

# Role of Appetite-Regulating Peptides in the Pathophysiology of Addiction: Implications for Pharmacotherapy

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**Abstract** Food intake and appetite are regulated by various circulating hormones including ghrelin and glucagon-like-peptide 1 (GLP-1). Ghrelin, mainly released from the stomach, increases food intake, induces appetite, enhances adiposity as well as releases growth hormone. Hypothalamic “ghrelin receptors” (GHS-R1A) have a critical role in food intake regulation, but GHS-R1A are also expressed in reward related areas. GLP-1 is produced in the intestinal mucosa as well as in the hindbrain in response to nutrient ingestion. This gut-brain hormone reduces food intake as well as regulates glucose homeostasis, foremost via GLP-1 receptors in hypothalamus and brain stem. However, GLP-1 receptors are expressed in areas intimately associated with reward regulation. Given that regulation of food and drug intake share common neurobiological substrates, the possibility that ghrelin and GLP-1 play an important role in reward regulation should be considered. Indeed, this leading article describes that the orexigenic peptide ghrelin activates the cholinergic–dopaminergic reward link, an important part of the reward systems in the brain associated with reinforcement and thereby increases the incentive salience for motivated behaviors via this system. We also review the role of ghrelin signaling for reward induced by alcohol and addictive drugs from a preclinical, clinical and human genetic perspective. In addition, the recent findings showing that GLP-1 controls reward induced by alcohol, amphetamine, cocaine and nicotine in rodents are over-

viewed herein. Finally, the role of several other appetite regulatory hormones for reward and addiction is briefly discussed. Collectively, these data suggest that ghrelin and GLP-1 receptors may be novel targets for development of pharmacological treatments of alcohol and drug dependence.

## Key Points

The data presented in this leading article collectively show that the orexigenic peptide ghrelin activates the cholinergic–dopaminergic reward link, an important part of the reward systems in the brain, implying that ghrelin may increase the incentive salience of motivated behaviors.

Central ghrelin signaling, as shown by ghrelin administration, ghrelin knockout mice as well as by pharmacological or genetical suppression of the ghrelin receptor (GHS-R1A), is required for alcohol mediated behaviors as well as for drug-induced reward in rodents, which is verified in human genetics studies.

In addition to regulation of food intake and glucose homeostasis, recent and novel data show that glucagon-like-peptide 1, another endocrine signal from the gut, mediates reward induced by alcohol, amphetamine, cocaine and nicotine in rodents.

In conclusion, peptides regulating appetite, such as ghrelin and GLP-1, may therefore constitute novel targets for development of pharmacological treatment strategies for addictive behaviors such as alcohol use disorders.

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## 1 Appetite Regulating Peptides

As discussed in several previous reviews, food intake and appetite are regulated by various circulating hormones and neuropeptides (see e.g. [1–3]). These signals include those produced by the gastrointestinal tract, such as ghrelin, peptide YY (3–36), oxyntomodulin, cholecystokinin and glucagon-like peptide-1 (GLP-1), in the brain, including galanin, orexin, neuropeptide Y (NPY), as well as those produced by adipose tissue e.g. adiponectin, leptin, interleukin-6 (for review see e.g. [2, 3] for overviews). Interestingly, these hunger-controlling hormones inform the present energy homeostasis to diverse neurobiological circuits, especially the hypothalamus, causing a physiological response (for review see e.g. [2, 3] for overviews). For several of these hunger-regulating hormones an increasing number of data, as reviewed herein, show that they also target brain areas intimately associated with reward and addiction. Taken together with the findings that regulation of food and drug intake share common neurobiological substrates [4, 5], the possibility that endocrine signals from the gut traditionally known to regulate food intake, energy and body weight homeostasis may play a role in reward regulation should be considered. Given that ghrelin and GLP-1 are fairly new modulators of drug-induced reward the involvement of these appetite-regulating peptides in reward and addiction processes are reviewed in this leading article. In addition, the role of several other hunger hormones in drug related behaviors is briefly discussed.

