



Maladaptive Eating Food Addiction, a Possible Mechanism of Genesis and Maintenance of Obesity and Diabetes

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Abstract

Introduction: The coexistence of obesity and type 2 diabetes mellitus (DMT2), clinically termed "diabetes," represents one of the most critical challenges to contemporary public health. The low success rates and frequent relapses associated with conventional treatments suggest the involvement of underlying maladaptive behavioral patterns that share clinical and neurobiological substrates with substance use disorders, operationalized as Food Addiction (FA).

Objective: To review and analyze the neurobiological, neuroendocrine, and behavioral mechanisms underlying food addiction and the phenomenon of "food noise," evaluating their direct implication in the genesis, maintenance, and treatment resistance of obesity and diabetes.

Development and Mechanisms: This review examines the critical transition from homeostatic hunger (regulated by the hypothalamus) to hedonic hunger, governed by the mesocorticolimbic dopaminergic pathway. Chronic consumption of hyperpalatable ultra-processed foods functions as a supraphysiologic stimulus that induces

massive dopamine release in the nucleus accumbens (NAc), driving an adaptive down-regulation of D2 receptors, hedonic tolerance, and a state of basal hypodopaminergia. This deficit weakens the top-down inhibitory control of the prefrontal cortex, impairing the capacity to modulate intense cravings. Additionally, functional neuroimaging studies confirm connectivity alterations within the reward and salience networks, displaying significant sex-dependent variations. Finally, we integrate the modulating role of peripheral signals (ghrelin, leptin, insulin, and incretins), the impact of gut microbiota via bacteriophages on neurotransmitter metabolism, and the concept of evolutionary mismatch.

Conclusions: Conceptualizing diabesity through the addiction paradigm dismantles the stigma of a lack of "willpower" and demands a shift in therapeutic approaches. Effective management of this condition requires integrated strategies combining behavioral psychotherapy (focused on anxiety regulation and mindful eating) alongside novel pharmacological tools (GLP-1/GIP receptor co-agonists), which are capable of mitigating food noise, restoring prefrontal executive function, and enabling the biological consolidation of sustainable healthy habits.

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Introduction

According to the World Health Organization (WHO), obesity is a chronic disease resulting from interactions between genetics, neurobiology, eating behaviors, and environmental factors related to access to healthy food. In 2022, one in eight people worldwide was obese. Since 1990, obesity has doubled among adults worldwide and quadrupled among adolescents. In 2022, 2.5 billion adults were overweight, of whom 890 million were obese. In 2022, 43% of adults aged 18 and over were overweight, and 16% were obese. By 2024, 35 million children under the age of 5 were overweight. In 2022, more than 390 million children and adolescents aged 5 to 19 were overweight, of whom 160 million were obese. It increased globally because countries experienced increased food security, socioeconomic development, changes in eating habits, sedentary lifestyles, and food systems with ultra-processed foods. These created obesogenic environments, contributing to a global public health crisis, with more than 1 billion obese people and increasing prevalence in almost every country [1]. As clinical and experimental diabetologists, the most frequent problem we observe is diabesity [1,2]. The coexistence of type 2 diabetes mellitus (T2DM) and

obesity is a 21st-century public health challenge due to its frequency, complications for the individual and society, the difficulty in its management, and a high rate of therapeutic failure [3-7]. Food addiction (FA) is a long-standing problem since Gold's pioneering research [8]. Replicated in laboratory animal models for addiction and eating disorders study of addictive metabolism, which delineate the key neurochemistry that fuels addiction and the influence that food has on the brain's anatomical reward pathways [9-11]. Fig 1

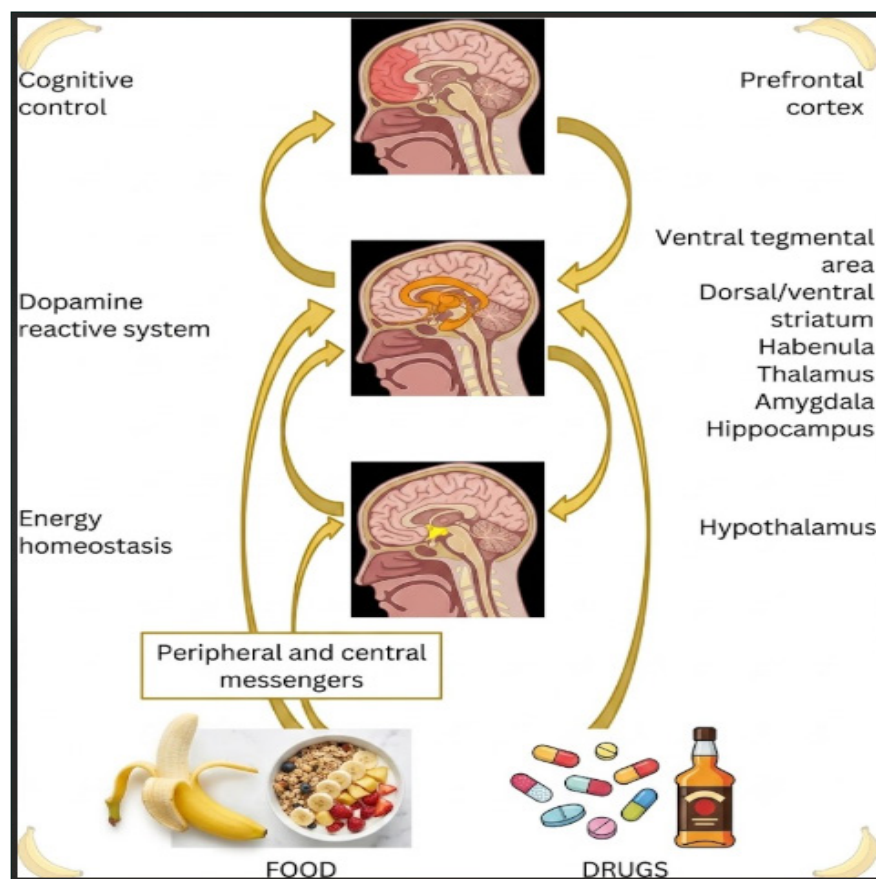


Figure 1: Neurocircuits related to metabolic control [11].

Stimuli generated by food activate and deactivate responses in the central nervous system (CNS), especially in the hypothalamus and hippocampus, where the body's needs, desires, nutritional history, and the opportunity to ingest food are interpreted. These neurochemical and neuroendocrine messengers include hormones, autacoids, neurotransmitters, and mRNA. This flow of information, stimulated by macronutrients and micronutrients, reaches the arcuate nucleus (Arc) and stimulates orexigenic or anorexigenic responses, as well as cravings. At the peripheral level, gastrointestinal hormones such as ghrelin in the greater curvature of the stomach are stimulated in response to appetizing thoughts (via vagus nerve), as well as luminal macronutrients and micronutrients, triggering orexigenic (appetite-increasing) responses in the brain at the level of the lateral hypothalamus (LHA), Figure 1. Furthermore, insulin and leptin (produced in adipocytes) reach the arcuate nucleus (ARC), stimulating anorexia through their effect on intermediate agents that act on the periventricular nucleus (PVN). Insulin and leptin also act on melanocortin 4 receptors (MC4R), exerting an anorexigenic effect on the nucleus accumbens (NAc). The NAc is located outside the hypothalamus at a higher level of CNS control over appetite, Figure 2. The NAc plays a key role in food addiction (FA) and appetite stimulation. Insulin and leptin can block the addictive influences of food at the level of the NAc, causing anorexia. Activation of the dorsal motor nucleus of the vagus nerve interacts with the intestine. Through this pathway, insulin and leptin indirectly stimulate the sympathetic nervous system, represented in the lower part of Figure 1. This tips the sympathetic/parasympathetic balance shown in Figure 2 to the left, favoring fatty acid oxidation and weight loss. Ghrelin replicates the effect described for insulin and leptin, but in the opposite direction; it increases appetite. This is why gastric curvature resection decreases its production, leading to satiety. In the Arc, ghrelin stimulates neuropeptide Y (NPY), which exerts an orexigenic (weight-inducing) effect on the NAc (opposite to that of MC4R) [11-14].

The Reward Circuit

To understand obesity from an addiction perspective, it is essential to differentiate between homeostatic

hunger (regulated by the hypothalamus to maintain energy balance) and hedonic hunger (driven by the corticolimbic reward system, independent of caloric needs, governed by the mesolimbic dopaminergic pathway, a circuit designed to motivate survival behaviors, such as the consumption of energy-dense foods).

Mesocorticolimbic Pathway

The mesolimbic pathway originates in dopaminergic neurons of the Ventral Tegmental Area (VTA) and projects its action to the NAc, the epicenter of pleasure and motivation processing. In ancestral conditions, the consumption of natural foods—fruits, roots—generated a moderate and controlled release of dopamine (DA) [11]. However, contemporary ultra-processed foods act as supraphysiological stimuli, altering this response. The synergistic combination of refined carbohydrates and free fatty acids triggers the massive and immediate release of dopamine in the NAc. A neurochemically analogous phenomenon to that observed after administering substances of abuse such as cocaine or ethanol, establishing an aberrant associative memory of "high reward." Thus, over time, more ultra-processed food is needed to generate more dopamine (DA), similar to what occurs with addiction.

Down-Regulation of D2 Receptors and Reward Deficit

Chronic and intermittent consumption of these hyperpalatable foods induces compensatory neuroplastic adaptations to protect the postsynaptic neuron from overstimulation. Functional neuroimaging (PET) studies have demonstrated a reduction in the availability of type 2 (D2) DA receptors in the striatum of morbidly obese individuals [15].

This down-regulation (adaptive decrease) of D2 receptors alters the dynamics of the circuit:

- **Hedonic Tolerance:** the person does not experience the same level of pleasure (reward) with a normal portion of food.
- **Dopaminergic Hypofunction:** a state of basal hypodopaminergic. To mitigate the discomfort caused by DA deficiency, the limbic system demands doses of the stimulus, transitioning from hedonic consumption to compulsive consumption [15].

Impaired Prefrontal Inhibitory Control

Dysregulation is not limited to the limbic system; it extends to the prefrontal cortex (PFC), responsible for executive functions and inhibitory control (behavioral "braking"). Dopaminergic projections from the ventral tegmental area (VTA) to the PFC (via the mesocortical pathway) are also altered by chronic glycolipotoxicity and neuroinflammation. Thus, the evaluation of long-term consequences versus immediate gratification is impaired. The PFC loses its capacity to modulate and curb impulsive demands from the nasopharyngeal nerve. This translates into craving and loss of control, where the person is aware of the self-induced metabolic damage but lacks the ability to stop eating.

Contribution of Neuroimaging

Neuroimaging in obesity allows visualization of alterations in the connectome of the reward network associated with decreased homeostatic control of eating behavior. Ravichandran et al. studied 150 individuals (men and women) with a high BMI ≥ 25 kg/m² as measured by resting functional magnetic resonance imaging. The Yale Food Addiction Scale (YFAS) was administered, and criteria for food addiction (YFAS symptoms ≥ 3 , significant impairment or distress) and eating behavior questionnaires were completed. They analyzed differences in connectivity and clinical variables. Individuals with food addiction had greater connectivity between brainstem regions and the orbitofrontal gyrus than individuals without food addiction. Women with food addiction had greater connectivity in salience and emotion regulation networks and less connectivity between the default mode network and the central executive network compared to men with food addiction. Increased connectivity between regions of the reward network was positively associated with scores on the General Food Cravings-Trait Questionnaire, indicating greater food cravings in individuals with eating disorders, suggesting dysregulation of the dopaminergic pathway, and greater connectivity in the locus coeruleus indicating maladaptive eating behaviors in individuals with AD. This could be a coping mechanism for anxiety and pathological stress. Sex differences in connectivity imply that women with AD engage more in emotional overeating and have less cognitive control compared to men [16].

Hormonal and Metabolic Crossroads

Neural systems evolved to motivate and reinforce the seeking, intake, and control of food use. The neural circuits underlying hedonic eating and drug addiction share similarities. The main circuits are: the mesolimbic dopaminergic system, opioid receptors, orexin, acetylcholine, and serotonin. In a person of normal weight, metabolic hormones modulate the dopaminergic pathway, inhibiting the "hedonic hunger" observed in humans and animal models of high-fat diets [17-19]. Excessive consumption of highly palatable foods (EPFs) is associated with eating disorders. EPFs stimulate brain reward pathways parallel to those activated by drug use, increasing the risk of dependence. The behavioral similarities between eating disorders and addictive drugs can be addressed in stages: loss of control over eating (binge eating), withdrawal, craving, sensitization, and cross-sensitization [20]. Compulsive intake of palatable foods is characteristic of eating disorders and shares features with drug use disorders. Processed sweet, fatty, and salty foods dominate our brain pathways; excessive intake of these foods reduces satiety and drives us to eat more than necessary. Assessed by the Yale Food Addiction Scale (YFAS) [21]. High sugar consumption activates brain reward circuits, a positive reinforcement mechanism, including the dopamine and endorphin systems, associated with satisfaction and pleasure. Chronic exposure to sugar alters these systems, leading to increased cravings and sugar dependence. This negatively impacts physical health, as it is associated with obesity and diabetes [22].

In drug addiction and overeating states, such as obesity and binge eating disorder (BED), there is an imbalance in circuits for motivation, reward salience, executive function, and self-control. Alterations in DA and glutamate (Glu) within the mesolimbic pathway are fundamental to these pathologies. Group I glutamate metabotropic receptors are expressed in mesolimbic pathways, modulating alterations in synaptic plasticity and neurotransmitter release observed in drug addiction, obesity, and TA [20].

