Obesity: Brain Mechanisms in Hypothalamic and Extrahypothalamic Regions

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Abstract

Obesity prevalence has reached epidemic proportions and obesity rates are expected to further rise in the coming decades. Such escalations pose significant risk for human health and have profound implications for costs to the individual and society. Successful treatment options for combating obesity have been limited to surgical practices which target peripheral organs such as the stomach or gastrointestinal tract. However, surgery is usually an option for cases that comprise a small percentage of the obese population. Pharmacological therapeutics, which would be applicable to the majority of human obesity, have been developed, but there have been no specific treatments with adequate efficacy to curb the escalating prevalence of obesity. Therefore, in efforts to discover novel therapeutics, it is imperative to advance our understanding of the brain's contribution to overeating and to lack of physical activity, which together comprise the main factors that give rise to the majority of obesity (i.e., diet-induced obesity). This chapter will focus on providing a brief background on obesity, followed by an overview of the main neurobiological obesity mechanisms as these have been

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described to date. Finally, an outlook on future approaches that perhaps show promise for obesity therapeutics will be discussed.

Keywords

Adiposity · Glucose · Insulin · Leptin · Brown adipose tissue · White adipose tissue · Ghrelin · Satiety · Metabolism · Energy intake · Energy expenditure · Hypothalamus · Nucleus accumbens · Orexin · Hypocretin · Melanin-concentrating hormone · Agouti-related peptide · Proopiomelanocortin · Dopamine · Thermogenesis · Autonomic · Reward · Reinforcement · Motivation · Sensory integration · Visceromotor · Cue · Hedonic

Brief Background

In 1990, the highest reported prevalence of obesity among adults in the United States was at approximately 15% (Mokdad et al. 1999). By 2000, this number had increased to 25% (Mokdad et al. 2003) and as of 2012, over 30% of adults and 17% of children and adolescents in the United States were reported as obese (Ogden et al. 2014). As of 2014, there are now three states with a prevalence of obesity greater than 35% (Fig. 1), and it is estimated that by 2030, over 50% of the US population will be obese (Finkelstein et al. 2012). This dramatic elevation in obesity prevalence constitutes a dire emergency for human health and carries significant societal and economic implications. Importantly, rising obesity rates are not limited to the United States but have also been observed in many other countries, a phenomenon that unequivocally grants obesity the capacity to be referred to as a global "epidemic".

In broad terms, obesity is a condition characterized by increased body weight due to excess adiposity brought upon by chronically elevated energy intake (i.e., amount of food consumed) and decreased energy expenditure (physical activity). Overeating is a critical factor that contributes to the vast majority of human obesity (i.e., diet-induced obesity). Food is of course necessary for survival and in addition to its nutritional benefits, it also contains powerful hedonic properties. Together, nutritional and hedonic reinforcement instill the reward, motivation, and "appetitive drive" which increases the likelihood of behavioral manifestations aimed at seeking and consuming food. Accordingly, aberrant nutritional, hedonic, and reward processing, especially in vulnerable populations are thought to underlie, in part, predisposition and development of diet-induced obesity.

In addition to food, metabolism also plays a critical role in obesity. Impairments in metabolism, even independent of feeding, can readily contribute to obesity via inefficient processing of energy utilization. Furthermore, in addition to metabolic deficits, obesity is often characterized by presence of additional features such as circulatory problems and cardiovascular disease, skeletal problems, dysregulated mood and motivation and depression, impaired insulin and glucose metabolism, and type 2 diabetes as well as certain psychiatric diseases.

