Psychopharmacology (2014) 231:2725–2740
DOI 10.1007/s00213-014-3640-0

REVIEW

The role of ghrelin in addiction: a review

Vassilis N. Panagopoulos · Elizabeth Ralevski

Received: 13 December 2013 / Accepted: 19 May 2014 / Published online: 20 June 2014

Abstract
Rationale Ghrelin is a fast-acting hormone that is produced primarily by the stomach and by the brain although in smaller quantities. The regulation and the secretion of ghrelin are complex and not limited to aspects of feeding. Ghrelin exerts powerful effects on multiple processes, and it has been demonstrated that it mediates the rewarding properties of food as well as of drugs of abuse.
Objectives The purpose of this review is to summarize the findings of preclinical and clinical studies related to ghrelin's possible role in addiction for each specific class of substances. Questions related to ghrelin's involvement in addiction are highlighted. Recurrent methodological issues that render the interpretation of the findings challenging are discussed. Also, the potential of targeting ghrelin as a pharmacologic treatment strategy for addiction is explored.
Results Ghrelin signaling is implicated in the mediation of behavioral and biochemical effects of drugs of abuse that are cardinal for the development of addiction, especially for alcohol, nicotine, and stimulants. The available literature implicating ghrelin in opioid or cannabis use disorders is currently limited and inconclusive.
Conclusions There is intriguing, although not always consistent, evidence for the involvement of ghrelin signaling in aspects of addiction, especially in the cases of alcohol, nicotine, and stimulants. Further research, particularly in humans, is recommended to replicate and expand on the findings of the current literature. Improved and novel methodologies that take into account the volatile and complex nature of ghrelin are required to clarify the inconsistencies of the findings.

Keywords Ghrelin · Alcohol · Nicotine · Stimulants · Opioids · Cannabis · Reward · Review

V. N. Panagopoulos
Department of Psychiatry, VA St. Louis Health Care System, 915 North Grand Blvd, St. Louis, MO 63106, USA

V. N. Panagopoulos
Department of Psychiatry, Washington University, 1 Brookings Dr., St. Louis, MO 63130, USA

E. Ralevski (✉)
Department of Psychiatry, VA Connecticut Healthcare System, Yale University School of Medicine, West Haven, CT, USA
e-mail: elizabeth.ralevski@yale.edu

Introduction

Ghrelin is a 28-amino acid orexigenic peptide hormone that was discovered in 1999 (Kojima et al. 1999). It is primarily produced by the stomach (Sakata et al. 2002), but the brain also produces it in smaller quantities (Cowley et al. 2003; Korbonits et al. 2001). Ghrelin is the endogenous ligand and an agonist of the previously orphan growth hormone secretagogue receptor type 1 (GHS-R_{1A}), and it induces a potent increase of growth hormone (GH) levels (Kojima et al. 1999, 2001). The active form of ghrelin is unique among known mammalian peptide hormones in that it contains an *n*-octanoyl posttranslational modification which is required for its effects on the GHS-R_{1A} (Kojima et al. 1999). This explains why it is known as acyl, acylated, or *n*-octanoyl ghrelin. A second related peptide, *des-acyl ghrelin*, which is identical with acyl ghrelin except for the absence of the *n*-octanoyl moiety, has also been identified. Des-acyl ghrelin does not bind GHS-R_{1A} and does not induce the release of GH (Hosoda et al. 2000; van der Lely et al. 2004). The sum of the concentration of both acyl and des-acyl ghrelin is referred to in the literature as *total ghrelin*.

The regulation of the secretion of ghrelin is complex and influenced by a variety of acute and chronic stimuli (Cummings et al. 2001). In the short term, ghrelin secretion

is stimulated potently by fasting or hypoglycemia (Toshinai et al. 2001; Tschop et al. 2000), and gastric ghrelin mRNA expression is upregulated by fasting, insulin, or leptin administration (Toshinai et al. 2001). The secretion of ghrelin is inhibited by refeeding after prolonged fasting and administration of glucose (Toshinai et al. 2001; Tschop et al. 2000), somatostatin analogues (Barkan et al. 2003), or insulin (Saad et al. 2002). In accordance with the above, in humans, an impressive increase of ghrelin levels preprandially has been documented, subsequently followed by a sharp decrease postprandially. Between meals, a progressive increase of ghrelin from its postprandial low levels has been observed prior to the ensuing preprandial sharp increase. On a more long-term basis, ghrelin levels are decreased in obesity (except for Prader-Willi syndrome-related obesity) (Cummings et al. 2002; Tschop et al. 2001) and increased in cachexia (Nagaya et al. 2001; Otto et al. 2001; Wisse et al. 2001).

Ghrelin as a circulating hormone has powerful effects on multiple systems (Kojima and Kangawa 2006). Apart from potently stimulating the secretion of GH (Kojima et al. 1999), the administration of ghrelin leads to an increased appetite level (Arvat et al. 2000; Wren et al. 2001), increased food intake, and weight gain (Asakawa et al. 2001; Druce et al. 2005; Tschop et al. 2000). Based on these findings, it has been proposed that ghrelin plays a major role in meal initiation by acting as a hunger signal transmitted from the stomach to the brain in response to the feeding state and energy balance of the body, thus participating in the long-term regulation of body weight and energy homeostasis (Cummings et al. 2001). The receptor that mediates most of ghrelin's actions, GHS-R_{1A}, is most abundantly expressed in the hypothalamus, and in particular the arcuate (Arc) and the ventromedial (VMH) nuclei, as well as the pituitary gland (Bennett et al. 1997; Guan et al. 1997; Howard et al. 1996; Zigman et al. 2006). The Arc nucleus of the hypothalamus contains neuropeptide Y (NPY)/agouti-related gene product (AgRP) co-expressing neurons and proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) co-expressing neurons that project to the lateral and paraventricular hypothalamus (Arora and Anubhuti 2006; Elmquist 2001). These groups of neurons are important segments of the homeostatic hypothalamic circuits that regulate appetite, food intake, and body weight (Bouret et al. 2004). It is believed that the orexigenic properties of ghrelin are mainly mediated by its ability to induce the depolarization of the NPY/AgRP neurons and to increase inhibition of the POMC/CART neurons of the aforementioned circuit (Schellekens et al. 2010; Zigman and Elmquist 2003). In turn, connections of the lateral hypothalamus to the VTA and the shell of the nucleus accumbens (NAcc) may be involved in the regulation of reward processing and feeding(Maldonado-Irizarry et al. 1995; Richardson and Aston-Jones 2012; Stratford and Wirtshafter 2012; Urstadt et al. 2013a, b). GHS-R_{1A} is unusual in that it shows a high constitutive activity, i.e., it demonstrates a high degree of basal downstream signaling activity independently of binding by its ligand, ghrelin (Mear et al. 2013). In addition, GHS-R_{1A} dimerizes various other receptors, e.g., the GHS-R_{1b} receptor and the dopamine 1 and 2 receptors (D_1 and D_2) (Schellekens et al. 2013b). The high constitutive activity and the ability for heterodimerization of the GHS-R_{1A} are believed to have important physiological effects on ghrelin signaling (Mear et al. 2013; Schellekens et al. 2013a, b). At the same time, both acyl and des-acyl ghrelin have actions that are independent of GHS-R_{1A} (Thompson et al. 2004). For instance, des-acyl ghrelin increases food intake with intracerebroventricular (ICV) but not peripheral administration (Toshinai et al. 2006). However, the exact function and physiologic importance of des-acyl ghrelin remain to be elucidated (Hosoda et al. 2000).

Ghrelin is not only involved in energy homeostasis, but is also implicated in the modulation of the rewarding aspects of food and the function of the reward system. First, ghrelin receptors are located on various neurons of the reward system, including the ventral tegmental area (VTA) (Abizaid 2009; Guan et al. 1997; Naleid et al. 2005). In addition, it has been shown in mice that ghrelin injections to the third ventricle, the VTA, or the laterodorsal tegmental area (LTDg) cause an increase of extracellular dopamine in the NAcc (Abizaid et al. 2006; Jerlhag et al. 2006, 2007). In fact, administration of ghrelin in the VTA triggers feeding, whereas administration of a GHS-R_{1A} antagonist in the VTA blocks the orexigenic effects of circulating ghrelin and reduces rebound feeding following fasting (Abizaid et al. 2006). Even the systemic administration of ghrelin increases the concentration of extracellular dopamine, dopamine turnover, and synapse formation in the NAcc (Abizaid et al. 2006; Jerlhag 2008), with this increase of dopamine happening specifically in the shell and not the core of the NAcc (Quarta et al. 2009). This anatomic distribution of dopamine increase is also observed with a range of drugs of abuse and palatable foods (Pontieri et al. 1995; Tanda and Di Chiara 1998). In addition, ghrelin stimulates locomotion not unlike natural and artificial rewards (i.e., drugs of abuse) do. The above effects are probably mediated by cholinergic neuronal input from the LTDg to the VTA, an area also stimulated by food (Jerlhag et al. 2006, 2012; Rada et al. 2000). Interestingly, systemic ghrelin administration can also induce conditioned place preference (CPP) (Jerlhag 2008) similar to substances of abuse. Lastly, based on functional imaging studies on humans, ghrelin can increase the activity of brain areas involved with reward processing during the presentation of food-related images (Malik et al. 2008). Based on the above evidence, ghrelin is thought to be augmenting the rewarding properties of food via its effects on the mesolimbic dopaminergic pathways of the reward system, thus influencing the motivation for acquiring food (Cummings et al. 2007; Jerlhag et al. 2007).

The mesolimbic reward system is influenced profoundly by substances of abuse after acute and chronic exposure (Nestler 2005). Since ghrelin appears to be augmenting behaviors that lead to the procurement of natural rewards such as foraging by acting as a hunger signal, it has been proposed that it may also be involved in augmenting behaviors that lead to obtaining artificial rewards, such as drug-seeking behaviors, by acting as a craving-inducing factor (Jerlhag et al. 2010). Additionally, several studies document a bidirectional relationship between food and drugs of abuse. First, food deprivation strengthens the effects of many drugs of abuse (Carroll 1998), and food intake reduces acquisition of certain classes of substances (Carroll and Lac 1998). Interestingly, intermittent and excessive consumption of sugar can lead to brain neuroadaptations and behaviors similar to the ones seen in addiction (Avena et al. 2008), and abnormalities in the reward system have been reported in imaging studies after prolonged and excessive consumption of food and substances of abuse (Holden 2001; Volkow et al. 2003a, b). Conversely, many drugs of abuse have powerful effects on food intake and can cause significant weight changes (Mohs et al. 1990). Lastly, hunger and craving for drugs have been described to have similar psychological qualities (Lee et al. 2006). Based on the above findings and observations, it has been postulated that the rewarding aspects of food and drugs of abuse share some of the same neuronal signaling pathways (DiLeone et al. 2003) and that ghrelin participates in the mediation of this bidirectional relationship.

