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Review

Moving beyond energy homeostasis: New roles for glucagon-like peptide-1 in food and drug reward

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ABSTRACT

Glucagon-like peptide-1 (GLP-1), a hormone and neuropeptide, is known to regulate energy homeostasis in part through an established central role in controlling food intake. Historically this central role has largely been attributed to GLP-1 receptor signaling in the brainstem and hypothalamus. However, emerging data indicate that GLP-1 also contributes to non-homeostatic regulation of food reward and motivated behaviors in brain reward centers, including the ventral tegmental area and nucleus accumbens. The hypothesis that GLP-1 signaling modulates reward circuitry has provided the impetus for studies demonstrating that GLP-1 attenuates reward for psychostimulants and alcohol. Here, we examine current evidence for GLP-1-mediated regulation of food and drug reward and use these findings to hypothesize mechanisms of action within brain reward centers.

1. Introduction

Numerous studies in animals and humans have established that glucagon-like peptide-1 (7–36) amide (GLP-1), an incretin hormone and neuropeptide, acts through both peripheral and central mechanisms to regulate energy homeostasis and feeding behavior (Kanoski et al., 2011; Turton et al., 1996). Importantly, central GLP-1 signaling has been linked not only to the regulation of energy homeostasis, but also to non-homeostatic reinforcing and motivational processes associated with food reward (Alhadeff et al., 2012; Dickson et al., 2012). Most notably, it was recently demonstrated that targeted activation of mesolimbic GLP-1 receptors decreases preference for palatable foods as well as the motivation to work for such foods (Alhadeff et al., 2012; Dickson et al., 2012; Dossat et al., 2011). While the exact mechanisms underlying the regulation of food reward are still under investigation, these findings have inspired the hypothesis that central GLP-1 signaling plays an additional role in the hedonic response to drugs of abuse. Several recent behavioral studies in animals have provided strong support for this hypothesis (Egecioglu et al., 2013a,b; Erreger et al., 2012; Graham et al., 2012; Shirazi et al., 2013). In this review, we examine the evidence that GLP-1 receptor agonists modulate the rewarding and reinforcing properties of palatable foods and drugs of abuse through regulation of established brain reward circuitries. Furthermore, we discuss potential mechanisms of action, with an emphasis on the involvement of the neurotransmitter dopamine (DA). Understanding the effects of GLP-1 on reward circuitries in the brain will allow us to better assess its utility as a pharmacotherapeutic for both obesity and substance use disorders.

2. GLP-1 and food: beyond energy homeostasis

GLP-1 is a peptide hormone produced by L-cells of the intestine in response to nutrient absorption within the gastrointestinal tract. While GLP-1's peripheral effects are many (Baggio and Drucker, 2007), it is most well-known for its glucoregulatory properties. As an incretin, GLP-1 promotes glucose-dependent insulin release by binding to receptors on beta pancreatic cells. The ability to potentiate insulin secretion has made long-lasting synthetic GLP-1 agonists powerful drugs for the treatment of type II diabetes. FDA-approved drugs in this class include exendin-4 (Ex-4) and liraglutide, which are resistant to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). Of interest, a percentage of obese diabetic patients taking these drugs lose weight, an effect that occurs primarily through reduced appetite and decreased food intake (Baggio and Drucker, 2007; Verdich et al., 2001).

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GLP-1 is also a neuropeptide produced by brainstem neurons in the nucleus of the tractus solitarius (NTS) which project widely to subcortical areas containing the GLP-1 receptor (Merchenthaler et al., 1999; Rinaman, 2010). The NTS, in turn, receives vagal afferents which provide information regarding taste and mechanical stretch of the gastrointestinal system (Berthoud, 2008).

As an outcome of the discovery of the potent anorectic effect of GLP-1 receptor agonists and the expression of GLP-1 receptors in the brain, studies began exploring GLP-1's central influence on food intake. They found that GLP-1 reduced appetite and induced weight loss when administered to the cerebral ventricles of rats (Tang-Christensen et al., 1996; Turton et al., 1996). They also discovered that central infusion of GLP-1 could activate c-Fos immunoreactivity in various nuclei of the brainstem and hypothalamus (Dijk et al., 1996), and that injection of GLP-1 directly into the paraventricular nucleus of the hypothalamus was sufficient to suppress feeding without inducing aversion (McMahon and Wellman, 1998). Thus, earlier research focused on the effects of GLP-1 on the hypothalamus and brainstem, regions highly involved in homeostatic metabolic control (Baggio and Drucker, 2007; Holst, 2004).

While this work established that GLP-1, in part, regulates the homeostatic control of feeding, it does not fully account for alterations in feeding behavior and food preference. For example, peripheral injection of GLP-1 long-lasting analogues in rodents reduces preference for sweets (Raun et al., 2007), while both peripheral and central infusions of GLP-1 analogues reduce motivation to work for food reward (Dickson et al., 2012). These findings suggest that GLP-1 also reduces food intake through regulation of food reward in non-homeostatic circuits. In fact, various reports indicate that GLP-1 receptors are expressed in components of the mesolimbic reward circuitry (Gu et al., 2013). Recently, research exploring the central modulation of food intake by GLP-1 has shifted away from homeostatic circuits and toward areas associated with reward, motivation, and stimulus salience. This shift in focus is timely, as obesity in the US has reached epidemic proportions and homeostatic control is clearly insufficient to prevent excessive food intake. In environments in which high fat and sugary foods are readily available, brain reward systems may override homeostatic systems (Niswender et al., 2011; Palmiter, 2007).

