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Genetic Variation in Satiety Signaling and Hypothalamic Inflammation: Merging Fields for the Study of Obesity

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Abstract

Although obesity has been a longstanding health crisis, the genetic architecture of the disease remains poorly understood. Genome-wide association studies have identified many genomic loci associated with obesity, with genes being enriched in the brain, particularly in the hypothalamus. This points to the role of the central nervous system (CNS) in predisposition to obesity, and we emphasize here several key genes along the satiety signaling pathway involved in genetic susceptibility. Interest has also risen regarding the chronic, low-grade obesity-associated inflammation, with a growing concern towards inflammation in the hypothalamus as a precursor to obesity. Recent studies have found that genetic variation in inflammatory genes play a role in obesity susceptibility, and we highlight here several key genes. Despite the interest in the genetic variants of these pathways individually, there is a lack of research that investigates the relationship between the two. Understanding the interplay between genetic variation in obesity genes enriched in the CNS and inflammation genes will advance our understanding of obesity etiology and heterogeneity, improve genetic risk prediction analyses, and highlight new drug targets for the treatment of obesity. Additionally, this increased knowledge will assist in physician's ability to develop personalized nutrition and medication strategies for combating the obesity epidemic. Though it often seems to present universally, obesity is a highly individual disease, and there remains a need in the field to develop methods to treat at the individual level.

Keywords

Polygenic obesity; hypothalamus; satiety; inflammation; neuronal genes; precision medicine

Introduction

Obesity is a major public health crisis, on the rise in the United States and worldwide. In 2018 nearly 20% of children and over 40% of adults in the United States were considered

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obese with the adult rate of obesity predicted to rise to 50% by 2030 [1–3]. Obesity is associated with numerous health, social, and economic consequences, both at an individual and societal level [4–6]. Increased adiposity correlates with an increased risk of total mortality, highlighting the need to better understand the disease to improve treatment development [4].

Obesity is a complex disease resulting from genetic and environmental factors. The heritability of obesity has been studied for a number of years, but much of the genetic architecture underlying the disease continues to elude us [7]. Estimates on the heritability of obesity range from 30% to 90%, with most falling around 70% [8]. Despite the prevalence of obesity, the genetics are still poorly understood—there are more than 900 known low-risk, common genetic variants associated with body mass index (BMI) and over 300 variants associated with waist-to-hip ratio (WHR), but this still only explains a small fraction of variability and many of the underlying causal genes remain unknown [7, 9, 10]. Genome-wide association study (GWAS) findings for obesity are enriched in the central nervous system (CNS), and many of these genes play a role in synaptic function and neurotransmitter signaling [7, 11–13]. Better understanding the genetics of obesity is key for four reasons:

1. to better understand the biology for obesity development and progression to reveal novel pathways and targets for pharmacotherapy [14, 15]
2. to advance prediction analyses for genetic risk scores to better highlight and inform at-risk patients and environments [16–18]
3. to improve pharmacogenetics so patients can be matched with the most effective drug for them [19, 20]
4. to expand understanding of disease heterogeneity of obesity for researchers, physicians, and the general public to improve patient outcomes and quality of life [21–23].

Many homeostatic processes become dysregulated when fat mass accumulates, but one of the greatest areas of interest is the inflammation associated with increased adiposity [24]. Obesity is associated with a chronic, low-grade inflammation called meta-inflammation [25, 26]. Work has shown that inflammation develops very early in the hypothalamus of the brain when on a high-fat diet (HFD), separate from significant increases in fat and weight [27–29]. Recent findings indicate a role of genetics in modulating inflammatory response, and that this response may play a role in disease progression [30, 31]. For example, a study published in 2020 identified that a central regulator of inflammatory cell function, *receptor-interacting serine/threonine-protein kinase 1* (*RIPK1*), is genetically associated with obesity and a potential therapeutic target for weight loss [32]. This review will focus on genetic contributions of neuronal genes to satiety signaling in obesity and the inflammatory response in the hypothalamus. Better connecting these two areas of research may reveal new pathways and targets for treating obesity and the numerous co-morbidities associated with it.

These are the first steps to developing personalized genomic strategies for treatment, as recent work shows that not everyone responds to a HFD in the same way [22, 23, 33]. More fully understanding the impact of genetic variation on obesity development, progression, and

resolution will shed light on a path toward personalized nutrition for treating the obesity epidemic.

Satiety Signaling

The hypothalamus has been a main area of research for the role of the brain in obesity, in part due to its large role in most forms of monogenic obesity and its critical function in satiety and food intake. This region regulates energy homeostasis and systemic metabolism by integrating peripheral anorexigenic (appetite-reducing) and orexigenic (appetite-stimulating) signals to determine appetite [34]. The melanocortin system, consisting of two functionally antagonistic neuronal populations within the arcuate nucleus (ArcN) of the hypothalamus is key to this regulatory function. One subset of neurons expresses the orexigenic neuropeptides: neuropeptide Y (NPY) and Agouti-related peptide (AgRP; NPY/AgRP neurons). The other subset expresses the anorexigenic peptides: pro-opiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART; POMC neurons).

