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Reward, dopamine and the control of food intake: implications for obesity

Nora D. Volkow[1], **Gene-Jack Wang**[2], and **Ruben D. Baler**[1]

[1]National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892, USA

[2]Medical Department, Brookhaven National Laboratories, Upton, NY 11973, USA

Abstract

The ability to resist the urge to eat requires the proper functioning of neuronal circuits involved in top-down control to oppose the conditioned responses that predict reward from eating the food and the desire to eat the food. Imaging studies show that obese subjects might have impairments in dopaminergic pathways that regulate neuronal systems associated with reward sensitivity, conditioning and control. It is known that the neuropeptides that regulate energy balance (homeostatic processes) through the hypothalamus also modulate the activity of dopamine cells and their projections into regions involved in the rewarding processes underlying food intake. It is postulated that this could also be a mechanism by which overeating and the resultant resistance to homoeostatic signals impairs the function of circuits involved in reward sensitivity, conditioning and cognitive control.

Introduction

One-third of the US adult population is obese [body mass index (BMI) ≥30 kg m^{-2}] [1]. This fact has far reaching and costly implications, because obesity is strongly associated with serious medical complications (e.g. diabetes, heart disease, fatty liver and some cancers) [2]. Not surprisingly, the health care costs alone owing to obesity in the US have been estimated at close to US$150 billion [3].

Social and cultural factors undoubtedly contribute to this epidemic. Specifically, environments that promote unhealthy eating habits (ubiquitous access to highly processed and junk foods) and physical inactivity are believed to have a fundamental role in the widespread problem of obesity (Overweight and Obesity Website of the Centers for Disease Control and Prevention; http://www.cdc.gov/obesity/index.html). However, individual factors also help determine who will (or will not) become obese in these environments. Based on heredity studies, genetic factors are estimated to contribute between 45% and 85% of the variability in BMI [4,5]. Although genetic studies have revealed point mutations that are over-represented among obese individuals [4], for the most part, obesity is thought to be under polygenic control [6,7]. Indeed, the most recent whole genome-wide association analysis study (GWAS) conducted in 249,796 individuals of European descent identified 32 loci associated with BMI. However, these loci explained only 1.5% of the variance in BMI [8]. Moreover, it was estimated that GWAS studies with larger samples should be able to identify 250 extra loci with effects on BMI. However, even with the undiscovered variants, it was estimated that signals from common variant loci would account for only 6–11% of the genetic variation in BMI (based on an estimated heritability of 40–70%). The limited explanation of the variance from these genetic studies is likely to reflect the complex

Corresponding author: Volkow, N.D. (nvolkow@nida.nih.gov).

interactions between individual factors (as determined by genetics) and the way in which individuals relate to environments where food is widely available, not only as a source of nutrition, but also as a strong reward that by itself promotes eating [9].

The hypothalamus [via regulatory neuropeptides such as leptin, cholecystokinin (CCK), ghrelin, orexin, insulin, neuropeptide Y (NPY), and through the sensing of nutrients, such as glucose, amino acids and fatty acids] is recognized as the main brain region regulating food intake as it relates to caloric and nutrition requirements [10–13]. In particular, the arcuate nucleus through its connections with other hypothalamic nuclei and extra-hypothalamic brain regions, including the nucleus tractus solitarius, regulates homeostatic food intake [12] and is implicated in obesity [14–16] (Figure 1a, left panel). However, evidence is accumulating that brain circuits other than those regulating hunger and satiety are involved in food consumption and obesity [17]. Specifically, several limbic [nucleus accumbens (NAc), amygdala and hippocampus] and cortical brain regions [orbitofrontal cortex (OFC), cingulate gyrus (ACC) and insula] and neurotransmitter systems (dopamine, serotonin, opioids and cannabinoids) as well as the hypothalamus are implicated in the rewarding effects of food [18] (Figure 1a, right panel). By contrast, the regulation of food intake by the hypothalamus appears to rely on the reward and motivational neurocircuitry to modify eating behaviors [19–21].

Based on findings from imaging studies, a model of obesity was recently proposed in which overeating reflects an imbalance between circuits that motivate behavior (because of their involvement in reward and conditioning) and circuits that control and inhibit pre-potent responses [22]. This model identifies four main circuits: (i) reward–saliency; (ii) motivation–drive; (iii) learning–conditioning; and (iv) inhibitory control–emotional regulation–executive function. Notably, this model is also applicable to drug addiction. In vulnerable individuals, the consumption of high quantities of palatable food (or drugs in addiction) can upset the balanced interaction among these circuits, resulting in an enhanced reinforcing value of food (or drugs in addiction) and in a weakening of the control circuits. This perturbation is a consequence of conditioned learning and the resetting of reward thresholds following the consumption of large quantities of high-calorie foods (or drugs in addiction) by at-risk individuals. The undermining of the cortical top-down networks that regulate pre-potent responses results in impulsivity and in compulsive food intake (or compulsive drug intake in addiction). This paper discusses the evidence that links the neural circuits involved in top-down control with those involved with reward and motivation and their interaction with peripheral signals that regulate homeostatic food intake.

