Neuron

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Review

The neurobiology of overeating

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https://doi.org/10.1016/j.neuron.2025.03.010

SUMMARY

Food intake serves to maintain energy homeostasis; however, overeating can result in obesity, which is associated with serious health complications. In this review, we explore the intricate relationship between overeating, obesity, and the underlying neurobiological mechanisms. We review the homeostatic and hedonic feeding systems, highlighting the role of the hypothalamus and reward systems in controlling food intake and energy balance. Dysregulation in both these systems leads to overeating, as seen in genetic syndromes and environmental models affecting appetite regulation when consuming highly palatable food. The concept of "food addiction" is examined, drawing parallels to drug addiction. We discuss the cellular substrate for addiction-related behavior and current pharmacological obesity treatments—in particular, GLP-1 receptor agonists—showcasing synaptic plasticity in the context of overeating and palatable food exposure. A comprehensive model integrating insights from addiction research is proposed to guide effective interventions for maladaptive feeding behaviors. Ultimately, unraveling the neurobiological basis of overeating holds promise for addressing the pressing public health issue of obesity.

INTRODUCTION

The prevalence of obesity is increasing globally.[1] In 2035, more than half of the adult population and 40% of children (ages 5–19 years) will be overweight (body mass index [BMI] > 25, World Obesity Atlas, 2024). Obesity, defined as a BMI > 30 kg/m^2 in adults (for children and adolescents: BMI at or above the 95th percentile for age and sex), affects both developing and developed countries, especially the United States, leading to severe health complications such as diabetes, cardiovascular diseases, and certain cancers.[2] The "obesity epidemics" increase morbidity and mortality, ultimately substantially decreasing the quality of life.

Overeating plays a more prominent role in the rise of obesity than decreased physical activity.[3] Sedentary lifestyles may contribute because of decreased energy spending, but while weight gain is undeniably driven by the difference between the energy spent and energy ingested, there is a consensus that enhancing physical activity may be insufficient to prevent overweight or restore normal weight in individuals with obesity. Physical activity, particularly when attempting to lose weight, invariably triggers an appetite that quickly compensates for and sometimes exceeds the energy spent.[4–7]

The increasing availability of calorie-dense foods has contributed to rising obesity rates in many populations. Foods that also combine high levels of fat and sugar, in particular, strongly promote overeating.[8] This nutrient combination rarely occurs in nature—with only a few exceptions, such as durian, coconut meat, and cashew nuts—but is characteristic of highly processed products[9] (e.g., milk chocolate or ice cream). Although milk also contains both fat and sugar, its relatively low caloric density explains why it is seldom consumed in excess. Humans can easily increase their daily caloric intake by ~500 kcal when exclusively offered an ultra-processed diet.[8] Palatable food with high caloric density may thus be the origin of an actual "food addiction"[10] (see Ziaudden and Fletcher[11]). The hypothesis posits that continued exposure to palatable food of high caloric density may override metabolic needs and cause a loss of control in regulating food intake in some individuals. While this scenario is appealing, its underlying neurobiological underpinnings have not been extensively tested.

This review examines the anatomy and physiology of neural systems governing feeding behavior and categorizes various forms of monogenic and polygenic obesity, which may map onto distinct neural circuits. We ask how these systems adapt when overeating and evaluate the literature on the food addiction hypothesis. The review will present evidence for synaptic plasticity in feeding circuits underlying overeating. We conclude by assessing the efficacy and limitations of current treatments and proposing a roadmap for future therapeutic approaches.

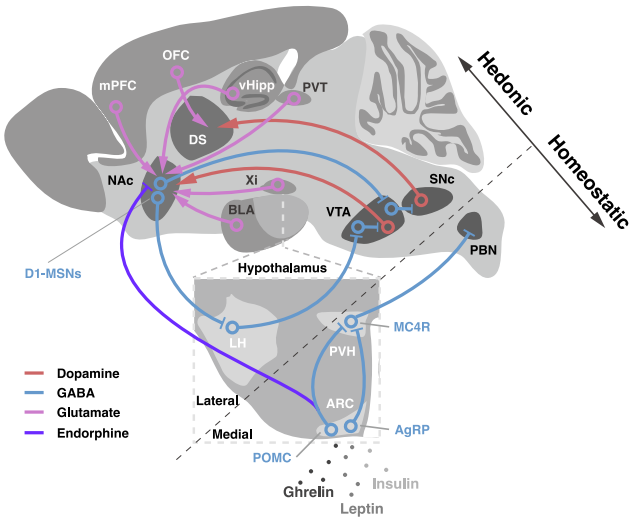

Figure 1. Schematics of homeostatic and hedonic circuits

The hedonic feeding system comprises the mesolimbic dopamine projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), where a population of D1R-expressing medium spiny neurons (D1R-MSNs) project to the lateral hypothalamus (LH), from where GABA neurons project on VTA GABA neurons, creating a disinhibitory circuit motive. Activation of this circuit by food can lead to positive reinforcement. The homeostatic system includes the arcuate (Arc) and paraventricular hypothalamus (PVH). The two major types of GABA neurons projecting from ARC to PVH are AgRP and POMC neurons, which are under the control of the hormones leptin, ghrelin, and insulin. PVH neurons express MC4 receptors and project to the parabrachial nucleus (PBN), which controls motor circuits of eating. The activity of AgRP neurons codes for hunger, which triggers food intake and may drive negative reinforcement. Some D1R-MSNs project back to the VTA preferentially connecting to GABA neurons, which relay the information to more dorsally projecting DA neurons. Within a few loops, this reaches the nigrostriatal projection. Orbitofrontal to dorsal projection neurons have been implicated in compulsive reward seeking. Several projections serve as the crosstalk between the homeostatic and the hedonic systems. These include ArgRP neurons projecting to the LH and POMC neurons projecting to the NAc, where they can release endorphins. BLA, basolateral amygdala; Xi, xiphoid body; PVT, paraventricular thalamus; mPFC, medial prefrontal cortex.