As food moves through the gut, signals are sent to the brain via mechanoreceptors, chemoreceptors, and hormones such as cholecystokinin (CCK), glucagon-like peptide (GLP)-1, peptide YY (PYY), and ghrelin (Figure 1) [35–39]. CCK, GLP-1, and PYY are examples of anorexigenic peptides, while ghrelin is a well-known “hunger hormone”, as have been reviewed elsewhere [36–40]. The gut-derived anorexigenic peptides CCK and GLP-1 bind to their respective receptors to stimulate POMC neurons, while PYY binds to its receptors on NPY/AgRP neurons to inhibit signaling (Figure 1) [41–43]. Ghrelin, on the other hand, stimulates NPY/AgRP neurons and modulates expression of adenosine monophosphate-activated protein kinase (AMPK) to promote appetite [44, 45]. Satiety signals can also originate from other tissues, such as leptin from the adipose tissue. Leptin is perhaps the best known satiety signal between the brain and peripheral tissues, and its genetic influence on obesity will be discussed in greater detail later. In the brain, leptin binds leptin receptors on both NPY/AgRP and POMC neurons, triggering the activation of the Janus family of tyrosine kinases (JAK)-signal transducer and activator of transcription (STAT) signaling [46]. In cases of normal signaling, leptin inhibits NPY/AgRP and stimulates POMC neurons, leading to a sense of satiety via the synthesis of POMC and POMC’s subsequent cleavage to the melanocyte-stimulating hormones, α-MSH and β-MSH (Figure 1) [46]. α-MSH can then bind two different melanocortin receptors, melanocortin-3 receptor (MC3R) and melanocortin-4 receptor (MC4R) of the paraventricular nucleus (PVN) of the hypothalamus [47, 48]. Of the two, MC4R is more widely distributed throughout the central nervous system, and has been connected to monogenic and polygenic forms of obesity [13]. Changes in the function of these neuronal populations is known to occur rapidly following HFD feeding, in as little as under a week [49].

Importantly, a key endpoint of communication in these hypothalamic pathways is the hindbrain, which has been identified as another key hub of energy balance and satiety signaling integration. For example, the PVN neurons described above engage both the nucleus of the solitary tract (NTS) and the central lateral parabrachial nucleus (cLPBN) of the hindbrain [50, 51]. In fact, the NTS likely processes and receives the greatest number of

energy status signals, and in turn communicates with the hypothalamus and the parabrachial nucleus [52, 53]. These include the signals from mechanoreceptors in the gut as well as many of the gut-derived hormones, such as CCK, GLP-1, ghrelin, and PYY, plus leptin from adipose (Figure 1) [54–56]. The hindbrain then integrates these multiple signals to control energy balance as reviewed elsewhere [52].

In conjunction to the role of the hypothalamus and hindbrain in homeostatic food intake and satiety, a growing body of evidence also implicates hedonic signaling in the obesity epidemic [12, 57, 58]. For example, genes within human GWAS obesity loci are enriched in the hippocampus [12]. The hippocampus may also play a role in meal size control [59], and hippocampal atrophy has repeatedly been linked to a HFD and obesity, and may alter responses to taste [60, 61]. In addition, the nucleus accumbens can influence food intake pathways, and has been the subject of study for obesity treatment [62–65]. A recent analysis showed strong gene expression enrichment of top obesity/BMI-associated loci in the insula and substantia nigra, regions involved in addiction, motivation, and reward-seeking behavior [66]. Furthermore, the hypothalamus connects with the insula in response to nutrient status and to drive the satiety response [67]. Work has demonstrated a positive relationship between higher BMI and greater hypothalamic gray matter volume and connectivity with the insula [68]. While hedonic signaling is not the focus of this review, it is important to mention its role and dysregulation in the development and maintenance of obesity. Very briefly, excessive dietary fat consumption disrupts the brain hedonic system by altering dopamine signaling to the point of overriding homeostatic mechanisms; more specific details have been described elsewhere [69]. These findings support research that indicates an association between obesity, obesity risk genes, and disordered eating patterns [70]. While further details lie outside the scope of this review, this highlights the necessity of expanding research to other neuron populations and different regions of the brain to determine the role of known genes and to continue identifying genetic factors influencing weight gain.

Monogenic Obesity Genes in the Brain

Ordinarily, the satiety signaling pathway is well-controlled. But deleterious mutations in any of the genes along the pathway often causes early onset, severe obesity, which has been extensively described elsewhere [71]. Of those genes expressed in the brain, the two that are perhaps the best studied are the *leptin receptor* (*LEPR*) and *MC4R*. Several single nucleotide variants in *LEPR*, including Lys109Arg and Gln223Arg are associated with severe obesity [72, 73]. Deficiencies in leptin and leptin receptor are extraordinarily severe but also rare, as is the case with most other mutations along the satiety signaling pathway in genes such as *PCSK1, ADCY3, POMC,* and *SIM1* [74]. The most common gene implicated in monogenic obesity is *MC4R:* early estimates suggested that approximately 2.5% of severely obese individuals have a deleterious mutation in *MC4R*, with exact rates varying by populations [75–77]. Most recent analyses demonstrate that approximately 7% of the total population and over 10% of obese patients have a coding variant in *MC4R* [78]. Nearly 20% of reported single nucleotide variations in the *MC4R* gene have been predicted to be pathogenic, or likely pathogenic, highlighting the predominance of *MC4R* in monogenic obesity [71]. New work has uncovered how 19 rare mutations in *MC4R* disrupt its trafficking and

signaling, including plasma membrane localization or interaction with $G\alpha_s$ protein [79]. While deleterious mutations in single genes along the satiety pathway explains a fair number of early onset, severe obesity cases, they do not explain the majority of obesity cases in the clinic, which typically present later in life. For most patients, individually small effects in many genes (polygenic obesity) culminate in an increased risk for obesity, rather than a large effect caused by just one gene. A select number of genes that are both present in the brain and have been implicated in polygenic obesity are discussed below.

Polygenic Obesity Genes in the Brain

As previously mentioned, GWAS has identified hundreds of variants that are associated with BMI and WHR [7, 9]. Although the causal genes for most loci remain unknown, many of the genes at or near these loci are enriched within the CNS, including the hypothalamus and pituitary gland, key sites of satiety regulation [12]. Genes are also enriched in the hippocampus and other areas of the limbic system that are likely to play a role in hedonic signaling of food intake [12, 13, 66]. Gene set enrichment and pathway analysis shows that CNS enriched genes are involved in synaptic function and neurotransmitter signaling [7, 12, 13]. Although to-date many genes identified through human GWAS act through neuronal processes to influence obesity, we have chosen three genes to describe in-depth: *FTO, MC4R,* and *ADCY3*.