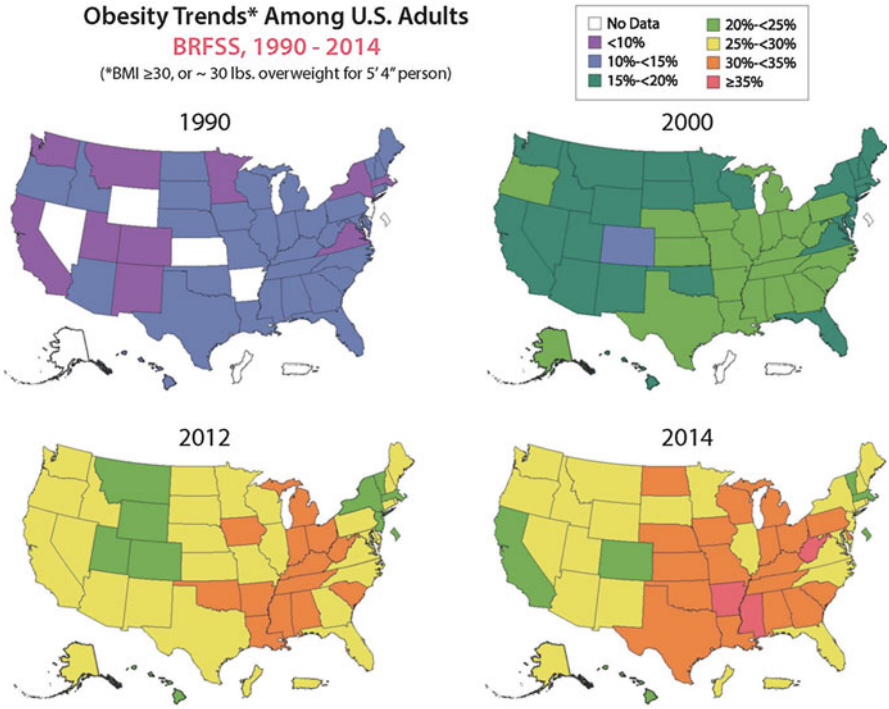

Fig. 1 Obesity prevalence rates in the United States from 1990 to 2014 (Adapted from the Centers for Disease Control, http://www.cdc.gov/obesity/data/prevalence-maps.html)

In some (and usually rare) cases, impairments in feeding and metabolism can arise from certain genetic mutations (e.g., leptin deficiency, melanocortin 4 receptor gene mutations) or pathological events (e.g., hypothyroidism); however, the vast majority of human obesity, especially the dramatic increase in recent years, is mostly attributed to interactions between genetic vulnerability that confers predisposition to overeating and unique environmental settings (i.e., chronic overconsumption of readily available, nutrient-dense food coupled with the modern-day sedentary lifestyle) (Fig. 2). Indeed, our recent environment, especially in developed countries, consists of a setting where nutritionally dense food is plentiful and physical exercise is limited. In this type of environment, brain mechanisms that originally evolved to prevent hunger, now promote overeating, which with chronic and repeated access to such food can lead to obesity. In this respect, obesity shares similarities with other disorders and diseases like substance abuse and drug addiction. Interestingly, similarities between obesity and drug addiction are not limited to views regarding willpower but also extend to similarities in neurobiology, and similar brain circuits that are implicated in obesity are also commonly associated with substance abuse and drug addiction (Volkow et al. 2013; Krashes and Kravitz 2014).

In general, overeating behavior is regulated by complex neural circuits which span a broad range of regulation of movement, satiety, reward, and learning, to

