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DRD2: Bridging the genome and ingestive behavior

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Abstract

Recent work highlights the importance of genetic variants that influence brain structure and function in conferring risk for polygenic obesity. The neurotransmitter dopamine (DA) plays a pivotal role in energy balance by integrating metabolic signals with circuits supporting cognitive, perceptual and appetitive functions that guide feeding. It has also been established that diet and obesity alter DA signaling leading to compulsive-like feeding and neurocognitive impairments. This raises the possibility that genetic variants that influence DA signaling and adaptation confer risk for overeating and cognitive decline. We consider the role of two common gene variants, FTO and TaqIA r**s1800497** in driving gene * environment interactions promoting obesity, metabolic dysfunction, and cognitive change via their influence on dopamine receptor subtype 2 signaling.

Keywords

Dopamine; Obesity; Genetics; ANKK1; inflammation; Cognition; Diet; Ingestive Behavior

From genome to ingestive behavior

Twin, adoption, and family studies indicate that 40–70% of Body Mass Index (BMI) variation is due to genetic factors [1]. Although estimates from genome-wide association (GWAS) (Box 1) studies tend to be lower, recent estimates based on simulations with whole-genome sequencing data also argue for 30–40% heritability for BMI [2]. While there is little doubt that much of these genetic contributions work through mechanisms directly regulating metabolism and energy balance, GWAS studies now highlight the importance of genetic influences on the central nervous system [3] and especially on circuits that support ingestive

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behavior. Furthermore, it is now recognized that diet induced obesity is associated with neurocognitive impairment [4, 5]. The mechanism behind this association is unknown. Here we consider the role of two common variants, the fat mass and obesity associated gene (FTO) and the TaqIA restriction fragment length polymorphism (RFLP, see glossary; rs1800497) in driving gene * environment interactions promoting obesity, metabolic dysfunction and cognitive impairment via their influence on dopamine receptor subtype 2 (DRD2) signaling. More specifically, we propose a model whereby individuals with one or more at-risk **alleles** have increased vulnerability for the deleterious effects of an unhealthy diet on dopamine (DA) dependent functions. These adaptations are in turn proposed to promote metabolic dysfunction and cognitive impairments, leading to an escalation in unhealthy eating.

BOX 1

Approaches to conducting genetic association studies

Genome-wide association study (GWAS)

The genotypes of people with a condition of interest (e.g. obesity) are compared with the genotypes of people without the condition (e.g. healthy weight) with the goal of identifying SNPs specifically associated with the condition.

Pros: Data-driven approach covers SNPs across the whole genome

Can identify novel candidate genes and biological pathways

Cons: Requires extremely large sample sizes of well-defined and carefully selected groups

Multiple comparisons introduced by examining millions of SNPs necessitate rigorous statistical correction to protect against false positives

Results are often difficult to interpret and cannot be used to infer causality

Candidate gene studies (CGS)

Genetic comparisons between groups with and without the condition of interest are only conducted on a limited number of SNPs. These SNPs are selected based on existing or theoretical knowledge of biological pathways involved in the condition.

Pros: Hypothesis-driven approach results in lesser chance of false positives than GWAS

Working from genes involved in known pathways generates more interpretable results

Cons: The selection of genes of interest is based on existing knowledge, which is by definition incomplete

Why Dopamine?

The role of dopamine (DA) signaling in ingestive behavior is multifactorial, encompassing cognitive, appetitive and metabolic domains, as well as their interactions (Box 2). Collectively these domains integrate information about the nutritional value and sensory properties of foods, as well as the state of the organism, to prioritize and adapt behavior to optimally acquire and store energy. Consequently, there are many pathways by which genetic variations that impact DA signaling can influence food intake and obesity. In addition, emerging work strongly suggests that adiposity, metabolic dysfunction and diets high in saturated fat and sugar produce adaptations in DA function at the molecular, cellular and circuit levels to impact DA-dependent functions ranging from working memory and compulsive behaviors [6–20] to food preference and nutrient sensing [21, 22] and regulation of glucose metabolism [23–26]. Thus DA genetic variants may influence intake not only by conferring initial risk but also by influencing brain adaptations [27, 28]. This sets the stage for a vicious cycle in which genetic predispositions influence brain function to promote an unhealthy diet and weight gain in obesogenic environments, which in turn impacts brain function to promote metabolic and cognitive dysfunction and further weight gain.