HOMEOSTATIC AND HEDONIC FEEDING SYSTEMS

It is common sense that the feeling of hunger signals a strong drive state that ultimately promotes eating. Eating relieves the negative affective state associated with hunger, fulfilling the criteria of negative reinforcement.[12,13] In most instances, individuals stop eating because they are sated, and the negative reinforcement drive dissolves. Highly palatable food, however, may override satiety and lead individuals to eat when they are no longer hungry. Consequently, by definition, the individual overeats (i.e., the caloric intake exceeds energy demands at a given moment), which may lead to weight gain if repeated. This may be an evolutionary advantage in animals, as it allows them to accumulate fat and replenish energy stored.[14] Conversely, the same system can stop food intake in a threat situation, thus exerting a sentinel function.[15,16] This interplay between hunger-driven eating and pleasure-driven overconsumption underscores the need to consider both homeostatic and hedonic systems (and their interplay) when examining the regulation of feeding behavior.

Feeding behavior is regulated by two closely intertwined systems: the homeostatic system, which ensures energy balance, and the hedonic system, which drives food consumption based on pleasure and reward.[17–19] Though often considered distinct, these systems overlap considerably in both function and anatomy, contributing to the complexity of overeating behaviors. In the former, the goal is to meet energy demands to keep body weight in a homeostatic range. Eating solely for enjoyment rather than energy needs may serve mental well-being but eventually can disrupt the body's energy balance and can contribute to weight gain. Ample work has identified the hypothalamus as a critical locus for controlling food intake, with some medial nuclei driving homeostatic control and lateral nuclei together with the mesolimbic system driving hedonic control (Figure 1).

HOMEOSTATIC FEEDING CIRCUITS

Within the medial hypothalamus, there are many interconnected nuclei, two of which have been directly implicated in homeostatic feeding: the N. arcuatus (arcuate nucleus; ARC) and the paraventricular nucleus (PVH).[20] Two key populations of γ-aminobutyric acid (GABA) neurons in the arcuate nucleus (ARC) mediate this process: agouti-related peptide (AgRP) neurons, which become active when hungry to promote feeding, and pro-opiomelanocortin (POMC) neurons, which inhibit feeding when energy stores are sufficient. Recent transcriptomics analysis with single-cell resolution has revealed an astonishing diversity among POMC and other hypothalamic cell types.[21] A molecular blueprint study showed ARC POMC neurons can be subdivided based on gene expression profiles into several unique cell types.[22] Integrating these findings with functional data highlights that the heterogeneity in gene expression may correspond to varied roles in energy balance, stress, and reward. The traditional view of POMC neurons as a homogeneous population must give way to a nuanced system where each subpopulation contributes uniquely to regulating energy homeostasis and beyond. More research will be needed to understand the functional diversity of POMC neurons fully.[23]

AgRP neurons are modulated by signals like low blood glucose and the hormone ghrelin, secreted by the stomach during fasting[13,24,25] but inhibited by leptin. A population of leptin receptor-expressing basonuclein 2 (BNC2)-positive GABA neurons make monosynaptic connections to AgRP neurons.[26] POMC neurons are activated by satiety signals such as leptin and insulin, released by adipose tissue and the pancreas, respectively, to reduce food intake.[27,28] These neurons project to many brain regions, including to the PVH,[29] where the balance between POMC and AgRP populations is tightly regulated according to the body's energy needs (Figure 2). Melanocortin 4 receptors (MC4R)-expressing neurons in the PVH thus integrate neuropeptide signals. AgRP axons release neuropeptide Y (NPY) to lower cyclic AMP (cAMP), while POMC axons release alpha-melanocyte-stimulating hormone (α-MSH) to increase cAMP in PVH MC4R neurons.[30] In a state-dependent manner, NPY and α-MSH peptides compete to control cAMP levels—NPY signaling is blunted by high α-MSH when satiated, while α-MSH signaling is blunted by high NPY when hungry. Energy

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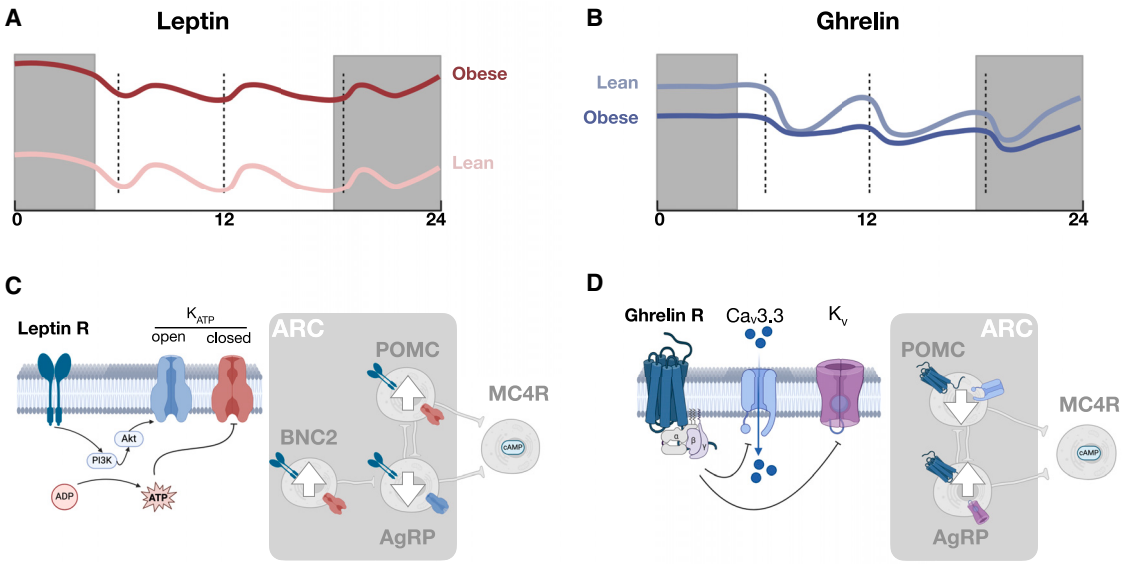