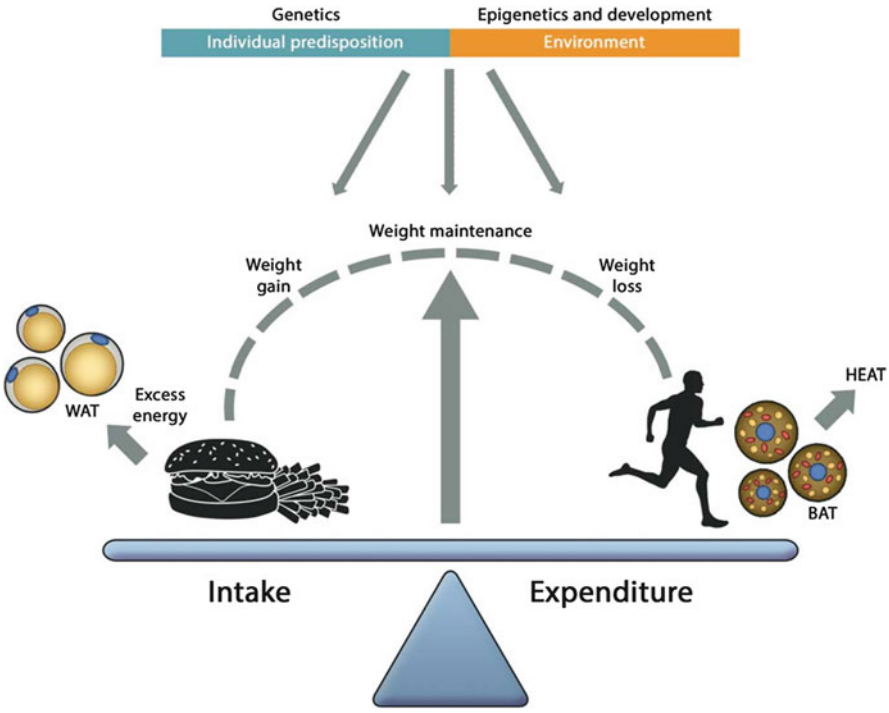

Fig. 2 Energy intake and expenditure are modulated by genetic and environmental factors (*WAT* white adipose tissue, *BAT* brown adipose tissue)

glucose regulation, autonomic system responses, temporal discounting, and complex decision-making. Indeed, in the past few decades, the notion of a neurobiological basis of obesity has gained significant acceptance. A major driving force for this perspective has been the experimental literature and recent research findings, which are summarized in the following sections.

Hypothalamic Mechanisms

The hypothalamus is undoubtedly the prototypical brain region implicated in obesity. This complex structure is comprised of several different subregions, each of which contains heterogeneous cell populations that influence feeding and energy homeostasis in various ways and degrees of complexity. Among such populations, of notable prominence is the central melanocortin system which is at the core of brain regulation of energy intake and expenditure. This system, comprised of pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons, is located in the arcuate nucleus of the hypothalamus (Fig. 3), a brain area situated at the most basal part of the hypothalamus, proximate to the median eminence, and thus strategically poised to receive energy input (e.g., glucose) and humoral signals

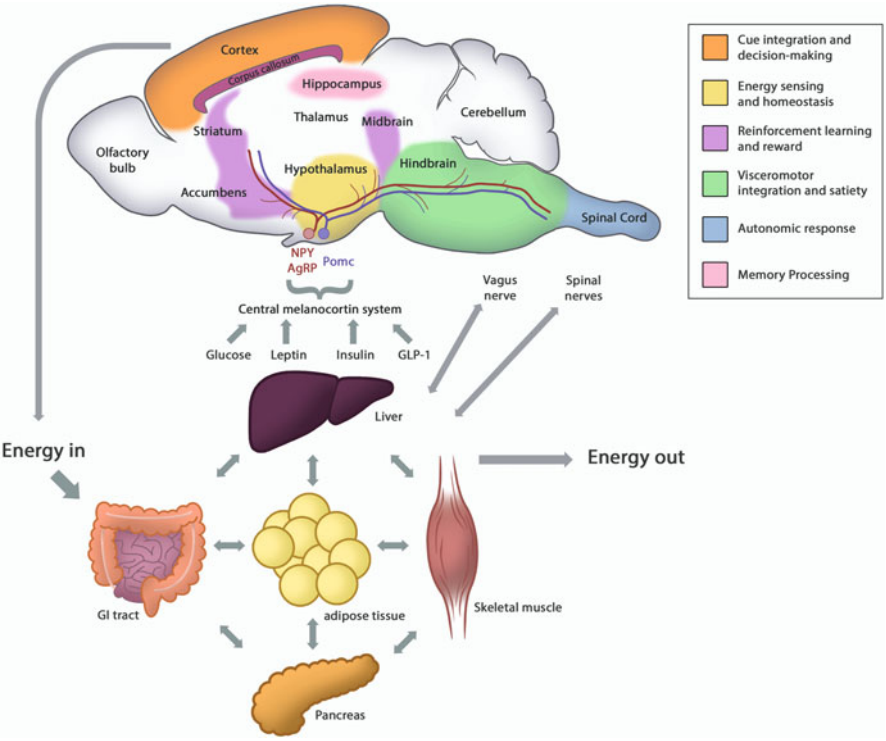

Fig. 3 Central and peripheral interactions regulating energy intake and expenditure

(e.g., leptin, ghrelin, insulin) from the periphery (Koch and Horvath 2014). Such signals activate or inhibit these arcuate neurons which can drive complex appetitive or aversive behaviors relevant to feeding and energy homeostasis via their projections to downstream circuits.

