Hankir MK, Ashrafian H, Hesse S, Horstmann A, Fenske WK. **Distinctive striatal dopamine signaling after dieting and gastric bypass.**Trends Endocrinol Metab. 2015;26:223-30.

The final publication is available at http://dx.doi.org/10.1016/j.tem.2015.03.005

Highlights

• Palatable foods elicit striatal dopamine release to strongly influence feeding.

• Obesity is associated with aberrant striatal dopamine signaling.

• Imbalance in striatal dopamine signaling may promote post-dieting weight regain.

• Surgery may correct striatal dopamine signaling to modify fat reward value.

Highly palatable and/or calorically dense foods, such as those rich in fat, engage the striatum to govern and set complex behaviors. Striatal dopamine signaling has been implicated in hedonic feeding and the development of obesity. Dieting and bariatric surgery have markedly different outcomes on weight loss, yet how these interventions affect central homeostatic and food reward processing remains poorly understood. Here, we propose that dieting and gastric bypass produce distinct changes in peripheral factors with known roles in regulating energy homeostasis, resulting in differential modulation of nigrostriatal and mesolimbic dopaminergic reward circuits. Enhancement of intestinal fat metabolism after gastric bypass may also modify striatal dopamine signaling contributing to its unique long-term effects on feeding behavior and body weight in obese individuals.

Keywords

obesity; dieting; gastric bypass; striatum; dopamine; reward

Obesity and post-dieting weight regain

The obesity pandemic continues to grow in industrialized and nonindustrialized nations alike, with recent estimates that as many as one-third of the world population is overweight or obese [1]. As one of the leading causes of morbidity and mortality, obesity poses a serious health and socioeconomic problem [2]. A central question that arises when attempting to understand obesity is why elevated fat mass once established is so resilient, as most individuals eventually regain weight lost by conventional means such as caloric restriction [3].

The reasons for weight regain seem to be twofold. First, the integrity of the homeostatic system is maintained in obesity and drives behavioral and physiological responses to return adipose tissue stores to the predieting (higher) steady state [4]. Second, energy-dense foods appear to become even more desirable following abstinence, and individuals most often relapse onto such

foods even in the absence of weight loss [5]. Consequently, postdieting weight regain constitutes one of the greatest challenges in dealing with the growing obese population today. Despite significant progress in our understanding of the neurobiology of energy homeostasis, little is known regarding how brain regions designed to promote weight stability are affected by overconsumption of high-energy foods and altered in diet-induced obesity (DIO).

Bariatric surgical procedures such as Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) are presently the most efficacious treatments for obesity [6], causing significant and long-term weight loss. This unique outcome for RYGB at least appears to be driven by changes in homeostatic and nonhomeostatic food processing (Box 1), which together may result in a reduced sense of hunger [7], reduced desire to eat [7], and reduced motivation to obtain high-energy foods [8]. Understanding how bariatric surgery overcomes homeostatic adiposity defense and targets central hedonic processing may enable the development of more effective and less invasive anti-obesity therapies in the future.

Box 1.
Homeostatic and Hedonic Feeding

The hypothalamus plays a fundamental role in the regulation of whole body energy homeostasis. Excess energy is stored as fat mass, which in turn controls caloric intake and energy expenditure [65]. A second superimposed system exists, sensitive to food that is being consumed, and this feedback system controls meal size and the sensation of satiety [65]. Although these different tonic and phasic control systems interact in complex ways, their overall integration in the hypothalamus is normally remarkably effective at maintaining relatively constant levels of adiposity. In contrast to what would be expected with such a robust homeostatic control system for energy balance, the world is in the midst of an obesity crisis. The problem seems to derive from how HF foods in particular can over-ride negative feedback signals acutely and then disrupt homeostatic signaling chronically. Following chronic consumption, an HFD causes a state of hypothalamic inflammation and resistance to peripheral adiposity signals leading to weight gain [66]. Therefore, it can be said that while a homeostatic system for maintaining constant energy balance is in place, it is vulnerable to attack and eventually shuts down in the face of a chronic HFD, leading to obesity.