## 2 Ghrelin

### 2.1 An Overview of Ghrelin and Its Function Within the Central Nervous System

Ghrelin, a 28-amino acid peptide, is mainly produced in and secreted from the stomach and other peripheral tissues [6]. However, there might be some production in parts of the brain [7–9]. Ghrelin was initially found to be involved in the hypothalamo-pituitary growth axis by increasing the release of growth hormone [6]. Extensive research has since then shown that circulating ghrelin has physiological roles for food intake and appetite in rodents as well as in humans [1, 10–12]. In addition, ghrelin regulates meal initiation [13] and increased ghrelin levels correlate with hunger scores in healthy subjects [14]. The findings that ghrelin increases adiposity by a mechanism that includes decreased fat utilization [15, 16] suggested that “ghrelin receptors” [i.e. growth hormone secretagogue receptor (GHS-R1A)] could be pharmacological targets for

treatment of obesity. Hypothalamic GHS-R1A were readily attributed to the ability of ghrelin to cause a release of growth hormone, but these receptors were later found to be important for ghrelin’s effect on fat accumulation, food intake as well as energy balance [7]. Interestingly, ghrelin and its receptor have since then been attributed several other physiological roles. Thus, this hormone regulates glucose levels, stimulates prolactin secretion, influences sleep and acts on the cardiovascular system (for review see [17]) and stimulates gastric motility in rodents [18]. In addition, ghrelin influences memory formation via hippocampal GHS-R1A [19] and increases anxiety- and depression-like behavior in rodents [20]. The findings that GHS-R1A are expressed throughout the reward systems [21–23], raised the hypothesis that ghrelin may have a role in reward regulation.

### 2.2 Ghrelin Activates the Cholinergic–Dopaminergic Reward Link

An important part of the reward systems in the brain is the cholinergic–dopaminergic reward link. It encompasses a cholinergic afferent projection from the laterodorsal tegmental area (LDTg) onto the ventral tegmental area (VTA) dopamine cells together with the mesolimbic dopamine system [i.e. the dopamine neurons from the VTA to nucleus accumbens (NAc)] (for review see [24]). This reward link is intimately associated with the reinforcing properties of natural rewards and addictive drugs [25–28] (for review see [24, 29]). The data presented in this leading article collectively show that ghrelin activates the cholinergic–dopaminergic reward link, implying that ghrelin may increase the incentive salience of motivated behaviors (for overview see Table 1).

The first study showing that ghrelin activates the reward systems showed that intracerebroventricular administration of ghrelin increased accumbal dopamine release and caused a locomotor stimulation in mice [30]. These data were extended and corroborated by the findings showing that local infusion of ghrelin into either the VTA or LDTg causes a locomotor stimulation and accumbal dopamine release [31] and that ghrelin administration locally into the VTA increases the dopamine turnover in NAc in rodents [32]. Furthermore, it was recently showed that peripheral or intra-LDTg ghrelin administration concomitantly increases ventral tegmental acetylcholine as well as accumbal dopamine release and that this synchronous neurotransmitter release is blocked by systemic injection of a GHS-R1A antagonist [33]. The findings that GHS-R1A are expressed on cholinergic cells in the LDTg [34] as well as on dopaminergic neurons in the VTA [32] further support that ghrelin can activate the reward systems via local mechanisms within the VTA and LDTg. A possibility that