The first and most significantly obesity-associated gene identified through GWAS is the aptly called *fat mass and obesity-associated* gene (*FTO*). A number of variants in *FTO* have been found in the first intron of the gene and are associated with increased body weight, body fat, energy intake, and other adiposity measures [80]. The best studied variant, rs9939609, has been found to increase risk for obesity 1.7-fold when subjects are homozygous for the obesity-risk “A” allele compared to the low-risk “T” allele [81]. However, the exact mechanism by which this allele increases obesity risk is still poorly understood. Early work demonstrated a relationship between the “obesity-risk” *FTO* variant and increased food—particularly fat—consumption in children [82, 83]. Research that followed suggested that variants in *FTO* may alter function of ghrelin, the appetite-promoting gut hormone, where subjects homozygous for the A allele had dysregulated circulating levels of acyl-ghrelin and a diminished postprandial appetite reduction (e.g., reduced satiety response) [84–86]. More recent data indicate that variants in *FTO* alter eating behavior not through ghrelin itself, but instead through how the central nervous system processes these satiety signals [85–87]. A current leading hypothesis suggests that this altered processing in the hypothalamus may be through connections between *FTO* and other genes, specifically *retinitis pigmentosa GTPase regulator-interacting protein-1-like* (*RPGRIP1L*) and the gene *Iroquois homeobox 3* (*IRX3*) [88, 89]. *RPGRIP1L* is located proximal to *FTO* and both are regulated by the *cut-like homeobox 1* (*CUX1*) transcription factor [90]. Enhancers in the first intron of *FTO*—where the most prominent obesity-related SNPs are located—act as long-range regulators for *IRX3* gene expression, where presence of these risk alleles in *FTO* led to increased expression of *IRX3* [90]. This connection has been of interest in recent years, and is more extensively reviewed elsewhere [88]. Importantly, it has recently been demonstrated that the *FTO* genotype may determine the

success of weight loss through lifestyle modification, and this may be in part by how these variants allow lifestyle changes to alter expression of *FTO* and *IRX3* [91, 92].

In addition to its association with monogenic obesity, variants in *MC4R* have been connected to polygenic obesity. As opposed to monogenic variants that truncate protein or severely alter protein folding/function, *MC4R* variants in polygenic obesity do not completely ablate or disrupt the protein. Indeed, certain polygenic variants within *MC4R* are beneficial: two coding region variants (Val103Iso and Iso251Leu) are negatively associated with obesity [93, 94]. These variants may affect signaling, as one study found that the presence of the Val103Ile variant led to a twofold decrease in antagonist (hAGRP) potency; other polymorphs were associated with differential responses to the endogenous agonists α-MSH and β-MSH [95]. Additional variants have been detected in GWAS, including the obesity-predisposing rs17782313, rs12970134, and rs476828 [96–98]. Just recently, a large study across 20,000 electronic MEdical Records and GEnomics (eMERGE) network participants and 77,000 independent individuals revealed 125 coding variants, including 30 novel variants [78]. This study confirmed not only the role of *MC4R* in polygenic obesity, but also heterogeneity in effect of the variants and prevalence in different populations [78]. The specific mutations in *MC4R* have been shown to influence the effectiveness of behavioral interventions and pharmacotherapy treatment. Patients with non-functional MC4R (monogenic obesity) do not respond well to bypass surgery but can respond to GLP-1 receptor agonism while patients with some functional MC4R (polygenic obesity) do respond to bypass surgery [99–102].

Other players in the melanocortin pathway also contribute to both monogenic and polygenic obesity, including *adenylate cyclase isoform 3* (*ADCY3*), which generates the secondary messenger cAMP [103]. While *ADCY3* was best known to participate in olfactory pathways, it has also been linked to adiposity and depression [104–108]. One early study identified a relationship between increased expression of *ADCY3* and improved metabolic health in the Goto-Kakizaki rat, where two functional point mutations in the promoter region increased *ADCY3* expression that, when combined with forskolin treatment, led to increased cAMP production in the islets, promoting systemic insulin sensitivity [109]. Follow-up studies identified polymorphisms in *ADCY3* that confer risk susceptibility to obesity [105, 106, 110]. At the same time, a separate study demonstrated that global *ADCY3* knock-out mice became obese due to leptin insensitivity, hyperphagia, and low locomotor activity—suggesting that the activity of *ADCY3* in the hypothalamus influenced body weight regulation [111]. Since these initial findings, a number of studies have validated the relationship between *ADCY3* function and adiposity: variants that increased expression and/or function of *ADCY3* promote decreased adiposity and better metabolic health, while variants that decreased expression and/or function predispose to weight gain [107, 112, 113]. Whether these effects are due to a change in food intake or to peripheral metabolism varies depending on the model used [107, 112, 113]. Our lab recently identified a variant in rat *Adcy3* that may be protective against obesity by altering transmembrane packing of the protein, and potentially altering membrane interactions and binding [114, 115]. Other work indicates that impaired signaling between MC4R and ADCY3 in the primary cilia of neurons can increase body weight [116]. Promisingly, it has been shown that genetic variation in *ADCY3* alters response to diet. In a randomized trial testing two

weight-lowering diets, presence of the G allele at rs10182181 correlated with an increased weight loss response on a low-fat diet, but a diminished response in a protein-rich diet [117]. This particular work highlights the importance an individual's genetic variation may have not only on developing obesity, but also on weight loss.

Obesity and Hypothalamic Inflammation

We know that genetics can contribute to dysregulated satiety signaling, but could genetic variation also affect the inflammation associated with obesity? It has been previously shown that a subset of the obese population have increased adiposity, but none of the metabolic complications, including reduced inflammation (e.g., metabolically healthy obese) [118, 119]. While adipose tissue is the best studied organ for obesity-associated inflammation, analyses have shown that HFD-induced inflammatory processes develop in the brain well before significant weight gain [27, 28]. There is also evidence that levels of reactive oxygen species (ROS) in the brain increase with diet-induced obesity (DIO) [120]. Hypothalamic inflammation has been connected to obesity since 2005, where the largest group of mRNAs modulated by a HFD was identified as immune-related proteins such as tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and c-Jun N-terminal kinase 3 (JNK3; also known as mitogen-activated protein kinase (MAPK)-10) [121].