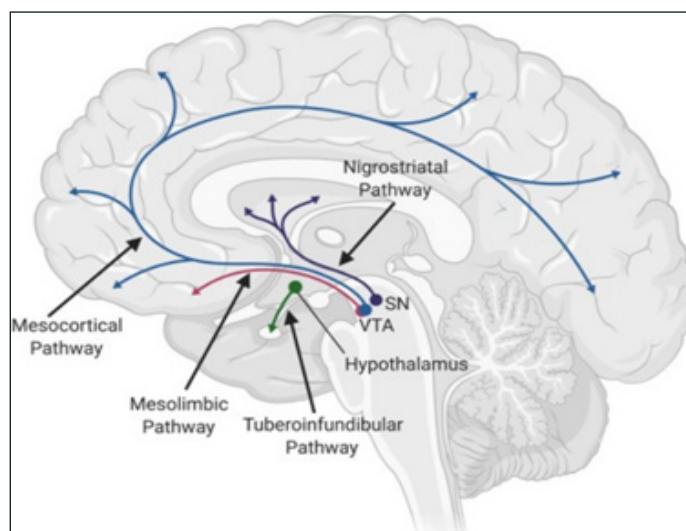


Figure 2: Mesolimbic circuit and its relationship to food addiction. Drug addiction, food addiction, obesity, diabetes, and binge eating disorder (BED) have a significant degree of overlap in the mesolimbic dopaminergic (DA) pathway.

A Rewards such as food and drugs act on the ventral tegmental area (VTA), increasing the activity of GABAergic and DA neurons. The VTA receives GABAergic input from D1 medium spiny neurons (MSNs), which have iGlu and group I metabotropic glutamate (mGlu) receptors located at the terminal. The VTA also receives Glu input from the prefrontal cortex (PFC) and the pedunculopontine tegmental nucleus (PPTg), and cholinergic input from the pedunculopontine nucleus (PPn) and the laterodorsal mesopontine tegmental nucleus (LDTn).

B. The MSNs of the nucleus accumbens (NAc) receive DA input from the VTA, Glu input from the PFC, thalamus, amygdala, and hippocampus (HPC), and GABA input from the ventral pallidum (VP). The MSNs also receive cholinergic modulation via cholinergic interneurons from the NAc.

C. GABAergic neurons in the VP receive input from D1 and D2 MSNs, DA input from the VTA, and cholinergic modulation from cholinergic interneurons [20].

The ventral tegmental area (VTA), composed of neurons located around the midline of the midbrain floor, produces DA. Immunohistochemistry and in situ hybridization in the VTA revealed that 55-65% of neurons express the enzyme tyrosine hydroxylase (TH, critical for DA synthesis), 30% are positive for glutamate decarboxylase

mRNA (GAD, necessary for GABA synthesis), and 2-3% express the vesicular glutamate transporter 2, vGluT2, for glutamate reuptake and packaging. There are neuronal subpopulations in the VTA that possess and release neurotransmitters, a phenomenon known as multiplexed neurotransmission, from different compartments within an axon, a terminal, or the same terminal, releasing simultaneously: (i) DA and Glu, (ii) Glu and GABA, or (iii) DA and GABA. Thus, they can transmit messages according to the neurotransmitter content and the timescale of their function, influencing pre- and postsynaptic changes, contributing to neuroplasticity and adaptation to environmental changes, improving adaptation, or generating obesity, diabetes, and other disorders. VTA neurons and glia play roles in positive and negative reinforcement, decision-making, working memory, incentive salience, and aversion. This behavioral heterogeneity reflects phenotypic characteristics of VTA neurons and the structures to which they are connected [20,23].

Contribution of neuroimaging to relating the effect of food on the cellular structure of neuronal nuclei responsible for producing “neurohormones” and their metabolic effects. Nolan-Poupart et al. used functional magnetic resonance imaging (fMRI) to determine whether the response to a palatable smoothie modifies neuroimaging. They predicted that increased responses in key reward regions—insula, striatum, midbrain, medial orbitofrontal cortex—and decreased responses in regions involved in self-control—lateral prefrontal cortex and lateral orbitofrontal cortex—would be associated with increased intake. They found a significant positive association between the milkshake response in the periaqueductal gray of the midbrain and voluntary milkshake intake. They observed strong bilateral responses in the insula upon milkshake consumption. They concluded that the midbrain response to palatable food is related to eating in the absence of hunger [24].

A. Significant response in the left and right mid-insula to unflavored milk. Bar graphs for unflavored solution (blue) and unflavored milk (red) (from the peak voxel). Time courses for unflavored solution (blue) and unflavored milk (red) (from the peak voxel). B. Positive correlation between the BOLD response and ad libitum intake. The midbrain response is positively

related to intake [24].

Opioid System

The opioid system acts synergistically with the dopaminergic system in energy, plasticity, and reward-related feeding. It is affected by maladaptive eating, overeating, hedonic eating, drugs, and interpersonal relationships—anything that can lead to addiction [25]. Studies in animals and humans explain that overstimulation of endogenous opioid receptors (EORs) expressed in brain regions (mesolimbic system) is implicated in phenotypes related to obesity and diabetes [26]. Thus, when examining the role of EORs in the development and persistence of maladaptive eating states, their ligands—endogenous opioids—must be considered. These include peptides, classified according to their binding to EORs: β -endorphin, which binds to the mu-opioid receptor (MOR) and the delta-opioid receptor (DOR), is derived from the proopiomelanocortin (POMC) gene and is produced in the nasopharyngeal nucleus [27]. It increases eating behavior by binding to the MOR in the NAc and decreases food intake by binding to the MOR in the anterior cingulate cortex (ARC). Furthermore, β -endorphin binds to MOR receptors, boosting the activation of the stress response coordinated by the hypothalamic-pituitary-adrenal (HPA) axis in anxiolytic responses, thus buffering the impact of stress [28].

Enkephalin, an endogenous opioid peptide, includes leu-enkephalin and met-enkephalin, produced in the striatum. It exerts its effects by binding to MOR and DOR receptors, coordinating hedonic feeding via circuits in the NAc and ventral pallidum. Recognized for their role in pain modulation, they decrease pain transmission and perception in the spinal cord, amygdala, and insula, promoting analgesia, stress reduction, and decreased activation of the hypothalamic-pituitary-adrenal (HPA) axis via MOR and DOR receptors [23].

Dynorphin A and dynorphin B, derived from the prodynorphin (Pdyn) gene, are endogenous opioids produced in the hypothalamus. They act via KOR receptors, with lower affinity for MOR and DOR receptors. Similar to enkephalins, dynorphins decrease the pain response and inhibit dopamine release in the midbrain. They drive eating behaviors, the direction of which can be modulated by emotional state through binding to KOR receptors. EOR receptors, which bind

to endogenous opioids, are influenced at different levels, leading to dysregulation. They play a convergent role, along with endogenous opioids, in excessive or insufficient consumption, as well as in caloric intake and its plastic and hedogenic effects.

EOR receptors participate in the overeating-obesity process by reinforcing food consumption in motivational states. Highly palatable foods with higher caloric value are more rewarding [29]. This was evolutionarily advantageous in environments of scarcity in modern times; however, these mechanisms contribute to overeating, obesity, and diabetes. EORs are poised to exert a lasting influence on food seeking and weight gain. Haghighi, A., et al., using genome-wide association studies (GWAS) in French-Canadian adolescents, identified a preventive effect against fat consumption and adiposity associated with the minor allele of the *Oprm1* gene, which encodes the morphine receptor (MOR) [30]. Conversely, decreased methylation of the *Oprm1* promoter was observed in obese individuals [31-36]. Fig 3.

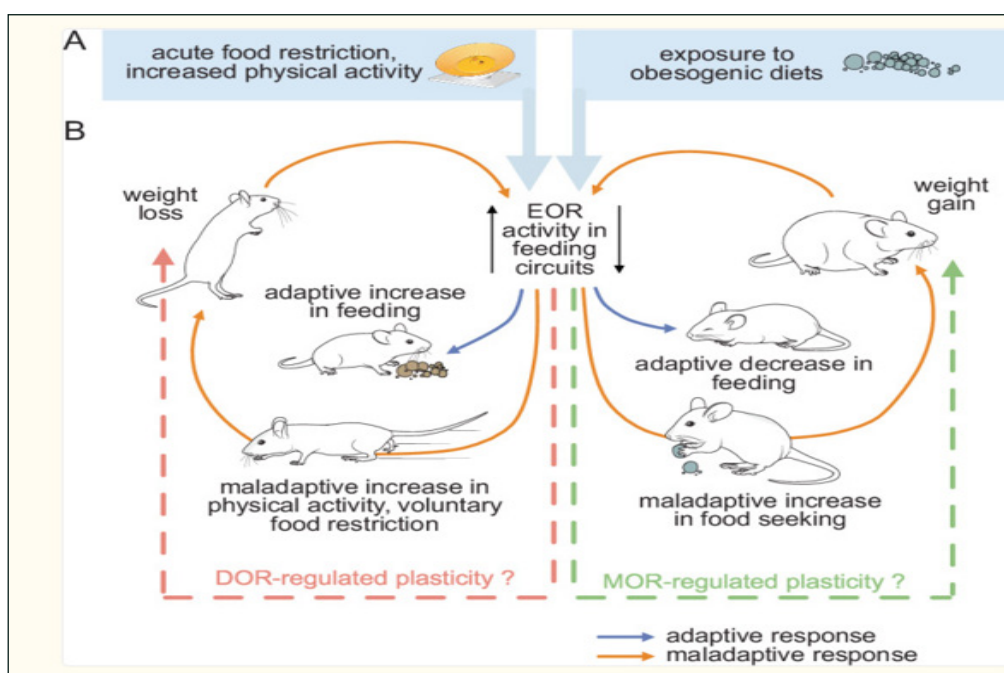


Figure 3: an Initial exposure to obesogenic diets or food restriction combined with physical activity initiates maladaptive cycles of weight gain (right) or loss (left) associated with decreased or increased activity of endogenous opioid receptors (EORs) in feeding circuits (orange arrows). Increased or decreased feeding states initially activate EOR-mediated plasticity mechanisms that further promote maladaptive eating, including increased food seeking or excessive physical activity and decreased caloric intake [23].

In clinical practice, it has been observed that the intake of highly processed foods increases the binding of endogenous opioid receptors and reduces enkephalin mRNA in the NAc [37,38]. A history of binge eating of ultra-processed foods, with repeated periods of high carbohydrate intake, causes hypersensitivity in opioid receptors of the NAc, hippocampus, cingulate cortex, and locus coeruleus affecting the learning process of food intake and increasing it, thus exacerbating the chronic complications of diabetes[39]. Because highly processed foods stimulate the release of hypothalamic opioids [40,41].

In clinical practice, it has been observed that the intake of highly processed foods increases the binding of endogenous opioid receptors and reduces enkephalin mRNA in the nucleus accumbens (NAc) [37,38]. A history of binge eating of ultra-processed foods, with repeated periods of high carbohydrate intake, causes hypersensitivity in opioid receptors of the NAc, hippocampus, cingulate cortex, and locus coeruleus, affecting the learning process of food intake and increasing it, thus exacerbating the chronic complications of diabetes.

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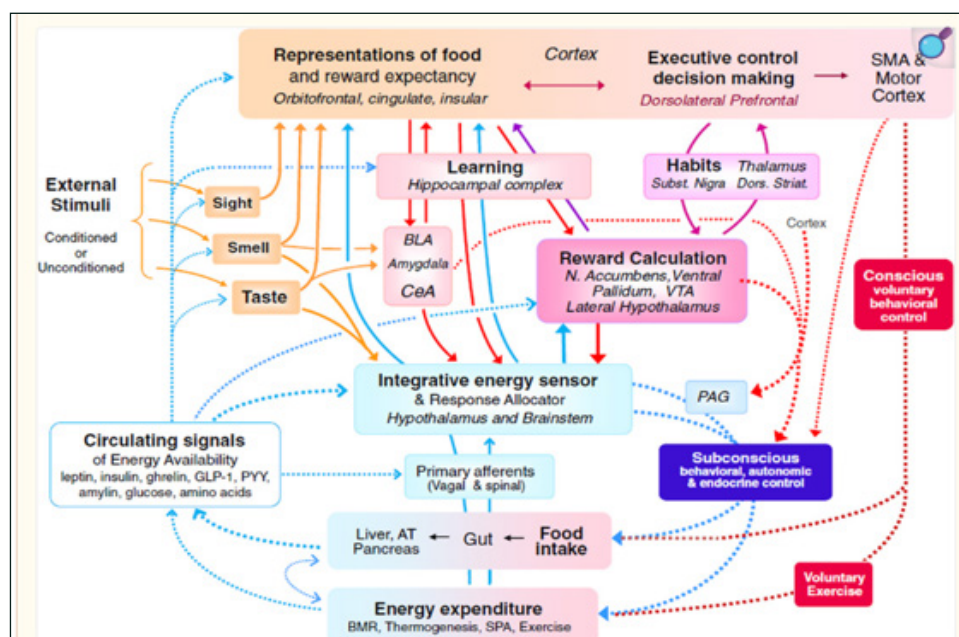


Figure 4: Systems and neural pathways involved in metabolic control, interactions between the homeostatic energy regulation system in the hypothalamus and brainstem (blue boxes and arrows in the lower half) and its connection with cognitive/emotional brain systems (red boxes and arrows in the upper half). The upward modulation of cognitive and emotional processes by metabolic signals and their derivatives is carried out by: a) circulating hormones and metabolites acting on the hypothalamus, brainstem, external sensory processing pathways, and components of the corticolimbic system, giving the affective tone of reinforcement or rejection to eating behaviors and habit formation (open blue arrows with dashed lines); b) vagal and spinal sensory information flows from the interior of the body to all levels of the neuroaxis, including the cortex (filled blue arrows with solid lines); and c) neuronal signals generated by the integrating hypothalamic energy sensor are distributed to areas involved in reward-based decision-making (filled blue arrows with solid lines). Taken together, these upward modulatory influences determine the salience level of the incentive directed toward specific nutrients. The downward modulation of food intake and energy expenditure by cognitive and emotional/reward systems is achieved by: a) direct external sensory input (taste, vision, hearing, smell) to the hypothalamic energy sensor and response allocator (dark yellow lines); b) input from the amygdala, cortex, and reward processing systems, especially the lateral hypothalamus, responsible for conditioned external cues that elicit intake (solid red lines and arrows); c) input from the cortex, amygdala, and basal ganglia to the extrapyramidal motor pathways of the midbrain (emotional motor system, dashed red lines and solid arrows); and d) the pyramidal motor system for voluntary behavioral control (dashed red lines on the right). N. Accumbens, nucleus accumbens; SMA, supplementary motor area; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; VTA, ventral tegmental area; PAG, periaqueductal gray matter; GLP-1, glucon-like peptide-1; PYY, peptide YY; AT, adipose tissue; SPA, spontaneous physical activity [41].

