Article published online: 2022-02-18

Obesity – A Matter of Motivation?

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Key words
Obesity, motivation, GLP-1, Dopaminergic midbrain

received 29.07.2021
revised 01.10.2021
accepted 26.10.2021
published online 18.02.2022

Bibliography
Exp Clin Endocrinol Diabetes 2022; 130: 290–295
DOI 10.1055/a-1749-4852
ISSN 0947-7349
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ABSTRACT

Excessive food intake and reduced physical activity have long been established as primary causes of obesity. However, the underlying mechanisms causing this unhealthy behavior characterized by heightened motivation for food but not for physical effort are unclear. Despite the common unjustified stigmatization that obesity is a result of laziness and lack of discipline, it is becoming increasingly clear that high-fat diet feeding and obesity cause alterations in brain circuits that are critical for the control of motivational behavior.

In this mini-review, we provide a comprehensive overview of incentive motivation, its neural encoding in the dopaminergic mesolimbic system as well as its metabolic modulation with a focus on derangements of incentive motivation in obesity. We further discuss the emerging field of metabolic interventions to counteract motivational deficits and their potential clinical implications.

Introduction

The growing obesity pandemic is one of the biggest health problems in the 21st century that gives rise to multiple comorbidities such as cancer or neurodegenerative diseases and thus dramatically increases mortality [1–3]. In the western world, excessive food intake beyond physiological needs as well as reduced physical activity are well established as main causes promoting obesity. However, the underlying mechanisms instigating this maladaptive behavior, which disregards or overrides homeostatic needs, are poorly understood. In everyday life, we constantly make decisions and adapt our behavior to our physiological needs and the surrounding environment – e. g., we decide to go to the bakery across the street to get a delicious sandwich avoiding lunch in the inhouse cafeteria. To ensure our physiological homeostasis and to adapt our behavioral responses, our brain constantly integrates information about the metabolic state (e. g., hunger) with external environmental cues (bakery vs. inhouse cafeteria). External cues can comprise varying motivational signals, which include the incentive value of

an expected reward (delicious sandwich vs. cafeteria lunch) but also the effort required to obtain the reward (distant bakery across the street vs. close inhouse cafeteria). Thus, everyday decisions in favor of or against food intake are based on cost-benefit analyses weighing the potential food reward against the cost of spending effort to obtain it.

The incentive theory of motivation regards motivational behavior to mainly depend on anticipated rewards and reinforcement; hence, incentive motivation refers to the processes that translate expected reward into the effort spent to obtain the reward [4–6]. Importantly, the subjective valuation of the magnitude of a reward depends on our internal state; a sandwich is regarded as more valuable in a hungry than a sated state [7]. Consequently, our motivation depends on the capacity of our brain to integrate internal state signals (hunger) with environmental cues (distance to bakery, value of sandwich) to guide our behavior.

There is increasing evidence that high-fat diet consumption and obesity perturbate the underlying neural processes leading to maladaptive behavior and motivational deficits. This mini-review aims to give a short overview of incentive motivation, its neural encoding in the dopaminergic mesolimbic system and its metabolic regulation with a focus on derangements of incentive motivation in obesity as one mechanism underlying excessive food intake and reduced physical activity. We further give an outlook on the emerging field of metabolic interventions to counteract motivational deficits and their potential clinical implications.

Encoding of incentive motivation in the dopaminergic midbrain

Incentive motivation is encoded by the mesolimbic dopaminergic system. Dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) encode both reward-driven learning and motivation to work for reward [8, 9]. Learning signals are encoded by phasic dopamine release in the NAc. On the other hand, dopamine release ramps up when we approach a reward reflecting reward expectancy [10]. The amount of dopamine, that is released during this ramping-up phase, provides information about the value of the anticipated reward and motivates the amount of effort required to obtain it [11–13]. While our understanding of the differential functions of dopamine in reward learning and motivation are mainly derived from animal studies, human brain imaging studies support these results, as changes in the activity of the NAc were observed to correlate with the subjective value of rewards and its anticipation [12, 14, 15]. Likewise, human pharmacological intervention studies lowering dopaminergic tone have provided evidence for lower effort spending and motivation [16–18].