Food is a potent natural reward and conditioning stimulus

Certain foods, particularly those rich in sugars and fat, are potent rewards [23] that promote eating (even in the absence of an energetic requirement) and trigger learned associations between the stimulus and the reward (conditioning). In evolutionary terms, this property of palatable foods used to be advantageous because it ensured that food was eaten when available, enabling energy to be stored in the body (as fat) for future need in environments where food sources were scarce and/or unreliable. However, in modern societies, where food is widely available, this adaptation has become a liability.

Several neurotransmitters, including dopamine (DA), cannabinoids, opioids and serotonin, as well as neuropetides involved in homeostatic regulation of food intake, such as orexin, leptin and ghrelin, are implicated in the rewarding effects of food [24–26]. DA has been the most thoroughly investigated and is the best characterized. It is a key neurotransmitter modulating reward (natural and drug rewards), which it does mainly through its projections from the ventral tegmental area (VTA) into the NAc [27]. Other DA projections are also

implicated, including the dorsal striatum (caudate and putamen), cortical (OFC and ACC) and limbic regions (hippocampus and amygdala) and the lateral hypothalamus. Indeed, in humans, ingestion of palatable food has been shown to release DA in the dorsal striatum in proportion to the self-reported level of pleasure derived from eating the food [28]. However, the involvement of DA in reward is more complex than the mere encoding of hedonic value. Upon first exposure to a food reward (or an unexpected reward), the firing of DA neurons in the VTA increases with a resulting increase in DA release in NAc [29]. However, with repeated exposure to the food reward, the DA response habituates and is gradually transferred onto the stimuli associated with the food reward (e.g. the smell of food), which is then processed as a predictor of reward (becoming a cue that is conditioned to the reward) [30,31]; the DA signal in response to the cue then serves to convey a 'reward prediction error' [31]. The extensive glutamatergic afferents to DA neurons from regions involved with sensory (insula or primary gustatory cortex), homeostatic (hypothalamus), reward (NAc), emotional (amygdala and hippocampus) and multimodal (OFC for salience attribution) modulate their activity in response to rewards and to conditioned cues [32]. Specifically, projections from the amygdala and the OFC to DA neurons and NAc are involved in conditioned responses to food [33]. Indeed, imaging studies showed that when non-obese male subjects were asked to inhibit their craving for food while being exposed to food cues, they decreased metabolic activity in amygdala and OFC [as well as hippocampus (see also Box 1), insula and striatum]; the decreases in OFC were associated with reductions in food craving [34].

Conditioned cues can elicit feeding even in sated rats [30] and, in humans, imaging studies have shown that exposure to food cues elicits DA increases in the striatum that are associated with the desire to eat the food [35]. In addition to its involvement with conditioning, DA is also involved with the motivation to perform the behaviors necessary to procure and consume the food. Indeed, the involvement of DA in food reward has been associated with the motivational salience or 'wanting' of food as opposed to the 'liking' of food [36] (Box 2), an effect that is likely to involve the dorsal striatum and perhaps also the NAc [37]. DA has such a crucial role in this context that transgenic mice that do not synthesize DA die of starvation owing to a lack of motivation to eat [37]. Restoring DA neurotransmission in the dorsal striatum rescues these animals, whereas restoring it in the NAc does not.

The hedonic ('liking') properties of food appear to depend on, among others, opioid, cannabinoid and GABA neurotransmission [36]. These 'liking' properties of food are processed in reward regions including lateral hypothalamus, NAc, ventral pallidum, OFC [9,27,38] and insula (primary taste area in the brain) [39]. Opioid signaling in NAc (in the shell) and ventral pallidum appears to mediate food 'liking' [40]. By contrast, opioid signaling in the basolateral amygdala is implicated in conveying the affective properties of food, which in turn modulate the incentive value of food and reward-seeking behavior, thus also contributing to food 'wanting' [41]. Interestingly, in rodents that have been exposed to diets rich in sugar, a pharmacological challenge with naloxone (opiate antagonist drug devoid of effects in control rats) elicits an opiate withdrawal syndrome similar to that observed in animals that have been chronically exposed to opioid drugs [42]. In addition, exposure of humans or laboratory animals to sugar produces an analgesic response [43], which suggests that sugar (and perhaps other palatable foods) has a direct ability to boost endogenous opioid levels. A research question that emerges from these data is whether, in humans, dieting triggers a mild withdrawal syndrome that could contribute to relapse.