Orexin

Orexins are synthesized in the lateral hypothalamus (LH), a key area connecting homeostatic and hedonic feeding. They participate in feeding behavior by stimulating food consumption ("orexin" means "appetite") [42]. They are associated with drug abuse due to their action on VTA and NAc neural circuits involved in the gratification of food and addictive drugs [43].

Acetylcholine

Acetylcholine (ACh) is released by interneurons that constitute less than 2% of the neurons in the NAc, where they have extensive axonal arborization. They synapse on the medium spiny output neuron [44]. ACh exhibits

opposing actions to DA in the striatum; anticholinergic (antimuscarinic) drugs antagonize M1 receptors [45]. Thus, DA exerts an inhibitory action on ACh interneurons in the striatum [46].

ACh in the NAc modulates feeding behavior. ACh increases at the end of a meal and after the ingestion of a palatable food, reaching a maximum after eating ceased [47,48]. Lesions of the cholinergic interneuron in the NAc with toxin (AF64A) increased food intake, suggesting that ACh in the NAc signals satiety [49]. Increased cholinergic interneuron activity in the NAc reduced the consumption of palatable foods. ACh from the NAc acted as a stop signal [50]. Food can be an aversive stimulus; through conditioned taste aversion, it was shown that the aversive stimulus (in this case, saccharin) would decrease DA release and increase ACh release [51-53].

Serotonin

Serotonin (5-hydroxytryptamine; 5-HT) is associated with reduced food intake. In the context of drug and sugar addiction, decreased 5-HT levels are associated with both depression and compulsive behavior, two disorders that influence addictive behavior [54]. Similarly, laboratory animals subjected to caloric restriction and intermittent access to highly processed foods show a significant reduction (71%) of 5-HT in the medial prefrontal cortex [55].

Leptin Resistance: Loss of the Homeostatic Brake

Leptin, a hormone derived from adipose tissue, plays a crucial role in regulating body weight, appetite, and behavior. It controls energy balance as an indicator of adiposity levels and modulates the reward system, associated with the desire for palatable foods. Obesity is characterized by increased adipose tissue mass associated with elevated leptin levels. The therapeutic potential of leptin for most forms of obesity is limited by leptin resistance and a narrow dose-response margin [56]. Secreted by adipose tissue according to fat reserves, it travels to the central nervous system (CNS) and provides information about energy adequacy. At the molecular level, leptin has receptors (Ob-Rb) in the anterior cingulate cortex (ACC), on dopaminergic neurons in the ventral tegmental area (VTA), and in other areas of the body. It inhibits dopamine secretion, reducing the hedogenic reward effect of food. In obesity, chronic hyperleptinemia saturates transporters across the blood-brain barrier, inducing defective JAK2/STAT3 pathway signaling and leading to leptin resistance. With the ventral tegmental area (VTA) deprived of this hormonal brake, the mesolimbic circuit misinterprets a state of constant starvation, exacerbating cravings and making the individual vulnerable to hyperpalatable food stimuli [57]. Fig 5

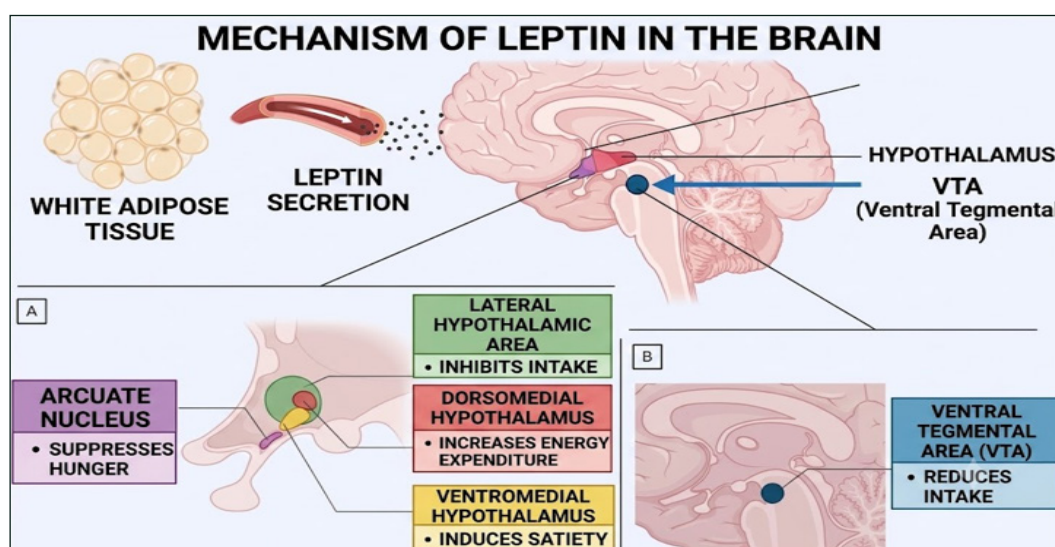


Figure 5: Function of leptin in the regulation of energy balance by the hypothalamus (A) and the ventral tegmental area (B). Direct effects of leptin on specific brain regions and its effects on first-order neurons. The action of leptin in the brainstem and periphery also regulates energy balance [56].

Ghrelin

Ghrelin, an orexigenic hormone originating in the greater curvature of the stomach, stimulates growth hormone secretagogue receptors (GHS-R1a) on dopaminergic neurons, increasing the firing rate of dopamine in the nucleus accumbens (NAc). Processing of preproghrelin and O-acylation by ghrelin O-acyltransferase (GOAT) generates acyl-ghrelin, an GHSR1 α agonist. Desacyl-ghrelin predominates in circulation and exerts context-dependent, GHSR1 α -independent, or low-potency effects, while truncated "mini-ghrelins" act as competitive antagonists. The advent of synthetic ligands, agonists, antagonists, and inverse agonists provided tools for elucidating GHSR1 α activity. Cryo-EM structures of GHSR1 α with peptide ligands and small molecules reveal a bipartite binding site, providing a framework for biased signaling, constitutive activity, and receptor selectivity. In addition to regulating food intake and growth hormone release, ghrelin modulates glucose homeostasis, gastric secretion and motility, cardiovascular tone, bone remodeling, renal hemodynamics, innate immunity, attenuates pro-inflammatory responses, and promotes repair phenotypes in macrophages [58,59]. In people with food addiction, ghrelin spikes no longer respond to fasting; they synchronize with contextual cues and stressful situations. Abizaid A et al. demonstrated that ghrelin alters the synaptic connectivity of mesolimbic dopaminergic cells, affecting the functional correlates of the mesolimbic reward circuit to modulate food intake [59]. It is a factor in the etiology of pathologies associated with both food and drugs of abuse. It has presynaptic action on GABA transmission associated with the initiation of synaptic plasticity, resulting in a synaptic equilibrium in proopiomelanocortin neurons dominated by GABA inputs [59].

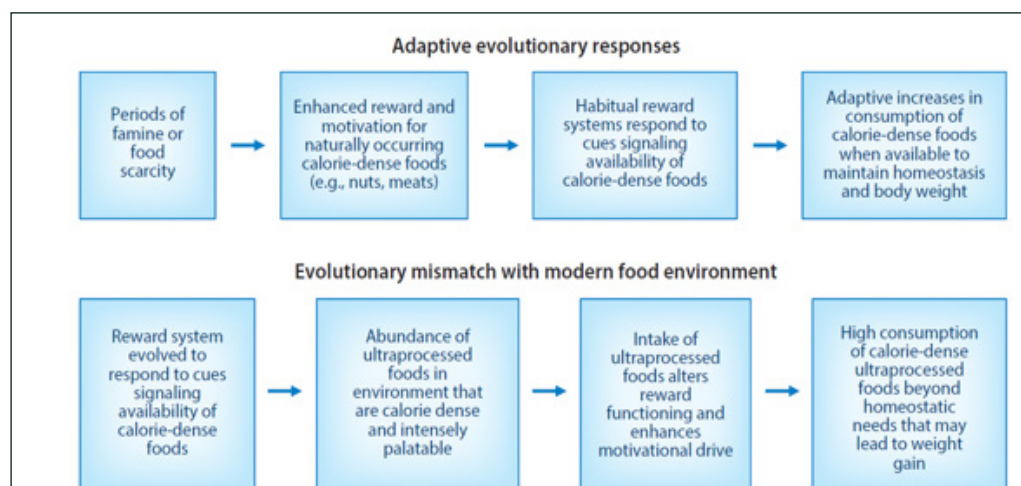


Figure 6: Model of dietary evolutionary mismatch: adaptive and maladaptive evolutionary responses in the modern food environment.

At this stage of civilization, in some parts of the world, there is a mismatch between biology and the food environment, leading to difficulties in controlling food intake and contributing to obesity and diabetes. Brain reward and motivation systems evolved to optimize the likelihood of humans obtaining sufficient calories. Thus, high-calorie foods—sugar and fat—activate reward and motivation systems: mesolimbic dopaminergic pathways and endogenous opioids, constituting, in their current excess, the mechanisms of glycolipotoxicity [60-62].

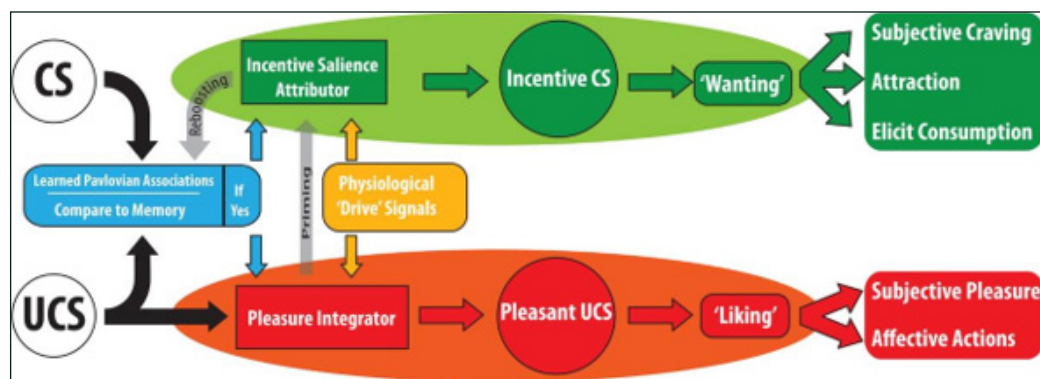


Figure 7: The motivational model separates reward “desire” (incentive salience) from “taste” (hedonic impact of sensory pleasure). This salience model derives from the concepts of incentive motivation. Normal hunger is a physiological “drive” signal to magnify the incentive “desire” and hedonic “taste” triggered by palatable foods and their associated cues, while satiety attenuates the multiplicative impact of cues and food. Regarding obesity, individuals with greater endogenous reactivity in mesolimbic circuits would have greater incentive salience for food and perhaps a greater hedonic impact, leading to a greater “desire” and/or “taste” for eating, thus promoting obesity [62].

Definitions of Some Terms Related to Desire and Taste.

Reward Terms [62]

Food reward: a process that includes taste (hedonic impact), desire (incentive motivation), and learning (associations and predictions). These often occur simultaneously, have separable psychological components, and involve separate brain systems, leading to their dissociation under certain conditions.

Hedonic spot: a brain site capable of amplifying pleasure and taste reactions when stimulated. These are located in the NAc, the ventral pallidum, and the brainstem. Each has a volume of 1 mm³ to 1 cm³ in humans, where neurochemical signals from opioids, endocannabinoids, benzodiazepines-GABA, or orexin amplify the hedonic impact of palatable foods. Applied to eating disorders, a key hedonic spot would alter the hedonic impact of food by modifying its consumption.

“Taste” (in quotation marks): An objective hedonic reaction detected in behavior or neuronal signals, generated by subcortical brain systems. A “taste” reaction to sweetness produces conscious pleasure by activating additional brain circuits, but a basic “taste” reaction can sometimes occur without subjective pleasure.

“Taste” (without quotation marks): The everyday sense of the word as a conscious, subjective feeling of pleasant pleasure.

“Desire” (in quotation marks): Incentive or motivational relevance to reward, triggered by reward-related cues. Attributing incentive salience to representations makes a cue and its reward more attractive, desirable, and likely to be consumed. The mesolimbic brain systems, especially those involving DA, are important for “desire.” Frequently, “desire” is associated with other reward components such as “taste” and learning, and with subjective desires; it can be dissociated from other components and from subjective desire.

Desire (without quotation marks): A conscious, cognitive desire for a declarative goal in the common sense of the word “desire.” This cognitive form of craving involves additional cortical brain mechanisms, beyond the mesolimbic systems, that mediate “craving” as incentive salience.

"Craving" without "taste": as in addictive incentive sensitization, a mechanism of drug addiction, food leads to compulsive levels of "craving." Mediated by changes in the brain's mesolimbic systems related to AD, sensitized "craving" can increase even if "taste" decreases for the same reward. If a similar brain mechanism applied to obesity and eating disorders, some people might compulsively crave and seek food without deriving any additional pleasure from it.