Following this line of reasoning, it appears likely that the examination of the ghrelin signaling system may provide valuable insights into the pathophysiology of addiction. This review summarizes the findings of preclinical and clinical studies relating to ghrelin's role in addiction as they apply to each specific class of substances.

Ghrelin and alcohol

Animal studies

Ghrelin has been the subject of several investigations utilizing animal experiments related to alcohol (see Table 1). According to a study examining the effects of ghrelin administration on mice exposed to alcohol for 9 weeks in the context of a two-bottle (alcohol/water) free-choice limited-access paradigm, ICV, VTA, or LTDg administration of acyl ghrelin increased alcohol intake, with this increase being higher with the VTA and LTDg route. This effect of ICV ghrelin administration was absent in GHS-R1A knockout mice. In addition, peripheral or ICV administration of a GHS-R_{1A} antagonist led to a decrease in alcohol consumption (Jerlhag et al. 2009). In contrast, in a study utilizing drinking in the dark procedures in relatively alcohol-naive mice (preexposed to alcohol for 3 days), the peripheral administration of ghrelin did not have an effect on alcohol consumption (Lyons et al. 2008). The divergent results could perhaps be explained by differences in the protocol of the studies. For instance, the mice used in the latter study were exposed to alcohol for a much shorter period of time in comparison to those in the former study prior to ghrelin administration. Perhaps different mechanisms are responsible for the reinforcing effects of alcohol in alcohol-naive mice in comparison to more chronically exposed animals.

Several studies have examined the effects of GHS-R_{1A} antagonists (Bahi et al. 2013; Landgren et al. 2011c; Suchankova et al. 2013b). Treatment of standard laboratory rats with a GHS-R_{1A} antagonist reduced the operant self-administration of 10 % alcohol and the number of active lever presses without affecting inactive lever presses. In the same strain, a GHS-R_{1A} antagonist reduced both alcohol consumption in the intermittent access 20 % alcohol two-bottle choice drinking paradigm and preference of alcohol over water. In an alcohol-preferring rat strain, a GHS-R_{1A} antagonist reduced alcohol intake and alcohol preference in the two-bottle choice limited-access drinking paradigm (Landgren et al. 2011c). Similar results were reported by Bahi and colleagues who showed that GHS-R_{1A} antagonism suppressed both operant alcohol self-administration and alcohol consumption in wild type but not in ghrelin/obestatin prepropeptide gene (ghrl) knockout mice (Bahi et al. 2013) and by Kaur et al. who demonstrated that a GHS-R_{1A} antagonist reduced preference for alcohol and alcohol intake in male mice undergoing a two-bottle choice experiment (Kaur and Ryabinin 2010). In a separate study, a single administration of a GHS-R_{1A} antagonist reduced alcohol intake in rats following voluntary alcohol consumption for 2 and 5 months with the effects being more pronounced after the 5-month-long exposure. Repeated treatment with a GHS-R_{1A} antagonist over 10 days resulted in a reduction of alcohol intake following 8 months of voluntary alcohol consumption and prevented the alcohol deprivation effect. Tolerance to the effects of the GHS-R_{1A} antagonist and rebound increase in alcohol intake were not observed (Suchankova et al. 2013b).

In terms of genetic evidence, it has been demonstrated that the alcohol-induced increase of dopamine in the NAcc is attenuated in ghrl knockout mice (Bahi et al. 2013; Jerlhag et al. 2011). Additionally, the alcohol-induced locomotor stimulation is attenuated in both heterozygote and homozygote ghrl knockout mice. ICV administration of acyl ghrelin increased alcohol, food, and fluid intake in wild type, heterozygote, and homozygote ghrl knockout mice to a similar degree. No baseline differences in alcohol or food intake between the three groups prior to treatment with ghrelin were detected (Jerlhag et al. 2011). Additionally, it has been shown that GHS-R1A gene expression is increased in a high-alcohol-consuming rat strain (AA) as compared to a low-

Table 1 Characteristics of ghrelin studies in animals

Study design	Substance	Results	Author(s)
Ghrelin administration	Alcohol	ICV, LDTg, or VTA administration of ghrelin increases alcohol intake	Jerlhag et al. (2009)
		Peripheral ghrelin administration does not increase alcohol intake	Lyons et al. (2008)
	Stimulants	Ghrelin administration enhances cocaine-induced CPP	Davis et al. (2007)
		Ghrelin administration enhances cocaine-induced hyperlocomotion	Wellman et al. (2005); Wellman et al. (2008)
	Opioids	Ghrelin administration augments heroin self-administration by increasing the break point	Maric et al. (2012)
	Cannabinoids	Ghrelin administration increases the endocannabinoid content of the hypothalamus	Kola et al. (2008)
Circulating ghrelin levels	Alcohol	High-alcohol-preferring rats (WHP) have lower ghrelin levels than low-alcohol-preferring rats (WLP) or Wistar PR and NP rats	Szulc et al. (2013)
		High-alcohol-preferring rats (AA) have similar baseline ghrelin levels to low-alcohol-preferring rats (ANA)	Landgren et al. (2011b)
	Stimulants	Positive correlation between peripheral total baseline ghrelin levels and the number of lever presses during reinstatement following exposure to cocaine-associated conditioned stimuli	Tessari et al. (2007)
Substance administration	Alcohol	Single administration of alcohol increases ghrelin levels in high-alcohol-preferring rats	Szulc et al. (2013)
		Long-term alcohol exposure (4 or 8 weeks) decreases ghrelin levels more for alcohol-preferring rats than controls	Szulc et al. (2013)
		Central ghrelin signaling mediates the alcohol-induced locomotor stimulation, NAcc dopamine increase, and CPP	Jerlhag et al. (2014)
		After long-term exposure, AA rats have significantly smaller reduction in plasma ghrelin levels than ANA rats	Landgren et al. (2011b)
	Nicotine	Administration of nicotine for 4 weeks increases acyl ghrelin levels	Tomoda et al. (2012)
	Stimulants	Acute administration of methamphetamine under ad libitum food access increases ghrelin levels; under food restriction, it decreases ghrelin levels	Crowley et al. (2005)
		Acute administration of methamphetamine has no effect on ghrelin levels	Kobeissy et al. (2008)
		Acute high-dosage (but not low dose) MDMA administration increases total ghrelin levels under ad libitum food access	Kobeissy et al. (2008)
GHS-R_{1A} antagonist administration	Alcohol	GHS-R_{1A} antagonism reduces alcohol consumption in rodents	Landgren et al. (2011c); Bahi et al. (2013); Kaur and Ryabinin (2010)
		Single administration and treatment over 10 days of a GHS-R_{1A} antagonist after chronic alcohol consumption (2–8 months) reduces alcohol intake	Suchankova et al. (2013b)
	Nicotine	GHS-R_{1A} antagonism attenuates the nicotine-induced locomotor stimulation, CPP, and dopamine release in the NAcc	Jerlhag and Engel (2011)
		GHS-R_{1A} antagonism attenuates nicotine-induced locomotor sensitization	Wellman et al. (2011)
	Stimulants	GHS-R_{1A} antagonism attenuates the stimulant-induced locomotor stimulation	Jerlhag et al. (2010); Clifford et al. (2012)
		GHS-R_{1A} antagonism attenuates CPP	Jerlhag et al. (2010)
		GHS-R_{1A} antagonism attenuates the dopamine increase in the NAcc	Jerlhag et al. (2010)
	Opioids	GHS-R_{1A} antagonism does not influence heroin self-administration and food-deprivation-induced heroin reinstatement but decreases inactive lever presses	Maric et al. (2012)
Substance antagonism	Cannabinoids	Cannabinoid receptor antagonism reduces acyl ghrelin levels in food-deprived rats	Cani et al. (2004)
		Cannabinoid receptor antagonism inhibits the ghrelin-induced increase of food intake	Tucci et al. (2004)
Substance-related gene manipulation	Cannabinoids	The ghrelin-induced increase in food intake, AMPK activity, and the endocannabinoid content of the hypothalamus is not observed in CB1 knockout mice	Kola et al. (2008)
Ghrelin-related gene manipulation or expression	Alcohol	Alcohol-induced locomotor stimulation and CPP are attenuated in ghrl knockout mice	Jerlhag et al. (2011); Bahi et al. (2013)
		GHS-R1A gene expression is increased in high-alcohol-preferring rats compared to that in low-alcohol-preferring rats after prolonged alcohol exposure	Landgren et al. (2011b)

Table 1 (continued)

Study design	Substance	Results	Author(s)
		Tolerance to the effects of the GHS-R_{1A} antagonist and rebound increase in alcohol intake are not reported	Suchankova et al. (2013b)
		Alcohol consumption is decreased in ghrl knockout mice	Bahi et al. (2013)
		Before exposure to alcohol, high-alcohol-preferring rats (WHP) have lower ghrelin than low-alcohol-preferring rats (WLP). Single administration of alcohol increases ghrelin levels in WHP but decreases it in WLP. Long-term exposure (4–8 weeks) decreases ghrelin levels more for alcohol-preferring rats than controls	Szulc et al. (2013)
	Stimulants	Ghrl knockouts show attenuated stimulant-induced locomotion stimulation	Abizaid et al. (2011)
		Ghsr knockouts show attenuated stimulant-induced locomotion stimulation	Clifford et al. (2012)
		Ghsr knockouts do not show the food-restriction-induced augmentation of food-associated anticipatory locomotion, but ghrl knockouts show an attenuated response	Clifford et al. (2011)
	Cannabinoids	In GHSR knockout mice, the ghrelin- or CB1-agonist-induced hypothalamic increase of AMPK activity is abolished	Lim et al. (2013)

ICV intracerebral ventricular, *LDTg* laterodorsal tegmental area, *VTA* ventral tegmental area, *MDMA* 3,4-methylenedioxy-*N*-methylamphetamine, *CB1* cannabinoid receptor, *ghsr* growth hormone secretagogue receptor gene, *WHP* Warsaw high-preferring rats, *WLP* Warsaw low-preferring rats, *PR* Wistar alcohol-preferring rats, *NP* Wistar non-preferring rats, *AA* Alko high-preferring rats, *ANA* Alko low-preferring rats, *ghrl* ghrelin/obestatin prepropeptide gene, *AMPK* AMP (adenosine monophosphate)-activated protein kinase

alcohol-consuming strain (ANA) in the NAcc, VTA, amygdala, prefrontal cortex, and hippocampus but not in the prefrontal cortex following a 14-week-long period of alcohol consumption. The two strains did not differ in their baseline preexposure plasma total ghrelin levels, but the AA rats showed a smaller reduction of ghrelin levels after alcohol exposure than the ANA rats (Landgren et al. 2011b). Furthermore, growth hormone secretagogue receptor gene (ghsr) expression was reduced in high-alcohol-consuming rats as compared to their low-consuming counterparts after 10 months of alcohol use and a series of treatments with a GHS-R_{1A} antagonist. A negative correlation between ghsr expression in the VTA and alcohol intake was observed. No differences in the methylation degree of a CpG island of ghsr were demonstrated between high- and low-alcohol-consuming rats following approximately 10 months of voluntary alcohol consumption. Of note, the aforementioned animals had undergone treatment with a GHS-R_{1A} antagonist with their last injection received 4 weeks prior to sample collection (Suchankova et al. 2013b). In another recent study, it was demonstrated that alcohol-induced CPP, locomotor stimulation, and voluntary alcohol consumption in a two-bottle choice drinking paradigm were decreased in ghrl knockout mice and mice receiving a GHS-R_{1A} antagonist when compared to controls (Bahi et al. 2013).