Endocannabinoids, predominantly through cannabinoid CB1 receptor signaling (in contrast to CB2 receptors), are involved with both homeostatic and rewarding mechanisms of food intake and energy expenditure [44–46]. Homeostatic regulation is mediated in part through

the arcuate and paraventricular nuclei in the hypothalamus and through the nucleus of the solitary tract in the brainstem, and the regulation of reward processes is mediated in part through effects in NAc, hypothalamus and brainstem. Therefore, the cannabinoid system is an important target in medication development for treatment of obesity and metabolic syndrome. Similarly, the modulation by serotonin of feeding behaviors involves both reward and homeostatic regulation and it has also been a target for the development of anti-obesity medications [47–50].

In parallel, there is increasing evidence that peripheral homeostatic regulators of energy balance, such as leptin, insulin, orexin, ghrelin and PYY, also regulate behaviors that are non-homeostatic and modulate the rewarding properties of food [50]. These neuropeptides might also be involved with cognitive control over food intake and with conditioning to food stimuli [51]. Specifically, they can interact with cognate receptors in midbrain VTA DA neurons, which not only project to the NAc, but also to prefrontal and limbic regions; in fact, many of them also express receptors in frontal regions and in hippocampus and amygdala [50].

Insulin, which is one of the key hormones involved in the regulation of glucose metabolism, has been shown to attenuate the response of limbic (including brain reward regions) and cortical regions in the human brain to food stimuli. For example, in healthy controls, insulin attenuated the activation of the hippocampus, frontal and visual cortices in response to food pictures [52]. Conversely, insulin-resistant subjects (patients with type 2 diabetes) showed greater activation in limbic regions (amygdala, striatum, OFC and insula) when exposed to food stimuli than did non-diabetic patients [53].

In the human brain, the adipocyte-derived hormone leptin, which acts in part though leptin receptors in hypothalamus (arcuate nucleus) to decrease food intake, has also been shown to attenuate the response of brain reward regions to food stimuli. Specifically, patients with congenital leptin deficiency showed activation of DA mesolimbic targets (NAc and caudate) to visual food stimuli, which was associated with food wanting, even when the subject had just been fed. By contrast, mesolimbic activation did not occur after 1 week of leptin treatment (Figure 2a,b). This was interpreted to suggest that leptin diminished the rewarding responses to food [19]. Another fMRI study, also done with patients with congenital leptin deficiency, showed that leptin treatment reduced the activation of regions involved with hunger (insula, parietal and temporal cortices) whereas it enhanced activation of regions involved in cognitive inhibition [prefrontal cortex (PFC)] upon exposure to food stimuli [20]. Thus, these two studies provide evidence that, in the human brain, leptin modulates the activity of brain regions involved not only with homeostatic processes, but also with rewarding responses and with inhibitory control.

Gut hormones also appear to modulate the response of brain reward regions to food stimuli in the human brain. For example, the peptide $YY_{3–36}$ (PYY), which is released from gut cells post-prandially and reduces food intake, was shown to modulate the transition of the regulation of food intake by homeostatic circuits (i.e. hypothalamus) to its regulation by reward circuits in the transition from hunger to satiety. Specifically, when plasma PYY concentrations were high (as when satiated), activation of the OFC by food stimuli negatively predicted food intake; whereas when plasma PYY levels were low (as when food deprived) hypothalamic activation positively predicted food intake [54]. This was interpreted to reflect that PYY decreases the rewarding aspects of food through its modulation of the OFC. By contrast, ghrelin (a stomach-derived hormone that increases in the fasted state and stimulates food intake) was shown to increase the activation in response to food stimuli in brain reward regions (amygdala, OFC, anterior insula and striatum) and their activation was associated with self-reports of hunger (Figure 2c,d). This was

interpreted to reflect an enhancement of the hedonic and incentive responses to food-related cues by ghrelin [55]. Overall, these findings are also consistent with the differential regional brain activation in response to food stimuli in satiated versus fasted individuals; activation of reward regions in response to food stimuli is decreased during the sated when compared to the fasted state [15].

These observations point to an overlap between the neurocircuitry that regulates reward and/or reinforcement and that which regulates energy metabolism (Figure 1b). Peripheral signals that regulate homeostatic signals to food appear to increase the sensitivity of limbic brain regions to food stimuli when they are orexigenic (ghrelin) and to decrease the sensitivity to activation when they are anorexigenic (leptin and insulin). Similarly, the sensitivity of brain reward regions to food stimuli during food deprivation is increased, whereas it is decreased during satiety. Thus, homeostatic and reward circuitry act in concert to promote eating behaviors under conditions of deprivation and to inhibit food intake under conditions of satiety. Disruption of the interaction between homeostatic and reward circuitry might promote overeating and contribute to obesity (Figure 1). Although other peptides [glucagon-like peptide-1 (GLP-1), CKK, bombesin and amylin] also regulate food intake via their hypothalamic actions, their extrahypothalamic effects have received less attention [12]. Thus, much remains to be learned, including the interactions between the homeostatic and the non-homeostatic mechanisms that regulate food intake and their involvement in obesity.