The effects of an HFD do not stop at the level of the hypothalamus, and homeostatic dysregulation is unlikely the sole determinant of the ongoing obesity issue in environments characterized by ubiquitous access to highly palatable, energy-rich foods. An important aspect thus is the hedonic properties of food, which lead to feeding when there is no nutritional need [5]. An anatomical substrate for a homeostatic–hedonic interaction for feeding derives from studies revealing that μ-opioid receptor activation in the ventral striatum drives consumption of

palatable HF food in otherwise sated rats by engaging a distributed network of regions within the hypothalamus [67]. The hypothalamus itself sends indirect projections to the ventral striatum to modulate hedonic feeding according to nutritional status [67]. Thus, there is considerable crosstalk between the homeostatic and hedonic systems, congruent with a highly integrated system governing food intake. Interestingly, transgenic mice with defective protein kinase A signaling in the striatum, are resistant to diet induced obesity (DIO) even in the face of an orexigenic neuropeptide profile in the hypothalamus. Despite having maintained preference for a HF diet, these mice consumed less than their wild type counterparts [68]. These results suggest that long-term regulation of striatal signaling can exert dominant effects on homeostatic and hedonic feeding and bodyweight.

Role of brain dopamine in feeding and obesity

Brain dopamine signaling is essential for the rewarding and reinforcing properties of artificial stimuli such as drugs of abuse and natural stimuli such as food, and impacts powerfully on goal-directed and habitual behaviors [9]. Accumulating evidence suggests that the brain dopamine system regulates whole body energy homeostasis. Dopamine-lesioned and genetically dopamine-deficient mice are profoundly aphagic 9 and 10, and feeding induces robust brain dopamine release [11]. Moreover, dopamine release is changed in various models of obesity including genetically obese mice [12] and obesity prone and DIO rats [13], as well as in obese humans [14]. These observations demonstrate both that aberrant brain dopaminergic transmission is associated with altered feeding behavior and that elevated fat mass is associated with aberrant brain dopaminergic transmission. It is therefore possible that restoration of normal brain dopamine function may effectively reverse detrimental feeding behavior and obesity.

The main dopaminergic projections in the central nervous system (CNS) arise from the ventral tegmental area (VTA) and substantia nigra (SN) of the midbrain, and terminate largely in the ventral and dorsal striatum forming the mesolimbic and nigrostriatal pathways respectively (Figure 1). As well as being anatomically segregated, these pathways are functionally divided and act in parallel to govern distinct processes. While these pathways have been extensively investigated in the context of drug addiction and motor function respectively, roles in food intake regulation have been assigned [9] with a focus almost exclusively on the mesolimbic pathway (Box 2). A recent human neuroimaging study revealed that the ventral and dorsal striatum can be dissociated based on adiposity and hedonic feeding in relation to dopamine 2 receptor (D2R) availability [15]. We present further evidence arguing that the mesolimbic and nigrostriatal dopaminergic pathways can be functionally dissociated in the regulation of energy balance, analogous to the proopiomelanocortin (POMC) and agouti-related peptide (AgRP) neuronal systems of the hypothalamic arcuate nucleus (ARC). We elaborate on how ventral striatal

dopamine generally promotes feeding on energy-dense foods. We then present the novel and perhaps slightly more contentious concept that dorsal striatal dopamine performs the opposite function decreasing feeding of energy dense foods and actually promoting feeding of less energy dense foods specifically by modifying the reward value of fat. Lastly, we apply this model to changes in hedonic feeding following weight loss after dieting and bariatric surgery, and hypothesize on the underlying mechanisms of surgically induced weight loss maintenance, with a focus on modifications in gut–striatal dopamine signaling.