In addition, it has recently been demonstrated by the use of artificial nucleotide binding technology that central ghrelin signaling (and not peripherally circulating ghrelin levels) is important for the mediation of alcohol reward including the alcohol-induced locomotor activity, NAcc dopamine increase, and CPP (Jerlhag et al. 2014). Results from studies that examine ghrelin levels in animal strains with varying degrees of preference for alcohol prior to and following exposure to alcohol show mixed results. For example, prior to alcohol exposure, one study found that Warsaw high-alcohol-preferring rats had lower levels of ghrelin when compared to Warsaw low-alcohol-preferring rats, Wistar high-alcohol-preferring (WHP) rats, or Wistar low-alcohol-preferring (WLP) rats (Szulc et al. 2013). Another study found that prior to alcohol exposure, there were no differences in ghrelin levels between Alko high-alcohol-preferring rats and Alko low-alcohol-preferring rats (Landgren et al. 2011b). The possibility that ghrelin is involved in determining the degree of alcohol preference for some high-alcohol-preferring strains but not for others could perhaps explain these discrepant results. In the aforementioned study by Szulc et al., a subsequent single administration of alcohol resulted in a directly proportional increase of total and acyl ghrelin levels in WHP rats and an inversely proportional decrease of total and acyl ghrelin levels in WLP rats and Wistar rats. Following more prolonged exposure to alcohol (4 or 8 weeks), acyl ghrelin levels decreased overall in comparison to baseline; Wistar alcohol-preferring rats (PR) had lower acyl and total ghrelin levels than Wistar alcohol-non-preferring rats (NP), and WHP had lower acyl and total ghrelin than WLP rats (Szulc et al. 2013). So, it appears that different strains demonstrate divergent

responses to a single administration of alcohol in terms of ghrelin levels. With more prolonged exposure to alcohol, ghrelin levels decrease across strains, but high-alcohol-preferring strains show a more pronounced decrease than low-alcohol-preferring strains.

Human studies

In humans, several lines of research have been conducted in connection to ghrelin and alcohol (see Table 2). Ghrelin administration has been shown to increase cue-induced craving in alcohol-dependent, heavy drinkers (Leggio 2013). Fasting plasma and gastric fundus acyl ghrelin levels were lower in patients with alcohol dependence admitted to the hospital for alcohol withdrawal as compared to those in controls. Patients who reported that they had their last drink longer than 24 h prior to admission were excluded from the study. (Badaoui et al. 2008). Similarly, fasting total ghrelin levels were lower in male patients with alcohol dependence who consumed at least 80 g of alcohol over the previous 24 h as compared to those in controls. There was a significant correlation between fasting total ghrelin levels and craving scores (Addolorato et al. 2006). Others have reported that fasting acyl plasma ghrelin levels were higher in male patients with alcohol dependence following at least 30-day-long abstinence in comparison to those in controls who had no history of alcohol dependence and abstained from alcohol for at least 72 h. In the alcohol dependence group, fasting acyl ghrelin was correlated positively with the duration of abstinence and negatively with daily alcohol intake prior to abstinence. The BMI was accounted for as a covariate in the analysis (Kim et al. 2005). In another study, patients with alcohol dependence had higher fasting total ghrelin levels at various time points within 10 days from getting hospitalized in comparison to controls. Early abstainers (who had their last drink 24–72 h beforehand) had higher fasting total ghrelin levels than active drinkers. No correlations were found between fasting total ghrelin levels and craving scores (Kraus et al. 2005). Methodological issues could perhaps explain the discrepant findings between this study and the findings of Addolorato et al. (Addolorato et al. 2006). There were differences in the following: total ghrelin levels in patients with alcohol dependence early in recovery, inclusion/exclusion criteria, the measurement of total and not acyl ghrelin levels, and the lack of controlling for all the factors that can influence ghrelin levels (please see "Discussion" section for further details). In a sample of 61 male inpatients with alcohol dependence, a positive correlation was observed between fasting acyl ghrelin and alcohol craving scores both at the onset of alcohol withdrawal and following 14 days of abstinence. Acyl ghrelin increased during these 14 days of abstinence in comparison to baseline. No correlation was observed between total ghrelin and craving scores; total ghrelin levels did not change significantly during the study period (Koopmann et al. 2012). According to a double-blind treatment study that evaluated ghrelin levels in patients with alcohol dependence assigned to baclofen or placebo for 12 weeks, baseline (following 3 days of abstinence) fasting total ghrelin levels were higher in the patients that ended up relapsing when compared with those who remained abstinent. Additionally, during these 12 weeks, total ghrelin levels decreased in the non-abstinent group and increased in the abstinent group. Baseline ghrelin levels were positively correlated with higher alcohol craving scores 6 and 12 weeks later (Leggio et al. 2012). In a study examining gender effects on ghrelin levels, it has been reported that total ghrelin levels were higher in female patients with alcohol dependence as compared to those in male patients following alcohol detoxification (on average 11.2 days after alcohol cessation) and after 3 weeks of subsequent rehabilitation. Various factors that influence ghrelin such as BMI and alcohol dependence severity were controlled for. No such difference was detected between males and females in the control group. Additionally, total ghrelin levels were higher in patients with alcohol dependence following alcohol detoxification as compared to those in controls; this difference was no longer detectable after 3 weeks of rehabilitation, especially because ghrelin levels decreased in male patients. Moreover, total ghrelin levels were higher in female patients with alcohol dependence following alcohol detoxification in comparison to those in female controls; this difference was not detected in males. Of note, the authors did not mention whether ghrelin measurements occurred following fasting (Wurst et al. 2007).

In several substance administration studies in healthy volunteers, acute administration of a moderate oral dose of alcohol resulted in a rapid and significant reduction of fasting total and acyl ghrelin which persisted for at least 5 h (Calissendorff et al. 2005, 2006; Zimmermann et al. 2006). Accordingly, the intravenous administration of alcohol in healthy social drinkers resulted in a blunting of the fasting-induced increase of plasma acyl ghrelin trending toward statistical significance (Leggio et al. 2013). Studies indicate that the aforementioned effects are independent of the caloric value of alcohol (Calissendorff et al. 2005; Nedvidkova et al. 2003).

In terms of genetic evidence, a single-nucleotide polymorphism (SNP) rs2232165 of the GHS-R1A gene has been associated with heavy alcohol consumption in a Spanish sample (Landgren et al. 2008). In a study on female patients with severe alcohol dependence in Sweden, SNPs of the pro-GHRL and the GHSR were not associated with alcohol dependence. According to the same study, the GHRL haplotype was associated with paternal alcohol dependence and reported alcohol withdrawal symptoms, whereas a GHSR haplotype was associated with type II alcohol dependence (more genetically driven)(Landgren et al. 2010). In a separate study

Table 2 Characteristics of ghrelin studies in humans

Study design	Substance	Results	Author
Ghrelin administration	Alcohol	Administration of ghrelin in alcohol-dependent heavy drinkers results in cue-induced craving	Leggio et al. (2013)
Circulating ghrelin levels	Alcohol	Recently detoxified alcoholics have lower ghrelin than controls, but some studies show increase in ghrelin	Badaoui et al. (2008); Kraus et al. (2005)
		Abstainers have higher ghrelin levels than controls	Kim et al. (2005)
		Abstainers have higher ghrelin levels than active drinkers	Kraus et al. (2005)
		There is a positive relationship between ghrelin levels and craving for alcohol	Addolorato et al. (2006); Koopmann et al. (2012); Leggio et al. (2012)
		During treatment (12 weeks), those that relapse have higher ghrelin than abstainers but over time abstainers' ghrelin levels increase while in non-abstainers, they decrease	Leggio et al. (2012)
		Female alcoholics have higher ghrelin levels after detoxification than male alcoholics and female controls. There is no difference in ghrelin levels between male alcoholics and male controls	Wurst et al. (2007)
	Nicotine	Smoking history is associated with higher fasting acyl and total ghrelin levels	Langenberg et al. (2005)
		Healthy, older (58-year-old) smokers have higher acyl ghrelin levels than non-smokers	Fagerberg et al. (2003)
		No association between smoking status and fasting total ghrelin levels	Poykko et al. (2006); Mutschler et al. (2012)
		A decrease of fasting acyl ghrelin levels 2 months after smoking cessation	Lee et al. (2006)
Substance administration	Alcohol	Alcohol administration lowers ghrelin levels in healthy controls	Calissendorff et al. (2006); Calissendorff et al. (2005); Zimmermann et al. (2006)
		Fasting-induced increase in ghrelin is blunted by intravenous alcohol administration	Leggio et al. (2013)
	Nicotine	Nicotine administration does not influence fasting total ghrelin in smokers but results in a decrease of fasting total ghrelin in non-smokers	Kokkinos et al. (2007)
		Acute smoking is associated with an increase in acyl ghrelin levels within the first hour after smoking	Fagerberg et al. (2003)
		Others have reported an increase in fasting total ghrelin in both non-smokers and smokers	Bouros et al. (2006)
Genetic associations	Alcohol	SNPs of the GHRL are not associated with alcohol dependence	Landgren et al. (2010)
		The Leu72Met polymorphism is not associated with alcohol dependence	Leggio et al. (2012)
		The A allele of the SNP rs2232165 of the GHS-R1a gene is associated with heavy alcohol consumption	Landgren et al. (2008)
	Nicotine	Two GHSR gene haplotypes are associated with smoking status	Landgren et al. (2010)
	Stimulants	The Leu72Met polymorphism of the GHRL is not associated with methamphetamine dependence	Yoon et al. (2005)
		Allele of the GHSR rs2948694 SNP is associated with methamphetamine dependence	Suchankova et al. (2013a)