Box 1. The role of the hippocampus in feeding behaviors

The hippocampus is not only central to memory, but is also involved in the regulation of eating behaviors through its processing of mnemonic processes (including remembering whether one ate, remembering conditioning associations, remembering where food is located, identifying interoceptive states of hunger and remembering how to relieve these states). For example, in rodents, selective lesions in the hippocampus impaired their ability to discriminate between the state of hunger and that of satiety [99] and, in female rats, it resulted in hyperphagia [100]. In humans, brain-imaging studies have reported activation of the hippocampus with food craving, a state of hunger, the response to food-conditioned cues and to food tasting [101]. The hippocampus expresses high levels of insulin, ghrelin, glucocorticoids and cannabinoid CB1 receptors, which suggests that this region also regulates food intake by non-mnemonic processes [102,103]. In addition, the hippocampus is implicated in obesity, as evinced by imaging studies showing that in obese but not in lean individuals, the hippocampus shows hyperactivation in response to food stimuli [104].

Box 2. Wanting versus liking: an important distinction

Brain reward systems involved with food intake distinguish a mechanism involved with motivating the desire for the food, referred to as ‘wanting’, versus a mechanism involved with the hedonic properties of the food, referred to as ‘liking’ [36]. Whereas the dopamine striatal system is predominantly (although not exclusively) implicated in ‘wanting’, the opioid and cannabinoid systems are predominantly (although not exclusively) implicated in food ‘liking’. Indeed, brain-imaging studies in humans have shown that the dopamine release triggered when humans encounter a food cue correlates with their subjective ratings of wanting the food [35]. Conversely, the activation of endogenous opioid or cannabinoid receptors appears to stimulate appetite in part by enhancing the ‘liking’ of the food (i.e. its palatability). Although these two mechanisms are separate, they act in concert to modulate eating behaviors.

Disruption in reward and conditioning to food in overweight and obese individuals

Preclinical and clinical studies have provided evidence of decreases in DA signaling in striatal regions [decreases in DAD2 (D2R) receptors and in DA release], that are linked with reward (NAc) but also with habits and routines (dorsal striatum) in obesity [56–58]. Importantly, decreases in striatal D2R have been linked to compulsive food intake in obese rodents [59] and with decreased metabolic activity in OFC and ACC in obese humans [60] (Figure 3a–c). Given that dysfunction in OFC and ACC results in compulsivity [reviewed 61], this might be the mechanism by which low striatal D2R signaling facilitates hyperphagia [62]. Decreased D2R-related signaling is also likely to reduce the sensitivity to natural rewards, a deficit that obese individuals might strive to compensate temporarily for by overeating [63]. This hypothesis is consistent with preclinical evidence showing that decreased DA activity in the VTA results in a dramatic increase in the consumption of high-fat foods [64].

Indeed, compared with normal-weight individuals, obese individuals who were presented with pictures of high-calorie food (stimuli to which they are conditioned) showed increased neural activation of regions that are part of reward and motivation circuits (NAc, dorsal striatum, OFC, ACC, amygdala, hippocampus and insula) [65]. By contrast, in normal-weight controls, the activation of the ACC and OFC (regions involved in salience attribution that project into the NAc) during presentation of high-calorie food was found to be negatively correlated with their BMI [66]. This suggests a dynamic interaction between the amount of food eaten (reflected in part by the BMI) and the reactivity of reward regions to high-calorie food (reflected in the activation of OFC and ACC) in normal-weight individuals, which is lost in obesity.

Surprisingly, obese individuals, when compared with lean individuals, experienced less activation of reward circuits from the actual food consumption (consummatory food reward), whereas they showed greater activation of somatosensory cortical regions that process palatability when they anticipated consumption [67] (Figure 4). The latter finding is consistent with a study that reported increased baseline glucose metabolic activity (a marker of brain function) in somatosensory regions that process palatability, including insula, in obese as compared with lean subjects [68] (Figure 3d,e). An enhanced activity of regions that process palatability could make obese subjects favor food over other natural reinforcers, whereas decreased activation of dopaminergic targets by the actual food consumption might lead to overconsumption as a means to compensate for the weak DA signals [69].

These imaging findings are consistent with an enhanced sensitivity of the reward circuitry to conditioned stimuli (viewing high-calorie food) that predict reward, but a decreased sensitivity to the rewarding effects of actual food consumption in dopaminergic pathways in obesity. We hypothesize that, to the extent that there is a mismatch between the expected reward and a delivery that does not fulfill this expectation, this will promote compulsive eating as an attempt to achieve the expected level of reward. Although the failure of an expected reward to arrive is accompanied by a decrease in DA cell firing in laboratory animals [70], the behavioral significance of such a decrease (when a food reward is smaller than expected) has, to our knowledge, not been investigated.