Contributions from Epidemiology

Food, Culture, Pleasure, Maladaptive Eating Epidemiological Mechanisms

Maladaptive eating comprises unhealthy eating patterns that jeopardize survival, including both overconsumption and underconsumption. These behaviors are often coordinated by endogenous opioid receptors (EORs), and when the synaptic circuits and mechanisms related to the control of nutritional intake are affected, they can lead to obesity and diabetes. Understanding whether repeated episodes of overeating, such as "cultural celebratory rituals" or "hedonic" binge eating, lead to obesity and diabetes [63] is crucial. These observations help explain how repeated episodes of overeating, whether as part of "cultural celebratory rituals" or "hedonic" binge eating, can affect the sensitivity of opioid receptors. The repeated release of these receptors can modify neural circuits in some individuals, risking maladaptation. As the saying goes, "genes load the gun, but the environment pulls the trigger." When a population migrates from its place of origin to different societies, the phenomenon of evolutionary mismatch occurs. Metabolic profiles change within a single generation. The Pima natives share the same genetic heritage, but they split geographically: one group remained in the Maycoba mountains (Mexico) and the other in Arizona (United States). In their place of origin, Mexico, they maintained a traditional agricultural lifestyle, with a diet based on corn and beans and high physical activity. Their metabolic profile showed a prevalence of type 2 diabetes of only 6% to 8%, normal cholesterol levels, and extremely low rates of obesity. In the Western environment (Arizona), they adopted the standard American diet (high in ultra-processed foods and saturated fats) and a sedentary lifestyle. They developed a metabolic profile where the prevalence of type 2 diabetes skyrocketed to 50% (one of the highest in the world), and obesity and

insulin resistance became the phenotypic norm. The Ni-Hon-San Study (Japanese Migration), a classic epidemiological study, followed Japanese men living in three distinct locations: Hiroshima/Nagasaki (Japan), Honolulu (Hawaii), and San Francisco (California). In Japan, those who had a traditional diet rich in fish, rice, and vegetables, and low in saturated fat, had a metabolic profile associated with coronary heart disease and low serum cholesterol levels. During the Hawaii-California transition, as the population migrated eastward and became more Westernized, their total cholesterol and triglyceride levels increased incrementally. The metabolic profile changed; Japanese people living in California had double the rates of cardiovascular disease compared to those who remained in Japan, matching the risk profile of the Caucasian American population. The South Asian Diaspora (MASALA and SABRE studies), immigrants from India, Pakistan, and Bangladesh who move to Western urban centers such as the UK or the US, exhibit a unique metabolic vulnerability known as the "Asian metabolic phenotype." Phenotypic change: Upon adopting a Western environment, these populations develop insulin resistance, type 2 diabetes, and cardiovascular disease at much younger ages and with a lower Body Mass Index (BMI) than Caucasians, along with an increase in ectopic fat. Data from the MASALA study (in the US) demonstrate that, when faced with a Western diet, South Asians preferentially accumulate fat viscerally and ectopically (in the liver and muscles) rather than in subcutaneous tissue. They have fatty livers and atherogenic dyslipidemia even while appearing "thin" externally. Studies led by the University of Minnesota in immigrant communities of Hmong and Karen ethnicities from Thailand to the US provided data on what happens in the first months after arriving in the West. Westernization of the gut: Upon arriving in the US, immigrants experience a massive and immediate loss of the diversity of their gut microbiota. Bacteria specialized in degrading native plant fibers die and are replaced by dominant western strains (*Bacteroides*). Metabolic consequences: the loss of microbial diversity precedes and directly predicts the onset of obesity and insulin resistance in the months following migration [64-70]. Clinical Understanding of the Problem: DSM-IV Criteria and the Yale Eating Disorder Scale (YFAS)

Penzenstadler L conducted a study on the Yale Eating Disorder Scale (YFAS) to objectify the addiction model and understand and treat obesity and diabetes. The Yale

Eating Disorder Scale (YFAS) symptom score is often used to assess the consumption of highly processed foods. While "food addiction" (FA) is not coded as an independent disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), compulsive consumption patterns share phenotypic equivalences with diagnostic criteria for Substance Use Disorder (SUD). The prevalence rate of FA varies among populations; a high symptom score is associated with a high body mass index. Symptoms vary; the most common is the inability to reduce or stop eating. The YFAS 2.0 allows for a continuum of severity, establishing different prevalence rates. detect the detection of mild and severe AC with 6 or more symptoms [72,73].

Table 1: DSM-IV-TR Criteria for Substance Dependence [71]

Use of the substance in larger amounts and over a longer period than intended.
Persistent desire or repeated unsuccessful attempts to stop using the substance.
Considerable time or activity is devoted to obtaining, using, and recovering from the substance.
Neglect or reduction of important social, occupational, or recreational activities.
Continued use despite knowledge of adverse consequences (e.g., failure to fulfill obligations, use in situations of physical risk).
Tolerance (significant increase in the amount used, significant decrease in the effect).
Characteristic withdrawal symptoms; use of the substance to relieve withdrawal symptoms. Presence of clinically significant impairment or distress

Table 2. Substance-Related Disorders and Addictions according to DSM-5 [71].

Use of the substance in larger amounts or for a longer period than recommended.
Wanting to cut down or stop using the substance, but being unable to do so.
Spending a lot of time obtaining, using, or recovering from the effects of the substance.
Having cravings and impulses to use the substance.
Being unable to fulfill responsibilities at work, home, or school because of substance use.
Continuing to use the substance even when it causes relationship problems.
Giving up important social, occupational, or recreational activities because of substance use.
Using the substance repeatedly even when it poses a danger.
Continuing to use the substance even when you know you have a physical or psychological problem that may have been caused or aggravated by the substance.
Needing more of the substance to get the desired effect (tolerance).
Developing withdrawal symptoms that can be relieved by using more of the substance.

Table 3: YFAS Scoring Guidelines [71]

The YFAS scoring is continuous for the first 16 questions, with scales from 0 to 4 (0: never, 1: once a month, 2: two or three times a month, 3: two to three times a week, 4: four or more times a week).
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Questions 17–25 are answered with yes or no.

In the YFAS 2.0, the 35 questions are continuous, with scales from 0 to 7 (0: never, 1: less than once a month, 2: once a month, 3: two or three times a month, 4: once a week, 5: two to three times a week, 6: four to six times a week, 7: every day).

Different cut-off points for each question:

Each criterion for substance use disorder (SUD) has several questions. If a question is answered affirmatively, the criterion is met and is scored 1. In YFAS, yes/no questions are scored 1 or 0. Clinical impairment or distress

is not added to the symptom count, but must be present in all cases. If it is not present, the criteria for food addiction are not met, even if other symptoms are present.

For diagnosis using YFAS, the symptom count must include at least 3 of the 7 criteria for food addiction and demonstrate clinical impairment or distress.

For assessment using YFAS 2.0, the symptom count must include at least 2 of the 11 criteria for food addiction and demonstrate clinical impairment or distress. (2 to 3 symptoms are considered mild, 4 to 5 moderate, and 6 or more severe.)

The Yale Food Addiction Scale and the DSM-5 criteria can be adapted to clinical practice, facilitating their applicability and therapeutic interventions, as we see in the following tables [71-73].

Table 4: Correlation between DSM and Clinical Criteria

DSM-5 Criteria (Substance Use Disorder)	Clinical Equivalent in Obesity / Food Addiction
Consumption in large quantities/prolonged time	Ingestion of massive portions of hyperpalatable foods, exceeding the point of gastric fullness and prolonging the episode (binge eating).
Persistent desire or unsuccessful attempts to control use	Chronic history of "diets" and attempts at caloric restriction that fail due to loss of inhibitory control.
Significant time spent obtaining/using	Obsessive meal planning, frequent visits to fast-food establishments, or nighttime food storage behaviors.
Craving (Intense or urgent desire)	Uncontrollable cognitive urge to consume a specific food (high in sugars/fats), triggered by negative emotional states or environmental cues.
Continued use despite physical/psychological consequences	Persistence in hypercaloric intake even when the patient has diagnosed serious comorbidities (Type 2 Diabetes, steatohepatitis, dyslipidemia).
Tolerance	Need to increase the quantity of ultra-processed foods or their caloric density to achieve the initial state of hedonic satiety.
Withdrawal	Manifestation of dysphoric symptoms (anxiety, irritability, headache, emotional lability) after abrupt deprivation of refined carbohydrates.

Table 5: Problems in the Use of Addictive Foods

Using the substance in larger amounts or for longer periods than recommended.
Wanting to cut down or stop using the substance, but being unable to do so.
Spending a lot of time obtaining, using, or recovering from the effects of the substance.
Experiencing cravings and impulses to use the substance.
Being unable to fulfill responsibilities at work, home, or school because of substance use.
Continuing to use the substance even when it causes problems in relationships.
Giving up important social, occupational, or recreational activities because of substance use.
Using the substance repeatedly, even when it poses a danger.
Continuing to use the substance even when aware of having a physical or psychological problem that may have been caused or aggravated by the substance.

Needing a larger amount of the substance to achieve the desired effect (tolerance). 11. Developing withdrawal symptoms, which can be relieved by using more of the substance.

Presence of clinical deterioration or significant distress

Table 6: Criteria for substance use disorder combined with YFAS questions. [71].

Criteria for the diagnosis of Substance Use Disorders (DSM-IV and DSM-5)	YFAS	YFAS2.0 – Questions [74]
Loss of control	1.-I notice that when I start eating certain foods, I eat much more than I intended.	1. When I started eating certain foods, I ate more than I intended.
	2.-I continue to eat certain foods even when I'm not hungry.	2. I continued eating certain foods even when I wasn't hungry.
	3. I eat until I feel physically unwell	3. I ate until I felt physically unwell.
Persistent desire, repeated unsuccessful attempts to reduce consumption of certain foods.	4. I worry about not eating certain foods or reducing my consumption of them.	4. I was worried about reducing my consumption of certain foods, but I ate them anyway.
	22. I want to reduce or stop eating certain foods.	25. I wanted to reduce or stop eating certain foods, but I couldn't.
	24. I have succeeded in reducing or stopping eating these types of foods.	31. I tried to reduce or stop eating certain foods, but I couldn't.
	25. How many times in the last year have you tried to reduce or stop eating certain foods altogether?	32. I tried to reduce or stop eating certain foods, but I failed.
Extensive time spent obtaining, using, and recovering.	5. I spend a lot of time feeling lethargic or fatigued after overeating.	5. I spent a lot of time feeling sluggish or tired from overeating.
	6. I consistently eat certain foods throughout the day.	6. I spent a lot of time eating certain foods throughout the day.
	7. When certain foods are unavailable, I go to great lengths to get them. I drive to the store to buy certain foods even if I have other options at home.	7. When certain foods weren't available, I went out of my way to get them. So, I went to the store to buy certain foods even though I had other things to eat at home.
		8. I ate certain foods so often or in such large quantities that I stopped doing other important things.

Given up important activities.	8. There were times when I ate certain foods so frequently or in such large quantities that I began eating instead of working, spending time with family or friends, or engaging in other important or recreational activities that I enjoy.	8. I ate certain foods so often or in such large quantities that I stopped doing other important things. These things could be working or spending time with family or friends.
	9. There were times when I ate certain foods so frequently or in such large quantities that I spent time dealing with negative feelings from overeating instead of working, spending time with family or friends, or engaging in other important or recreational activities that I enjoy.	10. I avoided work, school, or social activities because I was afraid of overeating there.
	10. There were times when I avoided professional or social situations where certain foods were available because I was afraid of overeating.	18. I felt so bad about overeating that I stopped doing other important things. These things could be working or spending time with family or friends.
	11. I sometimes avoided professional or social situations because I could not eat certain foods there.	20. I avoided work, school, or social gatherings because I couldn't eat certain foods there.
Use despite knowledge of adverse consequences.	19. I continued to consume the same types of food or the same amount of food despite having emotional and/or physical problems.	22. I continued eating the same way even though my diet was causing me emotional problems.
		23. I continued eating the same way even though my diet was causing me physical problems.
Tolerance	20. Over time, I discovered that I need to eat more and more to feel the way I want, for example, to reduce negative emotions or increase pleasure.	24. Eating the same amount of food no longer gave me as much pleasure as before.
	21. I discovered that eating the same amount of food no longer reduces my negative emotions or increases pleasurable sensations as it once did.	26. I needed to eat more and more to get the sensations I sought from eating. This included reducing negative emotions like sadness or increasing pleasure.

Withdrawal symptoms	2. I experienced withdrawal symptoms, such as agitation, anxiety, or other physical symptoms, when I reduced or stopped consuming certain foods. (Do NOT include withdrawal symptoms caused by reducing consumption of caffeinated beverages, such as soda, coffee, tea, energy drinks, etc.).	11. When I reduced or stopped eating certain foods, I felt irritable, nervous, or sad.
	13. I consumed certain foods to prevent anxiety, agitation, or other physical symptoms that were developing. (Please do NOT include the consumption of caffeinated beverages, such as soda, coffee, tea, energy drinks, etc.).	12. If I had physical symptoms from not eating certain foods, I would eat them to feel better.
	14. I noticed that I have a greater craving or impulse to consume certain foods when I reduce or stop consuming them.	13. If I had emotional problems from not eating certain foods, I would eat them to feel better.
		14. When I reduced or stopped eating certain foods, I had physical symptoms. For example, I had headaches or fatigue.
		15. When I reduced or stopped eating certain foods, I had intense cravings.
Continued use despite social or interpersonal problems		9. I had problems with my family or friends because I ate too much.
		21. I avoided social situations because people didn't approve of my eating habits.
		35. My friends or family were worried about my eating habits.
Impairment in daily functioning (work, school, home)		19. Eating too much prevented me from taking care of my family or doing household chores.
		27. I didn't do well at work or school because I ate too much.

Use in physically hazardous situations	15. My eating habits cause me significant distress.	28. I continued eating certain foods despite knowing they were physically dangerous. For example, I continued eating sweets despite having diabetes. Or I continued eating fatty foods despite having heart disease.
	16. I have trouble functioning effectively (in my daily routine, work/studies, social activities, family activities and health problems) because of food and eating.	33. I was so distracted by food that I could have hurt myself (for example, while driving, crossing the street, or operating machinery).
		34. I was so distracted thinking about food that I could have hurt myself (for example, while driving, crossing the street, or operating machinery).
Anxiety		29. I had such a strong craving for certain foods that I couldn't think of anything else.
		30. I had such intense cravings for certain foods that I felt the need to eat them immediately.
Clinically significant impairment		16. My eating behavior caused me a great deal of distress.
		17. I experienced significant problems in my life because of food and eating. These problems may have been related to my daily routine, work, school, friends, family, or health.
Unscored and unranked questions (introductory questions)	17. My eating habits have caused me psychological problems such as depression, anxiety, low self-esteem, or guilt.	17. I experienced significant problems in my life because of food and eating. These problems may have been related to my daily routine, work, school, friends, family, or health
	18. My eating habits have caused me significant physical problems or worsened an existing physical problem.	18. My food choices have caused me significant physical problems or worsened an existing physical problem.
	23. I have tried to reduce or stop eating certain types of food.	23. I have tried to reduce or stop eating certain types of food.