GHSR growth hormone secretagogue receptor gene, *GHRL* ghrelin/obestatin prepropeptide gene, *SNP* single-nucleotide polymorphism

with type I alcohol-dependent men and women (more environmentally driven), the authors examined the relationship between reward-related genes, four dimensions of temperament (novelty seeking, harm avoidance, reward dependence, and persistence), and three dimensions of character (self-directedness, cooperativeness, and self-transcendence) using the Temperament and Character Inventory scale (Cloninger 1994). No association between SNPs and type I alcohol dependence was found. However, ghrelin-related SNPs were associated with decreased self-directedness and alterations in self-transcendence (Landgren et al. 2011a). In another study, no association was demonstrated between the Leu72Met polymorphism of GHRL and alcohol dependence, and no differences were documented in terms of drinks per day, age of onset, duration of addiction, or family history of

alcoholism among patients with alcohol dependence with different GHRL polymorphisms (Leggio et al. 2012).

Summary

In the animal literature, central (Jerlhag et al. 2009, 2011) but not peripheral (Lyons et al. 2008) ghrelin administration can increase alcohol intake. The differing length of preexposure to alcohol may be the reason for the discrepant results of the above studies as mentioned above. Nevertheless, it is impressive and very pertinent to addiction that administration of ghrelin in areas of the reward circuitry of the brain can lead to an even more pronounced increase in alcohol intake. Different rat strains have different baseline ghrelin levels and react differently to a single administration of alcohol. It is possible that ghrelin is involved in determining the degree of alcohol preference for some high-alcohol-preferring strains but not for others. However, these differences disappear with longer exposures to alcohol. There is a decrease of ghrelin levels across strains. GHS-R_{1A} antagonism has been shown to decrease alcohol-induced CPP and locomotor stimulation, voluntary alcohol consumption, and alcohol preference. Even in animals chronically exposed to alcohol, both a single and repeated administration of a GHS-R_{1A} antagonist can reduce voluntary alcohol consumption and prevent the alcohol deprivation effect. Consistently, ghrl knockout mice have shown an attenuated alcohol-induced increase of dopamine in the NAcc, attenuated locomotor stimulation, and CPP and decreased alcohol consumption. These are consistent and promising findings indicating that ghrelin signaling plays a significant role in mediating the rewarding effects of alcohol.

In humans, studies with alcohol-dependent subjects show that there is a difference between abstainers and controls in that (1) abstainers have higher levels of plasma ghrelin than controls, (2) there is a relationship between ghrelin levels and abstinence, and (3) active drinkers have lower levels of ghrelin in comparison to abstainers. More recently, there are studies showing that there is a positive association between ghrelin levels and cravings. Studies with recently hospitalized alcohol dependent patients show that higher levels of ghrelin are associated with stronger cravings at least 12 h after their last drink. One treatment study that evaluated ghrelin levels longitudinally (over 12 weeks) in alcohol dependent patients found that higher baseline ghrelin levels predicted subsequent cravings and relapse. One could envision that if these findings are replicated, ghrelin levels could be utilized as a simple laboratory test that could distinguish patients with a higher probability for relapse early in recovery. In regard to genetic evidence, the associations of a polymorphism of the GHS-R1A gene with heavy alcohol consumption and of a haplotype of GHSR with type II alcohol dependence in female patients are encouraging but preliminary.

Ghrelin and nicotine

Animal studies

To date, only a few animal studies have examined the relationship between ghrelin and nicotine. Namely, according to a study on the effects of a 4-week-long exposure to cigarette smoke in ad libitum-fed rats, acyl ghrelin levels were significantly higher in comparison to those in controls, but des-acyl ghrelin levels were not influenced. Blood was collected following anesthesia 12 h after the end of smoke exposure. The weight of the smoking group was lower than that of the non-exposed one. The authors suggest that the increase in acyl ghrelin was likely due to the relative negative energy balance of the smoking group in comparison to the non-smoking group (Tomoda et al. 2012). According to a study that examined the influence of a GHS-R_{1A} antagonist on the effects of nicotine in mice, pretreatment with a single dose of a GHS-R_{1A} antagonist decreases the nicotine-induced locomotor stimulation, CPP, and release of extracellular dopamine in the NAcc (Jerlhag and Engel 2011). Similarly, another study reported that intraperitoneal pretreatment with a GHS-R_{1A} antagonist attenuated the nicotine-induced hyperlocomotor response in rats (Wellman et al. 2011).

Human studies

In humans, there is a series of studies examining ghrelin levels in smokers. According to a study on the metabolic syndrome, smoking history was associated with total ghrelin levels after controlling for other factors that influence ghrelin (e.g., BMI, age, and sex); the blood samples were collected following 12-h fasting, but it is unclear whether the acute effects of smoking were accounted for (Langenberg et al. 2005). In a study examining ghrelin levels and insulin sensitivity, smokers had higher acyl ghrelin levels than non-smokers. This association survived controlling for various factors that influence ghrelin (waist circumference, glucose infusion rate) but not others (body fat). Also, acute smoking was associated with an increase of acyl ghrelin levels within the first hour after smoking. Possible confounding factors included varied times from the last cigarette and its assessment relying on self-report (Fagerberg et al. 2003). In a study examining risk factors for atherosclerosis, no correlation between fasting total ghrelin levels and smoking status was found. Among current smokers, no correlation was detected between the amounts of cigarettes smoked daily and fasting total ghrelin levels. Of note, all smokers were instructed to abstain from smoking

during the morning prior to the study day (Poykko et al. 2006). In a study of healthy, treatment-seeking, smokers who successfully quit smoking during the study period, decreased fasting plasma acyl ghrelin levels were observed after 2 months of abstinence from smoking in comparison to baseline (prior to smoking cessation). The change of acyl ghrelin levels did not correlate with changes of other body composition parameters (Lee et al. 2006). According to a small study with male smokers and non-smokers (n=21), total ghrelin levels were not associated with nicotine withdrawal symptoms or tobacco craving 24 h after the onset of lab-verified nicotine abstinence, but there was a non-significant decrease of total ghrelin levels in comparison to baseline. No differences were detected in terms of total ghrelin levels between smokers and non-smokers. Of note, participants were asked to have only a light meal at least 2 h prior to the study sessions, but there was no prolonged fasting requirement, and other factors (e.g., BMI and age) were not controlled for (Mutschler et al. 2012).

In terms of the acute effects of smoking, it was demonstrated that smoking two consecutive cigarettes under controlled conditions did not have an effect on fasting total ghrelin plasma levels in smokers but induced a decline in non-smokers that was significant 30 and 60 min later. No differences were observed in the baseline (prior to smoking) fasting total ghrelin values between smokers and non-smokers. Of note, overnight abstinence from smoking was requested from all volunteers (Kokkinos et al. 2007). In another laboratory study with fasting, smoking, and non-smoking men and women, total ghrelin levels increased 2, 5, and 15 min after smoking one cigarette. One hour after smoking initiation, the effects of smoking subsided, and there was no significant difference between smokers and non-smokers in terms of total ghrelin levels (Bouros et al. 2006). One study that examined the genetics of alcohol dependence in female patients with severe alcohol dependence in Sweden reported that two haplotypes of the GHSR were associated with smoking status (Landgren et al. 2010).

Summary

In animals, the evidence is limited. One study showed nicotine administration increases acyl ghrelin levels. The other, GHS-R_{1A} antagonist attenuates some of the behavioral and biochemical effects of nicotine. In humans, the results of the literature are somewhat mixed. Most, but not all, studies show that (1) smokers have higher ghrelin levels than non-smokers and (2) smoking cessation leads to decreases in ghrelin levels. The results from nicotine administration studies are less clear. Some show that smoking increases ghrelin levels in both smokers and non-smokers; others show no change in smokers but either decreases or increases in ghrelin in non-smokers. It is challenging to reconcile these inconsistent findings unless one attributes them to methodological differences that can unduly influence the results. It should be noted that in many of these mainly cardiovascular and endocrinologic studies, ghrelin was not the main focus but rather a secondary outcome measure. As a result, many factors that influence ghrelin levels were not adequately controlled. For instance, abstinence prior to blood collection was assessed using only self-report measures. Differences in timing of measurement of ghrelin levels after the last cigarette, amount of cigarettes smoked by each group, and measurement of total instead of acyl ghrelin levels constitute additional methodological weaknesses of some of the above studies (please see "Discussion" section for further details). Of note, non-fasting ghrelin levels are of limited utility given the significant variation of ghrelin depending on the feeding state. Therefore, studies suffering from this methodological issue were not further reviewed here.

Ghrelin and stimulants

Animal studies

Davis and colleagues (2007) showed that pretreatment with acyl ghrelin enhanced the cocaine-induced CPP in rats at doses of cocaine below the threshold dose required to induce CPP in the absence of ghrelin pretreatment. Surprisingly, rats given a higher dose of cocaine did not show CPP when pretreated with ghrelin (Davis et al. 2007). These results suggest that acyl ghrelin may be capable of effectively reducing the threshold dose of cocaine required for CPP. It is unclear why a reversal of the action of ghrelin was observed in the higher cocaine dosage group. In a separate study, it was shown that pretreatment with ghrelin prior to cocaine administration in rats can enhance the cocaine-induced stimulation of locomotion (Wellman et al. 2005). This data provides a putative mechanism for the augmentation of the locomotor effects of cocaine that are observed in the context of food deprivation (Bell et al. 1997). Additionally, daily administration of ghrelin in rats for over 7 days has been shown to augment the effects of a single dose of cocaine on locomotion on the first day following the above 7-day period. This suggests that ghrelin mediates sensitization to the hyperlocomotor effects of cocaine (Wellman et al. 2008).