Figure 2. Divergent effects of leptin on neuronal activity

(A) Circulating leptin levels over 24 h. Levels are slightly higher during the night and increase after each meal. In individuals with obesity, the curves shift to higher levels overall.[33]

(B) Ghrelin decreases after each meal and is about 30% lower in individuals with obesity.[34,35]

(C) Leptin receptors are cytokine receptors that activate, among other signaling pathways, PI3K, which has two distinct effects. First, it can activate Akt, which binds to KATP channels to allow for K+ to flux out of the cell, leading to hyperpolarization.[36] Alternatively, it drives the synthesis of ATP, inhibiting KATP channels such that cells depolarize. BNC2 neurons and POMC neurons increase their firing in response to leptin (blue channels), whereas AgRP neurons are shut down (red channels).[26] The reciprocal GABA inhibition between POMC and AgRP neurons enhances the overall effect. In the downstream PVH α-MSH and NPY compete to regulate cAMP in MC4R neurons. Note that additional signaling pathways are not shown for simplicity.

(D) Ghrelin receptors inhibit Cav3.3 channels[37] and Kv7/KCNQ channels.[38] The former can explain decreased activity in POMC neurons, the later depolarization, and stronger firing of AgRP cells.

deficit signals activate AgRP neurons, promote feeding, and reduce energy expenditure. There are diverging interpretations, whether this is an innate or learned response. Food cues directly inhibit AgRP neurons and activate POMC neurons to adjust feeding behaviors in real time,[31] where, by contrast, another study[32] interprets the reduction in AgRP neuron activity as a learned reduction of negative-valence signals, framing it as relieving hunger-driven discomfort rather than an anticipatory switch to satiety. For the first, the rapid neuronal response to food is an innate and direct modulation that does not require prior learning. The latter suggests that AgRP neuron inhibition through external cues may involve Pavlovian learning, as animals can learn to associate sensory cues with hunger relief.

POMC neurons, on the other hand, suppress feeding and increase energy expenditure, activated by energy-sufficiency signals. Sensory food perception can affect hepatic metabolism via melanocortin release from POMC neurons via a sympathetic nerve signal.[39] Moreover, POMC and AgRP neurons are reciprocally connected. Reduction of POMC neuron activity may disinhibit AgRP neurons, leading to excessive hunger. Glucagon-like peptide-1 (GLP-1), secreted by intestinal L cells, reduces food intake by acting on GLP-1 receptors on AgRP and POMC neurons[40] and likely other brain regions like the nucleus of the solitary tract[41] and lateral septum (LS).[42,43]

Simultaneous activation of AgRP neurons and inhibition of POMC neurons resulted in a synergistic increase in food intake compared with when only one neuronal type was modulated. These conclusions based on chemogenetic manipulations[44] are confirmed by monitoring the neural activity of both cell types in feeding cycles across multiple time scales.[45]

HEDONIC FEEDING CIRCUITS

Homeostatic needs do not solely dictate the drive to eat. The hedonic feeding system is responsible for the consumption of food based on its rewarding properties, irrespective of energy balance. The lateral hypothalamic area (LHA) and its regulation of the mesolimbic dopamine system, particularly the ventral tegmental area (VTA) and nucleus accumbens (NAc), are central to this process.[46–48] GABA neurons in the LHA project to the VTA, where they disinhibit dopamine neurons,[49,50] driving food-seeking behavior and consumption of highly palatable foods, even when the body does not require energy.[13,51] VTA dopamine neurons integrate oral, gastrointestinal, and post-absorptive signals during ingestion,[52] which may provide a substrate for associative learning mechanisms between food or water sensory qualities and restoring fluid or nutrients. Consistent with this, dopamine release in the NAc, triggered by the sight, smell, or taste of desirable foods, further reinforces this behavior, promoting eating beyond physiological needs.[53,54] Direct intragastric delivery of a combined fat-sugar solution increases nigrostriatal dopamine release and overeating more strongly than fat or sugar alone.[6] Prolonged high-fat diet exposure reduces dopamine reuptake in rats.[55] In humans, D2 dopamine receptor binding is reduced in

subjects with obesity relative to controls,[56] and viral knockdown of striatal D2 receptors results in compulsive-like food seeking in rats,[57] further suggesting causal links between the brain dopamine systems and maladaptive feeding.

Additionally, a population of D1R-expressing medium spiny neurons (MSNs) of the NAc project to the LHA,[58] where they preferentially synapse onto GABA neurons.[47] At the onset of feeding, these cells fall silent, which enables feeding, and resume their activity upon termination of the feeding bout. Closed-loop optogenetic experiments of this circuit have demonstrated powerful control over feeding with rapid onset upon stimulation. A mouse will stop feeding instantaneously when the NAc-LHA projection is stimulated, even if hungry, and will readily initiate feeding when the projection is inhibited, even when sated. This demonstrated that the NAc-LHA projection can maintain food intake exceeding metabolic needs.

Glutamatergic neurons of the LHA also play a critical role in suppressing food intake via their projections to the lateral habenula and VTA. Ablation of LHA glutamatergic neurons increases food intake and body mass,[48] and the activity of these neurons becomes blunted over time in diet-induced obesity models.[59] The activity of some LHA neurons is also modulated by leptin or ghrelin administration,[60] although it is unclear if this is through a circuit or if there are direct effects within the LHA. Critically, optogenetic stimulation of LHA GABAergic and glutamatergic neurons bidirectionally produces reward seeking or aversive escape behaviors, further highlighting these systems' critical role in feeding and reward processing. High-fat diet exposure alters cell type-specific gene expression within the LHA, impacting both GABAergic and glutamatergic neurons.[59] These diet-induced changes in gene expression and neural activity within LHA neurons underscore the intricate crosstalk between homeostatic and hedonic systems, which is crucial for understanding the regulation of feeding behaviors. A recent normative framework postulates that need-encoding and motivation-encoding neurons are segregated within the medial and lateral hypothalamus, respectively, with AgRP neurons in the medial hypothalamus encoding need and leptin receptor-expressing neurons in the LHA encoding motivation.[61] The study applied a normative framework, experimentally validated by cell type-specific optogenetic manipulations to characterize the neural substrates of need and motivation within hypothalamic neuronal populations and settled on AgRP and lateral hypothalamus leptin receptor (LHLepR) neurons. Their model provides a temporal dynamic understanding of the basic properties of food intake. These insights emphasize that the functional and anatomical interplay between the medial and lateral hypothalamus may serve as a nexus for integrating homeostatic signals of need with hedonic drivers of motivation, facilitating adaptive feeding behaviors in response to dynamic internal and external cues.