Rodent studies show that a long-term HFD results in hypothalamic inflammation, which in turn induces hypothalamic leptin resistance that perpetuates the development of obesity through increased food intake [27, 122, 123]. High fat diets specifically enriched in saturated fats have been established to have a direct role in inducing this central inflammation [124]. Not all saturated fats increase inflammation equally, either. Rats consuming long-chain saturated fats derived from butter showed overall higher hypothalamic inflammation than rats consuming medium-chain saturated fats derived from coconut oil [124]. It has been postulated that these differences are due to the differential β-oxidation rates of long-chain and medium-chain fatty acids; long-chain saturated fatty acids are less prone to β-oxidation, and may therefore lead to increased lipotoxicity and inflammation [124, 125]. Hypothalamic inflammation has also been shown in human patients, and further positively correlated with serum inflammatory proteins such as IL-6 and C-reactive protein (CRP) [122, 123]. Inappropriate inflammation in the brain can disrupt numerous signaling pathways including the appetite control pathways, disturbing energy homeostasis. This disruption may perpetuate the development and progression of obesity and its sequelae. Furthermore, inflammatory-related hypothalamic abnormalities, such as microstructure and gliosis, are positively associated with obesity, and aberrations in brain volume and connectivity may be predictive of weight loss success [126–131]. To better understand obesity then, we must also consider the role of hypothalamic inflammation.

Inflammation is a key feature of the body's immune system responding to harmful stimuli, allowing injurious stimuli to be removed and initiating the healing process. Acute inflammation is generally protective, but in the case of obesity, the damaging stimuli cannot be so easily removed, leading to uncontrolled inflammation that becomes chronic and itself harmful. There are, of course, numerous pathways and interactions in inflammatory signaling pathways that have been well-described elsewhere [132]. We describe here only

select pathways as they relate to inflammatory genes with known genetic variants and connections to obesity.

The inflammatory response can be broadly summarized into four key steps: 1) stimuli recognition by cell surface pattern receptors, 2) signaling activation, 3) inflammatory marker release, and 4) recruitment of inflammatory cells. We will distinguish where in each of these steps the obesity-related genes discussed below are found.

Stimuli Recognition.

(Figure 2). Microbial structures (pathogen-associated molecular patterns, PAMPs), endogenous signals such as danger-associated molecular patterns (DAMPs), or cytokines trigger the inflammatory response by activating pattern-recognition receptors (PRRs). PRRs are expressed on immune and nonimmune cells alike, and one of the most highly conserved and best-studied families are the Toll-like receptors (TLRs). TLRs activate an intracellular signaling cascade that leads to nuclear translocation of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Increased adiposity contributes to increased TLR4 signaling, which is considered one of the main triggers for meta-inflammation [133].

Signaling Activation.

(Figure 2). MAPK. This family of serine/threonine protein kinases direct cellular responses to stimuli including the inflammatory cytokines TNF-α and IL-6. JNK is one of three mammalian MAPKs, and is activated by inflammatory stimuli (including ROS) and stress causing a signaling cascade through a MAPK kinase (MAPKK) and MAPKK kinase (MAPKKK). Activated JNK can phosphorylate the transcription factor activator protein (AP)-1 to result in regulation of the inflammatory response. JAK-STAT. The JAK-STAT pathway acts in inflammatory signaling as well as satiety signaling, responding to diverse signals including cytokines and leptin. Two receptor-associated JAKs are activated by a ligand and transphosphorylate, creating a docking site for two latent transcription factors, the cytoplasmic STATs. Once the STATs are phosphorylated, they dimerize and can translocate to the nucleus to regulate transcription of inflammatory genes, primarily cytokines. NF-κB. Following stimulation, PRRs activate IκB kinase (IKK), which regulates the NF-κB pathway by phosphorylating the inhibitory protein IκB. ROS have also been suggested to activate the NF-κB pathway through alternative IκB phosphorylation [134]. Phosphorylated IκB is degraded by the proteasome, subsequently releasing NF-κB for nuclear translocation. NF-κB can then activate gene transcription of pro-inflammatory cytokines.

Inflammatory Marker Release.

Inflammatory markers include inflammatory cytokines and chemokines, inflammatory proteins and enzymes, and ROS. Key pro-inflammatory cytokines include IL-1β, IL-6, and TNF-α. Perhaps the most notable inflammatory protein is CRP. These markers then go on to recruit inflammatory cells to the site of interest.

Inflammatory Cell Recruitment.

While the inflammatory response involves a highly coordinated network of several cell types, most immune cells associated with obesity-induced inflammation are macrophages, which are capable of phagocytosis, antigen presentation, and immune response modulation. Microglia are the brain's resident macrophages, with some participation by astrocytes in neuroprotection [135, 136].

Mechanistically, hypothalamic inflammation appears to be characterized by reactive gliosis, an increase in microglia infiltration and astrocyte proliferation, and has been found in rodent models, nonhuman primate models, and human models alike [122, 123]. Reactive gliosis observed in the hypothalamus may initially be protective in order to limit inflammation and neuron loss, and appearance of reactive gliosis corresponds with pro-inflammatory markers of the ArcN returning to basal levels [122]. As over-nutrition becomes chronic, the capacity of the supportive glial cells to control damage is overwhelmed and inflammation reoccurs [122]. Recent work has identified the mitochondrial uncoupling protein 2 (UCP2) as being a master regulator of microglial activation [137, 138]. A HFD induces UCP2-dependent microglial mitochondrial changes in dynamics and functions, resulting in ROS production and inflammatory activation [137, 138]. Separately, work has shown that activation of IKKβ/NF-κB signaling pathways in astrocytes of the hypothalamus are key in the development of hypothalamic inflammation, HFD-induced hyperphagia, and DIO susceptibility [139]. As hypothalamic inflammation and gliosis are evident in animals before the development of other metabolic symptoms, including weight gain, it has been suggested that hypothalamic inflammation is causative in the pathophysiology of obesity [123].