Abbreviations: YFAS – Yale Food Addiction Scale; DSM-IV and DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 4th and 5th editions; YFAS 2.0 – Yale Food Addiction Scale, version 2.0; mYFAS – Modified Yale Food Addiction Scale; mYFAS 2.0 – Modified Yale Food Addiction Scale, version 2.0; ED – eating disorder; FA – food addiction.

The functional limitation stems from an activity that, while potentially harmful, is the result of a voluntary decision (e.g., high-level sports) rather than a voluntary choice.

The behavior is characterized by a prolonged period of intense, time-consuming, and attention-consuming engagement, preventing the individual from attending to other aspects of life, without causing functional impairment or distress. Eating disorder (ED) results from a coping strategy that is harmful to the individual and their environment [75]. Behavioral aspects include: 1) functional impairment or distress as a direct consequence of the behavior; and 2) persistence over time. Functional impairment, significant distress, and persistence over time are detected in the YFAS. To avoid pathologizing, it is important to use exclusion criteria [76]. Structured interviews, such as the Yale interview, are useful for studying ED. Highly processed foods—with high levels of refined carbohydrates and fats, such as ice cream, pizza, and french fries—can trigger neurobiological and behavioral responses similar to those of addictive substances like alcohol and nicotine. Conversely, unprocessed foods—natural foods like fruits, vegetables, and whole grains, or minimally processed foods that do not substantially alter their nutritional content, such as frozen fruits—would trigger the same severe addictive process [77].

From a therapeutic perspective, if binge eating represents a maladaptive response to anxiety, clinicians could consider an integrated treatment model to simultaneously address difficulties related to anxiety and compulsive eating. An integrative approach is associated with better outcomes compared to a sequential or parallel approach [78,79]. Similarly, Oliveira E et al. identified a significant association between binge eating and anxiety; it is plausible that excessive food consumption may represent a maladaptive coping mechanism for managing anxiety symptoms, given that employing addictive behaviors

to regulate emotions is characteristic of addictions [79]. There would be two types of emotion regulation goals that motivate addictive behavior: reducing aversive emotional states such as anxiety (a form of negative reinforcement) or increasing positive affect through the introduction of a pleasurable stimulus (a form of positive reinforcement). Some addictive behaviors, such as alcohol abuse, would be more motivated by the first goal, while others, such as gambling, would be motivated by the second Food Noise [80-85].

This behavior involves hedonic hyperactivity, characterized by:

- Intrusive and recurrent thoughts: Constant internal monologue focused on what, when, and how much to eat, even immediately after consuming a full meal.
- Attentional Bias: Inability of the prefrontal cortex to shift attention away from food-related stimuli in the environment (smells, packaging, advertisements).
- Incentive Salience: The brain assigns excessive motivational and urgency value to environmental cues associated with ultra-processed foods.
- Response to pharmacological treatment with GL-1R
- Habits

Eating habits are “the result of more or less conscious, collective, and repetitive behavior that leads people to select, prepare, consume, and use certain foods or diets in response to social, cultural, and religious influences.” Children's long-term health and development are associated with dietary habits from the very beginning of life. Poor dietary habits are risk factors for overweight in childhood and adolescence, as well as for chronic diseases in adulthood such as obesity and diabetes. They are often related to the consumption of foods high in calories and fat, food selectivity, eating quickly, or eating in unsuitable environments. They are formed in childhood by a combination of genetic and environmental factors and can accompany the individual throughout adolescence and adulthood, as can the consequences of their dietary choices. They can be transmitted from generation to generation, influencing dietary patterns and nutritional status from the earliest stages of life as part of cultural heritage [86].

Influence of Parenting Styles on Food Socialization

Pleasure is essential in controlling the act of eating and shaping food choices, reinforced by the experience of consuming food [87]. Eating in company fosters

interaction between people, which is crucial for the development of eating habits. Food socialization is the process by which parents help their children adopt healthy eating practices, values, beliefs, and behaviors. Parents are the first and primary influence in the early stages of an individual's food socialization. Infants and preschool children depend entirely on their parents' guidance regarding appropriate food practices and preferences. As they grow and develop, children and adolescents enjoy greater independence, a variety of eating environments, eating companions, and food choices. While the parental environment remains of paramount importance during childhood and adolescence, food socialization needs change, parental control decreases, and peer influence becomes dominant. In adolescence, parents expect their children to have adopted the family traditions and values that guide their eating choices and behaviors as they become independent and autonomous adults.

Food socialization strategies can be classified according to how parents shape the eating habits their children will carry on as a legacy into the future. Four parenting prototypes have been defined, reflecting four feeding or parenting styles: 1) Authoritarian or responsive; 2) Authoritarian; 3) Permissive; 4) Neglectful or uninvolved. While authoritarian parents make healthy foods available and may gently encourage eating, permissive parents may provide healthy foods, expect children to eat whatever is put in front of them, and force them to eat. Responsive parents monitor their child's behavior and convey clear guidelines without resorting to intrusive or restrictive approaches. Parents with permissive, indulgent, and uninvolved profiles have few expectations regarding their children's eating behaviors. Permissive parents only provide foods they know their children will eat, are more tolerant, and avoid conflict, while uninvolved parents have a low degree of control and responsiveness, providing foods that are convenient at the time, without considering nutritional value or their children's preferences.⁸ In general, children of authoritarian parents achieve better results in terms of healthy eating and self-regulation [86].

Environmental and chemical pollutants, known as obesogens, can promote obesity. Examples include bisphenol A (BPA), phthalates, and dioxins, which belong to the group of compounds known as endocrine disruptors (EDCs). These have been defined by the Endocrine Society as “exogenous chemicals, or mixtures of chemicals, that interfere with any aspect of hormonal action” (Figure 5). The mechanisms by which obesogens exert their effects include: (i) altered adipocyte development; (ii) interference with hormone receptors; and (iii) promotion of inflammation. They can dysregulate adipocyte homeostasis by interacting with peroxisome proliferator-activated receptor gamma (PPAR γ) and the 9-cis retinoic acid receptor (RXR), leading to an increase in the number and size of adipocytes, impaired glucose uptake and insulin signaling, reduced expression of brown adipocyte markers, and inflammation [88]. They promote obesity by altering metabolic rate, energy homeostasis, and disrupting the hypothalamic regulation of appetite and satiety [89]. They mimic the effects of natural estrogens by binding to their receptors (ER α and ER β) and interfere with androgen receptors (AR) and thyroid hormone receptors (TR), disrupting the endocrine system [90,91]. Fig 13

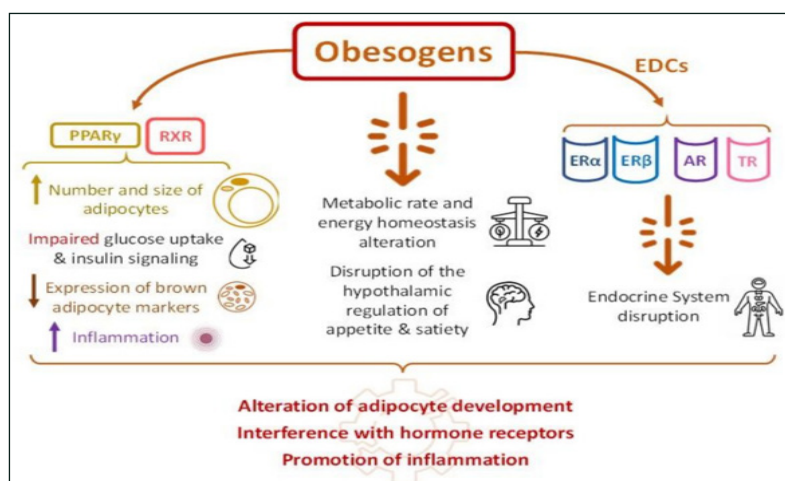


Figure 8: Mechanisms that mediate the harmful effects of obesogenic foods. AR, androgen receptor; EDC,

endocrine disruptors; ER α , estrogen receptor alpha; ER β , estrogen receptor beta; PPAR γ , proliferator-activated receptor gamma; RXR, 9-cis retinoic acid receptor; and TR, thyroid hormone receptor [90].

The psychology of addiction explains addiction based on incentive salience [92]. This implies that addictive desires do not differ in their nature from many of the desires of non-addicted individuals; the difference lies in how they are acquired, which affects their intensity. We understand them through the concept of "incentive salience." This refers to the quality by which something stands out, excels, or captures our attention above its surroundings. It comes from the Latin word *saliō* (to jump). In psychology and neuroscience, it is the brain mechanism that helps us prioritize stimuli. The salience network filters information, allowing us to focus on what is relevant to our survival or interests, both in addicts and non-addicts, contrasting these with more cognitive desires. The self-control challenge faced by addicts does not differ in essence from that faced by non-addicts, although the degree of difficulty can vary considerably. Self-control can be employed in three different stages, and examining how it might be strengthened helps to elucidate a general model of intentional action. Habit development in the context of food addiction is the mechanism by which an initially conscious and goal-oriented behavior (eating something tasty for pleasure) transforms into a compulsive and ingrained automatism [93].

Cravings for different foods do not always stem from explicit beliefs about how pleasurable they are to eat. Cravings do not need beliefs to exist; they can persist in their absence. Sometimes we perceive in our direct experience—to put it in a personal context—the desire to eat more of something (chocolates? overly sweet desserts? peanuts? potato chips?) even when we know we won't enjoy it and that it might make us nauseous. In addition to ultra-processed foods, this process is not a simple repetition of acts; it is a neurobiological hijacking that reconfigures the brain's circuitry. For teaching purposes, we can compare food to addictive drugs, of course remembering that there are differences. Addictive drugs artificially increase brain DA levels. Each drug acts differently: nicotine directly stimulates DA production, opiates decrease the production of substances that inhibit it, cocaine reduces the activity of the system that reabsorbs

dopamine after its release, and so on. Notably, they share one common characteristic: they all potentiate the effect of dopamine [93].

Development of an Addictive Habit

The development of habits in the context of food addiction is the mechanism by which an initially conscious and goal-oriented behavior (eating something tasty for pleasure) transforms into a compulsive and ingrained automatism. And addiction to ultra-processed foods is not simply a repetition of acts; it is a neurobiological hijacking that reconfigures the brain's circuits. The development of an addictive habit would have four sequential neurocognitive stages. Food addiction could be considered the endpoint of a series of stages, from "initial consumption"—the acquisition of the habit of ingesting a hedogenic food in response to a stressful event, whether unpleasant (loss, failure) or pleasant (celebrating an achievement or an important date)—to the loss of control over this behavior, which becomes habitual and, finally, compulsive. These transitions would depend on interactions between learning processes and the social environment [94,95].

The Cue: a stimulus that signals the brain to go into autopilot. In food addiction, cues are ubiquitous and can be divided into:

- Visual/Environmental: passing by a bakery, seeing a fast-food commercial, or simply sitting on the couch watching TV.
- Emotional (Hedonic Hunger): boredom, anxiety, loneliness, and frustration act as internal cues that the brain associates with the need for reward.

The Craving: the desire for the mental state that eating generates. It's the surge of dopamine that soothes the discomfort. The brain anticipates the reward before eating. In this phase, the person's attention narrows dramatically; they think only of the object of their addiction.

The Response (Routine): This is the habit itself, the physical "action," not the rational process. It could be unconsciously opening the refrigerator or searching the cupboard at midnight, ordering food through a mobile app, or buying a package of cookies at the kiosk. Because it is automated by the dorsal striatum, the person usually responds that they did it "without thinking."

The Reward: This is the outcome. Sugars, free fats, and other substances in food, often unknown to those who consume them, impact the bloodstream, stimulating the vagus nerve and releasing dopamine and endogenous opioids in the brain. The reward reinforces the habit: it teaches the brain that this response was effective in relieving the initial signal [94,95]. The Role of the Microbiota

Food addiction contributes to the obesity pandemic. The microbiome-addiction connection is linked to the action of Microviridae bacteriophages, particularly Gokushovirus WZ-2015a, observed in several human cohorts. Further analyses reveal that food addiction and Gokushovirus are related to serotonin and dopamine metabolism. Studies in murine models that received fecal microbiota and viral transplantation from human donors with a higher Gokushovirus load exhibit increased food addiction along with changes in tryptophan, serotonin, and dopamine metabolism in different brain regions, as well as alterations in dopamine receptors. Mechanistically, targeted tryptophan analysis shows lower concentrations of anthranilic acid (AA) associated with Gokushovirus. AA supplementation in mice decreases food addiction and alters pathways related to the neurotransmitter release cycle. In *Drosophila*, arachidonic acid (AA) regulates feeding behavior and ethanol preference, similar to addiction. Jurema Santos, G.C., et al. proposed that bacteriophages present in the gut microbiota contribute to regulating food addiction by modulating tryptophan and tyrosine metabolism. [96]

Human Genetics and Food Addiction

Substance use disorders (SUDs) such as food addiction are associated with moderate heritability (between 40% and 60%) [97,98]. Most studies focus on specific substances: tobacco or alcohol. However, SUDs often occur in association with other substances. Twin studies have indicated overlap in genetic influences affecting the risk of substance use disorders (SUDs), accounting for 74% to 80% of the genetic influences in alcohol use disorders (AUDs) and 62% to 74% of the genetic influences in other SUDs [99]. Genetic risk is considered substance-specific. Multivariate genome-wide association studies (GWAS) of SUDs have provided evidence that most of the genomic risk is shared [100-103]. Epidemiological and twin studies have shown that SUDs share phenotypic and

genetic influences with other disorders characterized by behavioral disinhibition. In twin studies, this underlying latent factor is highly heritable (~80%), more so than any of the disorders or traits studied individually. In the psychological literature, this spectrum of behaviors and disorders, including SUDs, is known as the externalizing spectrum. Efforts to identify genes involved in eating disorders often focus on individual disorders, despite the high rates of co-occurrence among them and with other externalizing traits [104].

What to do: Clinical Strategies for Habit Restructuring

Break the Cue (Stimulus Control): The addicted brain cannot resist a continuously exposed cue. The primary intervention is to modify the environment: eliminate ultra-processed foods from the home, change commuting habits, avoid certain restaurants, disable delivery app notifications, modify celebrations, and let family and friends know that their help is needed. **Replace the Response (Behavioral Intervention):** Habits are not eliminated, they are replaced. If the cue is work-related stress at 5:00 p.m. (Cue) and the craving is calm (Craving), the traditional response of eating a donut should be replaced by another behavior that also raises dopamine or lowers cortisol in a healthy way, such as a short walk, breathing exercises, or a phone call.