BOX 2

The gut-brain axis and cognition

An important recent discovery in the field of ingestive behavior is the ability of peripheral signals to directly impact cognitive processes. For example, intragastric administration of glucose results in an immediate rise in extracellular DA; however, when accompanied by concomitant intravenous injection of 2 deoxyglucose, which blocks the metabolism of glucose, the rise in extracellular DA is blocked and licking for a sugar reward is attenuated [29]. This indicates that dopaminergic responses, which are critical for learning and motivated behavior, depend upon a signal generated during the metabolism of glucose. In reciprocal influence, deep brain stimulation of dopaminergic brain areas modulates glucose metabolism and body weight in rodents [26] and in humans DA agonists have been used to successfully treat type 2 diabetes in some cases [25]. There is also evidence that gut-brain communication can be compromised by a high fat det. High fat feeding depletes levels of the fatty acid amide oleoylelthanolamide (OEA), blunts DA responses to nutrient ingestion and decreases the amount of work animals are willing to perform in order to receive a low fat emulsion. Remarkably, when OEA levels are restored by direct administered to the gut, DA responses to nutrient ingestion is recovered and animals will again work to obtain the low fat emulsion [21]. Since this effect depends upon the integrity of the vagal nerve, the findings suggest that nutrients influence perception and cognition by acting on afferent neural signals to impact dopaminergic signaling. Indirect evidence also exists in humans. Three weeks of supplementation with PhosphoLean™, which contains the precursor for OEA synthesis, decreases false alarm rate on a dopamine-dependent go/no-go task [30].

Why DRD2?

Dopamine signaling is regulated by a number of independent processes including dopamine production, pre- and postsynaptic dopamine receptors and presynaptic dopamine transporters. Genetic variations affecting any of these processes may therefore influence ingestive behavior and obesity. There are five types of dopamine receptors (DRD1-DRD5) grouped into two major subclasses: DRD2-like, including DRD2, DRD3, and DRD4; and DRD1-like, including DRD1 and D1RD5. Although, these receptors have different distribution patterns in the brain (Figure 1), they often interact to regulate neurotransmission [31]. We focus on DRD2 for four reasons. First, variations in the fat mass and obesity-associated (FTO) gene are the strongest **polygenic** determinants of adiposity [32] and inactivation of this gene impairs DRD2-dependent neurotransmission and function in rodents [33] and DRD2-dependent learning in humans [34]. Second, the TaqIA **RFLP,** which is associated with variation in DRD2 receptor density [35–38], was recently shown to interact with an FTO gene variant to influence adiposity, central and peripheral insulin resistance and DRD2-dependent learning [34, 39]. In both studies the influence of FTO on these **phenotypes** was found to be either greater in individuals who also possessed a copy of the TaqIA at-risk **allele** or dependent upon individuals also having this genotype. Third, although estimates vary depending upon ethnicity, roughly 50% (range 11% – 67% for rs8050136) of the European population carries an at-risk allele for FTO and approximately 35% (range 23%–56% for rs1800497) of these individuals can also be expected to carry the TaqIA at-risk allele (HapMap[1] and 1000 Genomes[2]). Genetic variants influencing DRD2 signaling therefore affect a significant portion of the population. Finally, there are consistent reports of decreased DRD2 following diet induced obesity [7], high fat diet in the absence of obesity [6], and metabolic dysfunction.

Dopamine-dependent functions influencing ingestive behavior

DA signaling is integral to a number of cognitive functions that are important for optimizing ingestive behavior (Table 1). The DA fronto-striatal loop plays a well-known role in working memory, cognitive flexibility, and associative learning [40]. Specifically, working memory and cognitive flexibility act as opposing influences to support the “on-line” stabilization of task-relevant representations while enabling the flexible updating of those representations in response to novel information [41]. Deficits in working memory and cognitive flexibility are in turn associated with cognitive inflexibility, impulsivity and compulsivity, all of which are associated with addictive like behaviors including overeating [42–46].

There is currently much debate over the precise role of DA in associative learning. While it is clear that several forms of associative learning are subserved by the fronto-striatal loop, including; (1) model based learning, where consideration of future values drive goal-directed behaviors; and (2) ‘model free” learning, where past learned values drive habit formation [47], the precise role of DA in these processes is intensely debated. DA has been argued to

[1]**HapMap:** A collaborative database that aimed to develop a haplotype map of the human genome by focusing on common SNPs. Has largely been supplanted by the 1000 Genomes Project. https://www.ncbi.nlm.nih.gov/probe/docs/projhapmap/

[2]**1000 Genomes Project:** A detailed public database of human genetic variation resulting from a collaborative project to perform whole-genome sequencing of at least one thousand participants from a number of ethnic groups. http://www.internationalgenome.org/

control the exertion of effort [48], the signaling of reward prediction errors [49], and the attribution of incentive salience to reward-related stimuli [50]. Regardless, of the exact role, the DA system plays a role in the switch from model-based (i.e. goal-directed/action – object responding) to model-free (i.e. habitual/stimulus – response responding) learning following repeated exposure to reinforcers including drugs and food [51–53] is a hallmark of addictive behavior [54] and observed in diet induced obesity [7].