Research suggests that a HFD determines microglial presence and activity in the ArcN independent of body weight [122, 140, 141]. Enteric gavage in mice with long-chain saturated fatty acids increased hypothalamic inflammatory markers and accumulation of hypothalamic microglia in a way that isocaloric gavages with medium-chain saturated fats or unsaturated fats did not [142]. Importantly, hypothalamic microglia have been identified as sensors of dietary saturated fatty acids that then control the intensity of the resulting inflammation [142]. Microglial content determines the intensity of the inflammatory response, mediate neuronal stress, and regulate satiety-signaling neurons when saturated fatty acid content is high to maintain consistent daily food intake [142]. Better understanding the response of microglia under different diet conditions in promoting and regulating hypothalamic inflammation may further reveal pathways to target for obesity treatment.

Genetic Variations in Inflammatory-related Genes Impact Obesity

In addition to identifying genes that are enriched in the CNS, human GWAS have also found variants within inflammation genes, including *TLR4* and *MAPK3* [12]. A recent study also identified inflammatory genes such as *Src homology 2 adaptor protein 3* (*SH2B3*) and *diacylglycerol lipase beta* (*DAGLB*) within genetic loci that are associated with increased adiposity and lower cardiometabolic risk, further suggesting a role of inflammation genes in metabolically healthy obese individuals [143]. In addition, as previously mentioned, variants near the central regulator of inflammatory cell function *RIPK1* have been connected to obesity [32]. Although genetic variation of inflammation genes and how they contribute to

the obesity epidemic is not well understood, we discuss three genes in-depth below: *SOCS3, JNK,* and *UCP2.*

The JAK-STAT pathway plays a prominent role in inflammatory signaling as well as satiety signaling. Activation of the JAK-STAT-SOCS3 signaling pathway by leptin has been highlighted in obesity research [144–146]. Binding and activation of STAT3 mediates the effects of leptin on energy homeostasis and neuroendocrine function and activates the negative feedback regulator, suppressor of cytokine signaling 3 (SOCS3), to limit leptin receptor action and reduce downstream MC4R activation [146]. Increased *SOCS3* expression is associated with increased leptin resistance, and SOCS3 over-activation has been linked to the development of insulin resistance in the brain and in peripheral tissues [146–148]. There is some evidence that demonstrates genetic variation in or near the *SOCS3* gene is associated with obesity traits, where decreased *SOCS3* expression is associated with improved leptin sensitivity and limited diet-induced weight gain [148–152]. Other studies have identified tentative interactions between variants in *SOCS3, IKBKB,* and *NFKB1* as affecting BMI and waist circumference [153]. This is particularly interesting as other research has shown that over-nutrition inappropriately activates the pro-inflammatory master switch IKKβ/NF-κB in hypothalamic neurons and promotes expression of *SOCS3,* further perpetuating dysregulation in leptin and melanocortin signaling [154]. Both JAK-STAT-SOCS3 and IKKβ/NF-κB pathways have shown some relation to TLR4 signaling [155–158]. While current research on the genetic variants of these genes is limited, this offers a promising avenue of research for hypothalamic inflammation under the context of obesity.

In addition to *SOCS3,* one candidate gene approach among obese patients found a common SNP in the *JNK* gene (rs1062225) that was associated with hypothalamic inflammation [123]. *JNK* codes for a MAPK that responds to inflammatory cytokines and may also regulate activation of the PI3K/Akt signaling pathway [159, 160]. Work has shown that constitutive JNK activation in NPY/AgRP neurons leads to adiposity via leptin resistance [161]. This may be through connections with SOCS3, as there is evidence that the downstream target of JNK, AP-1, has a response element in the *SOCS3* promoter region and can enhance *SOCS3* expression [162, 163]. The potential importance of the *JNK* gene for the inflammatory response in the hypothalamus is validated by the fact that inhibition of the JNK protein restored hypothalamic insulin signaling in HFD-fed rats and improved metabolic parameters [121]. Further evidence validating JNK signaling as being important for hypothalamic health is a recent study that confirmed *dual specificity phosphatase 8* (*DUSP8*), which governs JNK signaling, as a novel hypothalamic factor for type 2 diabetes (T2D) [164]. Genetic variants along the JNK signaling pathway have not been as well studied as previously mentioned genes under an obesity context, but these findings do demonstrate the importance of this pathway for hypothalamic and global metabolic health.

UCP2 is a mitochondrial protein known to be involved in energy homeostasis, that protects against ROS, promotes fatty acid oxidation, and is a master regulator of microglial activation [137, 138, 165–167]. Variants in the *UCP2* gene and promoter region have been connected to obesity, serum lipids, insulin resistance, and metabolic efficiency [168–170]. UCP2 is connected to ROS regulation, where decreased expression of *UCP2* has been related

to increased ROS accumulation and oxidative stress [171, 172]. UCP2 is also required for ghrelin to act on NPY/AgRP neurons, driven partially by the role of UCP2 in ROS scavenging [173]. But researchers have also shown that HFD-induced microglial activation in the hypothalamus is associated with increased expression of *UCP2* in the microglia, where ablating expression of *UCP2* in the brain microglia prevented DIO and improved metabolic parameters in male mice [137]. Separately, increased *UCP2* expression has been correlated with decreased risk for chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease, but increased risk for sepsis and inflammatory bowel disease [174–176]. Whether these inconsistencies are due to genotype differences, tissue-specific actions, or pathway-specific roles remains to be determined. Taken together, these data show that the relationship between *UCP2* and obesity must not only consider its haplotype, but also the tissue of study.