CROSSTALK BETWEEN HOMEOSTATIC AND HEDONIC SYSTEMS

Although often studied as separate entities, the homeostatic and hedonic feeding systems work together, with substantial crosstalk that modulates feeding behavior. Emerging evidence shows that the boundaries between these systems are flexible, and both systems are likely engaged during all feeding conditions. For instance, while food deprivation can activate homeostatic circuits, the rewarding properties of food are enhanced when hungry and can further drive consumption, even after energy needs are met. Signals from the hypothalamus can influence the mesolimbic reward pathway, and likely vice versa, creating a complex interaction between metabolic and reward circuits.[32,52,60] For example, while acting on AgRP neurons to stimulate hunger, ghrelin also enhances the activity of dopamine neurons in the VTA, linking hunger with reward.[62] Similarly, leptin has been shown to modulate dopamine signaling in the VTA, reducing food-seeking behavior in response to satiety.[63,64] These interactions suggest that overeating may arise from disruptions in the communication between these systems, where hedonic signals drive excessive consumption of palatable, high-calorie foods.

Another anatomical crosstalk between homeostatic and hedonic feeding systems relies on POMC neurons, which project from the arcuate (Arc) to the NAc.[65] When cleaved, POMC yields the predominant endogenous ligand of the μ opioid receptor (μOR), β-endorphin. Based on intra-cerebral injections of the opioid antagonist naloxone, NAc *μORs* have been implicated in the reinforcement effects of palatable food.[66] When μORs are blocked, rodents reduce sweet nutrient consumption but eat normal quantities of chow. The cells releasing endorphins and the relevant targets remain to be investigated. Several hypothetical circuit effects could contribute. Presynaptic μORs on glutamate terminals in the NAc can decrease the excitatory drive onto MSNs and alleviate the inhibition of downstream LHA neurons. μOR on D1R-MSNs could also affect reciprocal inhibition between D1R- and D2R MSNs. Moreover, μORs on cholinergic interneurons may silence these neurons, impacting dopamine release via presynaptic nicotinic receptors. Endorphins may, therefore, enhance the palatability of food by mediating interactions between homeostatic POMC-derived signals and hedonic μOR activity within the NAc (and likely other brain regions), linking energy balance mechanisms to reward-driven feeding behavior. This hypothesis, however, still needs empirical support.

The above examples illustrate shared pathways between the hypothalamus and reward circuits, yet much of the crosstalk remains unexplored. Future research should aim to disentangle the mechanisms through which homeostatic and hedonic signals integrate and how disruptions in this integration contribute to overeating and obesity. Understanding this dynamic interplay will be critical for developing interventions that can restore balance between these systems, potentially offering new strategies to combat overeating and obesity.

OVEREATING CAN RESULT FROM A DYSREGULATED HOMEOSTATIC FEEDING SYSTEM

Hypothalamic function is affected by several genetic syndromes associated with overeating (Figure 3; Box 1). Leptin deficiency is a rare genetic disorder affecting less than one in 1 million individuals.[67] Affected infants and toddlers are constantly hungry and eat up to 6000 kcal daily. Overeating can be treated by administering recombinant leptin, reducing hunger and food intake, but it

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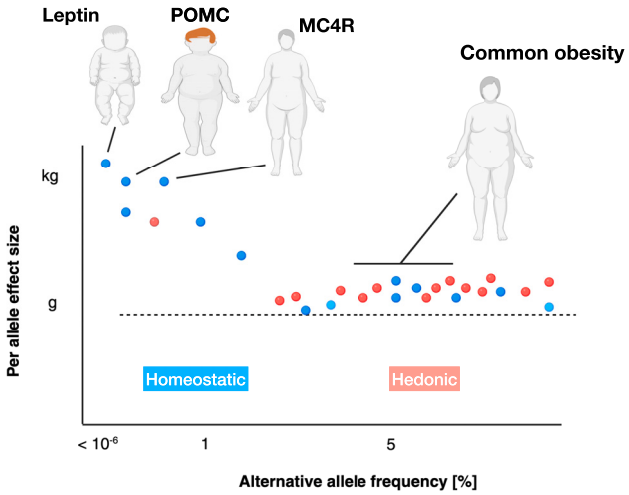

Figure 3. Monogenic *vs.* polygenic obesity: Schematic representation of the effect size as a function of the alternate allele frequency

Inspired by Akbari et al.[70]

Monogenic obesity is rare, but each gene variation has a large effect size and typically leads to obesity during childhood. Examples are loss-of-function mutations for leptin, leptin receptors, MC4R, or POMC and manifest with associated symptoms and signs (e.g., red hair in POMC deficiency). Polygenic obesity arises from cumulative variations in many hundreds of genes, each of which only contributes very little. The individuals affected are typically adults, and associated symptoms are the consequence of obesity (e.g., type 2 diabetes). Monogenic forms preferentially touch the function of the homeostatic system, while polygenic forms are caused by genes affecting the function of the hedonic and homeostatic systems. References in Box 1.

needs to be administered for life.[68] Leptin resistance, a slightly more frequent condition, refers to insufficient leptin receptor function, leading to overeating, albeit to a lesser degree.[69] Among the many physiological effects of leptin receptor activation, the inhibition of high-threshold channels like L-type voltage-gated calcium channels (VGCCs) and the activation of ATP-gated potassium (KATP) channels work together to suppress cellular activity during eating rapidly. KATP activation may result from the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) signaling pathway driven by leptin. In leptin-resistant individuals, this mechanism may be attenuated. Leptin deficiency may also lead to overeating via the altered control of BNC2 neurons onto AgRP neurons.[26] Indeed, when the leptin receptor is deleted in these neurons, mice overeat and become obese. This implies that in contrast to the effect on AgRP neurons, leptin receptors on BNC2 neurons normally would activate these cells.