Motivation in obesity – inconclusive results

In obese humans, alterations in the fronto-mesolimbic dopamine system (in particular within the dopaminergic projections from the VTA to the NAc) are related to an impaired reward system [19, 20]. A high-fat diet – interestingly even in the absence of obesity – induces downregulation of dopaminergic D2 receptors as described in animal studies [21, 22]. On a functional level, high-fat diet consumption also causes a devaluation of standard chow diet, which is encoded by reduced dopamine release from the VTA upon receival of standard food (amongst encoding by hypothalamic agouti-related peptide neurons), and thus diminishes the rewarding properties of food discovery [20]. In humans, the direct impact of a high-fat diet on the mesolimbic system in the absence of obesity has not been studied yet. The data comparing obese and healthy weight participants is consistent with the abovementioned animal literature. Human positron emission tomography (PET) studies revealed a negative correlation between body mass index (BMI) and striatal D2 receptor density or binding potential in obese and overweight humans [23, 24]. This reduced binding potential of striatal dopamine receptors seems to be associated with an altered striatal dopaminergic tone leading to an imbalance of anticipation and consumption of food reward [25, 26]. In comparison to lean individuals, humans with obesity show increased neural activation of the NAc when anticipating a reward but experience less activation of reward circuits from the actual food reward consumption [23, 27]. These changes in D2 receptor binding potential seem to be partly reversible by bariatric surgery-induced long-term weight loss [28–30]. In animals, bariatric surgery even seems to change the motivation for drug rewards via post-surgical increases in bile acid signaling, which reduces accumbal dopamine [31]. However, only little is known about incentive motivation in obese humans and findings portray a heterogeneous picture of effort spending in obesity.

Mathar et al. [32] assessed motivational differences between lean and obese humans in a cost-benefit decision-making paradigm, in which participants had to exert physical effort on a handgrip to win food and non-food reward. Obese participants were less willing to engage in physical effort in particular for high-caloric sweet snack food. In contrast, Epstein et al. as well as Giesen et al. suggest that obese humans may be willing to invest more effort to obtain high-caloric food than lean individuals [33, 34].

Metabolic modulation of the dopaminergic midbrain – animal results

These studies might rest upon incomplete assumptions about modulatory influences on midbrain dopaminergic function, as VTA dopaminergic neurons are not only involved in reward learning and motivation but are also sensitive to nutritional signals [35], post-ingestive effects of food [36, 37], and metabolic state signaled by peptidergic mediators [38–40]. Many orexigenic agents (such as Ghrelin) and postprandial anorexigenic peptides (such as glucagon-like peptide 1 (GLP-1), insulin or leptin) or their agonists can bind to receptors on dopaminergic neurons of the VTA/Nac [41] and hence modulate dopaminergic performance upon their activation affecting motivational behavior. In line, animal studies reveal that the hunger hormone ghrelin applied directly into the VTA increases dopamine levels in the NAc and thus induces motivational behavior for food rewards [42–45]. Correspondingly, in a state of overnight fasting with high endogenous levels of ghrelin, ghrelin receptor blockade in the VTA reduces the motivation to work for food reward [46, 47]. However, the effect of ghrelin on motivation seems to depend on the surrounding environmental cues. In a classical place preference task in rodents, peripheral injection of ghrelin in the absence of food-induced aversive

behavior [48], while in the presence of food, ghrelin instigated conditioned place preference [44, 48]) indicating that the interplay of endogenous metabolic signals and environmental perception shapes adaptive motivational behavior.

Contrary to ghrelin, postprandial hormones such as insulin or GLP-1 reduce motivated behavior for food rewards in mice by downregulating dopaminergic transmission [49]. Specifically, insulin action on dopaminergic VTA neurons depresses excitatory synaptic transmission [50], decreases dopamine concentrations by enhancing its clearance [51, 52], and reduces dopamine release into the NAc [53]. GLP-1 (and its analogues) reduces phasic dopamine release of VTA dopaminergic neurons in response to reward-indicating cues and attenuates synaptic drive onto mesolimbic dopamine neurons [54–56]. Amylin (and its receptor agonists), also seems to affect dopaminergic neurons in the VTA, reducing phasic dopamine action in the NAc and consequently food intake [57, 58]. Its complete role as a modulator of dopaminergic activity and hence motivation still requires further investigation with first data revealing an attenuating effect of Amylin receptor agonists on the rewarding properties of alcohol [59]. Similarly, the adipocytokine leptin, which circulates in proportion to body fat to signal the repletion of long-term energy stores, expresses its receptor on VTA dopaminergic neurons. However, ablation of these leptin receptors does not alter motivational behavior but increases anxiety-like behavior (as these neurons mainly project to the amygdala, which is highly implicated in anxiety) [60, 61]. Nonetheless, leptin reduces motivational behavior for food. The mode of action seems to be more indirect, however, with leptin receptor-bearing neurons of the lateral hypothalamus, decreasing mesolimbic dopaminergic function as a consequence of increased dopamine uptake in the NAc [62].