Connections between satiety signaling and inflammatory pathways

Very little work has been done to connect genetic variants in satiety signaling pathways to hypothalamic inflammation, and/or variants in inflammatory pathways to satiety signaling. Given the contributions of dysregulation in both pathways to the development and maintenance of obesity, this presents a large gap in knowledge. Described below are the known links between *FTO, MC4R,* and *ADCY3* and inflammation, as well as the connections between *SOCS3, JNK,* and *UCP2* and satiety (Figure 3).

Genes known to participate in satiety signaling have limited available evidence of also being connected to inflammation. The exact relationship between *FTO* and inflammation remains unclear. Early studies found that presence of the obesity-risk rs9939609 variant was associated with increased plasma CRP levels, independent of adiposity, as well as a predisposition in T2D patients towards inflammatory obesity [177, 178]. Another study found pleiotropic associations for a different *FTO* variant, rs1558902, with obesity measures and CRP [30]. However, subsequent studies investigating the relationship between *FTO* and inflammatory markers do not show significant associations [179, 180]. While at the time of this article there is no publicly available data on how *FTO* expression and activity are related to or affected by hypothalamic inflammation, research has found a connection between *FTO* and NF-κB activation in pancreatic β-cells, which may indicate a connection in the hypothalamus that has not yet been elucidated [181]. MC4R activation has been linked to anti-inflammatory and neuroprotective effects *in vitro*, and activating MC4R ameliorated the reactive phenotype in *in vitro* astrocytes [182–185]. Given the connection between astrocytes and the development of hypothalamic inflammation under HFD conditions, this also opens up the possibility that dysfunctional *MC4R* mutations may predispose or protect against hypothalamic inflammation as well as obesity. While much focus has naturally been on the role of *ADCY3* in the hypothalamus, there is some evidence indicating importance to its signaling in peripheral tissues as well [113]. Of particular note, haploinsufficiency of *Adcy3* in mice negatively altered fatty acid oxidation genes in white adipose tissue while separate work suggests that enhancing fatty acid oxidation in the hypothalamus reduced local inflammatory responses [113, 186]. Further work is needed to identify if changes in expression of *ADCY3* in the hypothalamus alter fatty acid oxidation, but this relationship may provide a link between *ADCY3* expression, hypothalamic inflammation,

and adiposity. Taken together, this indicates a need to better understand how genetic variants in known obesity-causing genes may also promote hypothalamic inflammation. The relationship between hypothalamic inflammation and obesity development cannot be ignored, and elucidating connections here may reveal new targets in known pathways.

There are also links between hypothalamic inflammation and satiety signaling that still need to be explored (Figure 3). Current evidence shows that hypothalamic inflammation is responsive to a HFD, and leads to obesity-associated problems [187]. Hypothalamic inflammation has been reported to disrupt hypothalamic hormonal (leptin, insulin, etc) signaling, leading to dysfunction of the central energy balance [154]. As has been reviewed elsewhere, hypothalamic inflammation has been shown to disrupt the hypothalamic endocrine systems to promote obesity, and may also activate the endocannabinoid system to promote overeating [29]. Expression changes in *SOCS3*, regulator of the JAK-STAT pathway, are well known to be instrumental to the development of leptin and insulin resistance and dysregulation of satiety signaling [29, 148, 188–191]. HFD feeding has also been connected to hypothalamic JNK activation, and a JNK-inhibitory peptide was once considered as a possible diabetes therapeutic [29, 161, 192–194]. Constitutive activation of JNK in NPY/AgRP neurons has been shown to induce hyperphagia and obesity in mice, and other studies have demonstrated a role of the JNK isoforms in feeding [161, 194]. Research has also shown that UCP2 modulates POMC and NPY/AgRP neuronal function, inhibiting glucose-induced activation in the former and promoting firing of the latter through its ROS regulators [195]. This work shows that hypothalamic inflammation affects satiety signaling and may explain its potentially causal role in DIO. It is therefore important to also consider genetic variants in these inflammatory-related genes in the context of obesity, as they may also explain a portion of a patient's predisposition to gaining weight. Better understanding the relationship between expression of inflammatory-related genes and dysfunction in these signaling pathways will illuminate our understanding of the connections between these two pathways as well as revealing potential drug targets.

Other Influences on Hypothalamic Inflammation

It is important to note that the gut-brain axis communicates not only satiety signals, but may also connect inflammation between the two tissues. Current research suggests that gut inflammation is another early consequence of a HFD and may have a causative role in obesity [28, 196]. The microbiome may be essential for mediating the relationship between nutritional components of a HFD and neuronal inflammation, and these changes in the gut-brain axis might induce the appetite and satiety dysregulation that promote the development of obesity [123]. As previously discussed, saturated fats have been well-connected to hypothalamic obesity [124, 125, 142]. Fatty acids also impact the gut microbiome. Human studies and other work have shown that a HFD alters gut microbiota, including reducing microbial richness and diminishing gut barrier integrity, both of which are ultimately associated with increased adiposity and worsened metabolic health [24, 28]. Studies in mice have investigated how different levels of saturation in fats affect the gut microbiome, and determined that diets richer in saturated fats have worsened outcomes [197, 198]. A study in humans also revealed that saturated fat content has a greater effect on microbe diversity compared to protein source [199]. Early changes in the gut microbiota influence

inflammation in the intestines, including an increased endotoxin production, and alter the permeability of the intestinal barrier that leads to endotoxin release and TLR4 activation elsewhere in the body [28, 133, 200]. Recent work has also shown that a switch to a fat-rich diet leads to a rapid and profound change in gut microbiota diversity and oxidative stress in the hypothalamus [201]. This body of work strongly suggests a connection between gut microbiota and the hypothalamus in the adaptation to HFD and regulating energy homeostasis, with the effect strongly driven by the content of saturated fatty acids in the diet. While not the focus of this review, fully understanding the connections between the gut and the brain is a key area of obesity research important for understanding and treating the disease.