**Table 1** Summary of articles addressing the role of ghrelin and GLP-1 signaling in alcohol and drug addiction

<b>Ghrelin administration</b>	→ Activates the mesolimbic dopamine system, specifically the cholinergic–dopaminergic reward link, in rodents	Jerlhag et al. [30] Abizaid et al. [32] Jerlhag et al. [31] Jerlhag [36] Jerlhag et al. [41] Quarta et al. [37] Jerlhag et al. [38] Jerlhag et al. [33] Wellman et al. [39] Hansson et al. [50] Jerlhag et al. [55]
	→ Causes a focal activation of a network including ventral tegmental area, nucleus accumbens and lateral hypothalamus in rats	
	→ Increases novelty seeking in rats	
	→ Increases alcohol intake in mice when administered into the third ventricle, ventral tegmental area or laterodorsal tegmental area	
	→ Slightly increases alcohol intake in alcohol naïve rats when administered peripherally	Lyons et al. [61] Wellman et al. [86] Davis et al. [87] Malik et al. [40] Leggio et al. [82]
	→ Augments cocaine-induced hyperlocomotion and conditioned place preference in rats	Jerlhag et al. [60] Bahi et al. [57] Jerlhag et al. [62]
<b>Ghrelin knockout mice</b>	→ Display attenuation of alcohol-induced reward as measured by locomotor stimulation, conditioned place preference and accumbal dopamine release	
<b>Prevention of ghrelin penetration into the brain</b>	→ Does not alter the rewarding properties of alcohol or alcohol intake in rodents	
<b>Plasma levels of ghrelin</b>	→ Are not different in high- and low-alcohol preferring rats	Landgren et al. [56] Szulec et al. [77] Calissendorff et al. [69] Calissendorff et al. [70] Zimmerman et al. [71] Leggio et al. [73]
	→ Are lower in high-alcohol preferring rats than in low-alcohol preferring rats	
	→ Are reduced by acute oral alcohol consumption in healthy volunteers	Addolorato et al. [74] Kraus et al. [76] Badaoui et al. [75] Kim et al. [78] Kraus et al. [76] Wurst et al. [79] Addolorato et al. [74] Wurst et al. [79] Koopmann et al. [80] Leggio et al. [81] Tessari et al. [88]
	→ Which are increased by fasting are suppressed by acute intravenous administration of alcohol in healthy nonsmoking social drinkers	
	→ Are suppressed in active drinking in alcohol-dependent individuals	
	→ Are increased in abstinent alcoholics	
	→ Are higher in alcohol dependent individuals with high craving scores than in those with low craving scores	
	→ Are increased in rats with high reinstatement of cocaine-seeking behavior	
<b>Polymorphisms in ghrelin related genes</b>	→ Are associated with high alcohol intake, personality traits important for alcohol dependence as well as with type II alcoholism	Landgren et al. [83] Landgren et al. [84] Landgren et al. [85] Landgren et al. [84] Suchankova et al. [95] Landgren et al. [68]
	→ Are associated with smoking as well as with amphetamine dependence in humans	
	→ Are associated with high sucrose intake	

Table 1 continued

<b>“Ghrelin receptor” (GHS-R1A) antagonist treatment</b>	→ Blocks the rewarding properties of alcohol in mice when administered centrally or peripherally	Jerlhag et al. [55]
	→ Decreases alcohol intake in rodents	Jerlhag et al. [55] Kaur and Ryabinin [58] Landgren et al. [56] Bahi et al. [57] Suchankova et al. [59]
	→ Decreases the motivation to consume alcohol as well as prevents relapse to alcohol drinking in rats	Landgren et al. [56]
<b>Ghrelin receptor (GHS-R1A) knockout mice</b>	→ Blocks the rewarding properties of amphetamine, cocaine or nicotine in rodents	Jerlhag et al. [89] Abizaid et al. [91] Clifford et al. [90] Wellman et al. [94]
	→ Display attenuation of the rewarding properties of alcohol as measured by locomotor stimulation, accumbal dopamine release as well as conditioned place preference → Display a reduction in cocaine-induced locomotor stimulation and sensitization	Jerlhag et al. [55] Clifford et al. [90] Abizaid et al. [91]
<b>Ghrelin receptor (GHS-R1A) expression</b>	→ Is detected in the nucleus accumbens, amygdala as well as on dopaminergic neurons in the ventral tegmental area and on cholinergic neurons in the laterodorsal tegmental area in rats	Abizaid et al. [32] Dickson et al. [34] Landgren et al. [23] Cruz et al. [66]
	→ Is altered in the ventral tegmental area following voluntary oral alcohol intake (3 or 10 months)	Landgren et al. [23] Suchankova et al. [59]
<b>Administration of GLP-1 analogues</b>	→ Decrease alcohol intake, alcohol seeking behavior and alcohol-induced reward in rodents	Egecioglu et al. [112] Shirazi et al. [113]
	→ Attenuate the rewarding properties of amphetamine and cocaine in rodents	Erreger et al. [115] Graham et al. [116] Egecioglu et al. [117]
	→ Prevent nicotine reward as well as block nicotine-induced expression of locomotor sensitization in mice	Egecioglu et al. [118]

ghrelin-induced reward could involve accumbal GHS-R1A should also be considered since GHS-R1A are expressed in this reward area [23].

