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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.

Keywords

Glucagon-like peptide-1; Reward; Food; Drugs of abuse; Alcohol; Psychostimulants; Dopamine; Transporter

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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; Egecioglu et al., 2013b; 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).

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 U.S. 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 hour 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 hour 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 hour chow intake, and the activation of GLP-1 receptors in the VTA maintained a significant reduction in food intake even 24 hours 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 hours).

"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 receptor, as pretreatment of animals with Ex-9 abolished the suppressive effect of intraventricular Ex-4 on operant conditioning for sucrose reward. Interestingly, this study also considered the operant responsiveness of rats that were "high reward responders" (on vehicle condition, earned 6 or more sucrose rewards in satiated state) versus "low reward responders" (earned 5 or fewer rewards). They found that the "high reward responders" earned fewer sucrose rewards when given Ex-4 in the VTA, while the "low reward responders" were unaffected. This suggests that some animals may be predisposed to the rewarding effects of food and that Ex-4 only attenuates motivated behavior in susceptible individuals. Furthermore, these data revealed that, at least at the doses used, Ex-4 was unable to reduce the number of rewards earned to the level of vehicle-treated animals in the "low responders" group. This finding is striking as it illuminates the intrinsic challenges to overcoming reward-seeking behavior in vulnerable individuals (Buckholtz et al., 2010; Flagel et al., 2010).

These collective findings point to a role for central signaling through the GLP-1 receptor not only in reducing food intake and palatability, but also the motivation to work for food. It should be noted that no aversive behaviors were identified in the aforementioned studies (Alhadeff et al., 2012; Dickson et al., 2012; Dossat et al., 2011), despite reports that aversion may partially account for a reduction in food intake (Thiele et al., 1997). It may be that aversion to GLP-1 is mediated by specific brain regions implicated in aversive responses (e.g. the central nucleus of the amygdala) (Dickson et al., 2012; Kinzig et al., 2002).

4. Central GLP-1 signaling modulates drug reward and motivation in animals

In recent years, several reports have made the case that food and drugs of abuse activate similar reward circuitries in the brain. Indeed, human brain imaging studies have demonstrated activation of mesolimbic reward areas in response to palatable food/food cues and drug reward (Kenny, 2011; Volkow et al., 2012), and the same deficiencies in striatal DA signaling have been noted in both obese and drug-dependent subjects (Volkow and Wise, 2005; Wang et al., 2001). Moreover, a growing body of literature suggests that enteric hormones and peptides with roles in feeding behavior, such as leptin, ghrelin, and insulin, are involved in drug reward (Daws et al., 2011; Dickson et al., 2011; Kenny, 2011). It is established that ghrelin, an orexigenic hormone, is in fact necessary for alcohol reward (Jerlhag et al., 2009). Insulin, as well, regulates the psychotropic effects of amphetamine (Owens et al., 2012; Williams et al., 2007) and has been proposed to be required for normal reward for food (Galici et al., 2003; Niswender et al., 2011; Speed et al., 2011).

Addiction to psychostimulant drugs, including cocaine and amphetamine, is characterized by compulsive seeking behavior and intense craving. These drugs augment extracellular DA, thereby enhancing and prolonging its effects intrasynaptically (Volkow et al., 2012). Cocaine blocks reuptake of DA from the synapse by blocking the DA transporter (DAT), while amphetamine promotes efflux of DA into the extracellular space. High levels of extracellular DA contribute to the reinforcing effects of and behavioral locomotor activation by psychostimulants. Excitingly, it was recently discovered that pretreatment with Ex-4

attenuates amphetamine- and cocaine-induced locomotion, suggesting that GLP-1 signaling reduces extracellular DA in response to psychostimulants (Egecioglu et al., 2013a; Erreger et al., 2012). Moreover, pretreatment with Ex-4 attenuates the rewarding effects of amphetamine and cocaine in a conditioned place preference (CPP) test (Egecioglu et al., 2013a; Graham et al., 2012), although preference for cocaine is not entirely abolished, suggesting that GLP-1-independent components of cocaine reward exist (Graham et al., 2012). Egecioglu and colleagues also measured reductions in amphetamine- and cocaine-stimulated accumbal DA release by microdialysis following peripheral Ex-4 injection (Egecioglu et al., 2013a). Of note, this result does not indicate whether this occurs as a direct result of accumbal GLP-1 receptor stimulation, or at the circuit level. While there have been no studies to date examining whether GLP-1 alters motivation for psychostimulants, these studies lend credence to the hypothesis that GLP-1 signaling overlaps with drug addiction.

