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Distinctive striatal dopamine signaling after dieting and gastric bypass

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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.

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.

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 [9,10], 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

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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.

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.

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