisfied with consumption of natural sugars [10]. Studies of rats show that excessive binging on sugar followed by deprivation creates a state of anxiety and suggested opiate-like withdrawal [11]. While both pathways have similarities, there is a need for more research to assess whether they are also interacting. That is, whether addictive drugs affect the emotional reaction to foods and vice versa. Such an interaction could have significance for efforts to combat drug abuse as well as obesity. A possible mechanism for such an interaction is the systemic inflammation associated with obesity which could affect the brain and promote changes that make individuals more susceptible to dopamine-related rewards.

### Genetic Polymorphisms Associated with Obesity and Food Addiction

Consumption of favorite foods increases dopamine concentrations in the nucleus accumbens, activating the meso-corticolimbic dopaminergic reward pathways of the brain, resulting in the reinforcing effects of euphoria or pleasure. These discoveries have been the result of advances in brain imaging including positron emission tomography scan and fMRI that enables visualization of brain activation on simply seeing images of favorite foods.

Since consuming food is critical to survival, it is perfectly reasonable that this activity would be highly valued within our inherited biological control mechanisms that evolved over eons of food scarcity and insecurity. Only in recent times has there been a surplus of calories available to all Americans including those in the lower socioeconomic strata. While these foods are inexpensive, they also have limited nutritional value and excess amounts of sugar and fat. Pleasurable responses to sugar and fat linked to activation of reward circuits in the brain activated by dopamine and other neurotransmitters can lead to food addiction and obesity in susceptible individuals as has been documented for drugs, alcohol, tobacco, sexual activity, and gambling.

## Dopamine Receptor *DRD2* Gene

The D2 dopamine receptor (*DRD2*) gene has most commonly been linked to alcoholism, although the gene has been associated with other addictive behaviors such as smoking, illicit drug use, gambling, and overeating. The *Taq1A* polymorphism, the most frequently studied polymorphism, is located more than 10 kilobase-pairs downstream from the coding region of the *DRD2* gene at chromosome 11q23. Recent studies have further localized the coding region of *Taq1A* within the coding region of a neighboring gene, *ANKK1* [12].

The D2 dopamine receptor, a G-protein-coupled receptor located on postsynaptic dopaminergic neurons, is centrally involved in reward-mediating and reward-deficiency pathways [13]. The *DRD2* gene encodes two molecularly distinct isoforms with distinct functions [14]. Signaling through dopamine D2 receptors governs physiologic functions related to locomotion, hormone production, and drug abuse. D2 receptors are also known targets of antipsychotic drugs that are used to treat neuropsychiatric disorders such as schizophrenia.

By a mechanism of alternative splicing, the D2 receptor gene encodes two molecularly distinct isoforms, D2S and D2L [15]. They are coexpressed in a ratio favoring the long isoform, D2L. D2L differs from D2S by the presence of an additional 29 amino acids within the third intracellular loop. Usiello et al. demonstrated that these receptors have distinct functions in vivo; D2L acts mainly at postsynaptic sites and D2S serves presynaptic autoreceptor functions [14].

There is evidence of a direct association in *Taq1A* A1 allele carriers with increased body fat and co-morbid substance use disorders. A clinical study found increased prevalence of *Taq1A* A1 allele in obese patients with other drug dependencies compared to non-abusing obese patients [16]. Among *Taq1A* A1 allele carriers, D2 receptor stimulation could potentially be effective in reducing craving and reward-seeking [17]. Individualized custom formulations of nutraceuticals have been proposed to “treat” individuals with known genetic deficiencies such as *Taq1A* A1 allele carriers [18].