The ability of GLP-1 to modulate the rewarding properties of drugs appears to extend to alcohol (Egecioglu et al., 2013b; Shirazi et al., 2013). Alcohol use disorders, like psychostimulant abuse, are characterized by compulsive use and seeking (Thanos et al., 2012). Alcohol promotes the firing of DA neurons in the VTA by impairing GABAergic inhibitory tone (Volkow et al., 2012). Egecioglu and colleagues found that low doses of intraperitoneal Ex-4 attenuate alcohol-induced locomotor stimulation in rodents and reduce accumbal DA release *in vivo* (Egecioglu et al., 2013b). They also found that Ex-4 reduced alcohol intake in a two-bottle choice model and impaired alcohol CPP under both acute and chronic treatment conditions. Finally, Ex-4 diminished alcohol seeking in a progressive ratio operant conditioning paradigm, suggesting a role for Ex-4 in drug motivation. Interestingly, the rats did not exhibit any rebound increases in ethanol consumption 48 hours after Ex-4 administration, implying that withdrawal symptoms may be attenuated by Ex-4. A second group also found significant reductions in ethanol CPP and intake following peripheral Ex-4 administration (Shirazi et al., 2013). Of interest, this study noted that the increased ethanol intake of high consumers (top 30%) over low consumers was completely abolished by peripheral GLP-1 administration in a 1 hour intermittent access drinking paradigm. Furthermore, this study showed that targeted microinjection of GLP-1 and Ex-4 into the VTA could significantly reduce ethanol intake. This is so far the only direct evidence that the VTA is an important site of GLP-1 action in drug reward.

Taken together, these studies suggest that GLP-1 attenuates drug reward from psychostimulants and alcohol, and that the effect may be mediated by decreases in stimulated accumbal DA release. While most of the aforementioned reports employed peripheral injections of GLP-1 analogues, we can speculate that the mesolimbic reward system is involved based upon known sites of action for the various drugs of abuse tested. Still, peripheral mechanisms cannot be ruled out. Additionally, it is also important to keep in mind that GLP-1 stimulates insulin release, which is known to regulate drug reward (Daws et al., 2011; Williams et al., 2007), and could potentially explain the reward attenuating effects of peripherally administered GLP-1 and its analogues. As a first pass, however, these behavioral studies provide key insights into the therapeutic potential of GLP-1 analogues in substance use disorders and establish a basis for future targeted studies.

5. Dietary and surgical manipulations altering plasma GLP-1 suggest that GLP-1 modulates food and drug reward

Although direct manipulation of GLP-1 signaling in animals provides the most valuable insights into its effects on reward systems, we may also learn something of the role of endogenous GLP-1 from states of altered blood plasma levels. One such condition is food restriction/deprivation. Since GLP-1 is released postprandially, GLP-1 levels are normally low during food restriction. We might expect that if GLP-1 signaling does reduce food and drug reward, that food restriction or fasting might increase susceptibility to the rewarding effect of food or drugs. Indeed, food restriction has been associated with enhancements in food and drug reward behavior. Food restriction promotes drug intake in humans (Hall et al., 1992) and provokes relapse to heroin and cocaine in animal self-administration models (Carroll, 1985; Comer et al., 1995; Shalev et al., 2002; Shalev et al., 2001). Food CPP is also more readily established under conditions of food restriction (Figlewicz et al., 2001). Additionally, when electrodes are implanted in various brain reward centers, animals tend to self-stimulate more when food restricted (Carr and Wolinsky, 1993; Figlewicz et al., 2001; Shalev et al., 2001). Knowing that food restriction reduces plasma levels of the anorexigenic hormones leptin and insulin and that both express receptors in brain reward centers (Figlewicz, 2003; Figlewicz et al., 2003), investigators hypothesized that replacement of these hormones could rescue potentiated reward. Under conditions of food restriction, intraventricular leptin replacement has been found to attenuate reinstatement of heroin seeking (Shalev et al., 2001), food CPP, and electrical self-stimulation of the lateral hypothalamus (Fulton et al., 2000). Importantly, leptin's effects appear to be specific to food deprivation stress, as it has no effect on footshock-induced reinstatement of heroin seeking (Shalev et al., 2001). Perhaps GLP-1 modulates enhanced food and drug reward in the fasting state. Currently, there are no published data directly comparing the reward-modulating effects of GLP-1 in food restricted vs *ad libitum* fed animals. For now, we can only draw an association between enhanced drug/food seeking behavior and low levels of GLP-1.