Analogous conditions exist in the POMC system, where deficiency also leads to overeating—the absence of α-MSH reduces the occupancy of MC4R on downstream neurons in the PVH.[77] Altered melanocortin signaling because of MC4R mutations is another cause of monogenic overeating.[90] GLP1, secreted by intestinal L cells, reduces food intake by acting on GLP-1 receptors on AgRP and POMC neurons[40] and likely other brain regions like the nucleus of the solitary tract[41] and LS.[42,43]

In line with the homeostatic-hedonic crosstalk described above, diminished POMC neuron activity could thus disinhibit dopamine neurons (because they release less GABA) in the mesolimbic pathway, enhancing the reinforcing effects of food. While complex, these forms of obesity share hunger as a predominant symptom, can often be efficiently treated by substituting the missing ligand, and relapse when treatment is stopped.

OVEREATING CAN RESULT FROM A DYSREGULATED HEDONIC FEEDING SYSTEM

Another cause of overeating is the consumption of highly palatable food without hunger. This is often called the "dessert effect"[91] because desserts are, by design, highly palatable, with a combination of sugar, fat, and salt that makes them extremely enjoyable. This palatability makes it difficult to resist eating them even when full. Hedonic eating is driven by the pleasure derived from food taste and is often linked to cravings and emotional

Box 1. One gene—many genes

In *monogenic forms of obesity*, a single gene strongly affects BMI. Genetic screening of large cohorts has identified a dozen genes that, when mutated, can drive obesity,[71] affecting primarily homeostatic feeding circuits. Examples include the genes for leptin (*LEP*) and the leptin receptor (*LEPR*), *POMC*, and *MC4R*. *MC4R* mutations are the most common forms of the overall exceedingly rare monogenic form of obesity. Loss-of-function mutations in *MC4R* manifest in severe childhood-onset obesity,[72–74] with a BMI effect size of 4.8 kg/m^2 corresponding to an average body weight increase of almost 18 kg.[75] By contrast, gain-of-function mutations have been linked to low BMI.[76] Deficiency in the POMC system also leads to overeating—the absence of α-MSH reduces the occupancy of MC4R on downstream neurons in the PVH.[77] Melanocortin binding to the receptor activates PVH neurons and induces satiety. MC4Rs expressed in other brain regions affect pain sensation, sexual function, anhedonia, and blood pressure regulation,[78–81] explaining the syndromic nature of MC4R mutations. Rare syndromic obesity can also arise from chromosomal deletion, which affects several genes. For example, Prader-Willi syndrome is caused by a partial deletion of chromosome 15 or abnormal DNA methylation, manifesting in weak muscle tone, hypogonadism, and hyperphagia.[82] *Common obesity is polygenic*, resulting from hundreds of polymorphisms that each have only a small effect.[70,83,84] A recent genome-wide association study (GWAS) with 800,000 individuals revealed many loci with per-allele effects lower than 0.04 kg/m^2, corresponding to less than 120 g for a person of average height.[85] To date, more than 1,500 genes have been implicated, many of which may affect the function of the mesolimbic reward system or upstream systems that can modulate addiction circuits, such as stress and anxiety systems.[86,87] Gene/environment studies confirmed increased obesity risk of previously identified loci such as fat mass and obesity-associated protein (FTO) but also showed that physical activity and a healthy diet can attenuate the effect of the FTO locus by 30% to 40%.[88,89]

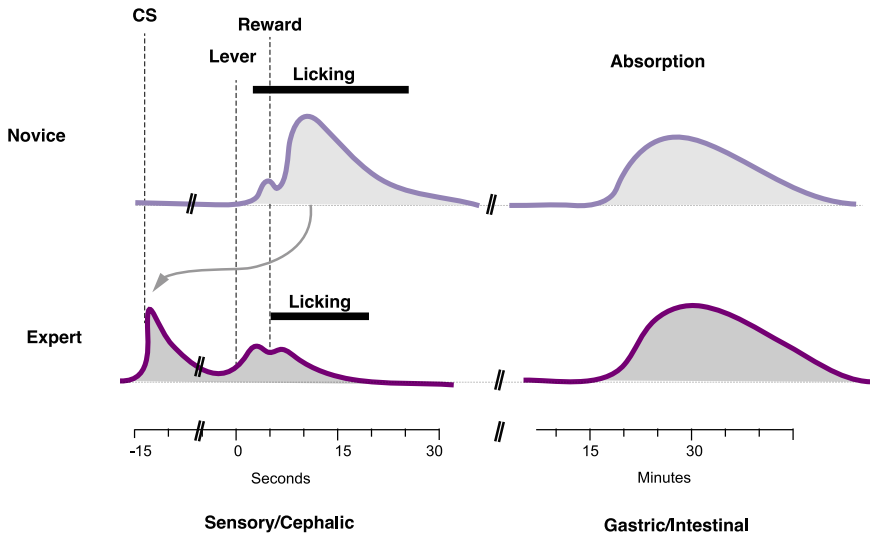

Figure 4. Dopamine transients during feeding

In animals eating a specific type of palatable food for the first time (novice), dopamine increases when innate proximal food cues arise, such as an odor, and is maximal when the animal starts licking (black bar). This sensory and cephalic phase lasts several tens of seconds. The gastric and intestinal phases of accumbal dopamine are observed tens of minutes later when the food is absorbed. In expert animals, the maximal dopamine transient is now shifted to the conditioned stimulus, and only a little increase is seen when the animal licks. The gastric and intestinal phases are unchanged. Based on data from Swift et al.,[6] Grove et al.,[52] Schultz et al.,[104] Roitman et al.,[105] and Tellez et al.[106]