Consumption of sweet or fat foods increases dopamine concentrations in the nucleus accumbens [19], activating the mesocorticolimbic dopaminergic reward pathways of the brain [20], resulting in the reinforcing effects of euphoria or pleasure. The A1 allele of the *Taq1A* polymorphism (rs1800497), located ~10 kb downstream of the *DRD2* gene [12] has been investigated for possible associations with habitual use of alcohol [21, 22], cocaine [23], nicotine [24–27], and opioids [28]. Evidence indicates that individuals carrying this allele have reduced brain D2 receptor density compared with other individuals [29–32]. Adolescent girls shown with pictures of palatable food had

weaker activation of the frontal operculum, lateral orbitofrontal cortex, and striatum if they are carriers of the *DRD2* *Taq1A* A1 allele or the *DRD4-7R* allele. These girls were also at risk for future weight gain [33].

Persistent substance abuse in individuals with the A1 allele may be a form of self-stimulatory behavior that compensates for insufficient dopamine activity [34]. The A1 allele has also been observed to be associated with obesity [35–37]. More research is needed to determine whether the *Taq1A* genetic polymorphism interacts with other well-known candidate genes for obesity including polymorphisms of the leptin receptor gene and others, and whether these interactive genetic effects could promote the development of obesity-associated inflammation. In turn, systemic inflammation could affect the brain leading to mild depression or other effects which promote continued addictive behaviors.

## Leptin Receptor *LEP-R* Gene

Other candidate genes for appetite control may interact with the *DRD2* A1 allele to increase the likelihood of overeating and obesity. The leptin receptor gene has polymorphisms that affect binding of leptin to the leptin receptor [38]. The leptin receptor gene (*LEP-R*, formerly *OB-R*) identified in 1995, is expressed in the hypothalamus and other organs, binds to free-circulating leptin released from adipose tissue, and plays a major role in metabolism and appetite signaling [39]. Genetic variants potentially affecting receptor structure, function, and binding to leptin include three single-nucleotide polymorphisms (SNPs) that result in amino acid substitutions (Lys109Arg (K109R) rs1137100; Gln223Arg (Q223R) rs1137101; and Lys656Asn (K656N) rs8179187) [40–42] located at highly conserved positions in the extracellular domain of the receptor protein.

Research from our group demonstrated an association between percent body fat and the *LEP-R* variant Lys109Arg [43]. Other studies reported linkage of Lys109Arg with fat mass [44], association with serum leptin levels in young Dutch men [45], an interaction between Lys109Arg and menopause with body mass index (BMI) [46], and fat mass loss in a caloric restriction intervention [47]. While the *DRD2* gene increases the likelihood of food addiction and obesity [36, 37], the *LEP-R* gene influences appetite control and has been associated with elevated levels of body fat and body composition [43–47]. The joint influence of *DRD2* and *LEP-R* could therefore predispose individuals to weight gain and obesity if risk alleles are carried from both genes.

Evidence for potential *DRD2* and *LEP-R* interaction has been demonstrated in mice lacking D2 receptors [48]. D2 receptor knock-out mice demonstrated leptin sensitivity, while wild-type mice had heavier body weights and were

leptin resistant. Further studies are needed to characterize the interplay between genes that encode for reward/pleasure neurotransmitters and energy balance regulation.

### Mu-Opioid Receptor Gene (*OPRM1*)

The mu-opioid receptor gene (*OPRM1*, located on chromosome 6q24) is one of four genes whose protein products bind to endogenous opioids. *OPRM1* is a member of the large family of transmembrane G-protein-coupled receptors. It is widely expressed in both brain and periphery [49]. The mu-opioid receptor is the primary site of action for the most commonly used opioids, including morphine, heroin, fentanyl, and methadone. By sequencing, DNA from 113 former heroin addicts in methadone maintenance and 39 individuals with no history of drug or alcohol dependence, five different SNPs in the coding region of the *mu-opioid* receptor gene were identified. The most prevalent SNP is a nucleotide substitution at position 118 (A118G), predicting an amino acid change at a putative N-glycosylation site. This SNP displays an allelic frequency of approximately 10% in the study population. Significant differences in allele distribution were observed among ethnic groups studied [50]. In a targeted study of food addiction, the functional A118G polymorphism of the mu-opioid receptor gene was found to be associated with binge eating disorders [51].