"Urge Surfing" techniques: teaching the person that craving is not an imperative command, but a physiological wave that lasts between 10 and 15 minutes. Through mindfulness, the person learns to observe the desire without acting on it, allowing the DA curve to naturally decline without having consumed the food [105-109].

Self-control [93]

Self-control exists as an independent system, a specialized psychological system that, when altered or damaged, hinders the ability to stop eating even after consuming enough to satisfy metabolic needs. Intentional action results from the interaction between desires, mediated by the self-control system. This implies considering self-control as the function of regulating which of a person's desires determine their behavior. In response to temptation, people spontaneously generate or retrieve arguments in favor of weak-willed action. If they lack the cognitive resources to overcome temptation, they conclude that the benefits of succumbing to temptation

are greater than they had thought, or that the costs of giving in are lower, or both, and act accordingly. Dill et al. propose three stages through which thought leads to action, which they call the deliberative stage, the volitional stage, and the implementation stage:

Deliberative stage: the agent makes a judgment about the best course of action. This is the crux of the self-control conflict: the deliberate challenge of arriving at a clear evaluative judgment despite the biased influence of the desire for incentives.

- **Volitional stage:** the agent chooses an intention to pursue. This is the point of the self-control conflict that Wallace identified: the volitional challenge of forcing oneself to pursue the end that has already been judged to be the best.
- **Implementation stage:** the agent selects the actions that implement the chosen intention. This is the central point of the self-control conflict: since habits are raw, unmotivated behavioral dispositions, they can lead to behaviors that contradict goals, even when one is fully committed to achieving them. Therefore, it is during the implementation stage that one must grapple with and overcome one's habits.

Implementing Self-Control: It is a challenge when one has a good goal that can be thwarted by a bad habit. Goal attainment can be hindered by habits that lead to behaviors incompatible with the goal. This problem becomes serious if, as in the case of addicts, the goal is to change an ingrained behavior stemming from the pursuit of a salience or incentive. Bad habits disrupt the addict's self-control, such as when they are habitually placed in situations that make food accessible or tempting. One strategy for self-control is to counteract the bad habit once it has been triggered. Overcoming a habit, which helps us as a mechanism for coping with frustrating situations, requires the ability to regulate attention to monitor the cues that trigger the habitual behavior.

Self-control strategy: plans of the type "if I encounter cue X, then I will perform action Y." People who formulate implementation intentions improve their goal attainment. The beneficial effects of implementation intentions are attributed to the association they create between the "if" condition and the "then" response. Participants who subsequently formulate implementation intentions show a strong association between the "if" condition and the "then" response,

reacting faster than controls to the words associated with the "then" response after being exposed to the "if" condition [110]. This association leads participants to quickly and automatically execute the planned "then" response upon encountering the specified "if" condition. The automaticity of this process explains why implementation intentions are equally effective (and in some cases more effective) when people experience executive control impairments caused by cognitive load, ego depletion, or old age [93, 111].

The Importance of Health Education, Physical Activity, and Socialization in Promoting Healthy Habits and Treating Food Addiction

Over the past ten years, the University Program of the Faculty of Medical Sciences at the National University of Córdoba, Argentina, in conjunction with the Argentine Diabetes Society and the Friends of Diabetes Group Foundation (NGO), has recognized the importance of health education combined with psychological support, adapted physical activity, and social participation. This approach helps participants understand the significance of food, its proper use, and recognize the dangers of its addictive nature. Adapted physical activity, based in our case on the practice of taekwondo (a martial art) where self-control and meditation are key principles, reinforces the learning process by engaging the body and mind. It fosters healthy habits such as class attendance, attention, and commitment, allowing participants to perceive the movements they will perform from the outside and the sensations they experience from the inside, especially the position of each part of their body. From an exercise physiology perspective, Taekwon-Do is a multimodal physical activity that combines three essential energy systems for the treatment of diabetes:

- **HIIT Effect (High-Intensity Interval Training):** The practice of high-intensity movements followed by recovery periods. Evidence shows that HIIT is significantly more efficient than continuous cardio in improving insulin sensitivity, reducing visceral fat, and stimulating mitochondrial biogenesis.
- **Eccentric Strength Training, Stabilization, Bone Mass, Muscle Mass, and Strength:** Maintaining stances (sogi), executing dynamic blocks, and the power required for kicks act as resistance training. This promotes muscle hypertrophy, prevents osteosarcopenia, and increases glycogen storage capacity.
- **Coordination, Flexibility, Balance, Visuospatial**

Memory, and Self-Control: Learning forms or patterns (tul/poomsae) demands a high level of neurocognitive engagement. This stimulates brain-derived neurotrophic factor (BDNF), improving neuroplasticity in patients whose central nervous system is often inflamed due to glucotoxicity.

- Development of socialization: attending classes provides a sense of order, and practicing with peers aids socialization[112-114]. Fig 9



Figure 9: Presentation of the Taekwon-do activity of the Learning to Live program. Figure 15 Translational Health Education activity of the Learning to Live program.

Role of Pharmacology

Incretinomimetic drugs, such as GLP-1 analogues (GLP-1Rs), have a place. GLP-1Rs such as semaglutide and exenatide were hypothesized by van Bloemendaal L. et al., that the reduction in food intake following activation of the glucagon-like peptide-1 receptor (GLP-1) is mediated by brain areas that regulate anticipatory and consummatory food reward. As part of a larger study, they determined the effects of GLP-1 receptor activation on brain responses to the anticipation and reception of chocolate milk compared to a tasteless solution. They studied obese individuals with type 2 diabetes mellitus (T2DM), as well as obese and lean individuals without T2DM, using functional magnetic resonance imaging (fMRI). The study included three fMRI sessions on separate visits during intravenous infusion of the GLP-1 receptor agonist exenatide, exenatide with prior GLP-1 receptor

blockade, or placebo, administered during somatostatin pituitary-pancreatic clamping. They observed that body mass index (BMI) was negatively correlated with brain responses to chocolate milk intake and positively correlated with the anticipation of its intake in brain areas that regulate reward, appetite, and motivation. Exenatide increased brain responses to chocolate milk intake and decreased the anticipation of its intake compared to placebo, which was accompanied by a reduction in food intake. Activation of the GLP-1 receptor decreases the anticipatory reward of food intake, thus reducing cravings, and increases the consummatory reward of food intake, preventing overeating [115]. Experience shows that GLP-1 receptors (GLP-1Rs) influence eating behavior through central neural pathways that also regulate compulsive and reward-driven actions. GLP-1Rs reduce appetite and modify food preferences, shedding light on the neural mechanisms underlying compulsive eating and offering potential therapeutic avenues for metabolic and behavioral disorders [116]. Hiranoka J et al. investigated the effects of oral semaglutide on changes in food preferences in Japanese individuals with type 2 diabetes (T2D). They conducted a retrospective, multicenter study of 75 T2D patients who received oral semaglutide. The primary outcome was the change in the score on the Brief Dietary History Questionnaire (BDHQ) three months after the initiation of oral semaglutide treatment. They observed a median age of 64.0 years, a BMI of 26.9 kg/m², and an HbA_{1c} of 7.6% (59 mmol/mol). The BDHQ results showed that total energy intake decreased. Among the individual nutrients, carbohydrates were the most significantly reduced. The CoEQ results showed decreases in cravings for sweets, chocolate or chocolate-flavored foods, and starchy foods; meal satisfaction; the frequency and intensity of food cravings; the difficulty in resisting food cravings; and the frequency of eating in response to food cravings (food noise) were significantly lower after 3 months. The authors concluded that in this population, treatment with oral semaglutide decreased total energy intake and modified food preferences. [117] Friedrichsen M, et al. investigated the effects of subcutaneous (s.c.) administration of semaglutide 2.4 mg once weekly on gastric emptying, appetite, and energy intake in obese adults, using a double-blind parallel-group trial with 72 obese adults, who were randomly assigned to receive semaglutide s.c. once weekly (with increasing doses up to 2.4 mg) or placebo for 20 weeks. Self-reported appetite scores and

responses to the Food Control Questionnaire (CoEQ) were recorded, and energy intake was measured during ad libitum lunch. The area under the concentration-time curve (AUC) of paracetamol from 0 to 5 hours after a standardized meal was found to be 8% higher with semaglutide 2.4 mg compared to placebo at week 20. Ad libitum energy intake was 35% lower with semaglutide compared to placebo (1736 vs 2676 kJ; estimated treatment difference: -940 kJ; $p < 0.0001$). Semaglutide reduced hunger and prospective food consumption and increased feelings of fullness and satiety compared to placebo. The CoEQ indicated better food control and less intense cravings with semaglutide compared to placebo, and body weight decreased by 9.9% with semaglutide and by 0.4% with placebo. The safety profile was consistent with that of semaglutide. In obese adults, weekly subcutaneous administration of 2.4 mg of semaglutide suppressed appetite, improved food control, reduced cravings, ad libitum energy intake, and body weight compared to placebo [118].

GLP-1R Mechanisms of Action

GLP-1 receptors are highly expressed in pancreatic β cells, where they play a key role in mediating glucose-dependent insulin secretion [119]. This action supports the hypoglycemic efficacy of GLP-1 receptors and their effectiveness in the treatment of obesity and diabetes. GLP-1 receptors are also located in the gastric mucosa and in enteric neurons distributed throughout the intestine [120,121]. The action mediated by pancreatic β cells shows insulinotropic effects of LP1-R, and activation of enteric GLP-1 receptors delays gastric emptying, attenuating postprandial glycemic peaks and prolonging satiety [122]. Fig 10

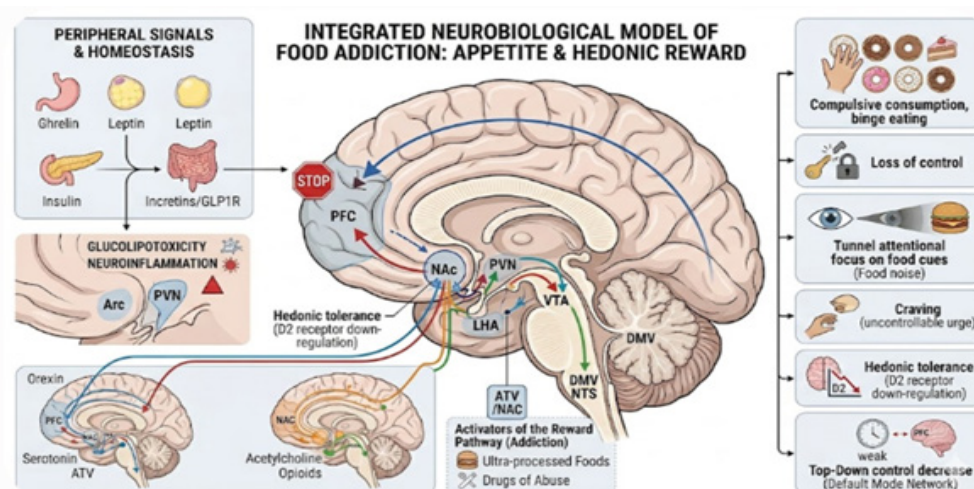


Figure 10: Site and mechanisms of metabolic and appetite-regulating actions of GLP-1 and GLP-1 receptors [113].

GLP-1 receptors access regions of the rhombencephalon indirectly via the vagus nerve, highlighting the essential role of these neuronal connections in the transmission of gastrointestinal signals to the central nervous system (CNS) [123]. GLP-1 receptors are abundantly expressed in vagal afferent neurons that innervate the stomach, which detect gastrointestinal distension and transmit this information to the nucleus of the solitary tract (NTS) [124]. The delay of gastric emptying by GLP-1 receptors depends on the presence of GLP-1 receptors in the stomach. This highlights the role of vagal afferents in mediating the metabolic and appetite-regulating effects of peripheral GLP-1, linking signals derived from the gut with central regulatory circuits [125].

GLP-1 receptors are expressed throughout the CNS, particularly in hypothalamic nuclei, septal regions, the brainstem, and, to a lesser extent, cortical structures [126]. GLP-1 receptor agonists exert their appetite-suppressing effects in these areas, linking peripheral metabolic signaling with the central regulation of feeding behavior. The gut and brain GLP-1 systems operate largely independently, with abundant mRNA transcripts for proglucagon (GCG), the precursor peptide of GLP-1, in the brainstem, especially in the nucleus of the solitary tract (NTS) [127]. GLP-1-producing neurons in the NTS project axonal terminals, innervating regions involved in autonomic

and metabolic control, such as the hypothalamic and thalamic nuclei and the NTS [128]. Brainstem-derived GLP-1, rather than gut-derived GLP-1, modulates GLP-1R-dependent signaling that regulates appetite and body weight [129]. It exists in low concentrations, is rapidly inactivated by DPP-4 enzymes, and is eliminated renally [130]. Thus, peripheral GLP-1 is unlikely to contribute significantly to the endogenous activation of central GLP-1Rs. Long-acting GLP-1 receptor agonists, liraglutide and semaglutide, which are resistant to degradation, show poor penetration into the CNS [131]. Tirzepatide, a dual agonist of GLP-1 and GIP receptors, does not appear to cross the blood-brain barrier efficiently [132].