Albeit ghrelin mainly is produced in the gastrointestinal tract [6] the possibility that circulating ghrelin reaches brain reward areas should be considered. Indeed, circulating ghrelin passes the blood brain barrier [35] and peripheral ghrelin administration induces a conditioned place preference, causes accumbal dopamine release and stimulates the locomotor activity in mice [36]. In support of the possibility that circulating ghrelin has central nervous effects are the findings showing that systemic ghrelin administration increase dopamine in the shell, rather than core, region of NAc [37]. The findings that VTA-infusion of a GHS-R1A antagonist blocks the ability of peripheral

ghrelin to increase food intake [32] and activate the mesolimbic dopamine system [38], suggest that, albeit peripheral route of administration, the ability of ghrelin to cause reward involves central nervous system. This is further substantiated by imaging data revealing that peripheral ghrelin administration causes a focal activation of a network of VTA, NAc and lateral hypothalamus in rats [39]. In healthy volunteers systemic ghrelin administration increases the response in reward related areas such as NAc to visual food as shown in human functional magnetic resonance studies [40] (for overview see Table 1).

The mechanisms regulating the ability of ghrelin to active the cholinergic–dopaminergic reward link are being elucidated. The first study showed that specific subtypes

( $\alpha 3\beta 2$ ,  $\beta 3$  and  $\alpha 6$ ) of the nicotinic acetylcholine receptor expressed within the VTA are crucial for ghrelin-induced reward [41]. Interestingly, antagonists to these subtypes also attenuate the reinforcing properties of alcohol in rodents [42–45] and reduce alcohol intake in heavy-drinking smokers [46, 47]. The findings that the ability of LDTg-ghrelin to increase accumbal dopamine is attenuated by an unselective nicotinic acetylcholine receptor antagonist into the VTA [33], further strengthen the contention that ghrelin activates the cholinergic–dopaminergic reward link. Other neurotransmitters may however be important for ghrelin-induced reward since the activity of mesolimbic dopaminergic neurons is controlled by various afferents. In support are the findings that a NMDA receptor antagonist, but not orexin or opioid receptor antagonist, attenuates ghrelin's ability to increase accumbal dopamine release, condition a place preference and cause a locomotor stimulation in mice [38]. Ghrelin increased food reward is modulated by NPY Y1 and opioid receptors in mice [48]. The findings that the mesolimbic dopamine system increases the incentive salience of motivated behaviors [49] and that ghrelin increases novelty seeking behavior in rodents and men [50] collectively imply that ghrelin signaling may influence the rewarding and motivational properties of addictive drugs and behavior.

### 2.3 The Role of Ghrelin Signaling in Alcohol Addiction

The findings that food deprivation augments drug reinforcement as well as increase self-administration of addictive drugs in rodents [51, 52] further support the hypothesis that common neurobiological mechanisms regulate food and drug reward [4, 5]. This is further substantiated by the findings that co-morbidities between alcohol use disorder and compulsive over eating in humans are common [53, 54]. As reviewed herein ghrelin, and its receptor have been suggested to be a gut-brain hormone of importance for addiction (for overview see Table 1).