In addition, the influence of circulating ghrelin levels on the effects of stimulants has also been assessed. Tessari and colleagues report a positive correlation between peripheral total baseline ghrelin levels and the number of lever presses during reinstatement of rats previously exposed to cocaine-associated conditioned stimuli (Tessari et al. 2007). Therefore, the authors of this study postulate that ghrelin may be involved in the food-restriction-induced sensitization to environmental cues that trigger drug-seeking behavior. It has been argued that the timing of the sessions in relation to the feeding

schedule and energy state of the rats was not controlled for strictly in this study (Cummings et al. 2007).

In terms of the acute effects of stimulants on ghrelin levels, it has been shown that administration of methamphetamine in rats with ad libitum access to food increases ghrelin plasma concentrations 2 h later as compared to that in placebo (Crowley et al. 2005). In contrast, when methamphetamine was administered 2 h prior to the presentation of food to rats with scheduled and restricted food access, it produced a small but significant reduction of ghrelin levels at the time of anticipated food presentation. It is unclear whether the total or the acyl portion of ghrelin was measured in this study (Crowley et al. 2005). This illustrates the complexities involved in the interpretation of ghrelin levels given that the effects of substances can vary depending on the exact feeding regimen of the experimental subjects. Additionally, in ad libitum fed rats, 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) has been shown to produce a significant increase of total serum ghrelin levels 6 h after successive administrations of dosages equivalent to a binge-like pattern of use as compared to controls and a significant increase 12 h later with the higher dose tested; the ghrelin levels returned to baseline at 24 h. Lower single doses did not produce a significant increase at any time point. In a separate experiment with the same design utilizing various dosages of methamphetamine, there was a trend increase of total ghrelin levels 6 h later, but the changes observed did not reach statistical significance at any time interval (Kobeissy et al. 2008).

There are several animal studies on stimulants that examine the effects of compromising the ghrelin signaling system. According to a study by Abizaid et al., ghrl knockout mice exhibit attenuated locomotion stimulation effects following single or repeated cocaine administration in comparison to their wild-type counterparts. There was a correlation between these effects and alterations in dopamine utilization in the striatum of wild-type mice. These alterations in dopamine utilization were not observed in the knockout mice unless they had been pretreated with ghrelin (Abizaid et al. 2011). Furthermore, rats pretreated with either a higher or a lower dose of a GHS-R_{1A} antagonist exhibit an attenuated increase of locomotion in response to cocaine. The lower dose of the antagonist induced an attenuated increase of locomotion only over the last 2 days of the experiment and not during the first 5 days. It should be noted that in the absence of cocaine, the higher but not the lower dose of the GHS-R_{1A} antagonist induced a suppression of locomotion per se. In a separate experiment, ghsr knockout rats also showed a decreased cocaine-induced hyperlocomotion response in comparison to wild-type rats (Clifford et al. 2012). Jerlhag et al. recently showed that a GHS-R_{1A} antagonist can attenuate the increase in locomotor activity, the increase of extracellular dopamine in the NAcc, and the CPP that are induced by either cocaine or amphetamine in mice (Jerlhag et al. 2010). In a later line of experiments, ghrl knockout, ghsr knockout, and wild-type mice were compared in terms of their locomotor response to a single administration of relatively low dosages of cocaine in the context of either food restriction or free access to food. Under food restriction, the wild-type mice group exhibited the expected food-associated increase in locomotion following vehicle administration, the ghsr knockout group did not show this response, and the ghrl group had an intermediate response. The wild-type group exhibited greater increases in locomotion in response to saline when under food restriction than when under the free-feeding condition, but the ghsr knockout mice did not exhibit this pattern of response. Following cocaine administration and while under food restriction, an increase in locomotion was observed in both knockout groups at the same level observed with the wild-type group. Following cocaine administration under ad libitum access to food, there were no changes in locomotion in any of the three groups. The above results suggest that the ghsr and ghrl are not required for the acute effects of low-dose cocaine on locomotion in the context of food restriction. However, it appears that the ghsr gene but not the ghrl is required for the food-restriction-induced augmentation of food-associated anticipatory locomotion (Clifford et al. 2011).

Human studies

To date, only a few genetic studies examined the relationship between stimulant use disorders and the ghrelin signaling system. Namely, according to a study of a Swedish population, there is an association between an allele of the GHSR rs2948694 SNP and methamphetamine dependence and an association between the GHRL rs4684677 SNP and the Addiction Severity Index (ASI) composite score of drug use (Suchankova et al. 2013a). In a study of the Korean population, no association was detected between the common Leu72Met polymorphism of the GHRL and methamphetamine dependence in patients participating in a parole and probation program (Yoon et al. 2005).

Summary

Accumulating data from animal studies indicates that ghrelin administration can enhance some of the biochemical and behavioral effects of stimulants. Also, consistent with findings in alcohol and nicotine, a GHS-R_{1A} antagonist attenuates the effects of stimulants. These findings in animals appear to be quite consistent and indicate that the ghrelin signaling system is a promising target for further research on stimulant use disorders. The results of stimulant administration studies are more mixed with experiments showing that methamphetamine and MDMA can increase ghrelin levels, decrease ghrelin levels, or have no effect. It is once again difficult to make sense of these conflicting results. Methodological issues may

be responsible for these discrepancies, e.g., measuring total rather than acyl ghrelin levels and allowing ad libitum food access rather than requiring prolonged fasting prior to ghrelin measurement. In humans, there is only one study that reported an association between an allele of the GHSR rs2948694 SNP and methamphetamine dependence. Further research will be required to examine whether the promising findings from the animal literature could be expanded to humans.

Ghrelin and opioids

The endogenous opioid system is involved in the regulation of the response to natural rewards including food (Skibicka and Dickson 2011). This is illustrated by the fact that μ-opioid receptor agonists can increase food intake (Mucha and Iversen 1986), palatability of food, and the willingness to work for obtaining food (Doyle et al. 1993; Grigson 2002). On the other hand, μ-opioid receptor antagonists can reduce the hedonic ratings of sugars and odors of palatable foods (Fantino et al. 1986; Yeomans and Gray 1997) and the preference for sweet high-fat food in humans (Drewnowski et al. 1992). At the same time, in rats, ghrelin can modulate pain by attenuating the development of carrageenan-induced hyperalgesia via an effect mediated by the central opioid receptors (Sibilia et al. 2006).

Animal studies

In a series of ghrelin administration experiments in rats, ICV administration of a higher but not a lower dose of ghrelin augmented the self-administration of heroin in a progressive ratio reinforcement schedule by increasing the break point. However, ghrelin did not produce a significant increase of active lever presses (the high-dose group trended toward statistical significance). It should be noted that the size of the groups was quite small (n=4 and n=11 for each group). In a separate experiment, a GHS-R_{1A} antagonist did not influence heroin self-administration but decreased the number of inactive lever presses. Following food deprivation, treatment with the GHS-R_{1A} antagonist did not attenuate food-deprivation-induced heroin reinstatement post extinction (Maric et al. 2012).

Human studies

To the best of our knowledge, there are no pertinent publications using human subjects.

Summary

Based on the results from a single animal study, ghrelin administration increases the break point for self-administration of heroin, but GHS-R_{1A} antagonism has not been shown to affect opioid self-administration (in contrast to its effects on alcohol self-administration).

Ghrelin and cannabinoids

Endocannabinoids are known to be involved in the regulation of appetite and food intake (Cota et al. 2003). Tetrahydrocannabinol and endogenous cannabinoids are well known to stimulate appetite (Kirkham 2005; Kirkham and Williams 2001), and cannabinoid receptor 1 (CB1) antagonists, e.g., rimonabant, reduce food intake (Black 2004). So, it is no surprise that a series of experiments have been devised to examine the connection of ghrelin and the cannabinoids.

Animal studies

First, it has been demonstrated that CB1 antagonists can reduce circulating acyl ghrelin levels in food-deprived rats (Cani et al. 2004). In fact, peripheral administration of a CB1 antagonist can inhibit GH secretion in a ghrelin-dependent manner (Al-Massadi et al. 2010). In a separate line of experiments examining the role of AMP-activated protein kinase (AMPK), an enzyme involved in the regulation of food intake and energy balance (Andersson et al. 2004), it was demonstrated that AMPK activity was influenced by both ghrelin and cannabinoids. It was consequently proposed that AMPK may be a mediator of the orexigenic effects of cannabinoids and ghrelin (Kola et al. 2005). Interestingly, in rats, a cannabinoid antagonist can block the orexigenic effect of central ghrelin administration (Alen et al. 2013; Tucci et al. 2004). In wild-type mice, central administration of ghrelin increased food intake, the activity of AMPK, and the hypothalamic endocannabinoid content. The cannabinoid antagonist, rimonabant, inhibited the ghrelin-induced increase of AMPK activity and of the hypothalamic endocannabinoid content. The ghrelin-induced increase in food intake, AMPK activity, and hypothalamic endocannabinoid content was not observed in CB1 knockout mice (Kola et al. 2008). Additionally, both the ghrelin- and the CB1-agonist-induced increase of AMPK activity in the hypothalamus were abolished in ghsr knockout mice (Lim et al. 2013).

Human studies

In humans, the number of relevant and available studies is limited. Namely, in a small study (n=8), hedonic eating, i.e., the consumption of food for pleasure, was associated with increased peripheral levels of ghrelin and the endocannabinoid 2-arachidonoylglycerol in healthy humans.

Summary

Based on the current available animal studies, it appears that the endogenous cannabinoid system and the ghrelin system interact in the regulation of food intake. Further research is required to investigate the implications of these intricate interactions to cannabis use disorders.

Discussion

A comprehensive review of the role of ghrelin in addiction leads to a number of main conclusions: (1) ghrelin has an impressive ability to augment the intake of alcohol and opioids in animal studies; (2) most remarkably, in the case of alcohol, nicotine and stimulants, GHS-R_{1A} antagonism, and manipulation of ghrelin-related genes in animal models can decrease substance intake and attenuate behavioral and biochemical effects that are considered important or even central for the development of addiction (e.g., increased dopamine release in the NAcc); (3) in humans, a very interesting finding is that individuals with alcohol dependence may differ in terms of ghrelin levels from healthy controls at various stages of recovery; and (4) in alcohol-dependent patients, ghrelin levels during early recovery may be predictive of future cravings and potentially of relapse risk. The above observations create hope for the discovery of a ghrelin-related pharmacological treatment for addiction, especially in the case of alcohol, nicotine, and stimulants. The active role of ghrelin in the function of multiple parts of the reward system, e.g., the VTA, LDTg, and NAcc, as described in this review, may explain why a ghrelin-based pharmacological treatment could prove effective for several different classes of substances of abuse. In addition, if ghrelin is indeed proven to play a major role in the sensitization to cue-triggered drug-seeking behavior, GHS-R_{1A} antagonists may be useful in protecting from relapse. In regard to cannabis and opioid use disorders, it would be premature to reach conclusions given the limited available evidence.