Why do GLP-1Rs and dual agonists exert effects on the CNS despite certain difficulties in crossing it? Because they act in areas of the CNS lacking a blood-brain barrier. The appetite-suppressing actions of GLP-1 receptor agonists and dual agonists are mediated by receptors located in circumventricular organs outside the blood-brain barrier. These are specialized regions that transmit peripheral signals to deep brain areas without the direct involvement of preproglucagon (PPG) neurons, which constitute the brain's endogenous source of GLP-1 [133]. Estévez V et al. studied metabolic syndrome (MS), a metabolic disorder related to obesity and insulin resistance, in a murine model of a high-fat diet. Insulin resistance is the main determinant of the development of chronic low-grade inflammation. This continuous inflammatory response culminates in neuroimmunoendocrine dysregulation responsible for the metabolic abnormalities and morbidities observed in people with MS. Events such as the accumulation of visceral adipose tissue, increased plasma concentrations of free fatty acids, tissue hypoxia, and sympathetic hyperactivity in individuals with metabolic syndrome (MetS) can contribute to the activation of the innate immune response, compromising cerebral microcirculation and the neurovascular unit (NV), leading to the onset or progression of neurodegenerative diseases. This study aimed to evaluate the effects of chronic treatment with a GLP-1 receptor agonist (semaglutide) on cerebral microcirculation and NVU integrity. They observed that semaglutide attenuated the metabolic disturbances induced by a high-fat diet (HFD) in mice fed HFD for 24 weeks. It also reversed the effects of the HFD on cerebral microcirculation by reducing capillary rarefaction and leukocyte interaction in postcapillary

cerebral venules. The group treated with DAG and semaglutide showed improved astrocyte coverage in the vessels. Thus, semaglutide can reverse microvascular rarefaction in metabolic syndrome by restoring the integrity of the neurovascular unit. Adverse dietary stimuli can compromise microglial homeostasis, an effect that is not reversed by semaglutide [134]. Restoring the integrity of the neurovascular unit. Adverse dietary stimuli can compromise microglial homeostasis, an effect that is not reversed by semaglutide [134].

The neurobiological mechanisms underlying the benefits of combined GLP-1 and GIPR receptor agonism with compounds such as tirzepatide include peripheral mechanisms, such as delayed gastric emptying, and central mechanisms, since the direct activation of central GIPR receptors—which have receptors in the ventral tegmental area, the nucleus accumbens (NAc), and the hippocampus—decreases the “addictive” effect of food (food noise) and craving in the habit loop, allowing the individual to regain prefrontal control and consciously build healthy habits, suppress or reduce food intake, and decrease body weight [135-137].

Conclusions

Obesity and diabetes are health and social problems that share neurobiological substrates and behavioral phenotypes with substance addiction, requiring adapted therapeutic strategies. The failure of approaches based exclusively on voluntary caloric restriction ("eat less and move more") is explained by their disregard for the mesocorticolimbic circuit and the automatization of behavior in the dorsal striatum. For the treatment of obesity and diabetes to be effective and sustainable, interventions must shift towards a translational model that integrates pharmacotherapy, reconfiguration of cognitive-behavioral habits, and patient participation and commitment.

References

1. World Health Organization (2025) Obesity and overweight.
2. Verde L, Annunziata G, Camajani E, Tarsitano MG, Savastano S, et al. (2026) Personalized Medical Nutrition Therapy and Physical Exercise: The Future of Diabetes Care. *Curr Obes Rep* 15: 20.
3. Kaufman F (2005) *Diabetes*. Bantam Press, New York, NY, USA.
4. Kapoor N, Sahay R, Kalra S, Bajaj S, Dasgupta A, et al. (2021) Consensus on Medical Nutrition

- Therapy for Diabetes (CoMeND) in Adults: A South Asian Perspective. *Diabetes Metab Syndr Obes* 14: 1703-1728.
5. Sinha A, Puri P, Pati S (2022) Social determinants of diabetes and its association with multimorbidity among older adults in India: a population-based cross-sectional study. *BMJ Open* 12: e061154.
 6. Xu J, Zhou H, Wang Z (2025) Accelerated biological aging mediates the associations of stress hyperglycemia ratio (SHR) with mortality in type 2 diabetes and obesity (diabetes). *Cardiovasc Diabetol* 24: 368.
 7. Shriner R, Gold M (2014) Food addiction: an evolving nonlinear science. *Nutrients* 6: 5370-5391.
 8. Gold M (2011) From bedside to bench and back again: A 30 year saga. *Physiol Behav* 104: 157-161.
 9. Alcantara IC, Tapia APM, Aponte Y, et al. (2022) Acts of appetite: neural circuits governing the appetitive, consummatory, and terminating phases of feeding. *Nat Metab* 4: 836-847.
 10. Murry S, Tulloch A, Gold M, Avena N (2014) Hormonal and neural mechanisms of food reward, eating behaviour and obesity. *Nat Rev Endocrinol* 10: 540-552.
 11. Volkow ND, Wang GJ, Tomasi D, Baler RD (2013) Obesity and addiction: neurobiological overlaps. *Obes Rev* 14: 2-18.
 12. Shriner R, Gold M (2014) Food addiction: an evolving nonlinear science. *Nutrients* 6: 5370-5391.
 13. Abizaid A, Liu ZW, Andrews ZB, Senior DE, Lee WA, et al. (2006) Ghrelin modulates the activity and synaptic input efficiency of dopaminergic neurons in the ventral tegmental area. *J Clin Invest* 116: 3229-3239.
 14. Gearhardt AN, Schulte EM (2021) Is food addictive? A review of the evidence. *Annu Rev Nutr* 41: 387-410.
 15. Volkow ND, Wang GJ, Telang F, Fowler JS, Thanos PK, et al. (2008) Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. *Neuroimage* 42: 1537-1543.
 16. Ravichandran S, Bhatt RR, Pandit B, Osadchiy V, Alaverdyan A, et al. (2021) Alterations in reward network functional connectivity are associated with increased food addiction in obese individuals. *Sci Rep* 11: 3386.
 17. Wallace CW, Fordahl SC (2022) Obesity and dietary fat influence dopamine neurotransmission: exploring the convergence of metabolic state, physiological stress, and inflammation on dopaminergic control of food intake. *Nutr Res Rev* 35: 236-251.
 18. Volkow ND, Wang GJ, Baler RD (2011) Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci* 15: 37-46.
 19. Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. (2001) Brain dopamine and obesity. *Lancet* 357: 354-357.
 20. Yohn SE, Galbraith J, Calipari ES, Conn PJ (2019) Shared Behavioral and Neurocircuitry Disruptions in Drug Addiction, Obesity, and Binge Eating Disorder: Focus on Group I mGluRs in the Mesolimbic Dopamine Pathway. *ACS Chem Neurosci* 10: 2125-2143.
 21. Qin D, Qi J, Shi F, Guo Z, Li H (2025) About Sugar Addiction. *Brain Behav* 15: e70338.
 22. Maqsood S, Ahmed F, Arshad MT, Ikram A, Abdullahi MA (2025) Comparative Analysis of Food Addiction and Obesity: A Critical Review. *Food Sci Nutr* 13: e70799.
 23. Sutton Hickey AK, Matikainen-Ankney BA (2025) Endogenous opioid receptors and the feast or famine of maladaptive feeding. *Nat Commun* 16: 2270.
 24. Nolan-Poupert S, Veldhuizen MG, Geha P, Small DM (2013) Midbrain response to milkshake correlates with ad libitum milkshake intake in the absence of hunger. *Appetite* 60: 168-174.
 25. Krupa H, Gearhardt AN, Lewandowski A, Avena NM (2024) Food Addiction. *Brain Sci* 14: 952.
 26. Burghardt PR, Rothberg AE, Dykhuis KE, Burant CF, Zubieta JK (2015) Endogenous opioid mechanisms are implicated in obesity and weight loss in humans. *J Clin Endocrinol Metab* 100: 3193-3201.
 27. Vohra MS, Benchoula K, Serpell CJ, Hwa WE (2022) AgRP/NPY and POMC neurons in the arcuate nucleus and their potential role in treatment of obesity. *Eur J Pharmacol* 915: 174611.
 28. Piloizzi A, Carro C, Huang X (2020) Roles of β -endorphin in stress, behavior, neuroinflammation, and brain energy metabolism. *Int J Mol Sci* 22: 338.
 29. Temple JL (2014) Factors that influence the reinforcing value of foods and beverages. *Physiol Behav* 136: 97-103.
 30. Haghighi A (2014) Opioid receptor mu 1 gene, fat

- intake and obesity in adolescence. *Mol Psychiatry* 19: 63-68
31. Pucci M (2019) Preclinical and clinical evidence for a distinct regulation of mu opioid and type 1 cannabinoid receptor genes expression in obesity. *Front Genet* 10: 523.
 32. Castro DC, Berridge KC (2014) Opioid hedonic hotspot in nucleus accumbens shell: mu, delta, and kappa maps for enhancement of sweetness “liking” and “wanting”. *J Neurosci* 34: 4239-4250.
 33. Pecina S, Berridge KC (2005) Opioid site in nucleus accumbens shell mediates eating and hedonic “liking” for food: map based on microinjection Fos plumes. *Brain Res* 863: 71-86.
 34. Kelley AE, Berridge KC (2002) The neuroscience of natural rewards: relevance to addictive drugs. *J Neurosci* 22: 3306-3311.
 35. MacDonald AF, Billington CJ, Levine AS (2003) Effects of the opioid antagonist naltrexone on feeding induced by DAMGO in the ventral tegmental area and in the nucleus accumbens shell region in the rat. *Am J Physiol Regul Integr Comp Physiol* 285: R999-R1004.
 36. Laurent V, Morse AK, Balleine BW (2015) The role of opioid processes in reward and decision-making: opioids and reward. *Br J Pharmacol* 172: 449-459.
 37. Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ (2002) Opioid modulation of taste hedonics within the ventral striatum. *Physiol Behav* 76: 365-377.
 38. Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF (2004) Opiate-like effects of sugar on gene expression in reward areas of the rat brain. *Mol Brain Res* 124: 134-142.
 39. Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, Schwartz GJ, Moran TH, Hoebel BG (2001) Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport* 12: 3549-3552.
 40. Boggiano MM, Chandler PC, Viana JB, Oswald KD, Maldonado CR, Wauford PK (2005) Combined dieting and stress evoke exaggerated responses to opioids in binge-eating rats. *Behav Neurosci* 119: 1207-1214.
 41. Berthoud HR (2012) The neurobiology of food intake in an obesogenic environment. *Proc Nutr Soc* 71: 478-487.
 42. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, et al. (1998) Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 92: 573-585.
 43. Cason AM, Smith RJ, Tahsili-Fahadan P, Moorman DE, Sartor GC, Aston-Jones G (2010) Role of orexin/hypocretin in reward-seeking and addiction: implications for obesity. *Physiol Behav* 100: 419-428.
 44. Meredith GE, Blank B, Groenewegen HJ (1989) The distribution and compartmental organization of the cholinergic neurons in nucleus accumbens of the rat. *Neuroscience* 31: 327-345.
 45. Xiang Z, Thompson AD, Jones CK, Lindsley CW, Conn PJ (2012) Roles of the M1 muscarinic acetylcholine receptor subtype in the regulation of basal ganglia function and implications for the treatment of Parkinson's disease. *J Pharmacol Exp Ther* 340: 595-603.
 46. DeBoer P, Abercrombie ED, Heeringa M, Westerink BHC (1993) Differential effect of systemic administration of bromocriptine and L-DOPA on the release of acetylcholine from striatum of intact and 6-OHDA-treated rats. *Brain Res* 608: 198-203.
 47. Mark GP, Rada P, Pothos E, Hoebel BG (1992) Effects of feeding and drinking on acetylcholine release in the nucleus accumbens, striatum, and hippocampus of freely behaving rats. *J Neurochem* 58: 2269-2274.
 48. Rada P, Avena NM, Hoebel BG (2005) Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. *Neuroscience* 134: 737-744.
 49. Mark GP, Shabani S, Dobbs LK, Hansen ST, Health O (2011) Cholinergic modulation of mesolimbic dopamine function and reward. *Physiol Behav* 104: 76-81.
 50. Aitta-aho T, Phillips BU, Pappa E, Hay YA, Harnischfeger F, et al. (2017) Accumbal cholinergic interneurons differentially influence motivation related to satiety signaling. *eNeuro* 4: 0328.
 51. Mark GP, Blander DS, Hoebel BG (1991) A conditioned stimulus decreases extracellular dopamine in the nucleus accumbens after the development of a learned taste aversion. *Brain Res* 551: 308-310.
 52. Mark GP, Weinberg JB, Rada PV, Hoebel BG (1995) Extracellular acetylcholine is increased in the nucleus accumbens following the presentation of an aversively conditioned taste stimulus. *Brain*

- Res 688: 184-188.
53. Wiss DA, Avena N, Rada P (2018) Sugar addiction: from evolution to revolution. *Front Psychiatry* 9: 545.
54. Harris GC, Aston-Jones G (2001) Augmented accumbal serotonin levels decrease the preference for a morphine associated environment during withdrawal. *Neuropsychopharmacology* 24: 75-85.
55. Chandler-Laney P, Castaneda E, Pritchett C, Smith M, Giddings M, et al. (2007) A history of caloric restriction induces neurochemical and behavioral changes in rats consistent with models of depression. *Pharmacol Biochem Behav* 87: 104-114.
56. Asgari R, Caceres-Valdiviezo M, Wu S, Hamel L, Humber BE, et al. (2025) Regulation of energy balance by leptin as an adiposity signal and modulator of the reward system. *Mol Metab* 91: 102078.
57. Fulton S, Pissios P, Manchon RP, Stiles L, Forgione L, et al. (2006) Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* 51: 811-822.
58. Polishchuk H, Guzik K, Kantyka T (2025) Beyond hunger: the structure, signaling, and systemic roles of ghrelin. *Int J Mol Sci* 26: 10996.
59. Abizaid A, Liu ZW, Andrews ZB, Shanabrough M, Borok E, et al. (2006) Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. *J Clin Invest* 116: 3229-3239.
60. Kenny PJ (2011) Common cellular and molecular mechanisms in obesity and drug addiction. *Nat Rev Neurosci* 12: 638-651.
61. Gearhardt AN, Schulte EM (2021) Is food addictive? A review of the evidence. *Annu Rev Nutr* 41: 387-410.
62. Berridge KC, Ho CY, Richard JM, Di Feliceantonio AG (2010) The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. *Brain Res* 1350: 43-64.
63. Sutton Hickey AK, Matikainen-Ankney BA (2025) Endogenous opioid receptors and the feast or famine of maladaptive feeding. *Nat Commun* 16: 2270.
64. Schulz LO, Bennett PH, Ravussin E, Kidd JR, Kidd KK, et al. (2006) Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S. *Diabetes Care* 29: 1866-1871.
65. Ravussin E, Valencia ME, Esparza J, Bennett PH, Schulz LO (1994) Effects of a traditional lifestyle on obesity in Pima Indians. *Diabetes Care* 17: 1067-1074.
66. Marmot MG, Syme SL (1976) Acculturation and coronary heart disease in Japanese-Americans. *Am J Epidemiol* 104: 225-247.
67. Kato H, Tillotson J, Nichaman MZ, Rhoads GG, Hamilton HB (1973) Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: serum lipids and diet. *Am J Epidemiol* 97: 372-385.
68. Kanaya AM, Herrington D, Vittinghoff E, Ewing SK, Liu K, et al. (2014) Understanding the high risk of diabetes among South Asians: the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. *J Diabetes Complications* 28: 518-523.
69. Shah AD, Kandula NR, Lin F, Allison MA, Carr J, et al. (2016) Less subcutaneous and more visceral adipose tissue in South Asians: The MASALA study. *Int J Obes* 40: 1154-1160.
70. Vangay P, Johnson AJ, Ward TL, Al-Ghalith GA, Shields-Cutler RR, et al. (2018) US immigration westernizes the human gut microbiome. *Cell* 175: 1187-1199.
71. Penzenstadler L, Soares C, Karila L, Khazaal Y (2019) Systematic review of food addiction as measured with the Yale Food Addiction Scale: implications for the food addiction construct. *Curr Neuropsychopharmacol* 17: 526-538.
72. Gearhardt AN, Corbin WR, Brownell KD (2009) Preliminary validation of the Yale Food Addiction Scale. *Appetite* 52: 430-436.
73. Gearhardt AN, Schulte EM (2021) Is food addictive? A review of the evidence. *Annu Rev Nutr* 41: 387-410.
74. Schulte EM, Gearhardt AN (2017) Development of the modified Yale Food Addiction Scale version 2.0. *Eur Eat Disord Rev* 25: 302-308.
75. Kardefelt-Winther D, Heeren A, Schimmenti A, van Rooij A, Muraige P, et al. (2017) How can we conceptualize behavioural addiction without pathologizing common behaviours? *Addiction* 112: 1709-1715.
76. Billieux J, van Rooij AJ, Heeren A, Schimmenti A, Muraige P, et al. (2017) Behavioural addiction open