In parallel to these activation changes in the reward circuitry in obese subjects, imaging studies have also documented consistent decreases in the reactivity of the hypothalamus to satiety signals in obese subjects [71,72].

Evidence of cognitive disruption in overweight and obese individuals

There is increasing evidence that obesity is associated with impairment on certain cognitive functions, such as executive function, attention and memory [73–75]. Indeed, the ability to inhibit the urges to eat desirable food varies among individuals and might be one of the factors that contribute to their vulnerability for overeating [34]. The adverse influence of obesity on cognition is also reflected in the higher prevalence of attention deficit hyperactivity disorder (ADHD) [76], Alzheimer disease and other dementias [77], cortical atrophy [78] and white matter disease [79] in obese subjects. Although co-morbid medical conditions (e.g. cerebrovascular pathology, hypertension and diabetes) are known to affect cognition adversely, there is also evidence that high BMI, by itself, might impair various cognitive domains, particularly executive function [75].

In spite of some inconsistencies among studies, brain-imaging data have also provided evidence of structural and functional changes associated with high BMI in otherwise healthy controls. For example, an MRI study done in elderly females using voxel-wise morphometry showed a negative correlation between BMI and gray matter volumes (including frontal regions), which, in the OFC, was associated with impaired executive function [80]. Using positron emission tomography (PET) to measure brain glucose metabolism in healthy controls, a negative correlation was also shown between BMI and metabolic activity in PFC (dorsolateral and OFC) and in ACC. In this study, the metabolic activity in PFC predicted the subjects' performance in tests of executive function [81]. Similarly, an NMR spectroscopic study of healthy middle age and elderly controls showed that BMI was negatively associated with the levels of *N*-acetyl-aspartate (a marker of neuronal integrity) in frontal cortex and ACC [79,82].

Brain-imaging studies comparing obese and lean individuals have also reported lower gray matter density in frontal regions (frontal operculum and middle frontal gyrus) and in post-central gyrus and putamen [83]. Another study, which found no differences in gray matter volumes between obese and lean subjects, did report a positive correlation between white matter volume in basal brain structures and waist:hip ratio; a trend that was partially reversed by dieting [84].

Finally, the role of DA in inhibitory control is well recognized and its disruption might contribute to behavioral disorders of discontrol, such as obesity. A negative correlation between BMI and striatal D2R has been reported in obese [58] as well as in overweight subjects [85]. As discussed above, the lower-than-normal availability of D2R in the striatum of obese individuals was associated with reduced metabolic activity in PFC and ACC [60]. These findings implicate neuroadaptations in DA signaling as contributors to the disruption of frontal cortical regions associated with overweight and obesity. A better understanding of these disruptions might help guide strategies to ameliorate, or perhaps even reverse, specific impairments in crucial cognitive domains.

For example, delay discounting, which is the tendency to devalue a reward as a function of the temporal delay of its delivery, is one of the most extensively investigated cognitive operations in relation to disorders associated with impulsivity and compulsivity. Delay discounting has been most comprehensively investigated in drug abusers who prefer small-but-immediate over large-but-delayed rewards [86]. The few studies done in obese individuals have also shown that these individuals display preference for high, immediate rewards, despite an increased chance of suffering higher future losses [87,88]. Moreover, a positive correlation between BMI and hyperbolic discounting, whereby future negative payoffs are discounted less than are future positive payoffs, was recently reported [89]. Delay discounting seems to depend on the function of ventral striatum (where NAc is

located) [90,91] and of the PFC, including OFC [92], and is sensitive to DA manipulations [93].

Interestingly, lesions of the OFC in animals can either increase or decrease the preference for immediate small rewards over delayed larger rewards [94,95]. This apparently paradoxical behavioral effect is likely to reflect the fact that at least two operations are processed through the OFC; one is salience attribution, through which a reinforcer acquires incentive motivational value, and the other is control over pre-potent urges [96]. Dysfunction of the OFC is associated with an impaired ability to modify the incentive motivational value of a reinforcer as a function of the context in which it occurs (i.e. decrease the incentive value of food with satiety), which can result in compulsive food consumption [97]. If the stimulus is highly reinforcing (such as food and food cues for an obese subject) the enhanced saliency value of the reinforcer will result in an enhanced motivation to procure it, which could appear as a willingness to delay gratification (such as spending time in long lines to buy ice cream).

However, in contexts where food is readily available, the same enhanced saliency can trigger impulsive behaviors (such as buying and eating the chocolate located next to the cashier even without previous awareness of the desire of such item). Dysfunction of the OFC (and of the ACC) impairs the ability to rein in pre-potent urges, resulting in impulsivity and an exaggerated delayed discount rate.