More recently, the DA projection from the ventral tegmental area to the hippocampus has been implicated in adaptive memory [55]. More specifically, this circuit enables the sculpting of memories towards events of motivational significance so that what is remembered is motivationally relevant and hence adaptive [55]. Whether this is altered in obesity is unknown but high fat fed rodents are impaired in contextual memory tasks where they must remember obtaining food rewards in locations with different features [56–58].

Finally, DA plays a critical role in metabolic sensing [59]. In particular, DA function has emerged as critical for the integrity of the “gut-brain” axis, which supports the transfer of signals about the energy and nutrition provided by nutrients to homeostatic and reward circuits that orchestrate their acquisition and metabolism. The gut-brain axis refers to the system of bidirectional communication between circuits in the brain and cellular sensors in the gastrointestinal tract (Box 1). Traditionally, ingestive behavior and nutrient metabolism were treated as operating with relative independence. However, recent work highlights their intimate relationship with direct regulation of perception and behavior by peripheral signals, and direct effect of central circuits including DA neurons on nutrient metabolism [21, 26].

TaqIA polymorphism (rs1800497)

The TaqIA **RFLP** is the most studied genetic variant related to DA signaling and obesity. In humans there are three variants: A1/A1, A1/A2 and A2/A2. Candidate gene studies (Box 2) show that approximately 30% of European, 60% of Asian and 41% of African (HapMap and 1000 Genomes) populations possess one or two copies of the A1 allele and those that do have roughly 30% fewer DRD2s in the striatum [36–38], though one study has failed to replicate this finding [60]. Many studies show that A1 carriers are more likely to have increased waist circumference [61], higher BMI and obesity [62, 63]. GWAS also implicate the variant in obesity. There are associations with waist circumference (p=0.01 for men and p=0.07 for women in GIANT[3]), fasting glycemia (p=0.02 in MAGIC[4]), insulin sensitivity (p=0.01 in MAGIC) and risk for type 2 diabetes (p=0.08) in DIAGRAM[5]). Of note, a meta-analysis of 33 studies with mostly small samples (under 100) reported no relationship between BMI and A1 allele status [64]. This finding is not surprising since this **SNP** explains only a small percent of the variance in BMI of the population, making larger samples, and more accurate measures of adiposity necessary to observe reliable associations. In addition to obesity the A1 allele is associated with a number of disorders in which DA

[3]GIANT: The Genetic Investigation of ANthropometric Traits. A consortium aiming to identify the genetic basis of human body size and shape. http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium
[4]MAGIC: The Meta-Analyses of Glucose and Insulin-related traits Consortium. A consortium that focuses on the genetic basis of Type 2 Diabetes. https://www.magicinvestigators.org/
[5]DIAGRAM: DIAbetes Genetics Replication And Meta-analysis. A consortium that works to identify genetic loci underlying glycemic traits. http://diagram-consortium.org/index.html

signaling is affected including attention deficit hyper activity disorder (ADHD) [65], addiction [66], alcoholism [67], poorer outcomes following traumatic brain injury [68, 69] and Parkinson's disease [70].

At the neurobehavioral level A1 carriers have widespread reduced glucose metabolism [71], reduced grey matter density in the substantia nigra, subthalamic nucleus and anterior cingulate cortex [72, 73], and reduced activity in the prefrontal cortex and striatum during reversal learning [74, 75], working memory [76] and receipt of monetary reward [77]. Being an A1 allele carrier is associated with greater impulsivity [78–84], poorer time estimation [78], steeper **delayed discounting** [40] poorer working memory [76, 84, 85], impaired reversal learning [74, 86, 87], impaired negative outcome learning [14, 34, 75] and poorer long term memory [88] (though see [89]).

These **endophenotypes** are in turn associated with overeating and risk of obesity. For example, carriers compared to non-carriers will work more for food, particularly if also obese, and those who are high in food reinforcement consume more snack food than non-carriers and A1 carriers who exhibit low food reinforcement [90, 91]. In addition, in a cohort of mostly healthy weight Asian American college students, A1 carriers compared to non-carriers reported greater fast-food and carbohydrate craving and if female this was accompanied by greater drive to consume highly palatable foods [92]. Furthermore, in carriers, but not non-carriers, there is a positive association between response in the orbitofrontal cortex to palatable food cues and future gain in body fat [93]. However, and in contrast, carriers also exhibit reduced responses in DA source and target regions to the receipt [93–95] or imagined receipt of an anticipated palatable food [96], and these responses also predict future weight gain [93, 95, 96].