POMC neurons are excitatory and release the melanocortin receptor peptide agonist, α-melanocyte-stimulating hormone (α-MSH), whereas AgRP neurons are inhibitory and release the AgRP peptide, neuropeptide Y (NPY), and GABA. α-MSH acts as an agonist at melanocortin receptors, whereas AgRP acts as an inverse agonist at these same sites. Among different subtypes, the melanocortin receptor 4 (Mc4R) in particular mediates a large component of feeding effects of POMC and AgRP/NPY neurons and is also implicated in obesity. Specifically, MC4R knockout (KO) mice display a robust obesity phenotype and the MC4R mutation comprises the most common cause of monogenic obesity in humans. POMC neurons are anorexigenic and their activation is associated with decreasing food intake, whereas AgRP/NPY neurons are orexigenic, and when stimulated, these neurons increase food intake and decrease energy expenditure.

The paraventricular nucleus of the hypothalamus (PVN), which is a critical downstream target of POMC and AgRP/NPY neurons, plays an important role in feeding (Shah et al. 2014; Garfield et al. 2015) and is implicated in obesity. This

region contains several different subsets of neurons that have been implicated in feeding and obesity including single minded 1 (Sim1) and oxytocin-expressing neurons. Early studies suggested that lesions to the ventromedial nucleus of the hypothalamus (VMN) produced hyperphagia and obesity (King 2006). The effects from such manipulations are of greater magnitude than lesions to other hypothalamic areas such as to the PVN and seem to be derived mostly via impaired metabolism. Like the PVN, the VMN receives considerable melanocortin input, and POMC activity in the VMN is known to regulate feeding behavior. The dorsomedial hypothalamus (DMH) is known to regulate food intake but also recently shown to regulate thermogenesis, mainly via the actions of NPY in this region, which include high-fat-diet-induced weight gain, glucose intolerance, and decreased energy expenditure (Bi et al. 2012; Bi 2013). The lateral hypothalamus (LH), a brain region with a critical role in motivation and reward, is also implicated in metabolic regulation and obesity (Burdakov et al. 2013). The LH contains orexin/hypocretin (ORX) neurons which promote arousal, reward seeking, and obesity resistance and melanin-concentrating hormone (MCH) neurons which promote sleep, physical inactivity, weight gain, and glucose metabolic deficits. In addition to ORX/MCH neurons, the LH contains a distinct group of neurons that express receptors for leptin and that seem to be involved in decreasing feeding and locomotor activity via effects of extrahypothalamic systems involved in reward and reinforcement such as the mesolimbic dopamine system (Burdakov et al. 2013).

The melanocortin system also influences feeding via projections to various extrahypothalamic sites such as the bed nucleus of the stria terminalis (BNST), paraventricular thalamus (PVT), and other regions (midbrain, brainstem, amygdala). In some of these targets, GABA and NPY have been shown to elicit rapid feeding responses while AgRP leads to delayed but longer feeding responses. Furthermore, POMC and AgRP/NPY neurons form loops with some of these downstream projection areas, which likely act to regulate feeding initiation/termination and other relevant behaviors.

Aside from their direct effects on stimulating feeding behavior and appetitive behaviors, both POMC and AgRP/NPY neurons are susceptible to energy signals, metabolism, and nutrients. Specifically, feeding, fasting, and weight loss reciprocally activate and inhibit POMC neurons and increase activity of AgRP/NPY neurons. As described earlier, the arcuate, via its proximity to the median eminence, is poised to receive information from the circulation via energy and nutritional messengers such as leptin, insulin, ghrelin, and glucose. For example, the anorexigenic peptide leptin, which is secreted from white adipose tissue and signals availability of fat stores, activates POMC neurons and inhibits AgRP/NPY neurons. Insulin inhibits both POMC and AgRP/NPY neurons (Varela and Horvath 2012). In contrast, the orexigenic peptide ghrelin activates AgRP/NPY neurons (Andrews 2011). It is important to note that not all POMC neurons respond to both leptin and insulin, as different subsets with unique responding to each of these messengers has been reported. AgRP/NPY neurons are highly active in the leptin-deficient *ob/ob* mouse, whereas leptin deficiency is associated with blunted responses of POMC neurons. Surprisingly, deletion of leptin receptors from POMC and AgRP/NPY

neurons only leads to mild obesity features (Varela and Horvath 2012), whereas deletion of leptin receptors from some other hypothalamic neuronal populations such as GABAergic nitric oxide synthase (nNOS) neurons cause severe hyperphagia and obesity (Leshan et al. 2012).