### Human Diets, Obesity, and Inflammation

Over the last 200 years, changes in the human diet and lifestyle have outstripped the ability of the genome to adjust to a changing environment and billions of people around the world are now overfat as a result [52–58]. While studies demonstrate that hunter–gatherers ate over 800 varieties of plant foods [59], Americans eat only about three servings per day which fail to provide the naturally occurring antioxidants, phytochemicals, vitamins, and minerals essential to good health. Highly processed foods with refined starches, sugars, fats, and oils often fail to contain essential nutrients found in nutrient-dense foods [60]. At the same time, labor-saving devices of all kinds and advances in transportation have made a highly sedentary lifestyle possible in just the last 30 years [61]. A global epidemic of obesity and chronic disease that is underestimated using the BMI is sweeping the globe as industrialization and improved standards of living are spreading to urban centers. Certain ethnic groups including African–Americans, Asians, Asian Indians, Latinos, Native Americans, and Eastern Europeans are genetically susceptible to Metabolic Syndrome resulting from the accumulation of visceral fat

with resulting inflammation [62]. It is estimated that in the next 10 years, the majority of all heart disease will be associated with type 2 diabetes mellitus [63].

The metabolic syndrome has emerged as an important cluster of risk factors for atherosclerotic disease. Common features are central (abdominal) obesity, insulin resistance, hypertension, and dyslipidemia, with high triglycerides and low high-density lipoprotein cholesterol. According to the clinical criteria developed by ATP III, it has been estimated that about one of every four adults living in the USA merits the diagnosis. The presence of the metabolic syndrome is highly prognostic of future cardiovascular events.

Chronic inflammation may represent a triggering factor in the origin of the metabolic syndrome: stimuli such as overnutrition, physical inactivity, and aging would result in cytokine hypersecretion and eventually lead to insulin resistance and diabetes in genetically or metabolically predisposed individuals. Alternatively, resistance to the anti-inflammatory actions of insulin would result in enhanced circulating levels of proinflammatory cytokines resulting in persistent low-grade inflammation. A generally enhanced adipose tissue-derived cytokine expression may be another plausible mechanism for the inflammation/metabolic syndrome relationship. The role of adipose tissue as an endocrine organ capable of secreting a number of adipose tissue-specific or enriched hormones, known as adipokines, may play a pathogenic role in metabolic syndrome. Although the precise role of adipokines in the metabolic syndrome is still debated, an imbalance between increased inflammatory stimuli and decreased anti-inflammatory mechanisms may be an intriguing working hypothesis. The chronic inflammatory state that accompanies the metabolic syndrome associates with both insulin resistance and endothelial dysfunction, providing a connection between inflammation and metabolic processes which is highly deleterious for vascular function. However, small amounts of weight loss which relieve the pressure for abdominal adipocytes to proliferate have been shown to reduce inflammation in patients with type 2 diabetes [64], and in two large trials to reduce the incidence of new cases of diabetes over 5 years by 58% in individuals with glucose intolerance and insulin resistance [65].

### Conclusion

Our brains are programmed to activate the pleasure centers of the brain on visualizing food and then eating it, to remember the food that was eaten in specialized memory neurons, and to activate our digestive processes including chewing and hormone secretion in preparation for digesting a delicious meal. Eating food is a life-giving event in the wild and so it is perfectly reasonable that this activity



would be highly valued within our inherited biological control mechanisms. However, when the stimuli are linked in susceptible individuals to increases in reward circuitry activity as detected in changes in dopamine and glucose metabolism, then neuronal plasticity could be altered in ways that both increase the tendency to eating disorders and obesity as well as drug addiction. Whether these pathways interact in susceptible individuals is unknown but has potential significance for efforts to prevent or treat chronic drug abuse through changes in diet and lifestyle including the treatment of obesity which may reduce brain inflammation.

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