eating.[92] Sweet and fat nutrients indirectly activate the reward system and promote several waves of dopamine release in the ventral and dorsal striatum.[6] Initially, dopamine release is primarily triggered during ingestion, likely driven by learned associations between sensory cues and the post-ingestive effects of food. This release is followed by a systemic response occurring several minutes later, driven by nutrient absorption in the stomach and intestines. The timing of this response depends on the food's composition, the nutrient absorption rate, and the activity of enteric nervous system neurons that respond to specific nutrients[52,93–95] (Figure 4). Over time, with repeated experiences, dopamine transients shift to predictive cues, such as the sight, smell, or taste associated with appealing foods.[96] The hypothesis is that cued dopamine signals, which may code for food value, can override fullness signals, leading to continued eating. Consistent with this, presenting conditioned stimuli previously associated with food elicits robust feeding in sated animals.[97] Two recent studies corroborate the critical role of the mesolimbic dopamine system in hedonic overeating. Disinhibiting dopamine neurons in the ventral tegmental area—by inhibiting the upstream glutamatergic neurons of the peri-locus ceruleus that project to VTA GABA neurons—prolongs ongoing food intake, a feeding-promoting mechanism that counteracts the appetite-suppressing effects of semaglutide.[98] Moreover, chronic consumption of a high-fat diet in mice diminishes the hedonic value of calorie-rich foods by disrupting neurotensin signaling in the projection from the lateral nucleus accumbens to the ventral tegmental area.[99] The other relevant circuits may involve the short-range hypothalamic regions (i.e., tuberal nucleus)[100] and more distant areas, such as the insula.[101–103]

Emotional factors modulate hedonic food intake. Stress, boredom, and other emotional states can lead people and animals to seek comfort in food. Desserts, often associated with comfort and indulgence, can be particularly appealing. Cultural norms and market forces can also play a role. In many cultures, dessert is a customary part of a meal, and people may eat it out of habit or tradition, regardless of hunger. The pervasive presence of these foods in the environment, including at schools, workplaces, and social gatherings, normalizes their consumption. Social norms and peer pressure can also encourage eating these foods.[107,108] In mice, transmission of food safety signals mediated by semiochemical transmission may lead to shifts in the food ingested.[109] This complex interplay between emotional, social, and environmental factors influencing hedonic food intake shares notable parallels with the mechanisms underlying addictive behaviors.

WHAT ADDICTION RESEARCH AND ANIMAL MODELS CAN TEACH US ABOUT OVEREATING AND OBESITY

Drug addiction is a global health challenge whereby vulnerable individuals seek and use drugs compulsively. Research over the last three decades has led to the emergence of a putative underlying circuit model. A current drug addiction model, therefore, posits that increases in mesolimbic dopamine are the initial step observed with all addictive drugs.[110,111] This is believed to be the mechanism underlying the strong reinforcing properties of drugs. The cellular correlate of drug adaptive behavior are forms of synaptic plasticity in the NAc, whereby dopamine modulates the induction of potentiation of glutamate afferents onto MSNs.[112,113] Some drugs also lead to negative reinforcement following extended use. This is particularly the case for opioids, which acutely inhibit a neural population in the central amygdala, which becomes hyperactive during withdrawal observed after chronic exposure.[114] Ultimately, compulsion is observed when more dorsal circuits are recruited.[115] Compulsive mice have a potentiated glutamate projection onto neurons of the dorsal striatum.[116] Although this addiction model is admittedly simplified, it highlights key elements that are also observed in common obesity. For example, positive and negative reinforcement can be loosely mapped onto the hedonic and homeostatic feeding systems. Moreover, evidence from human studies indicates that compulsive eating behavior is present in some individuals with obesity. In a population of patients referred for bariatric surgery, the prevalence of binge eating was 28.8%,[117] while in another study, the estimation was based on the observation of night eating disorder, which shares some commonalities with compulsion.[118] This is further supported by neuroimaging data

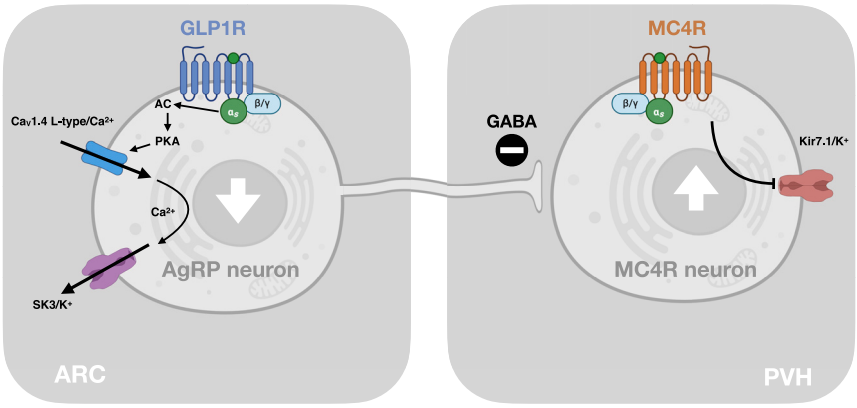

Figure 5. Mechanism of action of GLP-1 and MC4R agonists

AgRP neurons of the ARC express GLP1 receptors that couple to Gs proteins and activate the membranous adenylate cyclase (AC). PKA is activated downstream of cAMP, which increases calcium entry through Cav1.4 channels that eventually activate SK3 potassium channels and shut down neuronal activity.[139] As a result, these GABA neurons no longer inhibit MC4R neurons, and hunger decreases. Setmelanotide activates MC4R neurons via a G protein-independent direct interaction with Kir7.1 potassium channels.[140]

demonstrating considerable overlap in the neuronal substrates affected in both addiction and obesity.[119]

SYNAPTIC PLASTICITY AS A CELLULAR SUBSTRATE FOR OVEREATING

Our research and observations from others have shown that drug-evoked synaptic plasticity is the cellular substrate for addiction-related behavior. For example, strengthening excitatory synapses onto D1R-expressing MSNs is causally involved in locomotor sensitization. Similarly, palatable food can lead to enhanced synaptic drive of glutamate synapse onto dopamine neurons of the VTA[120] as well as alter excitatory synaptic transmission in the NAc,[121] but the significance of this finding for food intake remains elusive. When overeating is induced by acute food restriction (eating to catch up from an energy-depleted state), GABA transmission of D1R-MSNs onto LHA neurons may be depressed, opening the gate for enhanced food intake.[47,122] These findings are also corroborated by the direct stimulation of LHA GABA neurons, which trigger the motor program for eating, even without food. It is, therefore, plausible that changes in synaptic transmission underlie the overeating of palatable food. There is also evidence that plasticity of glutamate afferents onto AgRP neurons may contribute to the behavioral adaptations,[123] which has motivated the design of an aliphatic molecule activating GLP-1 receptors and, at the same time, inhibiting NMDA receptors (NMDARs).[124] The study demonstrates alterations in transcriptomic and proteomic responses within the hypothalamus that may be linked to glutamatergic signaling and synaptic plasticity. Still, more research is needed to see the emergence of a circuit model akin to the one described by drug addiction.