This pattern of observed effects has often been interpreted as evidence of enhanced anticipatory and blunted consummatory food reward [93], consistent with the incentive sensitization theory of addiction [50] and the anhedonia hypothesis of obesity [66] (Box 3). However, recent data refute the interpretation that reduced responses reflect anhedonia. First, dorsal striatal response to milkshake is associated with measures of impulsivity but not of food reward/reinforcement [97]. Second, a positive association between weight gain and dorsal striatal milkshake response in A1 carriers but not non-carriers was recently reported [98]. Critically, milkshake delivery in this study was unpredicted. Thus, response to the same food in the same DRD2 rich nucleus is positively or negatively associated with weight gain in A1 carriers depending upon whether the milkshake is expected or unexpected. This is an important observation because unpredicted, but not predicted outcomes generate error signals (Box 3). As such, it has been suggested that the decreased response to predicted milkshake corresponds to a weaker outcome signal while the increased response to unpredicted milkshake reflects an enhanced error signal. At the same time it is proposed that the enhanced responses to food cues reflect an overall heightened reward sensitivity in obesity [99].

BOX 3

Theories of DA function and dysfunction

DA as a learning signal

When the predicted outcome of an action or decision differs from the actual outcome it is adaptive for organisms to update future predictions to render them more accurate. According to learning theory, the generation of prediction errors (PE) is critical for driving this learning and phasic DA neuron firing is widely believed to code these PEs placing DA signaling at the center of associative learning. The original evidence supporting this theory came from electrophysiological investigations in the 90s. These experiments revealed that tonically active DA neurons increase their firing in response to the receipt of an unpredicted reward (positive PE) and decrease their firing response when a predicted reward is omitted (negative PE). However, after learning, when a reward is received as predicted DA neuron firing is unchanged. Instead the burst of activity occurs in response to cues that now predict the reward. Thus DA response signals predictions and prediction errors but not predicted outcomes [100].

Collectively, these findings suggest that the A1 allele is associated with enhanced error, but weaker reward outcome signal generation in the context of overall heightened reward sensitivity [99]. Supporting this interpretation, another study recently reported enhanced midbrain response in A1carriers vs. non-carriers upon the generation of positive error signals during a probabilistic learning task [34]. This study also showed that this heightened response was associated with poorer performance in negative outcome learning, which would be expected if reward outcome signals were diminished. Moreover, carriers failed to exhibit functional connectivity between midbrain and medial prefrontal cortex during the task, suggestive of a reduced transfer of DA learning signals to prefrontal circuits. Likewise, weaker reward outcome signals would also be expected to increase propensity for model free or habitual responding.

The findings also provide strong evidence that the A1 allele confers risk by producing baseline decreases in DA signaling resulting in differences in DA-dependent reinforcement and cognition. Consistent with this possibility pharmacological manipulation of DA signaling often produces distinct or opposing effects in carriers compared to non-carriers. For example, methylphenidate, which increases extracellular DA, is less effective at suppressing food intake in A1carrier vs. A1 non-carrier children with ADHD [101], whereas the DRD2 agonist bromocriptine is more effective at reducing craving and anxiety in A1 allele-carrying alcoholics [102]. In healthy individuals, bromocriptine, but not placebo administration increases activity in the nucleus accumbens during a reinforcement task and enhances performance in A1 carriers but not non-carriers. Similarly, administration of carbergoline, another agonist, during a reversal learning task produces increased activation in the medial orbitofrontal cortex, insula, ventral putamen and anterior cingulate cortex in A1 carriers but decreases response in these same areas in non-carriers [86]. Interestingly, providing monetary incentives, which presumably elicit DA release, improves performance on a working memory task in carriers but not non-carriers [85]. This suggests that like DA agonists, behavioral interventions that may increase DA signaling (e.g. exercise) may be

more effective in A1 carriers. Collectively, these studies are consistent with the inverted U-shaped action of DA function superimposed on baseline differences in DA signaling conferred by genotype (Box 4). Specifically, the effect of a DA agonist would move A1 carriers from suboptimal (low) to optimal (intermediate) and A1 non-carriers from optimal (intermediate) to suboptimal (high) dopaminergic functioning [86] thus producing opposing effects.

BOX 4

The inverted-U shaped DA action on cognition

To account for the considerable variability in the effects of pharmacological manipulation on cognition Cools and D'Esposito proposed that an individual's response depends upon their baseline level of DA signaling [41]. More specifically, they argue that the relationship between brain dopamine and cognitive function follows an inverted-U-shaped curve, where performance is optimal when DA levels are neither too low nor too high. Therefore pharmacologic manipulations may manifest in opposing or paradoxical effects on cognition. They further noted that the optimal level of DA signaling may vary across cognitive function since specific circuits might have different optimal DA levels. The implication of this model is that inter-regional and inter-individual differences in DA function must be considered to understand the relationship between central DA signaling, cognition and reward.