Another key influence on hypothalamic inflammation is the blood-brain barrier (BBB), which controls the passage of most blood components into the central nervous system [202]. Damage to this barrier can lead to leakage of unwanted substances into the brain that can propagate inflammation. Studies have demonstrated that a HFD typically leads to increased permeability of the BBB [203–205]. It has been shown that this effect differed between DIO and diet-resistant rats, indicating a potential impact of genetic variation [205]. The gut microbiome has been shown to affect BBB permeability [206, 207], and DIO-associated changes in the gut may then affect the BBB to propagate hypothalamic inflammation. Further connecting back to nutrients in the diet, a recent study showed that omega-3 polyunsaturated fatty acids were positively associated with BBB integrity and better brain health [208]. When investigating the role of hypothalamic inflammation on obesity, it is important to consider the many different factors that can determine the onset and severity of inflammation, whether they be genetic, environmental, or a mixture of both.

Conclusion

Concern for obesity and its prevalence is only rising: current trends suggest that an average of 50% of adults in the United States will be considered obese within ten years [1, 2]. It is well-known that much of what drives the obesity epidemic is the increase of calorie-rich foods high in saturated fats coupled with reduced physical activity [209, 210]. But obesity is a self-propagating cycle. Dietary fat causes an inflammatory response in the brain very quickly and in turn disrupts normal homeostatic processes [121, 211]. But not everyone responds to a HFD or obesity in the same way. Genetic variants in genes along both the satiety signaling and the inflammatory response pathways may explain individual susceptibility to gaining weight and/or suffering metabolic consequences. As new variants in brain genes are identified, it will be important to assess how these genes contribute to obesity. While hypothalamic inflammation is well-known to contribute to downstream events in the progression of obesity, many currently identified obesity-related genes that are involved in satiety signaling (*FTO, IRX3, MC4R, ADCY3*, etc) have not been evaluated for their role in the development and maintenance of inflammation, or how this inflammation affects their activity in turn. Further, genetic research on inflammatory-related genes (*SOCS3, JNK, UCP2*, etc) is limited. Connections between these pathways present the possibility of variants in multiple genes acting in tandem to predispose to or protect against obesity. Merging our knowledge of these fields will improve our understanding on

how obesity first develops under a HFD and how dysregulation of inflammatory pathways helps persist and worsen the disease.

In doing so, we can identify new potential targets for treating obesity. There are several main benefits to doing so. The first is that current treatments for obesity, which typically target satiety, are limited in number and efficacy and so developing new strategies is of high importance [212–214]. It has been shown in mice that reducing expression of inflammatory-related genes, including *TLR4* and *TNF-α,* can protect against DIO and associated comorbidities, opening up new pathways to target [215–218]. Better understanding the connection between satiety and inflammation will ensure that future treatment options are even more effective than those currently available. The second benefit is that studies have demonstrated that genetic variation can impact drug response to lipid lowering statins or sulfonylureas for treating T2D—this is likely to also be true for anti-obesity medication [19, 20]. Incorporating a patient's genetic variation into healthcare decisions will improve treatment and patient outcome. Genetic studies will also elucidate novel biological pathways and connections to help us understand underlying molecular mechanisms, enable polygenic risk scores to identify individuals most at risk, and inform pharmacogenetic analysis to determine which specific medications an individual will respond to best.

Each person is unique, with their bodies responding to a HFD and inflammatory signaling in different ways; we must strive to develop treatments that can ensure the best possible weight loss success for every individual. Using genetic information to advise patients is still a developing field [219, 220]. Although work is still needed to optimize the use of genetic information, increasing our understanding of the genetic variants and the biological pathways of obesity will help inform physicians of how best to use a patient's genetic information to help them reach their metabolic health and weight loss goals. Because obesity is so extraordinarily complex, the more we understand the connections between pathways and the roles individual variants may play, the better we can treat each individual patient.

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Highlights

- GWAS has identified numerous obesity-related genes as being enriched in the brain
- Genetic variants in genes along the satiety signaling pathway are known to contribute to obesity
- Recent studies have also identified genetic variants in inflammatory genes that contribute to obesity
- Connections between variants in satiety signaling and inflammation should be explored
- Personalized nutrition and medicine approaches improve obesity patient outcomes

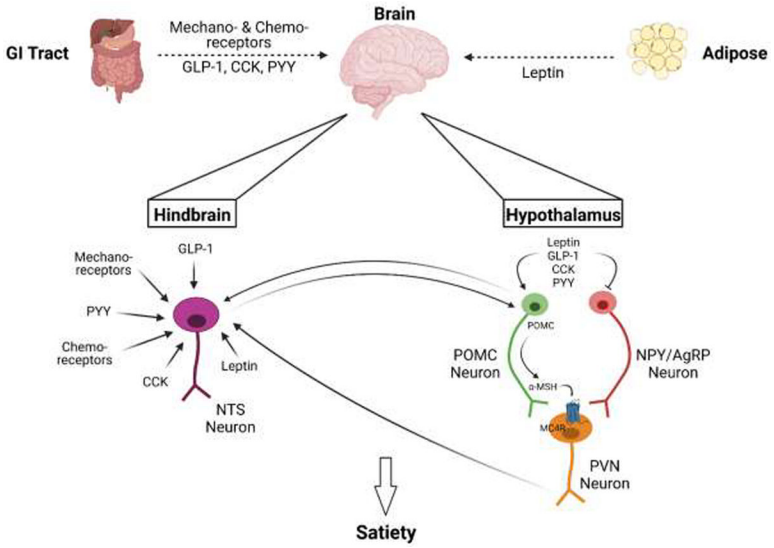

Figure 1. Broad Overview of Satiety Signaling.