In sum, the hypothalamic melanocortin system comprises a neurobiological system that plays a critical role in regulation of feeding and metabolism, and impairments to this system coincide with features of obesity such as increased hunger, overeating, and decreased metabolism. Further studies focusing on this system and its downstream projections will undoubtedly be relevant for expanding our understanding of the neurobiological regulation of obesity.

Brainstem and Spinal Cord

The brainstem integrates visceromotor and satiety signals from the periphery with energy-sensing hypothalamic and neuroendocrine circuitry to coordinate regulation of feeding and metabolism. However, in addition to these systems, the brainstem also relies on the autonomic nervous system to influence peripheral metabolism. In this regard, the hypothalamus communicates directly with visceromotor and autonomic brainstem nuclei and spinal cord to coordinate neuroendocrine and neuronal regulation of peripheral organs (Schneeberger et al. 2013; Abraham et al. 2014; Bisschop et al. 2015). This integration has considerable implications for obesity, especially with respect to regulation of forebrain feeding circuits, involvement of developmental metabolic programming (Elson and Simerly 2015), and consequently risk for obesity vulnerability.

Cortical Mechanisms

The cortex integrates visual, olfactory, taste, textural, and interoceptive cues signaling availability of food and guiding decision-making strategies for seeking and procuring food. Some of the most notable regions that have been implicated in obesity involve the insular (IC), orbitofrontal (OFC), anterior cingulate (ACC), and dorsolateral prefrontal (DLPFC) cortices (Pursey et al. 2014).

The IC is divided into two main parts, the larger anterior and the smaller posterior portion. The IC sends and receives direct connections to thalamus, the amygdala, and to somatosensory cortex and has been implicated in regulation of several processes related to feeding such as food reward, perception, taste processing, homeostasis/autonomic responses, interoceptive awareness, motor function (e.g., hand-eye coordination), swallowing, and gastric motility, among others (Frank et al. 2013). Obese individuals exhibit decreased functional connectivity of the IC (Kullmann et al. 2012) as well as increased IC activation during exposure to palatable food (Stice et al. 2008b). Moreover, increased IC activation to food was also observed in youth at risk for obesity (Stice et al. 2011), suggesting that IC activation to food may be a predisposing factor for obesity vulnerability.

The OFC (also known as ventromedial PFC) is located in the frontal lobe and plays a critical role in sensory integration, expectation, and emotional components of decision-making as well as relative motivational properties and value of food. Importantly, unlike the IC, the OFC does not seem to be implicated in food palatability. This structure shares many widespread connections to areas of the brain such as thalamus, striatum, and motor, limbic, and sensory cortices, and OFC volume and function have been implicated in obesity (Cohen et al. 2011; Shott et al. 2015). Moreover, obese individuals exhibit decreased OFC metabolic activity (Volkow et al. 2008), and in agreement with this, metabolic activity in the OFC negatively correlates with body mass index (BMI) (Volkow et al. 2009).

The ACC, also located in the frontal lobe, is involved in autonomic function, attention, motivation, reward, emotion, decision-making, and impulsivity. It is comprised of a dorsal and ventral portion. The dorsal portion shares connections with PFC, parietal cortex, and motor and visual systems, while the ventral portion is connected with more limbic regions such as the ventral striatum, amygdala, and hypothalamus. In relation to obesity, studies have reported that obese individuals exhibit decreased ACC volume (Raji et al. 2010) as well as decreased ACC functional responses during food presentation (Gearhardt et al. 2014).

The DLPFC, also located in the frontal lobe, is mainly involved in executive functions like working memory, cognitive flexibility, behavioral inhibition, impulsivity, and planning. The DLPFC shares connections with OFC, association cortices, as well as thalamus, hippocampus, and striatum. DLPFC brain activity in obese subjects predicts long-term weight management (Weygandt et al. 2015), and furthermore, DLPFC-thalamic anatomical connectivity (measured via diffusion-weighted MRI) is reported to be compromised in obese subjects (Gupta et al. 2015).