The current review of the available literature also raises recurrent, methodological issues that should be addressed when drawing conclusions regarding the role of ghrelin in addiction. As mentioned earlier, it is well documented that ghrelin levels fluctuate widely throughout the day in response to multiple factors, e.g., the exact feeding state. Therefore, these factors need to be controlled to the greatest possible extent when examining how acute or chronic exposure to substances of abuse affects ghrelin levels. Lack of controlling for these factors could perhaps explain the conflicting results of the above studies. For instance, food was available ad libitum during some of the above experiments, whereas it was restricted to varying degrees in others. In some studies, this was done by design, whereas in others, the feeding state was just not controlled for rigorously. Additionally, ghrelin measurements did not always follow prolonged fasting. This renders the interpretation of the findings challenging; it is not clear whether these results can be explained by the direct effects of the substance administered on ghrelin versus the exact feeding state of the subjects (Kobeissy et al. 2008). The timing elapsed from the administration of a substance to sample collection also differed significantly from study to study. This is particularly important for substances known to have acute but transient effects on ghrelin levels and a short half-life (e.g., alcohol or nicotine). Additionally, in many of the related studies, *total* ghrelin and not *acyl* ghrelin levels were assessed. Even though there is a correlation between the two, this constitutes an important methodological weakness. It should be mentioned that many of the reviewed studies were designed and executed just a few years after the discovery of ghrelin, at which time the importance of assessing *acyl* ghrelin was not well known or technically feasible.

In terms of future directions, implementing more rigorous and improved methodologies as described above would be of utmost importance to achieve a better understanding of the involvement of ghrelin in addiction. It could also be argued that measuring ghrelin levels or its effects in specific areas of the brain that are implicated in the pathophysiology of addiction rather than plasma levels may be more relevant to the study of addiction. Little is known about how the ability of GHS-R_{1A} to heterodimerize and its high constitutive activity affect ghrelin signaling (Schellekens et al. 2013a). Studying the high constitutive activity of GHS-R_{1A} with inverse GHS-R_{1A} agonists or discovering a way to alter its heterodimerization pattern with other receptors of the mesolimbic system may represent promising targets for future research.

Based on this review, there is intriguing evidence that suggests that ghrelin signaling is involved in aspects of addiction, especially in the cases of alcohol, nicotine, and stimulants. The available literature implicating ghrelin in opioid or cannabis use disorders is to date limited. Further research to replicate and expand on the above findings while strictly adhering to improved methodology will be required to clarify the inconsistencies of the available studies and widen our understanding of ghrelin and its relationship to addiction.

Conflict of interest The authors have no conflict of interest to report.

Funding Support for this manuscript was provided by the Mental Illness, Research, Education and Clinical Center (MIRECC) and by the National Center for PTSD, Clinical Neurosciences Division, VA CT Healthcare System, West Haven, CT, USA.

References

Abizaid A (2009) Ghrelin and dopamine: new insights on the peripheral regulation of appetite. J Neuroendocrinol 21:787–793. doi:10.1111/j.1365-2826.2009.01896.x

Abizaid A, Liu ZW, Andrews ZB, Shanabrough M, Borok E, Elsworth JD, Roth RH, Sleeman MW, Picciotto MR, Tschop MH, Gao XB, Horvath TL (2006) Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. J Clin Invest 116:3229–3239. doi:10.1172/JCI29867

Abizaid A, Mineur YS, Roth RH, Elsworth JD, Sleeman MW, Picciotto MR, Horvath TL (2011) Reduced locomotor responses to cocaine in ghrelin-deficient mice. Neuroscience 192:500–506. doi:10.1016/j.neuroscience.2011.06.001

Addolorato G, Capristo E, Leggio L, Ferrulli A, Abenavoli L, Malandrino N, Farnetti S, Domenicali M, D'Angelo C, Vonghia L, Mirijello A, Cardone S, Gasbarrini G (2006) Relationship between ghrelin levels, alcohol craving, and nutritional status in current alcoholic patients. Alcohol Clin Exp Res 30:1933–1937. doi:10.1111/j.1530-0277.2006.00238.x

Alen F, Crespo I, Ramirez-Lopez MT, Jagerovic N, Goya P, de Fonseca FR, de Heras RG, Orio L (2013) Ghrelin-induced orexigenic effect in rats depends on the metabolic status and is counteracted by peripheral CB1 receptor antagonism. PLoS One 8:e60918. doi:10.1371/journal.pone.0060918

Al-Massadi O, Gabellieri E, Trujillo ML, Senaris R, Pagotto U, Pasquali R, Casanueva FF, Seoane LM (2010) Peripheral endocannabinoid system-mediated actions of rimonabant on growth hormone secretion are ghrelin-dependent. J Neuroendocrinol 22:1127–1136. doi:10.1111/j.1365-2826.2010.02065.x

Andersson U, Filipsson K, Abbott CR, Woods A, Smith K, Bloom SR, Carling D, Small CJ (2004) AMP-activated protein kinase plays a role in the control of food intake. J Biol Chem 279:12005–12008. doi:10.1074/jbc.C300557200

Arora S, Anubhuti (2006) Role of neuropeptides in appetite regulation and obesity—a review. Neuropeptides 40:375–401. doi:10.1016/j.npep.2006.07.001

Arvat E, Di Vito L, Broglio F, Papotti M, Muccioli G, Dieguez C, Casanueva FF, Deghenghi R, Camanni F, Ghigo E (2000) Preliminary evidence that Ghrelin, the natural GH secretagogue (GHS)-receptor ligand, strongly stimulates GH secretion in humans. J Endocrinol Investig 23:493–495

Asakawa A, Inui A, Kaga T, Yuzuriha H, Nagata T, Ueno N, Makino S, Fujimiya M, Niijima A, Fujino MA, Kasuga M (2001) Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motilin. Gastroenterology 120:337–345. doi:10.1053/gast.2001.22158

Avena NM, Rada P, Hoebel BG (2008) Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev 32:20–39. doi:10.1016/j.neubiorev.2007.04.019

Badaoui A, De Saeger C, Duchemin J, Gihousse D, de Timary P, Starkel P (2008) Alcohol dependence is associated with reduced plasma and fundic ghrelin levels. Eur J Clin Investig 38:397–403. doi:10.1111/j.1365-2362.2008.01947.x

Bahi A, Tolle V, Fehrentz JA, Brunel L, Martinez J, Tomasetto CL, Karam SM (2013) Ghrelin knockout mice show decreased voluntary alcohol consumption and reduced ethanol-induced conditioned place preference. Peptides 43:48–55. doi:10.1016/j.peptides.2013.02.008

Barkan AL, Dimaraki EV, Jessup SK, Symons KV, Ermolenko M, Jaffe CA (2003) Ghrelin secretion in humans is sexually dimorphic, suppressed by somatostatin, and not affected by the ambient growth hormone levels. J Clin Endocrinol Metab 88:2180–2184. doi:10.1210/jc.2002-021169

Bell SM, Stewart RB, Thompson SC, Meisch RA (1997) Food-deprivation increases cocaine-induced conditioned place preference and locomotor activity in rats. Psychopharmacology 131:1–8. doi:10.1007/s002130050258

Bennett PA, Thomas GB, Howard AD, Feighner SD, van der Ploeg LH, Smith RG, Robinson IC (1997) Hypothalamic growth hormone secretagogue-receptor (GHS-R) expression is regulated by growth hormone in the rat. Endocrinology 138:4552–4557. doi:10.1210/endo.138.11.5476

Black SC (2004) Cannabinoid receptor antagonists and obesity. Curr Opin Investig Drugs 5:389–394

Bouret SG, Draper SJ, Simerly RB (2004) Formation of projection pathways from the arcuate nucleus of the hypothalamus to hypothalamic regions implicated in the neural control of feeding behavior in mice. J Neurosci 24:2797–2805. doi:10.1523/jneurosci.5369-03.2004

Bouros D, Tzouvelekis A, Anevlavis S, Doris M, Tryfon S, Froudarakis M, Zournatzi V, Kukuvitis A (2006) Smoking acutely increases plasma ghrelin concentrations. Clin Chem 52:777–778. doi:10.1373/clinchem.2005.065243

Calissendorff J, Danielsson O, Brismar K, Rojdmark S (2005) Inhibitory effect of alcohol on ghrelin secretion in normal man. Eur J Endocrinol 152:743–747. doi:10.1530/eje.1.01905

Calissendorff J, Danielsson O, Brismar K, Rojdmark S (2006) Alcohol ingestion does not affect serum levels of peptide YY but decreases both total and octanoylated ghrelin levels in healthy subjects. Metabolism 55:1625–1629

Cani PD, Montoya ML, Neyrinck AM, Delzenne NM, Lambert DM (2004) Potential modulation of plasma ghrelin and glucagon-like peptide-1 by anorexigenic cannabinoid compounds, SR141716A (rimonabant) and oleoylethanolamide. Br J Nutr 92:757–761

Carroll ME (1998) Acquisition and reacquisition (relapse) of drug abuse: modulation by alternative reinforcers. NIDA Res Monogr 169:6–25

Carroll ME, Lac ST (1998) Dietary additives and the acquisition of cocaine self-administration in rats. Psychopharmacology 137:81–89

Clifford S, Zeckler RA, Buckman S, Thompson J, Hart N, Wellman PJ, Smith RG (2011) Impact of food restriction and cocaine on locomotion in ghrelin- and ghrelin-receptor knockout mice. Addict Biol 16:386–392. doi:10.1111/j.1369-1600.2010.00253.x

Clifford PS, Rodriguez J, Schul D, Hughes S, Kniffin T, Hart N, Eitan S, Brunel L, Fehrentz JA, Martinez J, Wellman PJ (2012) Attenuation of cocaine-induced locomotor sensitization in rats sustaining genetic or pharmacologic antagonism of ghrelin receptors. Addict Biol 17:956–963. doi:10.1111/j.1369-1600.2011.00339.x

Cloninger CR (1994) Temperament and personality. Curr Opin Neurobiol 4:266–273

Cota D, Marsicano G, Lutz B, Vicennati V, Stalla GK, Pasquali R, Pagotto U (2003) Endogenous cannabinoid system as a modulator of food intake. Int J Obes 27:289–301. doi:10.1038/sj.ijo.802250