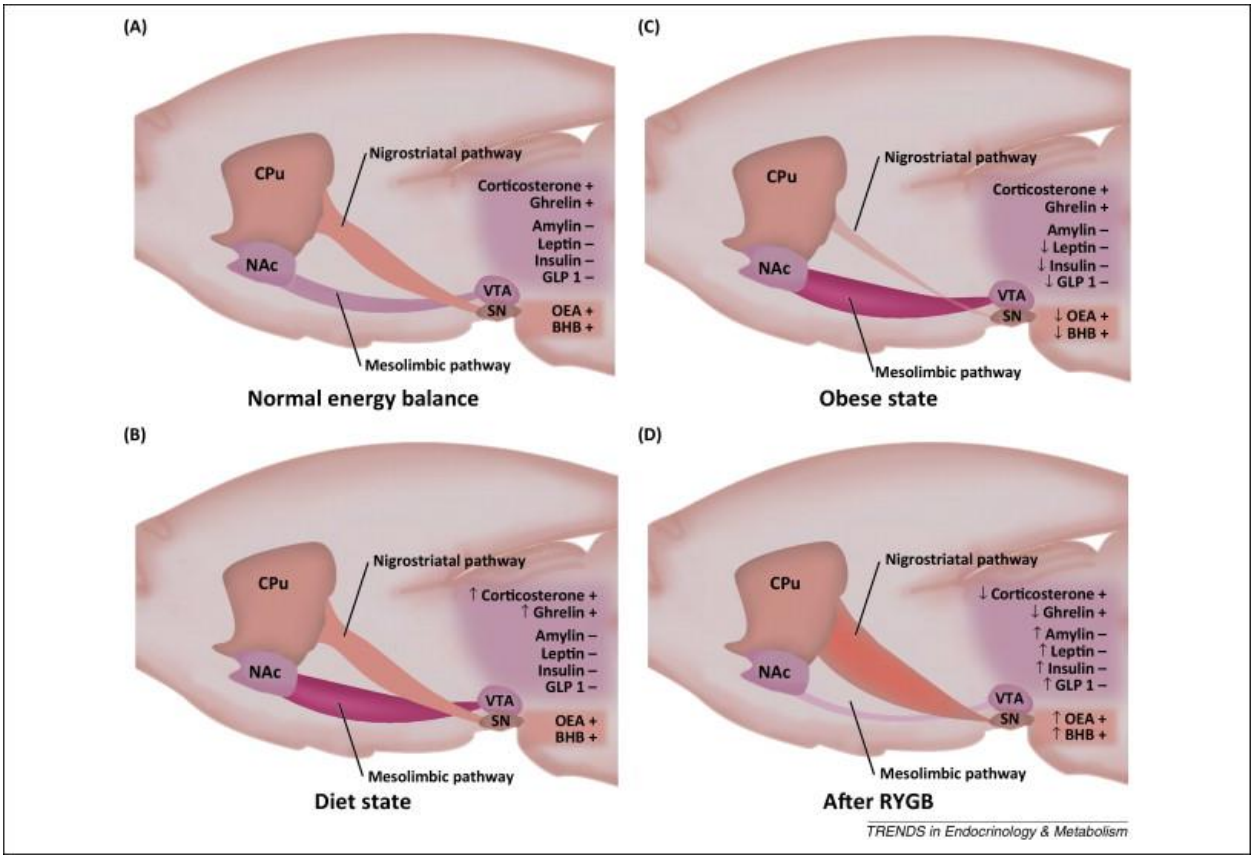

Figure 1 Modulation of mesolimbic and nigrostriatal pathways. (A) This panel shows the differential modulation of mesolimbic and nigrostriatal pathways by peripheral regulators of energy balance. In the normal state, anorexigenic factors such as leptin 12, 69 and 70, GLP-1 21 and 23, insulin 71 and 72, and amylin 57 and 58 act to decrease mesolimbic neuronal activity and/or ventral striatal dopamine release (−) to reduce hedonic feeding, while orexigenic factors such as ghrelin 16, 17 and 19 and corticosterone [33] perform the opposite function and act to increase mesolimbic neuronal activity and/or ventral striatal dopamine release (+) to promote hedonic feeding. OEA (and presumably also BHB) acting on vagal afferents arising from the gut [27] causes increased nigrostriatal neuronal activity and increased dorsal striatal dopamine release to reduce hedonic feeding. (B) A diet-induced obese state induces aberrant regulation of

mesolimbic and nigrostriatal pathways. Chronic consumption of an HFD results in leptin and insulin resistance [65]. This would be expected to increase mesolimbic tone (denoted by the strengthened projection), ventral striatal dopamine and hedonic feeding. Chronic consumption of an HFD also decreases OEA (and presumably also BHB) synthesis [59], resulting in decreased nigrostriatal tone (denoted by the weakened projection) [27], and dorsal striatal dopamine, and increased hedonic feeding. (C) Chronic caloric restriction causes dominant mesolimbic pathway signaling, leading to weight regain. Chronic caloric restriction results in a hyperghrelinemic 32 and 33 and hypercorticosteronemic 33 and 48, state, which would be expected to increase mesolimbic tone, ventral striatal dopamine and hedonic feeding. (D) RYGB surgery causes dominant nigrostriatal pathway signaling leading to long-term weight loss. RYGB results in the unique combination of increased circulating GLP-1 46 and 47 and amylin 46 and 47, and low ghrelin 46 and 47 and corticosterone [48]. Leptin and insulin sensitivities would also be restored and in the case of leptin is crucial for weight loss maintenance after surgery [73]. Together, this would be expected to decrease mesolimbic tone, ventral striatal dopamine and hedonic feeding. Additionally, RYGB may also increase OEA (and possibly also BHB) increasing mesolimbic tone, dorsal striatal dopamine and decrease hedonic feeding. Abbreviations: BHB, β hydroxybutyrate; CPu, caudate-putamen; GLP, glucagon-like peptide; HFD, high-fat diet; NAc, nucleus accumbens; OEA, oleoylethanolamide; RYGB, Roux-en-Y gastric bypass; SN, substantia nigra; VTA, ventral tegmental area.