Data from longitudinal studies examining the impact of the Taq1A A1 RFLP on weight gain are consistent with the pharmacological data, revealing opposing associations between response to food in DA source or target regions and weight gain as a function of genotype [93, 95, 98] (Figure 1). More specifically, caudate response to anticipated milkshake receipt is negatively associated with weight gain in carriers, but positively associated in non-carriers [93, 95], whereas the opposite is true amygdala response to milkshake in a sated state [98]. Whether these effects reflect cause or consequence of obesity is an open question. However, the dorsal striatal effects are most likely a consequence, since reduced responses are associated with weight gain but not risk for obesity as assessed through parental BMI [103]. Interestingly, since response to milkshake in this area is associated with impulsivity [97], it is possible that the A1 allele confers risk for adaptations in striatal circuits, which in turn in result in greater impulsivity. If so, then the one effect of the allele may be to increase risk for neural adaptations that lead to impulsivity and escalation of weight gain, which may explain why carriers have reduced success with weight loss interventions [104–106]. Relatedly, it is possible that adaptations occur in response to factors other than diet, adiposity or metabolic change, such as age, poor sleep quality, chronic stress, and physical inactivity [107]. Consistent with this notion, old but not young carriers compared to non-carriers show reduced dorsal striatal response and impaired performance during a memory task [88].

Molecular Mechanisms

The TaqIA RFLP is associated with a mutation producing a single amino acid change within the substrate binding domain of the ankyrin repeat and kinase domain containing 1 (ANKK1) protein [61] and is in **linkage disequilibrium** with the DRD2 locus [108].

Precisely how this mutation in the *Ankk1* gene locus influences DRD2 density and function is a subject of current investigation. One possibility is that the mutation affects ANKK1 activity, which then influences DA receptors through its biochemical actions. ANKK1 belongs to a large family of receptor-interacting protein (RIP) kinases, which serve as essential sensors of cellular stress, initiating responses to environmental factors, including nutrient ingestion, by activating transcription factors such as **NF-κB,** [109]. Chronic exposure to excessive nutritional lipids is known to trigger inflammatory-like response in the brain that are partially mediated by **NF-κB**, which n turn, acts a direct and indirect transcriptional regulator of DA receptor abundance and signaling. Accordingly, ***in silico*** analysis of the possible human protein-protein interactions reveals that among the ~30 predicted possible partners for human ANKK1 protein [110] half are found in pathways related to inflammatory responses including the **NF-κB, cytokine** pathways. Notably, in the brain ANKK1 is highly represented, if not uniquely expressed in astrocytes [111, 112]. Astrocytes can be targets for saturated fat-induced inflammatory responses and endoplasmic reticulum (ER) stress mediated through toll-like receptor (**TLR**) and **IKK/NF-κB** [113, 114] signaling pathways. In addition, **eicosanoids** derived from lipids are potent inducers of neural growth factor secretion by astrocytes, which also directly regulates DRD2 expression through an NF-κB dependent mechanism [115]. Moreover, high fat diet-mediated central inflammation increases DA neurons susceptibility to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [116]. Thus mechanisms exist to support a privileged connection between astrocytes and DRD2 bearing neurons resulting in selective effects of lipids on DRD2 via **inflammatory cascades** [117], similar to what has been previously described in the hypothalamus [118–122]. We therefore argue that mutation of ANKK1 mediates inflammatory-like responses that specifically affect DRD2 abundance and function, though there is some evidence that other DA receptor sub classes may also be affected [123].

Proposed Model

Altogether these observations converge towards the possibility that ANKK1 plays a role in mediating the effect of high fat diet on DRD2 expression via nutrient-induced inflammatory processes. We therefore propose a model whereby possession of the A1 allele enhances susceptibility to cellular inflammatory responses, which in turn alters DA signaling and DA-dependent cognition, metabolism and behavior (Figure 2). Given the central role that DA plays in integrating information about the nutritional value and sensory properties of foods, as well as the state of the organism, to prioritize and adapt behavior to optimally acquire and store energy, there are many possible pathways by which DA adaptations may confer risk for overeating and obesity. Likewise, A1 carriers would also be at risk for impairments in a variety of dopamine-dependent cognitive functions that are associated with obesity [4]. Accordingly, obese vs. lean carriers, but not non-carriers show reduced performance on a letter-number sequencing task that assesses executive functioning [124]. By extension, adaptations in DA signaling could also confer risk for other impulse control disorders and conditions where altered DA signaling contributes to pathology, such as diabetes and ADHD.

An important corollary of the model is that ANKK1 is linked primarily to diet rather than to adiposity or metabolic dysfunction. From this perspective, associations between genotype

and BMI and adiposity are secondary to the effect of diet. Likewise, this model predicts that a high fat diet also leads to impairments in DA-dependent cognition via influences on DRD2. This is an important consideration given emerging evidence that diabetes, obesity and diet are associated with cognitive impairments [4], and that many of these impairments rely upon DA signaling [125]. To date no study has directly evaluated the influence of diet on the association between the TaqIA A1 allele and adiposity, metabolic, and/or cognitive dysfunction. However, accumulating evidence from animal studies indicates that diet can influence DA signaling and function independently of body weight, adiposity and metabolic dysfunction [6, 21, 126]. Accordingly, circulating lipids directly modulate DA-mediated food reward [6–11] and obesity-associated cognitive dysfunction is improved by lowering circulating lipids independent of adiposity [127].