Hippocampus

Obesity and related metabolic diseases are associated with cognitive deficits and structural and functional impairments to the hippocampus (Stranahan 2015), and recent reports propose critical roles for this region in obesity and associated behaviors and metabolic states, particularly via effects of the hippocampus on energy regulation and feeding (Parent et al. 2014; Kanoski and Grill 2015). Indeed, the hippocampus, likely via its involvement in regulating episodic memory, is thought to play a role in timing of meals, food reward and flavor preference learning, and food-related memory processing (e.g., remembering the taste of a food or where food was initially found or stored). Not surprisingly, therefore, the hippocampus contains receptors for a number of neuropeptides and energy/satiety signals that are involved in feeding behavior and energy regulation (Parent et al. 2014) such as leptin, insulin, ghrelin, and others. Notably, leptin administration into the hippocampus impairs conditioned learning for food reward and lowers body weight (Kanoski et al. 2011). Conversely, visual and olfactory food reward stimulation in obese rats with deficient leptin signaling, via loss of functional leptin receptors, leads to significant and preferential decreases in hippocampal metabolism (Thanos et al. 2008). In

agreement with these findings, lesions to the hippocampus in rodents produce increases in feeding and weight gain (Davidson et al. 2008). Additional clinical evidence further support a role of the hippocampus in obesity. In particular, humans with hippocampal lesions do not remember eating and cannot determine their level of satiety (Parent et al. 2014), which can potentially serve as predisposing factors for overeating and consequently diet-induced obesity.

Striatal Mechanisms

Cortical integration and processing of sensory and interoceptive information pertaining to food and relevant stimuli is transmitted to other brain areas in order to initiate the appropriate goal-directed behavioral responses for procuring food. One such area is the striatum (Macpherson et al. 2014). Indeed, integrity of corticostriatal pathways is impaired in obese subjects, a phenomenon that has been specifically linked to BMI (Volkow et al. 2008, 2009). The striatum is comprised of a dorsal (caudate, putamen) and ventral (nucleus accumbens) division. The nucleus accumbens (NAc) is further divided into the core and shell components. Some of the most notable functions pertaining to the striatum include movement, motivation, hedonic and reward processing, postingestive reinforcement and reinforcement learning, processes critical for appetitive drive, and feeding regulation (Fig. 3). It is therefore not surprising that deficits in striatal structure, neurochemistry, and function have been observed in the context of obesity and eating disorders (Stice et al. 2008a; Raji et al. 2010; Kenny et al. 2013; Tomasi and Volkow 2013).

The striatum contains two main output pathways: the striatonigral pathway is associated with expression of dopamine D1 receptors (D1R) and the opioid peptide prodynorphin (Pdyn), while the striatopallidal pathway is associated with expression of dopamine D2 receptors (D2R) and proenkephalin (Penk) (Macpherson et al. 2014). The striatonigral pathway is generally associated with "Go" responses (e.g., movement initiation, behavioral responding) while the striatopallidal pathway is more closely linked with "No-Go" responding (e.g., movement termination, behavioral inhibition). Of these two pathways, striatopallidal disturbances in particular have been prominent in the context of obesity (Kenny et al. 2013). Importantly, such disturbances have been observed in both human and animal obesity models. Specifically, human morbid obese subjects and obese laboratory rodent models exhibit deficits in D2R binding in this region (Kenny et al. 2013).

In addition to D2R, the striatum also contains dense levels of mu-opioid receptors (MOR), which are associated with hedonics and taste processing and have also been implicated in obesity. In fact, impaired striatal D2R-MOR interactions have also been recently described in human obesity (Tuominen et al. 2015), and MOR binding availability seems to be implicated in weight loss changes due to bariatric surgery in obese patients (Karlsson et al. 2015). It is, however, important to note that similar studies investigating D2R binding availability have provided inconclusive results (Dunn et al. 2010; Steele et al. 2010; de Weijer et al. 2014). These studies collectively highlight that involvement of striatal D2R in obesity is complex and suggest

that striatal D2R impairments are more reflective of morbid obesity cases where subjects exhibit very high BMI (e.g., >40).