Box 2.

Mesolimbic dopamine signaling and hedonic feeding

Studies in rodents have consistently shown that elevated levels of ventral striatal dopamine increase the motivation to consume food; particularly energy-dense food [67]. The reinforcing nature of ventral striatal dopamine signaling has two distinct effects on energy-dense food intake: an immediate effect on consumption and an enduring effect on behavior. These two processes influence each other such that the reduced reward in response to food ingestion due to dopamine receptor blockade on one day, results in diminished motivation to obtain that reward on a subsequent day [9]. Similarly, the ability of sucrose, but not non-nutritive sucralose, to cause animals to remember positions where it was consumed, is associated with its ability to elicit ventral striatal dopamine release [74]. Studies in drosophila have further revealed that appetitive long term memory (LTM) develops with D-glucose but not its non-nutritive (yet similarly sweet) enantiomer L-glucose via a post-ingestive mechanism. The ability of D-glucose to cause appetitive LTM is abolished with dopamine receptor inhibition while dopamine neuron stimulation is sufficient to induce appetivite LTM with L-glucose [75].

Is there any evidence that targeting the circuitry that drives motivation to consume rewarding food in a behaviorally relevant context actually effects feeding? It has been shown that during the proximal and distal aspects of feeding that there are changes in ventral striatal dopamine

levels. Cues associated with food elicit a robust increase in ventral striatal dopamine release [76] and cue-induced operant behaviors to obtain a food reward are reduced following microinjections of GABA receptor agonists into the VTA or dopamine receptor antagonists into the ventral striatum [77]. Similarly, sham-feeding corn oil which increases ventral striatal dopamine release [78] is decreased by dopamine receptor antagonists [79]. Intriguingly, intragastric administration of fat (which bypasses the oral cavity and is thus purely post-ingestive) is associated with reduced ventral striatal dopamine [25]. Therefore it would appear that unlike the appetitive and consummatory phases of feeding, the urge to consume energy dense food is decreased once it has been digested, which is in line with a purely motivational signal that is adjusted in response to changes in homeostatic state.

Neuroendocrine regulation of food intake through the mesolimbic pathway

Circulating factors, which signal the long-term and short-term energy status of an organism, interact with the hypothalamus to regulate food intake and energy expenditure. A number of these factors also interact with the mesolimbic system to regulate hedonic feeding (Figure 1A). For instance, in rats, microinjection of the gastrointestinal orexigenic peptide ghrelin into either the VTA or NAc increases lever pressing to obtain a food reward [16]. Ghrelin increases the activity of dopaminergic VTA neurons in vitro [17] and systemic administration of ghrelin increases tonic dopamine release in the NAc shell (but not the core) of the ventral striatum [18]. Interestingly, the effect of microinjection of ghrelin into the VTA on food intake of laboratory chow is preserved, but its effect on operant behaviors to obtain a food reward is abolished when a dopamine receptor antagonist is microinjected into the ventral striatum [19]. These findings are consistent with previous observations that elevations in ventral striatal dopamine positively reinforces actions to obtain food, but not of food consumption itself [20].

Glucagon like peptide (GLP)-1 is an anorexigenic gut hormone released postprandially from the distal small intestine in proportion to the calorie intake of a meal. Microinjection of the GLP-1 receptor (GLP-1R) agonist exendin (Ex)-4 into the VTA and NAc suppresses feeding [21], while microinjection of the GLP-1R antagonist Ex-9 into the NAc increases feeding [22]. In the context of hedonic feeding and in direct contrast to ghrelin, lever pressing to obtain a food reward following microinjection of Ex-4 into the VTA and NAc is decreased [21]. Although GLP-1R activation in the VTA and ventral striatum has marked effects on hedonic feeding, it does not result in changes in phasic dopamine release, at least in the NAc core of the ventral striatum [23]. Instead, GLP-1R activation in presynaptic glutamatergic neurons causes increased glutamate release and activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype glutamate receptors in postsynaptic medium spiny neurons of the ventral striatum, to decrease food intake [23].