The first indication that ghrelin signaling regulates alcohol intake was from a study showing that peripheral or central administration of GHS-R1A antagonists (JMV2959 or BIM28163 respectively) reduces the intake of alcohol in mice consuming alcohol for 12 weeks [55]. In accordance are the findings that JMV2959 reduces high alcohol consumption in high-alcohol consuming Wistar as well as in alcohol-preferring (AA) rats [56], decreases voluntary alcohol consumption and preference in mice [57] and that peripheral administration of another GHS-R1A antagonist, D-Lys3-GHRP-6, reduces alcohol consumption in rats [58]. Moreover, acute systemic administration of the GHS-R1A antagonist, JMV2959, decreases alcohol intake in rats

voluntarily consuming alcohol for two, five and ten months and the ability of JMV2959 to reduce alcohol intake is more pronounced over time [59]. It was also found that repeated administration of JMV2959 decreased alcohol intake without inducing tolerance or rebound increase in alcohol intake after treatment termination [59]. Further support for an important role for ghrelin signaling in alcohol dependence are the findings that the GHS-R1A antagonist (JMV2959) reduces the motivation to consume alcohol as measured in the operant lever pressing model [56] as well as prevents the alcohol deprivation effect which reflects rebound drinking in rats [59]. In addition to alcohol intake, it has been shown that suppressed GHS-R1A function achieved by either genetical or pharmacological approaches (central or peripheral administration of a GHS-R1A antagonist (BIM28163 or JMV2959 respectively)) attenuates alcohol reward as measured by locomotor stimulation, conditioned place preference and accumbal dopamine release in mice [55].

Studies have also shown that central ghrelin administration, either into the third ventricle, the VTA or LDTg, increases alcohol intake in rats [55]. In accordance are the data showing that the alcohol-induced locomotor stimulation and dopamine release in NAc are attenuated in ghrelin knockout mice compared to wild type mice [60]. These data were later corroborated by others showing that ghrelin knockout mice have a disrupted alcohol reward as measured by locomotor stimulation, accumbal dopamine release and conditioned place preference [57]. Peripheral ghrelin administration only slightly increases alcohol intake in mice voluntarily consuming alcohol for only 3 days [61] implying that ghrelin signaling is more important in rodents exposed to alcohol for longer, rather than shorter, periods of time. Recent data show that Spiegelmer NOX-B11-2, which binds and neutralizes active (i.e. acylated) ghrelin in the periphery with high affinity and thus prevents its brain access, does not attenuate alcohol-induced reward in mice nor alcohol intake in rats [62], suggesting that circulating ghrelin in the plasma does not regulate alcohol intake or the rewarding properties of alcohol. On the contrary NOX-B11-2 reduced food intake in rats supporting a role for circulating ghrelin as a physiological regulator of food intake [62]. Given that ghrelin levels in the plasma are associated with alcohol craving (see later in Sect. 2.3) the possibility that circulating ghrelin is important for craving rather than reward should be considered. Taken together with the findings that ghrelin is produced centrally [7–9] it may be suggested that central ghrelin signaling regulates alcohol reward and consumption.

While previous studies pinpointed hypothalamic GHS-R1A to be important for ghrelin mediated food intake [12], the findings that ghrelin increases alcohol intake via local injections into either the VTA or LDTg [55], suggest that

the cholinergic–dopaminergic reward link is important for ghrelin signaling to regulate alcohol-mediated behaviors. GHS-R1A expression in the VTA is down regulated in high-compared to low-alcohol consuming rats supporting such a contention [59]. It has been shown that GHS-R1A alters the sensitivity of the mesolimbic dopamine system via its ability to heterodimerize with dopamine D1- and D2-like receptors [63, 64] as well as via its constitutive activity [65]. The possibility that ventral tegmental GHS-R1A, via such mechanisms, reduces the ability of addictive drugs to activate the mesolimbic dopamine system and thereby plays an important role for reward processes and for development of alcohol use disorder should therefore be considered. Other mechanisms or areas may also mediate the ability of GHS-R1A to regulate reward. Expression of GHS-R1A has been identified in other areas of the mesolimbic dopamine system such as the amygdala [23, 66]. It was recently revealed that ghrelin modulates GABAergic transmission in the rat amygdala by increasing inhibitory postsynaptic potential amplitudes in both naive and alcohol-dependent rats via pre- and post-synaptic mechanisms. Specifically, acute alcohol perfusion occluded the ghrelin-induced increase in GABAergic transmission whereas after repeated alcohol perfusion an enhanced ghrelin-induced inhibitory postsynaptic potential was observed in naive, but not alcohol-dependent rats. Application of GHS-R1A antagonists revealed tonic facilitatory activity of the GHS-R1A on GABAergic transmission in amygdala [66]. Further studies have shown that acute central administration of ghrelin increased serotonergic turnover as well as the expression of serotonin receptors in the amygdala in mice [67], suggesting that ghrelin signaling within the amygdala may regulate anxiety like behaviors.