MECHANISMS OF OBESITY TREATMENTS

Current pharmacological approaches primarily use GLP-1 receptor (GLP-1R) agonists to reduce food intake and body weight. Understanding their effects requires integrating the bioavailability of endogenous GLP-1[125] and pharmacological GLP-1R agonists, the expression loci for GLP-1 receptors, and the ensuing neural activity changes. The endogenous peptide is secreted by intestinal L cells and, among many other effects, reduces food intake by acting on central GLP-1 receptors. However, its effect is limited by the short half-life. Endogenous GLP-1 may act locally through neural pathways rather than as a circulating hormone,[126,127] influencing appetite suppression and gastric motility via enteric and sympathetic circuits. In this model, intestinofugal neurons secreting GLP-1 in the ileum would mediate appetite reduction by signaling to the hypothalamus through spinal afferents. GLP-1 is also produced and released by nucleus of solitary track (NTS) neurons,[128] some of which directly project to the hypothalamus to regulate satiety.[129] Central GLP-1-mediated effects are diverse, as the receptor is expressed across many brain regions. GLP-1R agonists can have long half-lives (up to 1 week[130]) but have poor blood-brain barrier (BBB) permeability. Some of the most prominent effects may thus arise in the circumventricular organs, largely devoid of a BBB, and select regions close to the ventricles, such as the LS and the Arc.

Nevertheless, multiple brain regions, such as the substantia nigra, VTA, amygdala, NAc, hippocampus, several regions of the hypothalamus (paraventricular nucleus of the hypothalamus [PVH], arcuate nucleus [ARC]), and hindbrain express GLP-1 receptors.[21] Brain-wide c-Fos monitoring of an acute application of a GLP-1 receptor agonist reveals a complex network of activated neurons, many of which may be indirectly affected.[131]

GLP-1 thus impacts food intake via central and peripheral mechanisms,[132] such as actions in the NTS.[133,134] Interestingly, some NTS GLP-1R-expressing neurons have been reported to directly project to both the VTA and NAc directly.[135,136] Recent findings suggest at least two distinct NTS populations of GLP-1R-expressing neurons, which can drive satiety or aversion[137] separately. This further implicates GLP-1 signaling in controlling hedonic feeding and reward processing. Overall, satiety terminates the meal and reduces the initiation of subsequent feeding.[93,138] GLP-1 Rs are expressed in AgRP and POMC neurons,[40] coupled to G proteins, activate adenylyl cyclase, and increase intracellular calcium. Because of the presence of calcium-dependent K conductances of the SK3 type (small conductance calcium-activated potassium channel 3), the net effect is reduced activity[139] within minutes of feeding (Figure 5).

Semaglutide and tirzepatide are examples of synthetic GLP-1R agonists. They are administered by subcutaneous injections or orally and reduce weight on average by 15%–20%.[141]

Please cite this article in press as: Stuber et al., The neurobiology of overeating, Neuron (2025), https://doi.org/10.1016/j.neuron.2025.03.010

Box 2. Impact of food offer on overeating

Certain foods' availability may impact obesity prevalence and help with treatment. Well-documented examples concern changes in the food offered in developing countries,[152] where the combined global burden of underweight and obesity has increased in most countries between 1992 and 2022. Obesity prevalence now outpaces the decline in underweight, particularly in countries across the Caribbean, Polynesia, Micronesia, and the Middle East. By contrast, underweight remains prevalent in South Asia and parts of Africa. Notably, 89% of countries for women and 73% for men had higher obesity rates than underweight in 2022. The double burden of being underweight and obesity continues to shift toward obesity, especially in school-aged children and adolescents. The food offered may also help to reduce obesity—for example, reducing sugar-sweetened beverage consumption in overweight and obese adolescents who received noncaloric beverages for a year. The experimental group saw a significant reduction in BMI and weight after the first year. However, at the two-year follow-up, these effects were not sustained. The study suggests that cutting sugar-sweetened beverages can temporarily affect weight but highlights the challenges in maintaining long-term benefits.[153]

Semaglutide does not pass the BBB but can access the brainstem, septal nucleus, and hypothalamus via the circumventricular organs.[131] As a result, direct and indirect c-Fos activation is observed in many brain regions, including hindbrain areas directly targeted by semaglutide and secondary areas without direct GLP-1R expression, such as the lateral parabrachial nucleus. GLP-1R agonists directly affect homeostatic appetite control centers, reducing hunger and food intake. Interestingly, during chronic GLP-1R agonist therapy, the orbitofrontal cortex shows increased activity when a subject is presented with palatable food cues,[142] which may increase the consumption of palatable food, favoring hedonic eating. GLP-1R agonists slow gastric emptying. This delayed digestion moderates the postmeal rise in blood sugar and prolongs the feeling of fullness. GLP-1R agonists may also have side effects (e.g., loss of muscle mass, anhedonia, and depression).

Glucagon (GCG), produced by intestinal L cells, pancreatic alpha cells, and neurons located within the nucleus of the solitary tract,[143] increases glycemia, and GCG receptor agonists can be used in conjunction with GLP-1R agonists to enhance weight loss.[144] This effect is attributed to GCG's peripheral lipolytic effects, which enhance fat metabolism.[145] Such a dual approach leverages central and peripheral mechanisms of GLP-1's glucose regulation and appetite suppression alongside GCG's peripheral effect to increase energy expenditure through lipolysis.