Also of note, all rodents are A1 homozygotes. Therefore genetic manipulations to knock out the gene encoding ANKK1 or even to introduce the A2 variant in the rodent will be essential to provide a mechanistic test of the model and possible molecular association with diet. However, human studies examining the impact of high fat feeding on carriers vs. non-carriers are possible and an important direction for future work. Large-scale studies aiming to disambiguate effects of genotype, diet, adiposity and metabolic dysfunction on DA signaling are also required.

FTO Gene Variants

Variations in the FTO gene are the strongest known genetic factor predisposing humans to polygenic obesity [32]. FTO is an enzyme that broadly regulates how the genetic code is translated from DNA into amino acids [128, 129] [130]. As such, the biological functions of FTO are diverse and incompletely understood, consistent with the link between FTO and non-obesity phenotypes, such as alcohol consumption and ADHD [131]. With respect to obesity the AA and AT genotypes are considered at risk compared to the TT genotype [32], with increased dietary intake from unhealthy eating behaviors [132–136] rather than metabolic dysfunction underlying the association [137, 138]. Interestingly accumulating evidence suggests that one pathway by which FTO affects adiposity is by influencing DA signaling. Specifically, the same variants associated with obesity have also been implicated in a number of DA-dependent behaviors and disorders [139, 140], while knocking out the *Fto* gene in mice results in impaired DRD2 control of neuronal activation and DA-dependent regulation of locomotor activity and reward sensitivity [33]. Furthermore, like the ANKK1 SNP, the influence of FTO on dopamine-dependent behavior can occur independent of obesity. This indicates that it is the mutation itself, rather than obesity associated with the mutation that influences DA signaling. This observation raises the possibility that FTO and ANKK1 may interact to confer susceptibility for adaptations in DA signaling related to diet induced obesity and metabolic dysfunction.

Consistent with this proposal, **epistatic** effects have been observed between FTO and ANKK1. For example, in a group of 92 individuals who were matched for age, BMI, and general intelligence but differed by FTO and ANKK1 genotype a gene dose effect was observed such that individuals with both at-risk alleles performed significantly worse on a probabilistic learning task performed in the fMRI scanner than individuals with only one or

neither at-risk allele [34]. Consistent with prior reports examining ANKK1, the effect was specific for negative outcome learning (i.e. genotype did not influence positive outcome learning), with A1 carriers performing worse than non-carriers and A1 carriers with the FTO at-risk SNP rs9939609 performing worse than those who did not have both at-risk alleles. Moreover, negative but not positive outcome learning was inversely related to prediction error responses in the midbrain. This finding indicates that FTO and ANKK1 interact to influence DA dependent learning that is impaired in obesity [14].

FTO/ANKK1 epistatic effects have also been observed on body composition and insulin sensitivity. More specifically, in a sample of 2245 individuals the FTO SNP rs 805136 only influenced body fat content, waist-to-hip ratio, insulin sensitivity and fasting insulin if they also carried the at-risk allele of the ANKK1 SNP [141]. Strikingly, a similar effect was observed with insulin action in the DRD2 rich caudate nucleus: FTO influenced insulin sensitivity only in A1 allele carriers. Thus there is evidence that FTO and ANKK1 SNPs interact to influence DA-dependent brain responses, behaviors, adiposity and metabolism. Although both variants are associated with DRD2, the precise mechanisms by which the interactions take place are unknown and also await development of an animal model. Moreover, these data raise the possibility that ANKK1 and FTO may interact to impact glucose metabolism and perhaps trigger a more global effect on cognition.

Concluding Remarks

We have reviewed evidence suggesting that two common genetic variants, ANKK1 and FTO confer risk for obesity and neurocognitive impairment by their mutual effects on DRD2. More specifically, we put forth the hypothesis that carrying the at-risk allele for the ANKK1 rs1800497 SNP increases susceptibility to DA adaptations related to high fat feeding, which then leads to weight gain, metabolic and cognitive dysfunction. We further highlight a potential role for the FTO rs805136 SNP in DA adaptations to diet and adiposity that ultimately impact cognition to confer additional risk. Direct tests of the model are needed, but if proven correct would suggest that the roughly 18% of the population with both at-risk alleles are at heightened risk for the deleterious effects of an unhealthy diet and would benefit from pharmacotherapies that prevent DRD2 adaptations. Towards this aim the development of an animal model is critical to identify molecular targets. Our model also suggests further focus on dopamine-adaptations as a causal link between neurocognitive impairment and diabetes and obesity is warranted and suggests that studies investigating this association should genotype their samples.

GLOSSARY

Agonist
A molecule that binds to, and activates, a receptor.

Allele
Alternative forms of the same gene.

Astrocytes

A type of cell in the central nervous system that is traditionally believed to perform support and maintenance for neurons but is now believed to play a more active role in cell signaling and computation.