Cowley M, Smith R, Diano S, Tschop M, Pronchuk N, Grove K, Stasburger C, Bidlingmaier M, Esterman M, Heiman M, Garcia-Segura L, Nillni E, Mendez P, Low M, Sotonyi P, Friedman J, Liu H, Pinto S, Colmers W, Cone R, Horvath T (2003) The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 37:649–661

Crowley WR, Ramoz G, Keefe KA, Torto R, Kalra SP, Hanson GR (2005) Differential effects of methamphetamine on expression of neuropeptide Y mRNA in hypothalamus and on serum leptin and ghrelin concentrations in ad libitum-fed and schedule-fed rats. Neuroscience 132:167–173. doi:10.1016/j.neuroscience.2004.11.037

Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS (2001) A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 50:1714–1719. doi:10.2337/diabetes.50.8.1714

Cummings DE, Clement K, Purnell JQ, Vaisse C, Foster KE, Frayo RS, Schwartz MW, Basdevant A, Weigle DS (2002) Elevated plasma

ghrelin levels in Prader Willi syndrome. Nat Med 8:643–644. doi:10.1038/nm0702-643

Cummings DE, Naleid AM, Figlewicz Lattemann DP (2007) Ghrelin: a link between energy homeostasis and drug abuse? Addict Biol 12:1–5. doi:10.1111/j.1369-1600.2007.00053.x

Davis KW, Wellman PJ, Clifford PS (2007) Augmented cocaine conditioned place preference in rats pretreated with systemic ghrelin. Regul Pept 140:148–152. doi:10.1016/j.regpep.2006.12.003

DiLeone RJ, Georgescu D, Nestler EJ (2003) Lateral hypothalamic neuropeptides in reward and drug addiction. Life Sci 73:759–768

Doyle TG, Berridge KC, Gosnell BA (1993) Morphine enhances hedonic taste palatability in rats. Pharmacol Biochem Behav 46:745–749

Drewnowski A, Krahn DD, Demitrack MA, Nairn K, Gosnell BA (1992) Taste responses and preferences for sweet high-fat foods: evidence for opioid involvement. Physiol Behav 51:371–379

Druce MR, Wren AM, Park AJ, Milton JE, Patterson M, Frost G, Ghatei MA, Small C, Bloom SR (2005) Ghrelin increases food intake in obese as well as lean subjects. Int J Obes 29:1130–1136. doi:10.1038/sj/ijo.0803001

Elmquist JK (2001) Hypothalamic pathways underlying the endocrine, autonomic, and behavioral effects of leptin. Int J Obes Relat Metab Disord 25(Suppl 5):S78–S82. doi:10.1038/sj.ijo.0801918

Fagerberg B, Hulten LM, Hulthe J (2003) Plasma ghrelin, body fat, insulin resistance, and smoking in clinically healthy men: the atherosclerosis and insulin resistance study. Metabolism 52:1460–1463

Fantino M, Hosotte J, Apfelbaum M (1986) An opioid antagonist, naltrexone, reduces preference for sucrose in humans. Am J Physiol 251:R91–R96

Grigson PS (2002) Like drugs for chocolate: separate rewards modulated by common mechanisms? Physiol Behav 76:389–395

Guan XM, Yu H, Palyha OC, McKee KK, Feighner SD, Sirinathsinghji DJ, Smith RG, Van der Ploeg LH, Howard AD (1997) Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. Brain Res Mol Brain Res 48:23–29

Holden C (2001) 'Behavioral' addictions: do they exist? Science 294:980–982. doi:10.1126/science.294.5544.980

Hosoda H, Kojima M, Matsuo H, Kangawa K (2000) Ghrelin and desacyl ghrelin: two major forms of rat ghrelin peptide in gastrointestinal tissue. Biochem Biophys Res Commun 279:909–913. doi:10.1006/bbrc.2000.4039

Howard AD, Feighner SD, Cully DF, Arena JP, Liberator PA, Rosenblum CI, Hamelin M, Hreniuk DL, Palyha OC, Anderson J, Paress PS, Diaz C, Chou M, Liu KK, McKee KK, Pong SS, Chaung LY, Elbrecht A, Dashkevicz M, Heavens R, Rigby M, Sirinathsinghji DJ, Dean DC, Melillo DG, Patchett AA, Nargund R, Griffin PR, DeMartino JA, Gupta SK, Schaeffer JM, Smith RG, Van der Ploeg LH (1996) A receptor in pituitary and hypothalamus that functions in growth hormone release. Science 273:974–977

Jerlhag E (2008) Systemic administration of ghrelin induces conditioned place preference and stimulates accumbal dopamine. Addict Biol 13:358–363. doi:10.1111/j.1369-1600.2008.00125.x

Jerlhag E, Engel JA (2011) Ghrelin receptor antagonism attenuates nicotine-induced locomotor stimulation, accumbal dopamine release and conditioned place preference in mice. Drug Alcohol Depend 117:126–131. doi:10.1016/j.drugalcdep.2011.01.010

Jerlhag E, Egecioglu E, Dickson SL, Andersson M, Svensson L, Engel JA (2006) Ghrelin stimulates locomotor activity and accumbal dopamine-overflow via central cholinergic systems in mice: implications for its involvement in brain reward. Addict Biol 11:45–54. doi:10.1111/j.1369-1600.2006.00002.x

Jerlhag E, Egecioglu E, Dickson SL, Douhan A, Svensson L, Engel JA (2007) Ghrelin administration into tegmental areas stimulates locomotor activity and increases extracellular concentration of dopamine in the nucleus accumbens. Addict Biol 12:6–16. doi:10.1111/j.1369-1600.2006.00041.x

Jerlhag E, Egecioglu E, Landgren S, Salome N, Heilig M, Moechars D, Datta R, Perrissoud D, Dickson SL, Engel JA (2009) Requirement of central ghrelin signaling for alcohol reward. Proc Natl Acad Sci U S A 106:11318–11323. doi:10.1073/pnas.0812809106

Jerlhag E, Egecioglu E, Dickson SL, Engel JA (2010) Ghrelin receptor antagonism attenuates cocaine- and amphetamine-induced locomotor stimulation, accumbal dopamine release, and conditioned place preference. Psychopharmacology 211:415–422. doi:10.1007/s00213-010-1907-7

Jerlhag E, Landgren S, Egecioglu E, Dickson SL, Engel JA (2011) The alcohol-induced locomotor stimulation and accumbal dopamine release is suppressed in ghrelin knockout mice. Alcohol 45:341–347. doi:10.1016/j.alcohol.2010.10.002

Jerlhag E, Janson AC, Waters S, Engel JA (2012) Concomitant release of ventral tegmental acetylcholine and accumbal dopamine by ghrelin in rats. PLoS One 7:e49557. doi:10.1371/journal.pone.0049557

Jerlhag E, Ivanoff L, Vater A, Engel JA (2014) Peripherally circulating ghrelin does not mediate alcohol-induced reward and alcohol intake in rodents. Alcohol Clin Exp Res 38:959–968. doi:10.1111/acer.12337

Kaur S, Ryabinin AE (2010) Ghrelin receptor antagonism decreases alcohol consumption and activation of perioculomotor urocortin-containing neurons. Alcohol Clin Exp Res 34:1525–1534. doi:10.1111/j.1530-0277.2010.01237.x

Kim DJ, Yoon SJ, Choi B, Kim TS, Woo YS, Kim W, Myrick H, Peterson BS, Choi YB, Kim YK, Jeong J (2005) Increased fasting plasma ghrelin levels during alcohol abstinence. Alcohol Alcohol 40:76–79. doi:10.1093/alcalc/agh108

Kirkham TC (2005) Endocannabinoids in the regulation of appetite and body weight. Behav Pharmacol 16:297–313

Kirkham TC, Williams CM (2001) Endogenous cannabinoids and appetite. Nutr Res Rev 14:65–86. doi:10.1079/NRR200118

Kobeissy FH, Jeung JA, Warren MW, Geier JE, Gold MS (2008) Changes in leptin, ghrelin, growth hormone and neuropeptide-Y after an acute model of MDMA and methamphetamine exposure in rats. Addict Biol 13:15–25. doi:10.1111/j.1369-1600.2007.00083.x

Kojima M, Kangawa K (2006) Drug insight: the functions of ghrelin and its potential as a multitherapeutic hormone. Nat Clin Pract Endocrinol Metab 2:80–88. doi:10.1038/ncpendmet0080

Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K (1999) Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402:656–660

Kojima M, Hosoda H, Matsuo H, Kangawa K (2001) Ghrelin: discovery of the natural endogenous ligand for the growth hormone secretagogue receptor. Trends Endocrinol Metab 12:118–122

Kokkinos A, Tentolouris N, Kyriakaki E, Argyrakopoulou G, Doupis J, Psallas M, Kyriaki D, Katsilambros N (2007) Differentiation in the short- and long-term effects of smoking on plasma total ghrelin concentrations between male nonsmokers and habitual smokers. Metabolism 56:523–527. doi:10.1016/j.metabol.2006.11.012

Kola B, Hubina E, Tucci SA, Kirkham TC, Garcia EA, Mitchell SE, Williams LM, Hawley SA, Hardie DG, Grossman AB, Korbonits M (2005) Cannabinoids and ghrelin have both central and peripheral metabolic and cardiac effects via AMP-activated protein kinase. J Biol Chem 280:25196–25201. doi:10.1074/jbc.C500175200

Kola B, Farkas I, Christ-Crain M, Wittmann G, Lolli F, Amin F, Harvey-White J, Liposits Z, Kunos G, Grossman AB, Fekete C, Korbonits M (2008) The orexigenic effect of ghrelin is mediated through central activation of the endogenous cannabinoid system. PLoS One 3 doi:10.1371/Journal.Pone.0001797

Koopmann A, von der Goltz C, Grosshans M, Dinter C, Vitale M, Wiedemann K, Kiefer F (2012) The association of the appetitive peptide acetylated ghrelin with alcohol craving in early abstinent alcohol dependent individuals. Psychoneuroendocrinology 37:980–986. doi:10.1016/j.psyneuen.2011.11.005

Korbonits M, Bustin SA, Kojima M, Jordan S, Adams EF, Lowe DG, Kangawa K, Grossman AB (2001) The expression of the growth hormone secretagogue receptor ligand ghrelin in normal and abnormal human pituitary and other neuroendocrine tumors. J Clin Endocrinol Metab 86:881–887