Neuroendocrine regulation of food intake through the nigrostriatal pathway

The crucial role of dorsal striatal dopamine in feeding is well established. Early studies revealed that nigrostriatal (as opposed to mesolimbic) lesions result in severe aphagia [10], and in mutant dopamine deficient aphagic mice who lack tyrosine hydroxylase (TH), the rate-limiting enzyme involved in dopamine production, virally mediated gene transfer of TH into the dorsal striatum (as opposed to the ventral striatum) is sufficient to rescue feeding [24]. These findings suggest that dorsal striatal dopamine functions in a similar fashion to ventral striatal dopamine to affect food intake. However, more recent evidence implicates dorsal striatal dopamine in the suppression of hedonic food intake by acting as a reward receipt signal. For instance, consumption of palatable food in lean humans causes dopamine release in the dorsal striatum, as revealed by positron emission tomography (PET)–magnetic resonance imaging (MRI), which is in close correlation to self-reported food pleasantness [11]. In mice, intragastric delivery of fat leads to tonic dopamine release in the dorsal striatum [25]. Interestingly, mice adjust the volume of fat ingested according to concentration, which itself is in direct proportion to tonic dopamine release [25]. These data suggest that dorsal striatal dopamine acts as a homeostatic signal to maintain constant levels of fat ingestion. The reasons for the discrepancy between the lesion and molecular studies and the dopamine measurement studies are presently unclear, but may be due to motor deficits in pharmacologically lesioned animals and developmental compensation in transgenic animals.

There are reports of diminished dorsal striatal function in response to high fat food intake in obesity as adjudged by human functional MRI studies [26]. These data suggest that obesity is associated with reduced sensitivity to food reward receipt (mostly in the form of fat), likely caused by dysfunction of dorsal striatal dopamine signaling, which may lead individuals to compensate for by overindulgence of high-fat (HF) foods (Figure 1B). This raises the question, if dorsal striatal dopamine is restored in obese individuals, would this lead to a restoration of HF food reward receipt facilitating body weight loss? Indeed, in chronically HF-fed mice that have diminished dorsal striatal dopamine release, systemic administration of the lipid signaling molecule oleoylethanolamide (OEA) resulted in reduced HF food intake and body weight loss, with an associated elevation of dorsal striatal dopamine [27]. The effect of OEA on dorsal striatal dopamine was not seen in vagotomized mice, or in mice lacking the peroxisome proliferator receptor (PPAR)α, of which OEA is a natural ligand. Crucially, the suppression of HF food intake in response to OEA was abolished when a mixed dopamine receptor antagonist was microinjected into the dorsal striatum. Dorsal striatal dopamine signaling, thus, can be considered as a central sensor or ‘counter’ of ingested calories (in the form of fat at least) providing negative feedback due to reward receipt, much like the nutrient-sensing mechanisms in the hypothalamus that lead to satiation [28] (Figure 1A). A conserved role for dopamine in nutrient selection is suggested by studies performed on Drosophila, which reject diets low in essential amino acids due to dopamine neuron nutrient sensing [29].

As mentioned above, the nigrostriatal pathway plays dual roles in motor and reward function. Obese individuals are more likely to develop Parkinson's disease (PD) and obese mice are more prone to nigrostriatal neurodegeneration and loss of dorsal striatal dopamine [30]. In a preclinical model of early stage PD, rats with partial lesions to the nigrostriatal pathway treated with Ex-4 show restoration of dorsal striatal dopamine release [31]. It is conceivable thus that GLP-1 interacts with the nigrostriatal dopamine pathway to also regulate hedonic feeding in obesity.

How dieting may affect the mesolimbic pathway to regulate hedonic feeding

Chronic food restriction results in changes in some of the peripheral factors described above which could potentially affect mesolimbic signaling and promote weight regain through increased hedonic feeding (Figure 1C). For instance, in mice, food restriction results in increased circulating ghrelin levels and weight regain is attenuated in ghrelin knockout (KO) animals under free refeeding conditions [32]. This effect is only observed on an HF diet (HFD) and not on standard chow [32]. In stress-induced hyperghrelinemic mice, the increased rewarding effect of HF foods are absent in ghrelin receptor KOs and is restored when the receptor is re-expressed in TH-containing neurons in the VTA [33]. Together, these observations further implicate a role for mesolimbic dopamine signaling in ghrelin induced hedonic feeding and weight gain.