There is a possibility that the orexigenic peptide reduces alcohol intake due to alcohol's caloric rather than rewarding properties. This appears less likely since the GHS-R1A antagonist JMV2959 reduces the intake of saccharine, another reward without calories [68], suppresses parameters strictly reflecting reward namely locomotor stimulation and conditioned place preference [55] as well as attenuates reward induced by other addictive drugs without caloric content (see Sect. 2.4).

Studies showing alterations in plasma levels of ghrelin in patients with alcohol dependence as well as in high- and low-alcohol preferring rats support a role for ghrelin signaling in alcohol mediated behaviors. Initially it was shown that acute oral alcohol intake reduces the secretion of ghrelin in healthy volunteers [69–71]. Interestingly, the reduction of ghrelin by acute oral alcohol intake is not affected by gastroprotective sucralfate, implying that the appetite-stimulating effect of alcohol is not mediated by ghrelin [72]. The findings that acute intravenous administration of alcohol in healthy nonsmoking social drinkers

suppresses fasting-induced increase in ghrelin, but does not alter circulating ghrelin levels, suggest that alcohol may act directly in the stomach by preventing the release/secretion of ghrelin as well as via systemic effects in humans [73]. In line are also the findings that active drinking in alcohol-dependent individuals suppresses both ghrelin levels and fundic ghrelin production [74–76]. In support are the data from a rodent study showing that high-alcohol preferring rats have lower plasma levels of ghrelin than low-alcohol preferring rats do [77]. However this was not verified in another study showing no difference between ghrelin levels in high- and low-alcohol preferring rats [56]. In abstinent alcoholics several studies have shown that the levels of ghrelin are increased [76, 78]. This was also shown in abstinent female alcoholics [79]. Moreover, higher ghrelin levels correlate with higher craving levels in patients with alcohol use disorder [74, 79], suggest that ghrelin may increase the incentive value of motivated behaviors. Supportively, a recent study demonstrated that the plasma concentration of active ghrelin (previous studies have investigated total ghrelin) was positively correlated to alcohol craving and that the plasma levels of active ghrelin increased significantly during early abstinence [80]. In support are the findings showing that the baseline ghrelin levels correlate with self-reported craving scores in alcohol dependent individuals and that blood ghrelin levels are increased in alcohol dependent subjects who abstained from alcohol when compared to non-abstinent alcohol dependent subjects [81]. In support of ghrelin playing a role in the neurobiology of alcohol craving are the recent data showing that intravenous administration of exogenous ghrelin increases alcohol craving in alcohol-dependent heavy-drinking individuals [82]. In addition, human genetic data show that high alcohol consumption in humans is associated with a single nucleotide polymorphism in the GHS-R1A gene [83]. Data from a cohort of Swedish females with alcohol dependence show that paternal alcohol dependence as well as with type II alcohol dependence is associated with haplotypes of the preproghrelin and GHS-R1A genes [84]. Moreover, polymorphisms of the ghrelin signaling system are associated with important personality traits of individuals with alcohol dependence namely decreased self-directedness and alterations in self-transcendence [85].