Food for thought

It would appear, from the collected evidence presented here, that a substantial fraction of obese individuals exhibit an imbalance between an enhanced sensitivity of the reward circuitry to conditioned stimuli linked to energy-dense food and impaired function of the executive control circuitry that weakens inhibitory control over appetitive behaviors. Regardless of whether this imbalance causes, or is caused by, pathological overeating, the phenomenon is reminiscent of the conflict between the reward, conditioning and motivation circuits and the inhibitory control circuit that has been reported in addiction [98].

Knowledge accumulated during the past two decades of the genetic, neural and environmental bases of obesity leaves no doubt that the current crisis has sprouted from the disconnect between the neurobiology that drives food consumption in our species and the richness and diversity of food stimuli driven by our social and economic systems. The good news is that understanding the deep-seated behavioral constructs that sustain the obesity epidemic holds the key to its eventual resolution (see also Boxes 3 and 4).

Box 3. Future basic research directions

- A better understanding of the interaction at the molecular, cellular, and circuit levels between the homeostatic and reward processes that regulate food intake.
- Understanding the role of genes in modulating the homeostatic and the reward responses to food.
- A better understanding of the involvement of other neurotransmitters, such as cannabinoids, opioids, glutamate, serotonin and GABA, in the long-lasting changes that occur in obesity.
- Investigating the developmental aspects of the neurobiology underlying food intake (homeostatic and rewarding) and its sensitivity to environmental food exposure.

- Understanding the epigenetic modifications in neuronal circuits involved with the homeostatic and rewarding control of food intake in the fetal brain in response to exposure to food excess and food deprivation during pregnancy.
- Investigating neuroplastic adaptations in homeostatic and reward circuits associated with chronic exposure to highly palatable foods and/or to high quantities of calorie-dense food.
- Investigating the relationship between homeostatic and hedonic processes regulating food intake and physical activity.

Box 4. Future clinical research directions

- Studies to ascertain whether the greater activation of reward-associated areas in response to food-related cues in obese individuals underlies their vulnerability for overeating or reflects a secondary neuroadaptation to overeating.
- It is suggested that enhanced dopaminergic neurotransmission contributes to improved eating behavior through optimization and/or strengthening of cognitive control mechanisms mediated in part through the PFC; however, further research is needed into the currently ill-defined mechanisms involved.
- Diet alone is seldom a path to successful (i.e. sustainable) weight loss. It would be instructive to address whether: (i) dieting can trigger a withdrawal syndrome that increases the risk of relapse; and (ii) the decreased leptin levels associated with diet-induced weight loss lead to hyperactivation of reward circuitry and compensatory food seeking behaviors.
- Research to determine the neurobiology that underlies decreases in food craving and hunger following bariatric surgery.

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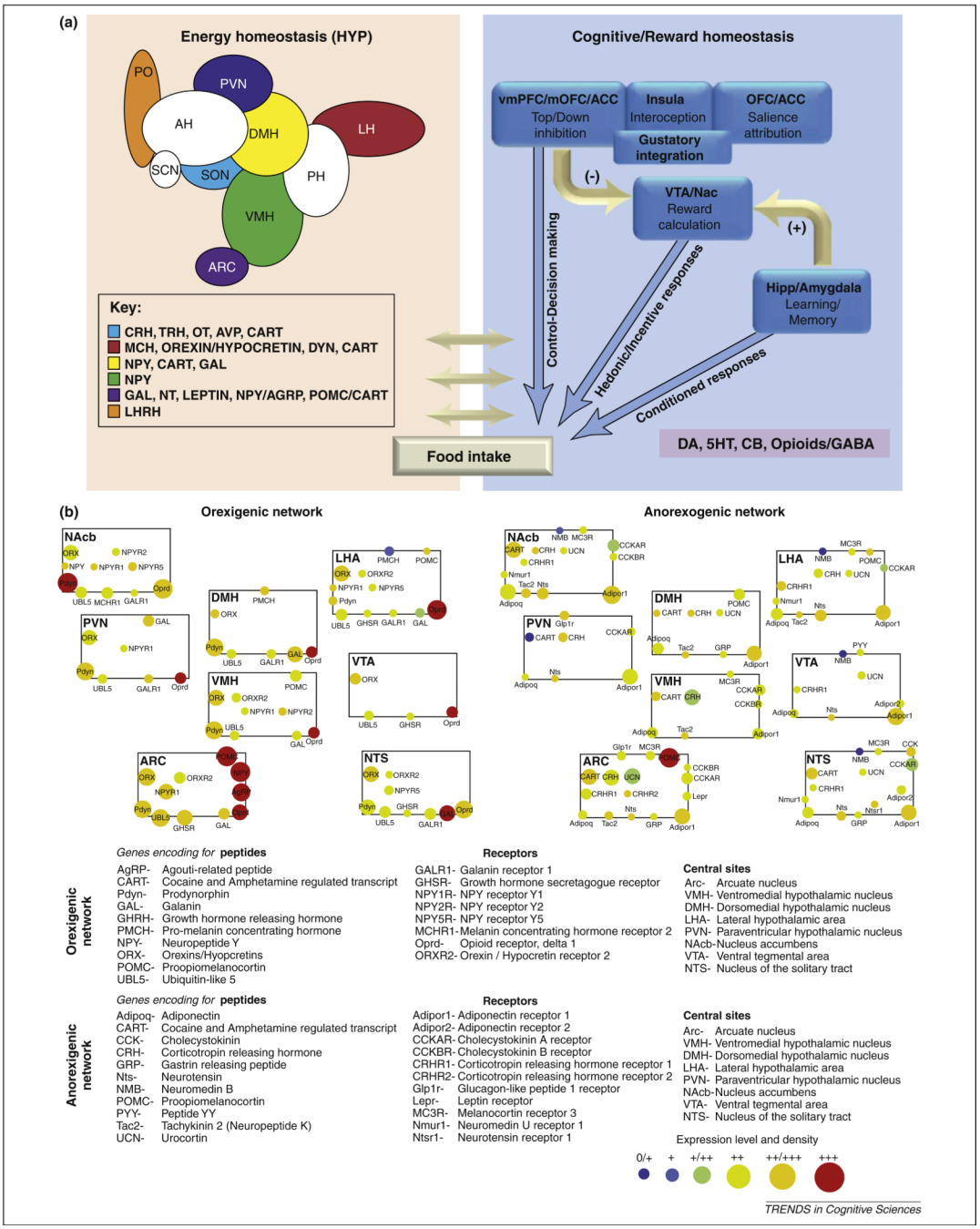