The circulating levels of the stress hormone corticosterone also increase following both an acute fast and chronic food restriction [33]. Microinjection of corticosterone into the VTA increases tonic dopamine release in the ventral striatum and systemic corticosterone increases palatable food intake [33], thus implicating an important role of the hypothalamic-pituitary-adrenal (HPA) axis activation in hedonic feeding and very likely postdieting weight regain as well.

RYGB alters the hedonic value of high fat food

Studies on humans and rodent models have consistently shown that RYGB promotes switching of preference from energy-dense foods to healthier alternatives, with patients stating that they prefer consumption of fruits and vegetables and actively avoid fatty foods [34]. In this context, in patients, consumption of low-fat foods is higher than that of HF foods post-surgery [35], and craving for energy-dense foods, particularly those high in fat content, is reduced [36]. Brief access lick tests reveal that RYGB-operated rats have a preference for lower concentrations of corn oil solution over higher ones [37] and in 24-h two bottle preference tests, RYGB rats prefer low over high concentrations of an Intralipid fat emulsion [38]. Also, in chronic feeding studies, RYGB rats have a lower preference for HFD over laboratory chow when presented with both

diets simultaneously [37]. Together, these observations suggest that RYGB modifies the hedonic value of fat via both pre- and postingestive processes.

It cannot be overlooked that a learned aversion to HF foods develops after gastric bypass surgery. Few studies have been candid about the fact that patients often report severe discomfort in response to consuming high fat meals, sometimes even associated with a dumping syndrome [39]. In keeping with this, in rats after RYGB, oral gavage of corn oil induces a conditioned taste aversion [38] and meal-induced neuronal activity in the area postrema, a region implicated in the development of visceral illness, is increased [40]. Therefore, learned aversion might be a contributor to reduced HF food intake after surgery. Nevertheless, independent changes in reward processing in the striatum might also take place in response to calorie-rich foods, particularly those high in fat content.

Evidence that RYGB surgery effects striatal dopamine signaling

Given the documented effects of RYGB on the reward value of food, interest has grown in assessing potential modifications in striatal processing. PET studies with radiolabelled raclopride and fallypride, which are both selective D2/D3R antagonists, have provided conflicting results, with reports of an increase [41] and a decrease [42] in dorsal striatal D2/D3R availability respectively at 6 weeks after RYGB on morbidly obese (average BMI ~45) women. A single-photon emission computed tomography (SPECT) study with radiolabeled iodobenzamide, another selective D2/D3R antagonist, showed no changes in dorsal striatal D2/D3R availability again at 6 weeks after RYGB on morbidly obese (average BMI ~45) women [43].

A significant limitation of these studies is that they neither provided a distinction between receptor expression levels and endogenous dopamine levels [44], nor a quantitative measure of feeding-induced changes in striatal dopamine release [11] after surgery. One way to assess this would be to use the preclinical models of RYGB in rodents and to determine feeding-induced extracellular tonic or phasic dopamine levels in the striatum after surgery-induced weight loss through the use of in vivo microdialysis or fast scan cyclic voltammetry respectively. Although no such studies have been performed to date, it was shown recently that dopamine levels were increased, ex vivo, in the dorsal striatum of RYGB-operated mice, compared to obese sham-operated controls [45]. Despite the lack of information on changes in dopamine levels according to feeding state, these preliminary results suggest that RYGB might restore dorsal striatal dopamine function (Figure 1D). Future studies on the effect surgery has on ventral striatal dopamine, are warranted (Box 4).

How RYGB may affect the mesolimbic and nigrostriatal pathways to regulate hedonic feeding

RYGB results in signature changes in some of the peripheral factors described above (Box 3). In contrast to calorie restriction however, the resulting profile may affect mesolimbic and nigrostriatal signaling in such a way as to promote weight loss maintenance through decreased hedonic feeding (Figure 1D). Indeed, some obesity treatments are thought to target the mesolimbic pathway to exert their effects on body weight [33]. The circulating levels of the anorexigenic gut hormones GLP-1 and peptide tyrosine tyrosine (PYY) increase following RYGB in both rodent and human studies 46 and 47, whereas circulating ghrelin levels decrease in rodent and most (but not all) human studies 46 and 47. Interestingly, unlike for animals, which lose weight after chronic food restriction, circulating corticosterone levels remain low after RYGB in rats [48].

Box 3.