The striatum receives dense projections from the midbrain including dopamine-releasing neurons from the substantia nigra (SN) and ventral tegmental area (VTA). The SN dopamine neurons project mainly to the dorsal striatum which is associated with mediating habitual and compulsive feeding behaviors relevant to obesity. In contrast, VTA dopamine neurons project mainly to the NAc (mesolimbic pathway) and cortex (mesocorticolimbic pathway) and are implicated in food reward, food reinforcement learning, as well as postingestive reinforcement (de Araujo et al. 2012; van Zessen et al. 2012), critical processes that drive formation of food preferences. Obesity is associated with blunted midbrain dopamine signaling to both dorsal and ventral striatum (Geiger et al. 2009; Naef et al. 2015). Since these circuits are implicated in reward and reinforcement, it has been suggested that obese individuals are characterized by a state of reduced sensitivity to the rewarding effects of food, which effectively leads to food overconsumption (Wang et al. 2001). Other relevant inputs to striatum originate from hypothalamus and specifically from the LH. In particular, feeding is influenced by both direct and indirect LH projections to ventral striatum, and mainly to the shell of the NAc (Urstadt and Stanley 2015), suggesting that along with integrating reward and reinforcement learning information, the striatum also receives information on energy balance from the LH.

Notably, the location of the striatum (between cortex and hypothalamus) constitutes a critical attribute for this region as a critical component of the neurocircuitry relevant to obesity. In addition to cortex and hypothalamus, however, the mesocorticolimbic, mesolimbic, and striatal output systems also receive information from other areas such as the hippocampus and amygdala which are also implicated in obesity, likely via their involvement in memory and affective processing (Carnell et al. 2011). Collectively, these circuits likely interact in a complex and synergistic manner for regulating normal behaviors relevant to obesity, as well as dysregulated obesity-related behaviors in the context of pathology.

Outlook

As mentioned in the prior sections, obesity rates have reached alarming levels and are expected to escalate over the next few decades. Aside from the detrimental health cost incurred to the individual, obesity also has significant economic implications (e.g., it is estimated that obese individuals incur approximately 42% greater health care costs than normal-weight individuals (Finkelstein et al. 2009)). As such, it is critical to develop treatment methods and approaches for addressing these escalations in obesity prevalence. Most pharmacological treatments that have been developed to date have been largely unsuccessful, likely due to the fact that obesity is a multidimensional condition with complicated etiology and is characterized to a large extent by individual differences in metabolism and in the regulation of overeating. Of the successful treatment approaches to date, bariatric surgery methods have been the treatment of choice, especially for morbid

or severe obesity cases. Nevertheless, bariatric surgery is unsuccessful in as much as 20–40% of obese patients, who typically fail to lose weight or regain their lost weight. Furthermore, bariatric surgery can have significant health complications and in some cases can result in death. Most of the inefficacy of bariatric surgery is due to patients continuing to overeat, since bariatric surgery itself is not enough to maintain weight loss. One potential area of therapeutic promise is neuromodulation. Neuromodulation can be aimed at modifying neural circuits and mechanisms involved in overeating and motivation in order to decrease overeating and enhance physical activity. Moreover, these approaches are amenable to address interindividual variation which is observed in obese subjects. In particular, techniques that may hold promise include real-time fMRI, transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and more invasive techniques like deep brain stimulation (DBS) and vagus nerve stimulation (Val-Laillet et al. 2015). Along with neuromodulation approaches, neuroimaging can be concurrently used to monitor neural functioning and responses to food in efforts of predicting weight gain and monitoring weight loss in response to therapeutics. For example, it has been shown that measuring responsivity of several brain areas including the dorsal striatum, ventral striatum, hypothalamus, thalamus, amygdala, and midbrain to food using fMRI (Stice et al. 2008b; Geha et al. 2013; Sun et al. 2015) can predict future weight gain. Finally, integrating neuroimaging with other approaches such as genetics, cognitive, and other biological measures (e.g., biomarkers) along with neuromodulation may hold significant promise for combating escalating rates of obesity over the next decades.

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