Delayed Discounting
The cognitive phenomenon where the relative value of a reward decreases as the delay in receiving it increases.

Eicosanoids
A type of signaling molecule that regulates the function of other cells.

Endophenotype
Heritable behavioral and/or neurocognitive traits that are associated with, or convey risk for, a syndrome.

Epistasis
A form of interaction between genes, where the presence of a certain allele for one gene modifies or masks the expression of a different gene.

In silico analyses
A computer-based data mining–based method for determining proteome-wide protein-protein interactions (PPIs). This method is based on the ability of a program to predict – based on the literature and known sequence of the protein-the possible physical interaction between proteins. This method is typically used to narrow down potential partners involved in a signaling cascade.

Inflammatory cascade
A series of cellular events that are triggered by an immune reaction and that result in pathological inflammation.

Linkage disequilibrium
The tendency of certain alleles of different genes to be inherited together at a rate greater than chance.

Lipids
A class of hydrophobic organic molecules that encompasses fats and oils.

NF-κB: (nuclear factor kappa-light-chain-enhancer of activated B cells)
NF-κB is a protein complex that acts as a master transcriptional regulator of the mRNA cellular response to various stimuli, including nutrients. It is fundamental for the control of immune responses and regulates cell survival/death, cytokine production, and response to free radical damage. NF-kB mediates the inflammatory response to nutrient overload in the brain [122, 142–144] and directly controls DRD2 expression [145].

Polygenic
Type of inheritance where the contributions of multiple genes determine a single characteristic.

Restriction fragment length polymorphism (RFLP)

A variation in a genetic location of interest that can be revealed by the digestion of the gene with restriction enzymes. Different gene variations are reflected by different lengths of the DNA fragments after digestion.

Single Nucleotide Polymorphism (SNP)

A variation in a single nucleotide at a specific position in the genome.

Toll like receptors (TLR)

A family of membrane receptors that recognize structures such as microbes and mediate immune responses. In the CNS TLR are expressed on neurons and glia [146, 147] and mediate diet-induced inflammation through various mechanism including direct binding of fatty acids [148–151].

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Outstanding Questions

Is diet associated with changes in dopamine-dependent function in humans? If so, is this independent of changes in adiposity and/or metabolic function?

To what extent does ANKK1 contribute to the susceptibility for diet induced impairments in cognition? How do these cognitive changes influence ingestive behavior?

Is the roughly 18% of the population carrying the at-risk alleles for both FTO and Taq1A A1 polymorphism at increased risk for metabolic and neurocognitive dysfunction associated with dopamine signaling?

What are the molecular pathways by which nutrient induced pro-inflammatory signals interact with ANKK1 to influence DRD2?

Are the predicted negative effects of diet on cognition reversible?

Trends Box

1. Dopamine integrates metabolic signals with circuits regulating behavior.
2. The *Ankk1 and Fto* gene variants interact to influence dopamine dependent functions.

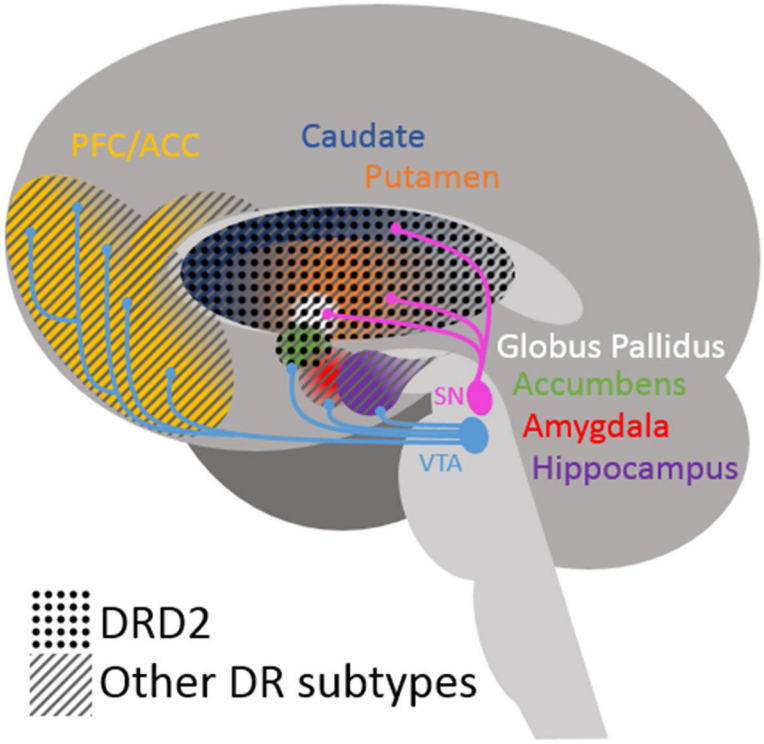

Figure 1. Dopamine receptor subtype distributions

Simplified schematic of brain dopamine pathways and distribution of DRD2 and other dopamine receptor subtypes in areas important for reward. DRD2 shows the greatest differential expression in striatal areas. SN = Substantia Nigra, VTA = Ventral Tegmental Area, PFC = Prefrontal Cortex, ACC = Anterior Cingulate Cortex.