Collectively, the orexigenic peptide ghrelin seems to enhance motivational behavior in rodents by upregulating dopaminergic transmission in the mesolimbic system, whereas postprandial and anorexigenic peptides (such as insulin, GLP-1, leptin, and probably amylin) have the opposite effect on dopaminergic function and motivation[63]. However, the food itself, which is used as a reinforcer in motivational paradigms, exerts a time-dependent effect on dopamine release with an immediate orosensory and delayed post-ingestive dopaminergic response [37]. Considering the multitude and complexity of modulatory influences on the dopaminergic mesolimbic system, the above-portrayed roles of peptidergic hormones in the regulation of motivation might be multifaceted with varying effects depending on nutritional/metabolic state.

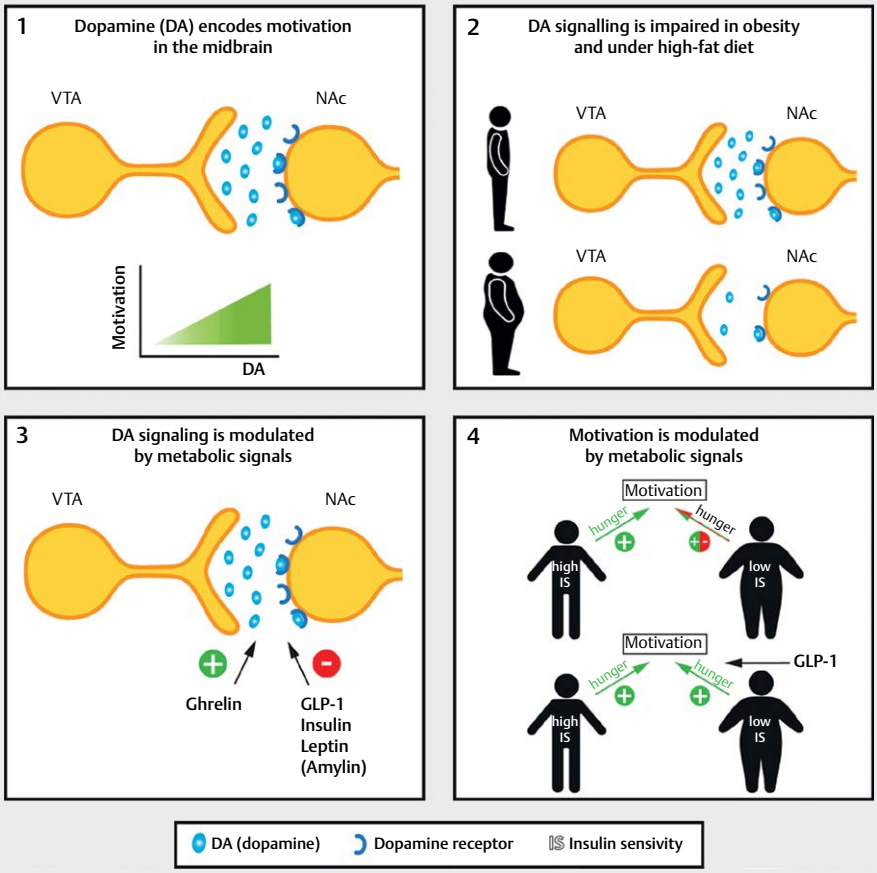
Metabolic modulation of motivational behavior in humans and its derangements in obesity

While the modulatory effect of metabolic peptides on the dopaminergic neurocircuitry and motivational behavior is well documented in rodents, evidence for a modulatory role of peripheral peptides or metabolic state affecting motivational behavior in humans is scarce. We, therefore, set up a randomized, placebo-controlled study to assess the effect of GLP-1 on motivation in lean and obese individuals while capturing their metabolic state, i. e., their hunger level and insulin sensitivity. Participants exerted force on a hand-grip to win food and monetary rewards. We could show that hunger increases incentive motivation in lean humans but not in obese humans indicating that motivational irregularities in obesity are state-dependent. We further observed that the effect of hunger on incentive motivation is modulated by the peripheral insulin sensitivity of the individual with impaired peripheral insulin sensitivity reducing the motivational effect of hunger [64]. These results are in line with previous studies showing that altered insulin sensitivity impacts dopaminergic projections of the midbrain and denote a dysfunctional integration of metabolic signals and external cues within the mesolimbic system as the foundation of impaired motivational drive in obesity [65]. The aforementioned heterogeneous results about incentive motivation in obese humans showing both increased and decreased effort spending for rewards might thus be a consequence of neglecting metabolic state, in particular, insulin sensitivity and fasting time/hunger. We further demonstrate that administration of the GLP-1 analogue liraglutide normalizes the motivational effect of hunger in insulin-resistant humans. Most importantly, this holds true for both food and monetary reward, indicating that the modulatory effect of GLP-1 on motivational behavior exceeds a mere food scenario and might prove beneficial in other disorders with motivational deficits [64].