Another example of altered blood GLP-1 levels that has been used to speculate on GLP-1's role in reward is bariatric surgery. Basal and postprandial circulating GLP-1 increases after surgery, particularly following roux-en-y gastric bypass (RYGB) (Ashrafian and le Roux, 2009; Korner et al., 2005). Patients who undergo RYGB lose significant weight, exhibit decreased appetite, and show greater interest in consuming low fat than high fat foods (Ochner et al., 2011b; Thomas and Marcus, 2008). According to Ochner and colleagues, 20–45% of post-RYGB weight loss may be unexplained by change in stomach size and increases in metabolism (Ochner et al., 2011a). It has been suggested that weight loss after RYGB may be enhanced by changes in food intake behaviors mediated by enteric hormones like GLP-1. This is physiologically plausible since GLP-1 secretion is enhanced by faster delivery of food contents to the gut following the bypass procedure (Baldinger et al., 2007; Klockhoff et al., 2002; Moran and Dailey, 2011; Ochner et al., 2011a). In support of this notion, RYGB "good responders" (~40% weight loss) secreted significantly more GLP-1 in response to a post-operative test meal than "poor responders" (< 20% weight loss) (le Roux et al., 2007; Moran and Dailey, 2011). Functional magnetic resonance imaging (fMRI)

studies in patients before and after RYGB have revealed reductions in mesolimbic pathway activation (including the VTA, ventral striatum, and dorsomedial prefrontal cortex) following combined audio and visual energy-dense food cues (Ochner et al., 2011b). PET studies have also revealed alterations in D2 DA receptor availability and extracellular DA following RYGB (Dunn et al., 2010; Steele et al., 2010). It appears, therefore, that there is at least some correlative link between elevations in GLP-1 following RYGB and alterations in reward activation. Additional work will be required to draw a causal relationship.

Interestingly, associations have also been made between bariatric surgery and alcohol use disorders (AUDs). Several small-scale studies have suggested, perhaps unconvincingly, that patients develop *de novo* alcohol dependence following surgery (Buffington, 2007; Davis et al., 2013; Ertelt et al., 2008; Sogg, 2007), while a large clinical study of 6,165 patients which analyzed alcohol intake on a 4 point scale showed that patients who had previously consumed alcohol “occasionally” or “frequently” had significantly *decreased* their alcohol intake score as a group (Davis et al., 2012). No changes were noted in patients who had not used alcohol before surgery. This same publication also studied the effect of RYGB on alcohol consumption in rats selectively bred to consume ethanol. Before surgery, sham rats consumed comparable amounts of alcohol to RYGB rats. After surgery, the RYGB rats consumed significantly less alcohol than sham-operated rats. The authors postulated that the reduction in ethanol consumption following RYGB may have been the result of elevated GLP-1. Indeed GLP-1 levels increased selectively in the RYGB rats following ethanol oral gavage. Furthermore, intraperitoneal injection of Ex-4 reduced ethanol consumption in sham rats but not in RYGB rats, presumably because endogenous GLP-1 levels are already elevated in RYGB rats and intake is already low. However, treatment with Ex-9 did not modulate ethanol consumption in either RYGB or sham rats (Davis et al., 2012). The lack of response to a GLP-1 receptor antagonist calls into question the hypothesis that elevated endogenous GLP-1 is responsible for the decrease in alcohol consumption observed following RYGB. Furthermore, the effect of RYGB on alcohol consumption in rodent models appears to be inconsistent, as two other studies found the opposite effect (Davis et al., 2013; Thanos et al., 2012). Still, these findings suggest potential avenues for future study.