- definition 2.0-using the open science framework for collaborative and transparent theoretical development. *Addiction* 112: 1723-1724.
77. Schiestl ET, Wolfson JA, Gearhardt AN (2022) The qualitative evaluation of the Yale Food Addiction Scale 2.0. *Appetite* 175: 106077.
78. Karapareddy V (2019) A review of integrated care for concurrent disorders: cost effectiveness and clinical outcomes. *J Dual Diagn* 15: 56-66.
79. Oliveira E, Kim HS, Lacroix E, de Fátima Vasques M, Durante CR, et al. (2020) The clinical utility of food addiction: characteristics and psychosocial impairments in a treatment-seeking sample. *Nutrients* 12: 3388.
80. De Castro V, Fong T, Rosenthal RJ, Tavares H (2007) A comparison of craving and emotional states between pathological gamblers and alcoholics. *Addict Behav* 32: 1555-1564.
81. Tavares H, Zilberman ML, Hodgins DC, El-Guebaly N (2005) Comparison of craving between pathological gamblers and alcoholics. *Alcohol Clin Exp Res* 29: 1427-1431.
82. Burger KS, Sanders AJ, Gilbert JR (2016) Hedonic hunger is related to increased neural and perceptual responses to cues of palatable food and motivation to consume: evidence from 3 independent investigations. *J Nutr* 146: 1807-1812.
83. Duhne M, Volkow ND (2025) The cognitive burden of hedonic hunger: neurobiological mechanisms underlying 'food noise'. *Trends Cogn Sci* 29: 214-226.
84. Jensterle M, Rizzo M, Haluzík M, Janež A (2025) Efficacy of GLP-1 receptor agonists on 'food noise' and intrusive food thoughts in patients with obesity: a neurocognitive perspective. *Lancet Diabetes Endocrinol* 12: 115-124.
85. Goldstone AP, Precht CG, Scholtz S, Miras AD, Chhina N, et al. (2014) Ghrelin mimics fasting to enhance reactivity of human bio-imaging reward circuitry to high-calorie foods. *Am J Clin Nutr* 99: 1310-1319.
86. Fisberg M, Gioia N, Maximino P (2024) Transgenerational transmission of eating habits. *J Pediatr (Rio J)* 100: S82-S87.
87. Haines J, Haycraft E, Lytle L, Nicklaus S, Kok FJ, et al. (2019) Nurturing children's healthy eating: position statement. *Appetite* 137: 124-133.
88. Egusquiza RJ, Blumberg B (2020) Environmental obesogens and their impact on susceptibility to obesity: new mechanisms and chemicals. *Endocrinology* 161: bqaa024.
89. Mocnik M, Marcun Varda N (2021) Obesogens in children-an uncharted territory. *Metabolites* 11: 882.
90. Núñez-Sánchez MÁ, Jiménez-Méndez A, Suárez-Cortés M, Martínez-Sánchez MA, Sánchez-Solís M, et al. (2023) Inherited epigenetic hallmarks of childhood obesity derived from prenatal exposure to obesogens. *Int J Environ Res Public Health* 20: 4711.
91. Micic D, Polovina S, Micic D, Macut D (2021) Endocrine disrupting chemicals and obesity: the evolving story of obesogens. *Acta Endocrinol* 17: 503-508.
92. Robinson T, Berridge K (2008) The incentive sensitization theory of addiction: some current issues. *Philos Trans R Soc Lond B Biol Sci* 363: 3137-3146.
93. Dill B, Holton R (2014) The addict in us all. *Front Psychiatry* 5: 139.
94. Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 8: 1481-1489.
95. Graybiel AM (2008) Habits, rituals, and the evaluative brain. *Annu Rev Neurosci* 31: 359-387.
96. Jurema Santos GC, Góis Leandro C, Oliveira TLP (2026) Associations between food addiction symptoms, food intake and BMI-for-age in children from a low-income region: a structural equation modeling approach. *Eur J Clin Nutr* 80: 515-523.
97. Sacks JJ, Gonzales KR, Bouchery EE, Tomedi LE, Brewer RD (2015) 2010 national and state costs of excessive alcohol consumption. *Am J Prev Med* 49: e73-e79.
98. Verhulst B, Neale MC, Kendler KS (2015) The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. *Psychol Med* 45: 1061-1072.
99. Kendler KS, Myers J, Prescott CA (2007) Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. *Arch Gen Psychiatry* 64: 1313-1320.
100. Hatoum AS, et al. (2023) Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders. *Nat Ment Health* 1: 210-223.
101. Hatoum AS, et al. (2022) The addiction risk factor: a unitary genetic vulnerability characterizes

- substance use disorders and their associations with common correlates. *Neuropsychopharmacology*.
102. Khan Y, et al. (2025) Transdiagnostic and disorder-level genome-wide association studies enhance precision of substance use and psychiatric genetic risk profiles in African and European ancestries. *Biol Psychiatry*.
103. Miller AP, Bogdan R, Agrawal A, Hatoum AS (2024) Generalized genetic liability to substance use disorders. *J Clin Invest*.
104. Poore HE, Chatzinakos C, Leger B, et al. (2026) Multivariate genetic analyses of 2.2 million individuals reveal broad and substance-specific pathways of addiction risk. *Nat Ment Health* 4: 582-593.
105. Wood W, Neal DT (2007) A new look at habits and the habit-goal interface. *Psychol Rev* 114: 843-863.
106. Wood W, Mazar A, Neal DT (2022) Habits and goals in human behavior: separate but interacting systems. *Perspect Psychol Sci* 17: 590-605.
107. Bouton ME (2021) Context, attention, and the switch between habit and goal-direction in behavior. *Learn Behav* 49: 349-362.
108. Brewer JA, Elwafi HM, Davis JH (2013) Craving to quit: psychological disorder and distinct neurobiological mechanisms of mindfulness training as a treatment for addictions. *Curr Top Behav Neurosci* 13: 415-432.
109. Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F (2009) Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology* 56: 3-8.
110. Adriaanse MA, Gollwitzer PM, De Ridder DTD, de Wit JBF, Kroese FM (2011) Breaking habits with implementation intentions: a test of underlying processes. *Pers Soc Psychol Bull* 37: 502-513.
111. Bayer UC, Achtziger A, Gollwitzer PM, Moskowitz GB (2009) Responding to subliminal cues: do if-then plans facilitate action preparation and initiation without conscious intent? *Soc Cogn* 27: 183-201.
112. Díaz-Gerevini GT, Parisi C, Reartes G, Priotto S, Repossi G, et al. (2026) Cognitive Frailty in Older Adults with Diabetes Mellitus: Bases for its Approach. *J Adv Clin Neurol Res*. 3071-0731.
113. Moiz A, Fillion KB, Tsoukas MA, Yu OH, Peters TM, et al. (2025) Mechanisms of GLP-1 receptor agonist-induced weight loss: a review of central and peripheral pathways in appetite and energy regulation. *Am J Med* 138: 934-940.
114. Díaz-Gerevini GT, Campanella C, Reartes GA, López C, Priotto S, et al. (2025) Beneficial effects of the "Learning to Live" program on the psychoaffective health of diabetic and non-diabetic older adults from Carlos Paz, Córdoba, Argentina in times of the COVID-19 pandemic. *Pinelatioamericana* 1: 26-35.
115. van Bloemendaal L, Veltman DJ, Ten Kulve JS, Groot PF, Ruhé HG, et al. (2015) Brain reward-system activation in response to anticipation and consumption of palatable food is altered by glucagon-like peptide-1 receptor activation in humans. *Diabetes Obes Metab* 17: 878-886.
116. O'Connor RM (2026) Revisiting food addiction in the era of GLP-1-based obesity pharmacotherapy via neural reward pathways linking feeding and substance use. *Front Behav Neurosci* 20: 1805953.
117. Hironaka J, Ushigome E, Kondo Y, Hashimoto Y, Osaka T, et al. (2025) Changes in food preferences after oral semaglutide administration in Japanese patients with type 2 diabetes: KAMOGAWA-DM cohort. *Diab Vasc Dis Res* 22: 14791641251318309.
118. Friedrichsen M, Breitschaft A, Tadayon S, Wizert A, Skovgaard D (2021) The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes Obes Metab* 23: 754-762.
119. Tornehave D, Kristensen P, Romer J, Knudsen LB, Heller RS (2008) Expression of the GLP-1 receptor in mouse, rat, and human pancreas. *J Histochem Cytochem* 56: 841-851.
120. Broide E, Bloch O, Ben-Yehudah G, Cantrell D, Shirin H, et al. (2013) GLP-1 receptor is expressed in human stomach mucosa: analysis of its cellular association and distribution within gastric glands. *J Histochem Cytochem* 61: 649-658.
121. Drokhlyansky E, Smillie CS, Van Wittenberghe N, Ericsson M, Griffin GK, et al. (2020) The human and mouse enteric nervous system at single-cell resolution. *Cell* 182: 1606-1622.e23.
122. Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, et al. (2024) Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Signal Transduct Target Ther* 9: 234.
123. Brierley DI, de Lartigue G (2022) Reappraising the role of the vagus nerve in GLP-1-mediated

- regulation of eating. *Br J Pharmacol* 179: 584-599.
124. Williams EK, Chang RB, Storchlic DE, Umans BD, Lowell BB, Liberles SD (2025) Sensory neurons that detect stretch and nutrients in the digestive system. *Cell* 188: 3623-3624.
125. Abbott CR, Monteiro M, Small CJ, Sajedi A, Smith KL, et al. (2005) The inhibitory effects of peripheral administration of peptide YY(3-36) and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway. *Brain Res* 1044: 127-131.
126. Dossat AM, Kokoska MM, Whitaker-Fornek JR, Sniffen SE, Kulkarni AS, et al. (2023) Glucagon-like peptide-1 receptors in the gustatory cortex influence food intake. *J Neurosci* 43: 4251-4261.
127. Holt MK, Richards JE, Cook DR, Brierley DI, Williams DL, et al. (2019) Preproglucagon neurons in the nucleus of the solitary tract are the main source of brain GLP-1, mediate stress-induced hypophagia, and limit unusually large intakes of food. *Diabetes* 68: 21-33.
128. Tuesta LM, Chen Z, Duncan A, Fowler CD, Ishikawa M, et al. (2017) GLP-1 acts on habenular avoidance circuits to control nicotine intake. *Nat Neurosci* 20: 708-716.
129. Merchenthaler I, Lane M, Shughrue P (1999) Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J Comp Neurol* 403: 261-280.
130. Drucker DJ, Asa S (1988) Glucagon gene expression in vertebrate brain. *J Biol Chem* 263: 13475-13478.
131. Moore PW, Malone K, VanValkenburg D, Rando LL, Williams BC, et al. (2023) GLP-1 agonists for weight loss: pharmacology and clinical implications. *Adv Ther* 40: 723-742.
132. Rhea EM, Babin A, Thomas P, Omer M, Weaver R, et al. (2024) Brain uptake pharmacokinetics of albiglutide, dulaglutide, tirzepatide, and DA5-CH in the search for new treatments of Alzheimer's and Parkinson's diseases. *Tissue Barriers* 12: 2292461.
133. McLean BA, Wong CK, Campbell JE, Hodson DJ, Trapp S, Drucker DJ (2021) Revisiting the complexity of GLP-1 action from sites of synthesis to receptor activation. *Endocr Rev* 42: 101-132.
134. Gabery S, Salinas CG, Paulsen SJ, Ahnfelt-Ronne J, Alanentalo T, et al. (2020) Semaglutide lowers body weight in rodents via distributed neural pathways. *JCI Insight* 5: 133429.
135. Estado V, Obadia N, Chateaubriand PH, Figueiredo V, Curty M, et al. (2025) Semaglutide restores astrocyte-vascular interactions and blood-brain barrier integrity in a model of diet-induced metabolic syndrome. *Diabetol Metab Syndr* 17: 2.
136. Zhang Q, Delessa CT, Augustin R, Bakhti M, Collden G, et al. (2021) The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling. *Cell Metab* 33: 833-844.e5.
137. Enyew Belay K, Jemal RH, Tuyizere A (2024) Innovative glucagon-based therapies for obesity. *J Endocr Soc* 8: bvae197.