Outlook: Metabolic treatment of motivational deficits in psychiatric diseases

As GLP-1 normalized motivation in insulin-resistant humans but did not affect motivation in insulin sensitive participants, GLP-1(analogues) might comprise therapeutic potential for motivational dysfunctions in dopaminergic disorders, which are associated with metabolic impairments such as insulin resistance. Insulin resistance is a shared abnormality among many patients with type 2 diabetes mellitus and major depression [66] hence, GLP-1 could be cautiously hypothesized to improve dopaminergic functioning in depression and hence depressive symptom burden in patients suffering from both depression and insulin resistance. Furthermore, GLP-1 receptor polymorphism has been associated with anhedonia – the lack of motivation, which is a core symptom of depression. In a first meta-analysis, treatment of diabetic patients with GLP-1 analogues resulted in a significant reduction of depression scores [67]. However, this meta-analysis is based on eight publications only with heterogeneous cohorts so that the result must be interpreted with caution. While the GLP-1 analogue Liraglutide is already approved as weight loss medication in Germany [68], randomized controlled clinical trials on the efficacy and safety of GLP-1 analogues as a treatment for motivational deficits in diabetic or insulin-resistant patients suffering from depression are lacking.

In animal studies, GLP-1 also reduces the reinforcing efficacy of drugs of abuse so that a potential therapeutic benefit of GLP-1 analogues could also be suspected for detoxification therapies [69]. For instance, GLP-1 analogues were shown to reduce cocaine, amphetamine, alcohol, and nicotine use in animals [70]. Interventional studies in humans are fervently awaited.



▶ **Fig. 1** Encoding of motivation in the dopaminergic midbrain. Notes. 1) Dopamine (DA) encodes motivation in the midbrain; dopaminergic neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) with higher dopaminergic tone encoding higher motivation. 2) Dopamine signaling is impaired in obesity and under high-fat diet. The binding potential of dopaminergic D2 receptors is reduced in obesity and high-fat diet (in animal studies) causing a reduced dopamine release from the VTA upon receival of standard food and thus diminishing the rewarding properties of food discovery. 3) Dopamine signaling is modulated by metabolic signals as shown in animal studies. Ghrelin applied into the VTA increases dopamine levels in the NAc and hence motivation; glucagon-like peptide 1 (GLP-1), insulin, leptin and (probably) amylin reduce motivated behavior for food rewards in mice by downregulating dopaminergic transmission. 4) In humans, motivation increases with increasing hunger levels in normal weight humans with good insulin sensitivity, while in obese humans with reduced insulin sensitivity hunger does not affect motivation. Intervention with GLP-1 does not affect motivation in insulin sensitive humans but normalizes the effect of hunger on motivation in insulin resistant humans.

Summary

In summary, both external cues and internal state signals are integrated into the dopaminergic mesolimbic system to guide our everyday motivational behavior (see ▶ **Fig. 1**). Dopamine release in the NAc ramps up as a reward approaches, encoding reward expectancy. Metabolic peptide hormones – such as insulin, GLP-1, leptin, or ghrelin – modulate dopaminergic transmission thus regulating motivational behavior, that is, hunger augments motivation to exert effort for rewards. In obesity, insulin resistance reduces the motivational effect of hunger, indicating that a dysfunctional integration of metabolic signals with external cues seems to lead to derangements of incentive motivation representing one possible mechanism underlying excessive food intake and reduced physical activity in obesity. Concomitantly, interventions with metabolic messengers offer new opportunities to reverse motivational deficits. In obese humans, for example, intervention with GLP-1 normalizes motivational behavior. Future clinical research directions should therefore include the safety and efficacy of clinical interventions with metabolic mediators in pathologies associated with motivational insufficiencies.

Conflict of interest

The authors declare that they have no conflict of interest.

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