## 2.4 The Role of Ghrelin Signaling in Drug Dependence

Data from several publications reviewed herein suggest that ghrelin signaling has an important role for reward in general (for overview see Table 1). It was initially showed that peripheral ghrelin administration augments cocaine-induced locomotor stimulation [86] as well as conditioned

place preference to cocaine in rats [87]. In accordance are the data showing a positive correlation between elevated levels of ghrelin and increased cocaine seeking behavior in rats [88]. Pharmacological suppression of GHS-R1A by means of JMV2959 reduces the rewarding properties of amphetamine and cocaine as measured by locomotor stimulation, accumbal dopamine release and conditioned place preference [89]. In addition, either genetic or pharmacologic suppression of GHS-R1A attenuates cocaine-induced locomotor stimulation as well as sensitization in rats [90, 91]. Food restriction, which elevates ghrelin levels [92], augments amphetamine- and cocaine-induced hyperlocomotion, enhances cocaine-seeking behavior and increases self-administration of cocaine or amphetamine in rats [51]. Furthermore, the GHS-R1A antagonist JMV2959 decreases the rewarding properties of nicotine [93] as well as prevents nicotine induced locomotor sensitization in rodents [94]. Human genetic data show an association between a single nucleotide polymorphism in the GHS-R1A gene and smoking as well as with amphetamine dependence [84, 95]. Taken together a role of ghrelin and its receptor in the reinforcing properties of addictive drugs may be implied.

### 3 Glucagon-Like Peptide 1 (GLP-1)

#### 3.1 A Brief Overview of GLP-1 and Its Function Within the Central Nervous System

GLP-1 is produced in the intestinal L-cells [96] as well as in the hindbrain [97] in response to nutrient ingestion [98]. Increasing evidence shows that central or peripheral GLP-1 administration reduces food intake in rodents and man [99–103]. In addition, this incretin peptide [104] regulates glucose-dependent insulin secretion [105], gastric emptying and glucagon secretion [106, 107]. GLP-1 analogues have therefore been approved for treatment of type II diabetes. Initial studies showed that hypothalamic as well as brainstem GLP-1 receptors are required for the anorexic and gluoregulatory effects of GLP-1 [99, 108, 109]. The findings that GLP-1 receptors are expressed through out the mesolimbic dopamine system [110] and that GLP-1 containing neurons project directly to the VTA and NAc [111], suggest that the role of GLP-1 extends beyond food intake and glucose regulation and may include reward regulation as reviewed in this leading article.

#### 3.2 Role of GLP-1 in the Pathophysiology of Addiction

There are to date a few initial publications suggesting that GLP-1 receptors have a role in reward regulation (for

overview see Table 1). Indeed, treatment with a GLP-1 analogue, exendin-4, at a dose with no effect per se, prevented the rewarding properties of alcohol as measured by locomotor stimulation and accumbal dopamine release in mice [112]. This initial study also showed that conditioned place preference, reflecting reward, for alcohol was attenuated by both acute and chronic treatment with exendin-4 in mice. Furthermore, exendin-4 treatment decreased alcohol intake, using the intermittent access 20 % alcohol two-bottle-choice model, as well as reduced alcohol seeking behavior, using the progressive ratio test in the operant self-administration model, in rats [112]. These novel data imply that GLP-1 receptors could be pharmacological targets for treatment of alcohol dependence in man. The findings were later corroborated by others showing that exendin-4, by peripheral or local VTA infusion, decreases alcohol intake in rats and that systemic exendin-4 injection attenuated alcohol induced conditioned place preference in mice [113]. Moreover, gastric bypass, which reduces ghrelin and increases GLP-1 plasma levels, reduces alcohol intake in both humans and rats [114]. In addition to alcohol, GLP-1 receptors appear to be important for reward induced by addictive drugs. Indeed, exendin-4 attenuates amphetamine-induced locomotor stimulation and cocaine-induced conditioned place preference in rodents [115, 116]. In support are the recent data showing that exendin-4, attenuates the reinforcing properties of cocaine as well as amphetamine as measured by locomotor stimulation, accumbal dopamine release and conditioned place preference in mice [117]. In accordance are the findings that exendin-4, in addition to preventing nicotine reward, blocks nicotine-induced expression of locomotor sensitization in mice [118]. To investigate the role of GLP-1 receptors for drug addiction further additional studies are warranted. For instance the role of other GLP-1 analogues, including liraglutide and exenatide, on alcohol reward, alcohol intake, relapse to alcohol drinking, cue-induced relapse drinking should be investigated. In addition, the role of the enzyme, dipeptidyl peptidase-4, which eliminates GLP-1, for alcohol- and drug-induced reward should be elucidated. Associations between plasma levels of GLP-1 and alcohol craving as well as alcohol use disorder should be studied. Associations between polymorphisms in GLP-1 related genes and alcohol dependence should be examined in human genetic studies. Given that GLP-1 analogues, such as exenatide and liraglutide, are approved for the treatment of diabetes type II these reviewed data are of clinical interest since GLP-1 analogues could be used in treatment of drug dependence. When used for addiction therapy the possibility that a reduced alcohol intake is driven by nausea, rather than abolished reward, should be considered. Reports show that treatment with GLP-1 analogues