Figure 1.

Regulation of food intake relies on multichannel communication between overlapping reward and homeostatic neurocircuits. **(a)** Schematic diagram of the crosstalk between the homeostatic (hypothalamus, HYP) and reward circuits that control food intake. The HYP is central to energy balance and several of its nuclei are involved in energy regulation [arcuate (ARC), dorsomedial (DMH) ventromedial (VMH) and lateral HYP (LH)] integrating orexigenic and anorexigenic signals from the periphery and the CNS and communicating these to regions from the reward circuitry. For example, orexin neurons in LH are influenced by leptin and ghrelin and, in turn, project to reward regions via OX1 and OX2 receptors. Several key neuropeptides produced in various hypothalamic nuclei are indicated:

corticotrophin-releasing hormone (CRH), tyrotrophin-releasing hormone (TRH), oxytocin (OT), vasopressin (AVP), cocaine- and amphetamine-regulated transcript (CART), NPY, agouti-related protein (AgRP), proopiomelanocortin (POMC), galanin (GAL), neurotensin (NT), leptin, orexin, luteinizing hormone-releasing hormone (LHRH) and melanin-concentrating hormone (MCH). By contrast, top-down inhibition of feeding depends heavily on the PFC, including OFC and ACC. The amygdala ascribes emotional attributes and, together with memory and learning circuitry, generates conditioned responses. This circuit is subject to strong influence coming from cortical and mesolimbic input. Many of the orexigenic and anorexigenic peripheral signals directly influence neural computations not only in hypothalamus, but also in mesocorticolimbic structures (amygdala, OFC and hippocampus). Conversely, many classic neurotransmitters (DA, CB, opioids, GABA and serotonin) are produced as a result of mesocorticolimbic activity and influence the HYP. For comprehensive reviews, see [26,105]. **(b)** Expression of orexigenic and anorexigenic genes in the central circuitry (data derived from the Allen Brain Atlas; http://www.brain-map.org). Each box represents a brain region and the circles indicate expression levels of genes in the region. Circle sizes represent expression density ('+' expression is sparse to '+++' expression throughout the entire area). Colors represent expression levels (dark blue < light blue < turquoise < light green < orange < red). The location of each gene symbol in the boxes does not correlate with the distribution of that gene within the brain region it represents. Gene symbols without circles are mentioned when only expression density or level is >0. POMC is a precursor for an orexigen, β-endorphin, and for an anorexigen, α-melanocyte-stimulating hormone. Reproduced, with permission, from [106].

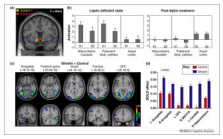

Figure 2.

Leptin decreases whereas ghrelin increases reactivity to food stimuli in brain reward areas. **(a, b)** Brain images showing areas where leptin reduced the activation (NAc-caudate) in two subjects with leptin deficiency. **(b)** Histogram for the activation response to food stimuli in subjects with leptin deficiency before and after leptin treatment. **(c)** Ghrelin increases reactivity to food stimuli in brain reward areas, as indicated by SPM images showing brain areas where activation by food stimuli was greater with ghrelin than with saline; and **(d)** a histogram of limbic areas for the response to food stimuli after saline (controls; red bars) and after ghrelin (blue bars). Modified, with permission, from [19] **(a, b)** and [55] **(c, d)**.