Long-term mediators of energy balance, RYGB surgery and the mesolimbic pathway

Leptin released from adipose tissue and insulin from pancreas, are the two circulating hormones signaling long-term energy stores to the brain. Both have recently been implicated in regulating hedonic feeding by interacting with their cognate receptors in neurons of the mesolimbic pathway. Viral mediated knockdown of the leptin receptor in the VTA leads to increased preference for sucrose and HF foods [69]. Leptin decreases the activity of VTA neurons in vivo and in vitro [69] and central administration decreases ventral striatal tonic dopamine release in vivo [70]. Similarly, microinjection of insulin into the VTA decreases sucrose and HF food intake [72], and in brain slices, insulin has a long-term depressive effect on excitatory glutamatergic transmission in the VTA. This effect is occluded when animals eat a high-calorie meal, which causes insulin release and supports the notion that insulin causes the same plastic changes in VTA neurons in vivo [71]. The impact of insulin on dopamine release in the ventral striatum is not known and requires further investigation. However, these results suggest that both insulin and leptin decrease VTA neuronal activity and dopamine release in the ventral striatum to decrease the reward value of high sugar/fat foods. In obesity, circulating levels of leptin and insulin are elevated, together with resistance to receptor-mediated signaling. One may hypothesize then that leptin/insulin resistance could result in elevated ventral striatal dopamine release, contributing to increased hedonic feeding.

RYGB and weight loss both restore sensitivity to leptin and insulin. Recent evidence suggests that it is unlikely that restored leptin signaling plays a critical role in the early weight loss after surgery. Indeed, RYGB fatty Zucker rats that lack a functional leptin receptor exhibit the initial weight loss [80]. However, leptin might be required for weight loss maintenance at the later stages after RYGB, as leptin-deficient ob/ob mice eventually regain weight after the procedure

[73]. The role of insulin signaling on RYGB-mediated weight loss has yet to be determined and cannot be ruled out. By extension, both leptin and insulin could exert their effects on hedonic feeding and bodyweight maintenance after RYGB via dampening the activity of the mesolimbic dopaminergic pathway.

Box 4.
Outstanding questions

• Does RYGB modify/restore dopamine release in the ventral/dorsal striatum? Would these effects of RYGB extend to different sub-regions within the ventral/dorsal striatum?

• How would RYGB affect dopamine release in other brain regions such as the prefrontal cortex?

• Do the different bariatric surgical procedures differ in how they affect striatal dopamine signaling?

• Would changes in dorsal striatal dopamine signaling after RYGB break negative feeding habits observed in obesity?

• Would changes in striatal dopamine signaling after RYGB cause changes in hedonic feeding and bodyweight?

• Which gut factors could provide a link between rerouted nutrient passage in the gut and modified striatal dopamine signaling after RYGB? Would different factors be involved with different nutrients thereby causing different effects on striatal dopamine release?

• How would knowledge of changes in gut-dopamine signaling after RYGB in preclinical models apply to human patients and could this lead to novel treatment strategies for obesity?

Although GLP-1 and PYY have been considered the prime candidates driving changes in feeding and bodyweight after RYGB surgery, contradictory results have been obtained from recent pharmacological and KO studies in rodents. Chronic central infusion of a neuropeptide Y2 receptor (Y2-R) antagonist did not affect the surgery phenotype in rats with regards to feeding and body weight [49], and GLP-1R KO mice lose as much weight after RYGB as wild-type mice, and show no differences in food preference tests [49]. As unexpected as these results may be, the role of these hormones in RYGB driven weight loss and their interaction with the mesolimbic and nigrostriatal pathways ought not to be dismissed. For instance, GLP-2 receptor (GLP-2R) signaling could compensate for the deleted GLP-1R gene in KO mice. Also, gastric distension stimulates a population of hindbrain NTS neurons that express GLP-1 [50], which has been shown to project to the VTA and NAc [51]. Considering the reduced size of the gastric

pouch after surgery, the role of GLP-1 as a neuropeptide as opposed to a hormone in suppressing feeding may be more plausible, especially given the short half-life of GLP-1. Selective ablation of GLP-1R-expressing neurons in the mesolimbic pathway using GLP-1 conjugated to the neurotoxin saporin may provide key answers [52].