6. Potential dopaminergic mechanisms of GLP-1-mediated alterations in food and drug reward

As evidenced by the relative scarcity of studies on the modulation of reward by GLP-1, this field of study is in its infancy. Therefore it is impossible to present clear mechanisms by which GLP-1 is acting on reward circuits. However, we hypothesize that GLP-1 signaling alters DA homeostasis in the mesolimbic reward system. This assertion is most strongly supported by 1) the reduction in motivated behaviors elicited by GLP-1 agonists, particularly when injected directly within dopaminergic reward circuits, 2) the attenuation of psychostimulant- and alcohol-stimulated accumbal DA release, and 3) the finding that Ex-4 reduces psychostimulant- and alcohol-induced locomotion, a behavioral proxy for DA signaling.

Alterations in DA homeostasis within the mesolimbic reward system can be mediated by either postsynaptic or presynaptic mechanisms in either the VTA or NAc (or both). Since GLP-1 receptors are expressed within the VTA, GLP-1 signaling could alter firing rates of dopaminergic neurons, which would modulate DA release in the NAc and potentially other projection sites, including the amygdala and the prefrontal cortex. Firing rates of DA cells are an important component of reward and stimulus saliency and can be influenced by hormonal signaling (Chaudhury et al., 2013; Labouebe et al., 2013; Palmiter, 2007; Volkow et al., 2009). Currently, we do not know if GLP-1 receptors are located on dopaminergic or GABAergic neurons in the VTA, but alterations in the firing properties of either neuronal type could influence dopaminergic output. Such a mechanism would be similar to that observed for the hormone leptin. Leptin significantly reduces DA neuronal firing rate within the VTA *in vivo* and in slice preparations (Hommel et al., 2006), while central leptin infusion attenuates extracellular DA by microdialysis (Krugel et al., 2003). An alternative (but not mutually exclusive) mechanism is that GLP-1 alters DA signaling and homeostasis directly within the NAc. Again, the existence of GLP-1 receptors in this brain region makes this a plausible hypothesis, although we do not know with certainty whether the key receptors are expressed pre- or postsynaptically. Presynaptic GLP-1 receptor signaling within the NAc might influence DA homeostasis by acting through the DAT. The DAT is normally responsible for clearing DA from the intrasynaptic space but its activity can be impaired by the actions of abused psychostimulants. It is important to note that other peripheral hormones are capable of modulating DAT function. Insulin, for example, has been shown to regulate the effects of amphetamine by altering DAT surface expression and amphetamine-induced DA efflux in a phosphoinositide 3-kinase-dependent manner (Carvelli et al., 2002; Speed et al., 2011; Williams et al., 2007). Furthermore, insulin attenuates amphetamine-induced behaviors (Marshall, 1978). This lends credibility to the hypothesis that these same dopaminergic mechanisms of hedonic regulation are employed by GLP-1 agonists. If in fact DA mediates the effects of central GLP-1 on motivated behaviors, this information could fuel inquiry into the potential of the brain GLP-1 receptor or its signaling intermediates as therapeutic targets for obesity and substance use disorders.

7. GLP-1 as a potential therapeutic for obesity and substance use disorders

Obesity and substance abuse disorders are both major public health concerns. Currently, more than one third of U.S. adults are obese (Ogden et al., 2012) and the economic burden of drug abuse in the U.S. is estimated at nearly $600 billion annually (Harwood et al., 2004). The impact of these conditions is compounded by the fact that we have very few effective therapies to treat either condition. Behavioral therapies, although effective for some patients, have not provided a systemic solution (Breland et al., 2012). Thus, the search for successful pharmacotherapeutics has intensified. GLP-1 analogues have emerged as promising candidates for the treatment of both conditions.