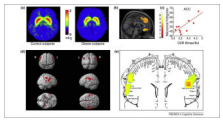

Figure 3.

Hyperphagia could result from a drive to compensate for a weakened reward circuit (processed through dopamine regulated corticostriatal circuits) combined with a heightened sensitivity to palatability (hedonic properties of food processed in part through the somatosensory cortex). **(a)** Averaged images for DA D2 receptor (D2R) availability in controls (*n*=10) and in morbidly obese subjects (*n*=10). **(b)** Results from SPM identifying the areas in the brain where D2R was associated with glucose metabolism, these included the medial OFC, ACC and the dorsolateral PFC (region not shown). **(c)** Regression slope between striatal D2R and metabolic activity in ACC in obese subjects. **(d)** Three-dimensionally rendered SPM images showing the areas with higher metabolism in obese than in lean subjects ($P < 0.003$, uncorrected). **(e)** Color-coded SPM results displayed in a coronal plane with a superimposed diagram of the somatosensory homunculus. The results (*z* value) are presented using the rainbow scale where red > yellow > green. When compared with lean subjects, obese subjects had higher baseline metabolism in the somatosensory areas where the mouth, lips and tongue are represented and which are involved with processing food palatability. Modified, with permission, from [22] (a–c) and [68] (d,e).

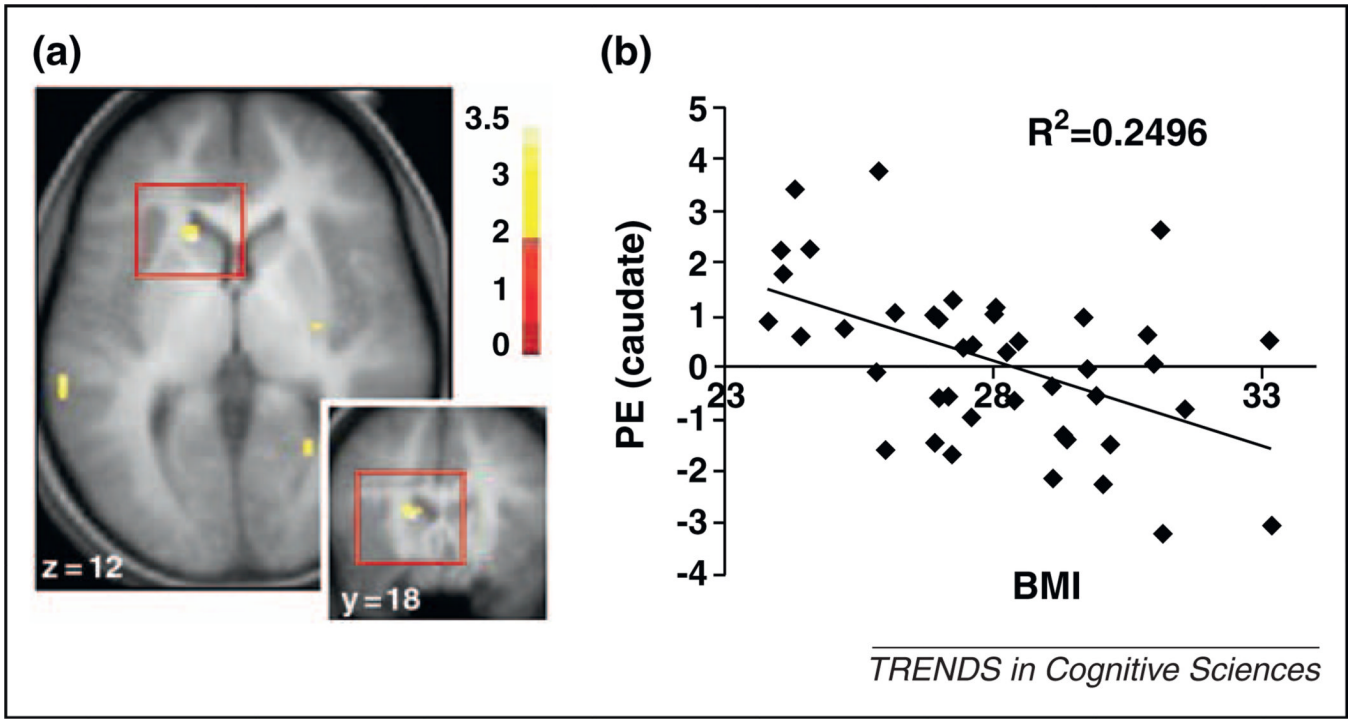

Figure 4.

Obese subjects have a decreased response in DA target regions when given food compared with that recorded in lean subjects. **(a)** Coronal section of weaker activation in the left caudate nucleus in response to receiving a milkshake versus a tasteless solution; **(b)** Correlation between the difference in activation and BMI of the subjects. Modified, with permission, from [67].