Several additional active principles with central and peripheral targets are clinically approved and often used in combination with GLP-1R agonists. A bimodal molecule that combines NMDAR antagonism with GLP-1R agonism carried the hope of effecting synaptic plasticity only in the neurons relevant for overeating. Still, the circuit adaptations need to be further investigated to establish a causal link.[124] A glucose-dependent insulinotropic polypeptide (also called gastric inhibitory polypeptide, GIP) receptor agonists and GCG (coded by the GCG gene) receptor agonists act synergistically with semaglutide to enhance weight loss.[146] GIP is synthesized by intestinal K-cells and is secreted primarily in response to food intake, with a notable increase following meals rich in fats. GIP plays a role in regulating body weight and food consumption by activating the GIP receptor (GIPR) signaling pathway.[147] Interestingly, GIPR agonists and antagonists can induce weight loss, a seemingly paradoxical phenomenon. One possible explanation is that prolonged GIP exposure may lead to receptor desensitization, ultimately causing an antagonistic effect.[148] Most importantly, these treatments and GLP-1 monotherapy are typically transient, and patients often regain weight upon discontinuing the treatment. The mechanism of the ephemeral effect remains elusive but may be explained by the acute inhibitory effect on AgRP neurons. At the societal level, this transient efficacy underscores the need for long-term strategies that address biological

Box 3. Food addiction—a controversial concept

Striking parallels between drug addiction and overeating in obese individuals have been described.[154] Both conditions are associated with escalation of use, a feeling of loss of control, social and personal distress,[155] and adverse physiological consequences due to excessive intake. A key symptom of drug addiction is the compulsive nature of the consumption of the addictive substance. While compulsion is a term that has many definitions, it can operationally be understood as the seeking and intake of a substance (including foods), even when this is associated with major negative consequences.[115] Whether compulsive overeating occurs due to exposure to palatable food remains controversial,[3] but see Fletcher and Kenny.[156] The hypothesis posits that continued exposure to palatable food of high caloric density may override metabolic needs and cause a loss of control in some individuals. Two key assumptions—yet to be empirically tested—are (1) that certain foods have qualities analogous to addictive drugs and (2) that specific individuals carry an individual vulnerability to lose control, akin to persons with substance-use disorder. Neither of the two is fully established. The concept of food addiction has also been critiqued as the "medicalization of common eating behaviors."[157] *While the circuit model of addiction may be helpful to parse circuits of overeating, the concept of food addiction is not empirically supported by neurobiological investigations. While the similarities between these two pathological behaviors are striking, it should be cautioned to treat maladaptive feeding as an addiction.*

Box 4. Setmelanotide is a novel treatment for a rare form of monogenic obesity

MC4R is a member of the melanocortin receptor family (MCRs), a class-A G-protein-coupled receptor (GPCR) subgroup consisting of five subtypes (MCR1–5) that mediate multiple physiological effects in humans.[158] MC4R is an unusual GPCR as it has both an endogenous agonist and an endogenous antagonist.[159] α-MSH, derived from POMC, binds to MC4Rs and has anorexigenic effects. Conversely, AgRP antagonizes MC4Rs to stimulate appetite.[160] MC4R is abundant throughout the mammalian central nervous system (CNS) and is highly expressed within the paraventricular nucleus (PVH). The MC4R agonist setmelanotide treats genetic obesity caused by a single-gene mutation.[161] The MC4R couples to Gs proteins, but the receptor also inhibits Kir7.1 potassium channels directly.[140] As a result, upon setmelanotide treatment, PVH neurons depolarize, and food intake decreases.

mechanisms and behavioral and environmental factors contributing to weight regain.

FUTURE RESEARCH

The current mouse models offer a mechanistic investigation to delineate the relevant circuits of hedonic overeating and understand how this may override homeostatic control. The proposed circuit model for overeating is an essential step toward a comprehensive understanding of the disorder and may enable novel rational therapeutic approaches. Additional considerations of obesity that need to be integrated in the future are the effects of stress, social separation, and social incentives to eat. The microbiome and epigenetic mark in fat cells[149] is a topic of growing interest and has recently garnered significant attention.

The ingested food directly shapes the gut flora, and gut-brain signaling may lead to changes in feeding circuit function. The mechanistic insight will facilitate the interpretation of genetic studies of the highly polygenic common obesity by providing novel categories for gene ontology studies. The translatability of animal studies has been challenged because food addiction has been investigated as a heterogeneous concept, and causality in the development and maintenance of obesity was challenging to establish.[150,151] Finally, individual vulnerability to overeating remains a formidable challenge and will have to be considered when making recommendations for food regulations (Box 2).

CONCLUSIONS

The neurobiology of overeating involves complex interactions between homeostatic and hedonic feeding systems, genetic predispositions, and environmental factors. Understanding the neural circuits and synaptic mechanisms underlying these behaviors is essential for developing effective interventions for obesity and related health conditions. Future research should identify the synaptic circuit adaptations responsible for overeating and parse the relative contributions of homeostatic and hedonic feeding systems. Establishing a comprehensive model of overeating, integrating insights from addiction research, will provide a solid foundation for addressing this critical public health issue.

ACKNOWLEDGMENTS

G.D.S. was supported by R37DA03270 and R01DA038168. C.L. is an ERC advanced grant awardee and is supported by the Swiss National Science Foundation. We thank Julian Hintz, Anna Ramisch, and Eva Wang for critically reading the manuscript and helping with the figures. In Figures 2, 3, 4, and 5, we used templates from BioRender (agreement numbers: *NT282M0HYT*, *ED282M0MBH*, *GM282M0DK2*, *SP282M08UU*, and *EL282LZYUT*).

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

While preparing this work, the authors used large language models (ChatGPT-4o and o1) for spelling and grammar checks, as well as for literature searches. The author(s) reviewed and edited the content as needed and take full responsibility for the final publication.

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