The brain incorporates signals from multiple organs, primarily the gut and adipose, to determine appetite (dashed arrow). The gut communicates fullness via mechanoreceptors, chemoreceptors, and hormones including glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and peptide YY (PYY). The adipokine leptin is also secreted from white adipose tissue to instigate anorexigenic signals. These signals are integrated in the hypothalamus and the hindbrain. In the hindbrain, neurons of the nucleus of the solitary tract (NTS) receive these signals and can then communicate with neurons in the hypothalamus (solid arrows). In the hypothalamus, there are primarily two neuronal populations: anorexigenic pro-opiomelanocortin (POMC) neurons and orexigenic neuropeptide Y/Agouti-related peptide (NPY/AgRP) neurons. Anorexigenic peptides inhibit NPY/AgRP neurons and stimulate POMC neurons, which then synthesize POMC to be subsequently cleaved to α-melanocyte-stimulating hormone (α-MSH), which then primarily binds to melanocortin-4 receptor (MC4R) of the paraventricular nucleus (PVN) neurons, which then releases downstream signals, including to the NTS, to induce satiety and restrict eating. Created with BioRender.com.

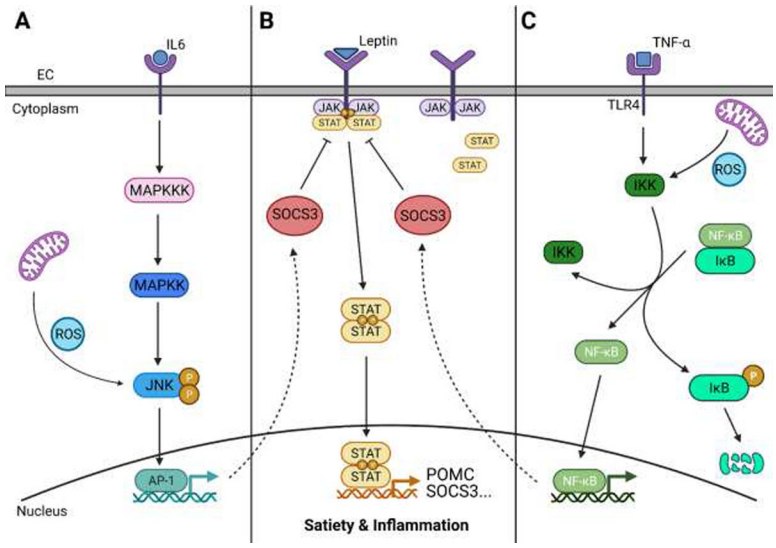

Figure 2. Broad Overview of Relevant Inflammatory Pathways: JNK, JAK-STAT, and NF-κB Signaling.

Pattern recognition receptors (PRRs), expressed on immune and non-immune cells, can be activated by many different signals, including cytokines. A) c-Jun N-terminal kinase 3 (JNK3) also known as mitogen-activated protein kinase (MAPK)-10, is activated when inflammatory cytokines begin a kinase signaling cascade via a MAPK kinase (MAPKK) and MAPKK kinase (MAPKKK) (solid line). JNK may also be activated by reactive oxygen species (ROS) produced by mitochondria. Activated JNK phosphorylates transcription factors, including activator protein-1 (AP-1), which then regulate the inflammatory response. AP-1 also has a response element in the promoter region of suppressor of cytokine signaling 3 (SOCS3) (dashed line). B) When a ligand, such as leptin, binds to the receptor, two receptor-associated Janus family of tyrosine kinases (JAK) proteins are brought in close contact and transphosphorylate, creating a docking site for the cytoplasmic JAK-signal transducer and activator of transcription (STAT) proteins. The JAK proteins then phosphorylate the STAT proteins, which dimerize and translocate to the nucleus to regulate transcription for satiety signaling pathways (e.g., pro-opiomelanocortin, POMC) and the inflammatory response. SOCS3 inhibits the JAK-STAT pathway and down-regulates leptin signaling. C) The PRR for NF-κB, typically Toll-like receptor 4 (TLR4), activates IκB kinase (IKK), a protein complex that phosphorylates the protein IκB, releasing it from the NF-κB complex. ROS may also activate IKK. NF-κB then translocates to the nucleus to activate gene transcription of many pro-inflammatory cytokines. Increased activation of NF-κB in POMC neurons has also been associated with increased expression of SOCS3 (dashed line). Created with BioRender.com.

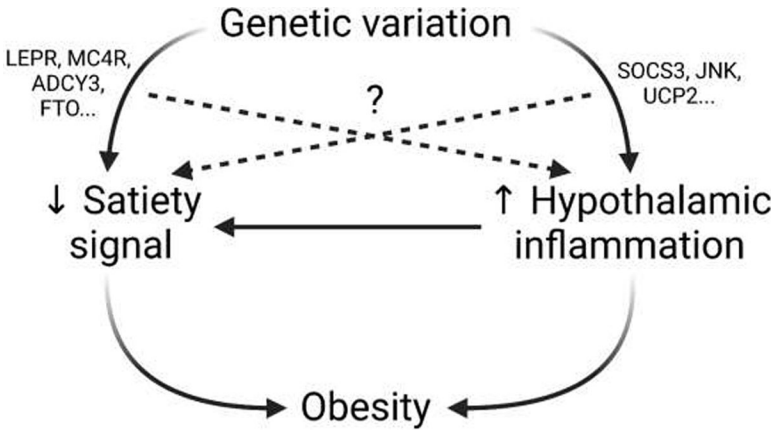

Figure 3. Graphical Abstract.

It is known that genetic variation can alter satiety signaling and hypothalamic inflammation, and that dysfunction in both of these pathways contributes to the development and progression of obesity (solid line). It is also known that hypothalamic inflammation dysregulates satiety signaling (solid line), further contributing to weight gain. What remains to be determined is the extent to which genetic variations in satiety-signaling genes (*LEPR, MC4R, ADCY3, FTO,* etc) contribute to development of inflammation, and how variations in inflammatory-related genes (*SOCS3, JNK, UCP2,* etc) might alter satiety signaling (dashed line). Better understanding the connections between these two pathways will reveal new drug targets for obesity treatment, and will allow physicians to gain a wider perspective on how genetic variants will affect metabolic health. Created with BioRender.com.