In the case of PYY, peripheral rather than central Y2-Rs may play a more prominent role in surgery-induced feeding suppression. In support of this, a study utilizing a rat model of relapse onto HF food following chronic food restriction, showed that HF-pellet- and cue-induced reinstatement of lever pressing for HF food were both abolished by systemic PYY administration, with the former effect being reversed by systemic, but not intra ARC Y2-R antagonist administration [53]. It is noteworthy that vagal afferents are stimulated by PYY [54], which has been shown to result in decreased VTA neuronal activity [55] and dopamine turnover in the ventral striatum [56]. Although it is hard to extrapolate rodent findings to human physiology, these results raise the question, are patients, after RYGB surgery, less susceptible to relapse to hedonic feeding because of elevated post-surgery levels of PYY negatively regulating the mesolimbic dopaminergic pathway?

Another peripheral candidate affecting the mesolimbic dopaminergic pathway is the pancreatic hormone amylin, whose circulating concentration is increased after surgery in rats [46]. The amylin receptor complex is expressed in the VTA and ventral striatum and microinjection of the receptor agonist or antagonist into the VTA decreases and increases food intake respectively [57]. Intra-VTA amylin receptor agonist treatment also decreases lever pressing for a sucrose reward [57]. A subsequent study revealed that microinjection of amylin into the VTA reduces phasic dopamine release in the NAc core and knockdown of the amylin receptor in the VTA increases body weight on an HFD [58]. These results suggest that amylin physiologically suppresses hedonic feeding to regulate energy homeostasis, in rats.

A highly interesting metabolic candidate that might affect the nigrostriatal pathway after surgery is OEA. OEA synthesis in the duodenum and jejunum peaks within half an hour of consuming a meal and is specifically increased by intragastric delivery of dietary lipids [59]. Intestinal OEA synthesis decreases with chronic consumption of an HFD, even in the absence of obesity [59]. Although not currently known, RYGB may restore OEA levels in the remaining gut (distal jejunum/proximal ileum) by rerouting nutrient (fat) passage to ultimately restore dorsal striatal dopamine and decrease fat intake. Similar to RYGB, OEA changes the preference for HF food to low fat food [27]. Also, the effects of RYGB and OEA on weight loss are dependent on intact vagal afferent signaling 27 and 60.

A potential role for intestinal fatty acid oxidation (FAO) in RYGB-induced weight loss also merits discussion. Pharmacological inhibitors of FAO have long been known to stimulate HF feeding, whereas stimulation of intestinal FAO suppresses feeding [61]. Consistent with this, both OEA and synthetic PPARα agonists that suppress appetite, increase the expression of enzymes involved in FAO in the gut and FAO products such as the ketone body β hydroxybutyrate (BHB) in the portal vein 62 and 63. As fatty acids also serve as natural ligands of PPARα [64], the increased fat accessing the distal gut after surgery could therefore ultimately result in increased intestinal FAO generating increased BHB and suppression of HF food intake. In support of this hypothesis, a priming effect of OEA has been observed as administration alone does not elicit dorsal striatal dopamine release, and fat must also be subsequently delivered to the gut for its full effects [27]. Therefore, RYGB may increase OEA and/or intestinal FAO to modify the reward value of fat.

Concluding remarks and future research perspectives

Progress has steadily been made in identifying brain systems involved in the hedonic effects of energy dense food and the adaptations that occur in response to their overconsumption and the ensuing weight gain. We have summarized evidence suggesting that the mesolimbic and nigrostriatal dopamine pathways play distinct roles in hedonic feeding. The radically different outcomes of RYGB and dieting on the hedonic value of high calorie (particularly HF) food and weight loss maintenance is possibly due, in part, to differential regulation of these pathways. The unique ability of RYGB to cause a profound and enduring change in our relation with food is likely a result of modifications to homeostatic, hedonic, and aversive systems in the CNS.

Further insight into how the altered profile of peripheral factors in combination interact with the CNS to cause and maintain weight loss after bariatric surgery will undoubtedly aid in the development of novel anti-obesity therapies. Molecules such as OEA and GLP-1, which engage the hypothalamus and the striatum to decrease food intake and hedonic feeding, respectively, represent promising pharmaceutical candidates, as they will allow for a dual-pronged approach for treating obesity.

Acknowledgments

We would like to thank Professor Ivan de Araujo for his valuable input and critical comments on an earlier version of this manuscript. We would also like to thank Mara Sandrock for producing the figures. The work of MKH, SH, AH and WKF is supported by the IFB Adiposity Diseases, Federal Ministry of Education and Research (BMBF), Germany, FKZ: 01E01001 (http://www.bmbf.de).

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