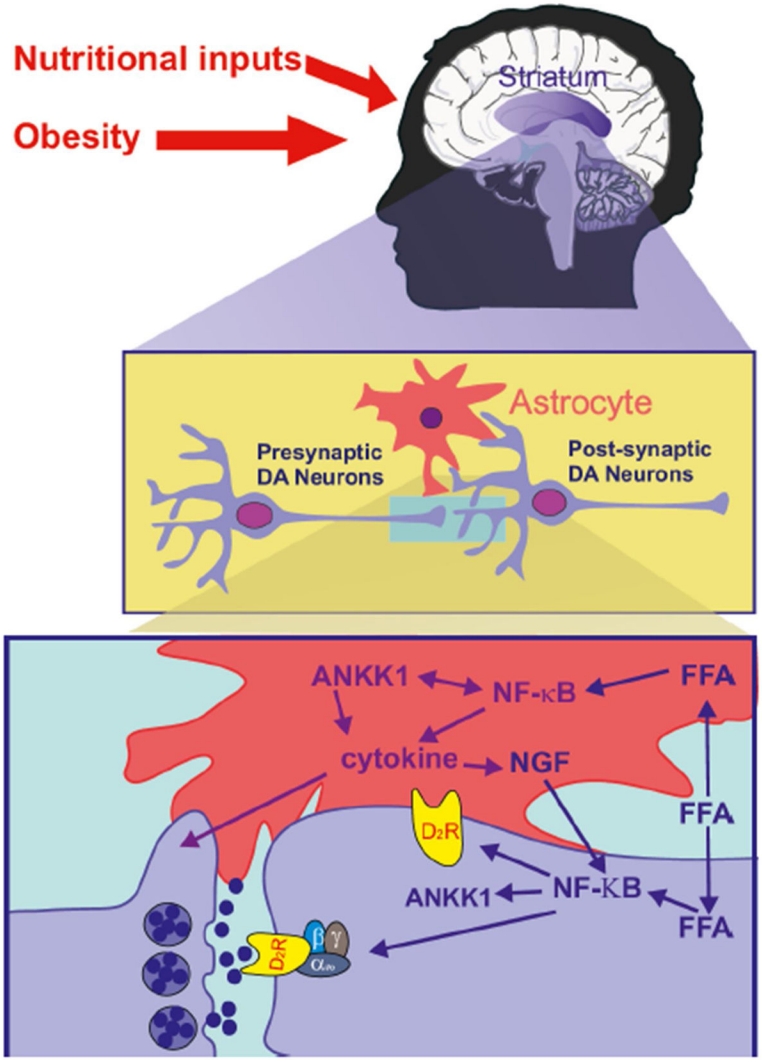

Figure 2. Potential mechanism associating ANKK1 and DRD2 signaling

Nutritional inputs such as free fatty acids (FFA) promote the action of pro-inflammatory signaling in astrocytes and neurons. This results in activation of NF-kB (the nuclear enhancer of kappa-light-chain-enhancer of activated B cells). Through astrocyte-neuronal signaling NF-kB regulates the transcription of the DA D2 receptor (D2R). In addition, within the astrocyte NF-kB signaling promotes a cytokine-mediated production of the neural-growth factor (NGF), a potent inducer of neural D2R abundance. ANKK1 is predicted to physically interact with NF-kB in the astrocyte and in the neuron. As such, ANKK1 mutations (*TaqI*A A1) could directly impact cellular responses mediated by NF-kB, including regulation of D2R signaling and receptor expression [117]). The circles in the cleft represent dopamine release.

Table 1

Tools for assessing DA-dependent neurocognitive functions

Function	Definition	Assessment
Working memory	Performs temporary maintenance and manipulation of information held “on-line” for immediate use	N-back, digit span, Sternberg working memory task, letter- number sequencing, Austin Maze
Response inhibition	Suppression of inappropriate behaviors; Can also be measured via its opposing trait, impulsivity	Stop-signal task, go/no-go, Stroop task, self-report questionnaires (BIS/BAS, BIS- 11)
Cognitive flexibility	Ability to generalize and adapt cognitive strategies to novel environmental contexts	Wisconsin Card Sorting Task, Trail-Making Test
Incentive motivation	Willingness to work towards receiving a reinforcing goal or reward	Progressive ratio, self-reported wanting/craving of a stimulus or to engage in a behavior
Associative learning	Acquisition and retention of new stimulus-cue or behavior-stimulus associations	Classical and operant conditioning