3. Central GLP-1 signaling modulates food reward and motivation in animals

Obesity is a complex condition that arises from a combination of environmental, genetic, and socioeconomic factors. Emerging evidence suggests that food reward may be an important etiological factor, as obese individuals disproportionately consume high energy foods and exhibit enhanced motivation to work for rewarding food stimuli (Mela, 2006). Imaging studies demonstrate a possible neurobiological basis for these behaviors. Obese subjects, when compared with normal-weight subjects, show increased activation of certain brain reward centers in response to calorie-dense food cues (Stoeckel et al., 2008). At the same time, obese individuals exhibit decreased activation of the caudate nucleus in response to consumption of a palatable milkshake (Stice et al., 2008), which may be related to a lower availability of D2 DA receptors within the striatum (Wang et al., 2001). It has been posited that such reductions in receptor availability attenuate dopamine signaling, predisposing individuals to pathological overeating (Wang et al., 2001). DA has an established role in feeding behavior (Palmiter, 2007). In particular, increases in extracellular DA appear to be associated with desire for palatable foods (Volkow et al., 2002).

Based on the understanding that dysfunction of reward pathway activation may contribute to obesity and alterations in perceived food reward, research has begun to examine how GLP-1 alters reward circuits to influence feeding behavior. Such studies require specific and targeted activation of GLP-1 receptors in brain reward centers. The mesolimbic DA pathway, from the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens (NAc) in the medial forebrain, has a definitive role in incentive motivation for both drugs of abuse as well as food (Avena et al., 2006; Kalivas and Volkow, 2005; Wise, 2006). DA released in the NAc binds to postsynaptic DA receptors to activate neuronal efferents involved in the motor components of reward seeking. The GLP-1 receptor appears to be expressed both in the VTA and the NAc based upon studies of GLP-1 immunoreactivity, autoradiographic binding, *in situ* hybridization, and direct neural tracing between these areas and the NTS (Alhadeff et al., 2012; Dossat et al., 2011; Göke et al., 1995; Gu et al., 2013; Merchenthaler et al., 1999; Rinaman, 2010). Furthermore, exogenous intraperitoneal injection with the synthetic GLP-1 analogue, Ex-4, induces Fos activation in the NAc (Gu et al., 2013). These findings underscore the relevance of targeted manipulations to GLP-1 signaling in these discrete reward areas to the study of GLP-1 signaling in feeding behaviors.

Direct injection of Ex-4 into the VTA or NAc core has been shown to alter multiple aspects of food reward. First, GLP-1 signaling in the VTA appears to be important in determining the palatability of food ("liking"). In one study, injection of subthreshold doses of Ex-4 into the VTA or NAc core, but not the NAc shell, of food-deprived rats resulted in a significant suppression of sucrose intake at multiple time points compared to vehicle-injected animals (Alhadeff et al., 2012). Ex-4 also shifted their preference for high fat food to regular chow when injected into the VTA, NAc core, and NAc shell, resulting in a reduced 24 h weight gain. Depending on the time of exposure and location of injection, the GLP-1 receptor-specific antagonist, exendin-(9-39) amide (Ex-9) (Göke et al., 1993), increased or had no effect on high fat diet intake. This suggests that endogenous GLP-1 signaling maintains a degree of control over food intake and preference. In another study, it was found that GLP-1 injected into the NAc core reduced 2 h regular chow intake and induced c-Fos expression relative to saline, but no effect was observed in the NAc shell. Again, Ex-9 had the opposite effect on chow intake (Dossat et al., 2011). Finally, Ex-4 injected into the VTA, but not the NAc shell, reduced 24 h chow intake, and the activation of GLP-1 receptors in the VTA maintained a significant reduction in food intake even 24 h after injection (Dickson et al., 2012). The combined results of these three important studies indicate that (1) the VTA and NAc core are important targets for GLP-1-mediated reduction in sucrose and high fat food preference, (2) the NAc shell is likely not an important site of action for GLP-1 in regard to food palatability, although it may still play a role in motivated behaviors (Dickson et al., 2012), (3) endogenous GLP-1 signaling in mesolimbic reward areas may be important for controlling perceived food palatability, and (4) the effects of GLP-1 receptor signaling on reward may be relatively long-lived (>24 h).

"Wanting", or the motivation to obtain rewarding stimuli, is another important aspect of feeding behaviors and is dissociable from "liking" (Berridge and Robinson, 1995; Berridge et al., 2009; Berthoud and Morrison, 2008). Motivation for food is typically assessed through an operant learning paradigm called progressive ratio operant conditioning. In this task, the animal must press a lever progressively more times to receive consecutive rewards. This test has been used to assess motivational incentive following targeted injection of Ex-4 into the VTA or NAc (Dickson et al., 2012). After VTA injection, Ex-4 reduced the number of sucrose rewards obtained in a dose responsive manner, but injection into the NAc only resulted in a reduction at the highest dose. The effect of Ex-4 on motivated feeding behavior was specific to the GLP-1

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