While peripheral GLP-1 has a half-life of less than two minutes due to rapid inactivation by the enzyme DPP-4 (Deacon et al., 1995), the synthetic analogues show resistance to DPP-4 and have much longer half lives. As such, these drugs, when injected systemically, are able to cross the blood-brain barrier to affect central signaling (Kastin and Akerstrom, 2003). It is also possible that endogenous GLP-1 or its long-lasting analogues are influencing central

signaling through vagal transmission (Abbott et al., 2005; Kakei et al., 2002; Kanoski et al., 2011; Rinaman, 2010; Williams, 2009). Therefore, GLP-1 analogues in their current form are a viable option for the treatment of reward system impairments.

As a potential therapeutic for obesity, GLP-1 analogues have already shown great potential. Although they are currently only approved for the treatment of type II diabetes in the U.S., GLP-1 analogues have shown efficacy in reducing weight loss in this population with minimal side effects (Vilsboll et al., 2012). Still, the exact circuitry and homeostatic or hedonics mechanisms underlying GLP-1-induced weight loss are unclear. Further investigation into central GLP-1 mechanisms of reward modulation may help to identify additional targets for the treatment of obesity.

As a potential therapeutic for substance use disorders, we must further explore which aspects of drug reward are modulated by GLP-1. The development of substance use disorders involves at least 1) susceptibility to the drug in naïve individuals, 2) the potentially damaging physiological effects of the drug, 3) the enjoyment of the drug, 4) the motivation to work to obtain more of the drug, 5) learning to associate the drug with environmental cues, 6) withdrawal effects from the drug, and 7) susceptibility to relapse in prior users. In designing therapies against substance use disorders, it is important to characterize the intervention at each of these levels. For example, it would be inappropriate to prescribe a therapy that decreases the rewarding effects of a drug but increases motivation to consume it. Based on currently available reports, we can make assertions about how GLP-1 might influence some of these components, but for others few data exist. We know from the animal behavioral studies presented here that Ex-4 attenuates the pharmacological effects of psychostimulants and alcohol (Egecioglu et al., 2013a; Egecioglu et al., 2013b; Erreger et al., 2012), reduces the rewarding properties of psychostimulants and alcohol (Egecioglu et al., 2013a; Egecioglu et al., 2013b; Graham et al., 2012), and attenuates alcohol seeking behavior (Egecioglu et al., 2013b). Egecioglu and colleagues also found that there was no rebound ethanol consumption after treatment, suggesting that Ex-4 may attenuate withdrawal symptoms to alcohol. Relapse models were not used in any of the reports cited. Similarly, no studies directly addressed GLP-1's effect on susceptibility to addiction in naïve animals. However, one study showed that RYGB attenuated ethanol consumption in alcohol-naïve rats (Davis et al., 2012), indicating that GLP-1 could play a role in the acquisition of drug-taking behavior.

8. Concluding remarks

In summary, GLP-1 and its analogues attenuate the hedonic properties of food, alcohol, and psychostimulants and reduce the motivation to obtain food and alcohol in rodents (Alhadeff et al., 2012; Dickson et al., 2012; Dossat et al., 2011; Egecioglu et al., 2013a; Egecioglu et al., 2013b; Erreger et al., 2012; Graham et al., 2012). The literature reviewed herein suggests that GLP-1 regulates feeding behavior and drug abuse, in part, through classical reward circuits. In particular, GLP-1 appears to modulate the function of the mesolimbic reward system. We propose that it most likely does so by altering DA neurotransmission. Here we have reviewed a shift in paradigm from a homeostatic mechanism of action to a motivational view of GLP-1's role in appetitive behaviors, a shift that is overdue in the realm of food

reward/obesity and a shift that will drive research into GLP-1 as a therapeutic for substance abuse.

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Highlights

- Behavioral studies suggest GLP-1 signaling regulates both food and drug reward.
- The VTA and NAc are important anatomical targets for such regulation.
- GLP-1 signaling likely modulates dopamine neurotransmission.
- The GLP-1 receptor may be a therapeutic target for substance abuse/addiction.