is associated with an increased risk of pancreatitis, which may be a concern for patients with alcohol use disorder whom already display a risk for pancreatitis. Another concern may be that these substances are administered by subcutaneous injection.

#### 4 Other Appetite-Regulating Hormones and Drug Related Behaviors

In addition to ghrelin and GLP-1 several other gut-brain hormones traditionally known to control food intake have been shown to modulate the responses to drugs of abuse. In brief, inhibition of leptin pathways decreases preference for alcohol [119] and leptin increases alcohol intake [120] as well as enhances the motivation to consume alcohol following alcohol withdrawal [121]. Elevated leptin levels have been demonstrated in male alcoholics [122] as well as in high alcohol-preferring mice [123]. Initial studies showed that an orexin receptor antagonist reduced self-administration of alcohol, prevents reinstatement of alcohol-seeking induced by both visual and olfactory cues in alcohol preferring rats [124] as well as attenuates stress-induced reinstatement for alcohol-seeking in Long-Evan rats [125]. Activation of orexin neurons is associated with context-driven renewal of alcohol-seeking in rats [126]. However, as reviewed elsewhere the role of orexin for alcohol-induced reward appears to be more complex (for review see [127]). Central administration of orexin reinstates cocaine, morphine as well as heroin seeking behavior [128–130]. In human studies, the plasma levels of the anorexigenic peptides leptin as well as orexin are associated with nicotine craving [131]. Administration of either of these peptides blocks reward induced by psychostimulant drugs [132–134]. It was initially shown that NPY-deficient mice show increased alcohol consumption, compared with wild-type mice [135]. In addition, a NPY2 antagonist suppresses alcohol intake in both naïve [136] and postdependent animals [137]. Local infusion of a viral vector designed to overexpress NPY into the amygdala reduces alcohol intake [138]. Moreover, NPY blocks the reinstatement of alcohol-seeking induced by yohimbine in rats [139]. The serum levels of adiponectin are significantly elevated in patients with alcohol dependence at admission for alcohol detoxification as well as after one week of withdrawal treatment [140]. This study also showed that alcohol craving was significantly associated with adiponectin [140]. In addition, cholecystokinin decreases alcohol intake in rodents [141–143]. In accordance are the data showing that a selective cholecystokinin-A receptor antagonist reduced the consumption of alcohol, whereas a specific cholecystokinin-B receptor antagonist decreases the intake of cocaine in rats [144]. In addition, central

administration of the orexigenic peptide galanin increases whereas a galanin antagonist reduces alcohol intake in rats [145, 146].

#### 5 Conclusion

Alcohol use disorder is one of the major causes of illness and death in society, and the economic costs are extensive (for review see [147, 148]). Today, only a few medications are approved for treatment of alcohol dependence and clinical trials suggest that the effect of these pharmacological agents is moderate (for review see [147, 148]). Furthermore, it is a heterogenous disorder where treatment possibly should be individualized. There is therefore a need for additional and more effective medications. This leading article presents a review of the data showing that gut-brain peptides such as ghrelin and GLP-1 appear to have a broader role than body weight homeostasis. Indeed, these hormones regulate alcohol as well as drug-induced reward and both GHS-R1A and GLP-1 receptors may therefore constitute novel targets for development of pharmacological treatment strategies for addictive behaviors such as alcohol use disorders.

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