Kraus T, Schanze A, Groschl M, Bayerlein K, Hillemacher T, Reulbach U, Kornhuber J, Bleich S (2005) Ghrelin levels are increased in alcoholism. Alcohol Clin Exp Res 29:2154–2157

Landgren S, Jerlhag E, Zetterberg H, Gonzalez-Quintela A, Campos J, Olofsson U, Nilsson S, Blennow K, Engel JA (2008) Association of pro-ghrelin and GHS-R1A gene polymorphisms and haplotypes with heavy alcohol use and body mass. Alcohol Clin Exp Res 32: 2054–2061. doi:10.1111/j.1530-0277.2008.00793.x

Landgren S, Jerlhag E, Hallman J, Oreland L, Lissner L, Strandhagen E, Thelle DS, Zetterberg H, Blennow K, Engel JA (2010) Genetic variation of the ghrelin signaling system in females with severe alcohol dependence. Alcohol Clin Exp Res 34:1519–1524. doi:10.1111/j.1530-0277.2010.01236.x

Landgren S, Berglund K, Jerlhag E, Fahlke C, Balldin J, Berggren U, Zetterberg H, Blennow K, Engel JA (2011a) Reward-related genes and personality traits in alcohol-dependent individuals: a pilot case control study. Neuropsychobiology 64:38–46. doi:10.1159/000324992

Landgren S, Engel JA, Hyytia P, Zetterberg H, Blennow K, Jerlhag E (2011b) Expression of the gene encoding the ghrelin receptor in rats selected for differential alcohol preference. Behav Brain Res 221: 182–188. doi:10.1016/j.bbr.2011.03.003

Landgren S, Simms JA, Hyytia P, Engel JA, Bartlett SE, Jerlhag E (2011c) Ghrelin receptor (GHS-R1A) antagonism suppresses both operant alcohol self-administration and high alcohol consumption in rats. Addict Biol 17:86–94. doi:10.1111/j.1369-1600.2010.00280.x

Langenberg C, Bergstrom J, Laughlin GA, Barrett-Connor E (2005) Ghrelin and the metabolic syndrome in older adults. J Clin Endocrinol Metab 90:6448–6453. doi:10.1210/jc.2005-1358

Lee H, Joe KH, Kim W, Park J, Lee DH, Sung KW, Kim DJ (2006) Increased leptin and decreased ghrelin level after smoking cessation. Neurosci Lett 409:47–51. doi:10.1016/j.neulet.2006.09.013

Leggio L (2013) Studying the role of feeding-related pathways in alcoholism via human laboratory studies. Alcohol Alcohol 48:27–27

Leggio L, Ferrulli A, Cardone S, Nesci A, Miceli A, Malandrino N, Capristo E, Canestrelli B, Monteleone P, Kenna GA, Swift RM, Addolorato G (2012) Ghrelin system in alcohol-dependent subjects: role of plasma ghrelin levels in alcohol drinking and craving. Addict Biol 17:452–464. doi:10.1111/j.1369-1600.2010.00308.x

Leggio L, Schwandt ML, Oot EN, Dias AA, Ramchandani VA (2013) Fasting-induced increase in plasma ghrelin is blunted by intravenous alcohol administration: a within-subject placebo-controlled study. Psychoneuroendocrinology. doi:10.1016/j.psyneuen.2013.09.005

Lim CT, Kola B, Feltrin D, Perez-Tilve D, Tschop MH, Grossman AB, Korbonits M (2013) Ghrelin and cannabinoids require the ghrelin receptor to affect cellular energy metabolism. Mol Cell Endocrinol 365:303–308. doi:10.1016/j.mce.2012.11.007

Lyons AM, Lowery EG, Sparta DR, Thiele TE (2008) Effects of food availability and administration of orexigenic and anorectic agents on elevated ethanol drinking associated with drinking in the dark procedures. Alcohol Clin Exp Res 32:1962–1968. doi:10.1111/j.1530-0277.2008.00784.x

Maldonado-Irizarry CS, Swanson CJ, Kelley AE (1995) Glutamate receptors in the nucleus accumbens shell control feeding behavior via the lateral hypothalamus. J Neurosci 15:6779–6788

Malik S, McGlone F, Bedrossian D, Dagher A (2008) Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab 7: 400–409. doi:10.1016/j.cmet.2008.03.007

Maric T, Sedki F, Ronfard B, Chafetz D, Shalev U (2012) A limited role for ghrelin in heroin self-administration and food deprivation-induced reinstatement of heroin seeking in rats. Addict Biol 17: 613–622. doi:10.1111/j.1369-1600.2011.00396.x

Mear Y, Enjalbert A, Thirion S (2013) GHS-R1a constitutive activity and its physiological relevance. Front Neurosci 7:87. doi:10.3389/fnins.2013.00087

Mohs ME, Watson RR, Leonard-Green T (1990) Nutritional effects of marijuana, heroin, cocaine, and nicotine. J Am Diet Assoc 90:1261–1267

Mucha RF, Iversen SD (1986) Increased food intake after opioid microinjections into nucleus accumbens and ventral tegmental area of rat. Brain Res 397:214–224. doi:10.1016/0006-8993(86)90622-0

Mutschler J, Graf N, Spanaus KS, Rossler W, Hergan K, Binkert CA, Gutzeit A (2012) Circulating ghrelin levels are not associated with craving and withdrawal symptoms in acute nicotine withdrawal. Psychiatr Danub 24:229–230

Nagaya N, Uematsu M, Kojima M, Date Y, Nakazato M, Okumura H, Hosoda H, Shimizu W, Yamagishi M, Oya H, Koh H, Yutani C, Kangawa K (2001) Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: relationships between ghrelin and anabolic/catabolic factors. Circulation 104:2034–2038. doi:10.1161/hc4201.097836

Naleid AM, Grace MK, Cummings DE, Levine AS (2005) Ghrelin induces feeding in the mesolimbic reward pathway between the ventral tegmental area and the nucleus accumbens. Peptides 26: 2274–2279. doi:10.1016/j.peptides.2005.04.025

Nedvidkova J, Krykorkova I, Bartak V, Papezova H, Gold PW, Alesci S, Pacak K (2003) Loss of meal-induced decrease in plasma ghrelin levels in patients with anorexia nervosa. J Clin Endocrinol Metab 88:1678–1682

Nestler EJ (2005) Is there a common molecular pathway for addiction? Nat Neurosci 8:1445–1449. doi:10.1038/nn1578

Otto B, Cuntz U, Fruehauf E, Wawarta R, Folwaczny C, Riepl RL, Heiman ML, Lehnert P, Fichter M, Tschop M (2001) Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa. Eur J Endocrinol 145:669–673

Pontieri FE, Tanda G, DiChiara G (1995) Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. Proc Natl Acad Sci U S A 92:12304–12308. doi:10.1073/pnas.92.26.12304

Poykko SM, Kellokoski E, Ukkola O, Kauma H, Paivansalo M, Kesaniemi YA, Horkko S (2006) Plasma ghrelin concentrations are positively associated with carotid artery atherosclerosis in males. J Intern Med 260:43–52. doi:10.1111/j.1365-2796.2006.01661.x

Quarta D, DiFrancesco C, Meletto S, Mangiarini L, Heidbreder C, Hedou G (2009) Systemic administration of ghrelin increases extracellular dopamine in the shell but not the core subdivision of the nucleus accumbens. Neurochem Int 54:89–94

Rada PV, Mark GP, Yeomans JJ, Hoebel BG (2000) Acetylcholine release in ventral tegmental area by hypothalamic self-stimulation, eating, and drinking. Pharmacol Biochem Behav 65:375–379

Richardson KA, Aston-Jones G (2012) Lateral hypothalamic orexin/hypocretin neurons that project to ventral tegmental area are differentially activated with morphine preference. J Neurosci 32:3809–3817. doi:10.1523/jneurosci.3917-11.2012

Saad MF, Bernaba B, Hwu CM, Jinagouda S, Fahmi S, Kogosov E, Boyadjian R (2002) Insulin regulates plasma ghrelin concentration. J Clin Endocrinol Metab 87:3997–4000

Sakata I, Nakamura K, Yamazaki M, Matsubara M, Hayashi Y, Kangawa K, Sakai T (2002) Ghrelin-producing cells exist as two types of cells, closed- and opened-type cells, in the rat gastrointestinal tract. Peptides 23:531–536. doi:10.1016/S0196-9781(01)00633-7

Schellekens H, Dinan TG, Cryan JF (2010) Lean mean fat reducing "ghrelin" machine: hypothalamic ghrelin and ghrelin receptors as therapeutic targets in obesity. Neuropharmacology 58:2–16. doi:10.1016/j.neuropharm.2009.06.024

Schellekens H, Dinan TG, Cryan JF (2013a) Taking two to tango: a role for ghrelin receptor heterodimerization in stress and reward. Front Neurosci 7:148. doi:10.3389/fnins.2013.00148

Schellekens H, van Oeffelen WE, Dinan TG, Cryan JF (2013b) Promiscuous dimerization of the growth hormone secretagogue receptor (GHS-R1a) attenuates ghrelin-mediated signaling. J Biol Chem 288:181–191. doi:10.1074/jbc.M112.382473

Sibilia V, Lattuada N, Rapetti D, Pagani F, Vincenza D, Bulgarelli I, Locatelli V, Guidobono F, Netti C (2006) Ghrelin inhibits inflammatory pain in rats: involvement of the opioid system. Neuropharmacology 51:497–505. doi:10.1016/j.neuropharm.2006.04.009

Skibicka KP, Dickson SL (2011) Ghrelin and food reward: the story of potential underlying substrates. Peptides 32:2265–2273. doi:10.1016/j.peptides.2011.05.016

Stratford TR, Wirtshafter D (2012) Evidence that the nucleus accumbens shell, ventral pallidum, and lateral hypothalamus are components of a lateralized feeding circuit. Behav Brain Res 226:548–554. doi:10.1016/j.bbr.2011.10.014

Suchankova P, Jerlhag E, Jayaram-Lindstrom N, Nilsson S, Toren K, Rosengren A, Engel JA, Franck J (2013a) Genetic variation of the ghrelin signalling system in individuals with amphetamine dependence. PLoS One 8:e61242. doi:10.1371/journal.pone.0061242

Suchankova P, Steensland P, Fredriksson I, Engel JA, Jerlhag E (2013b) Ghrelin receptor (GHS-R1A) antagonism suppresses both alcohol consumption and the alcohol deprivation effect in rats following long-term voluntary alcohol consumption. PLoS One 8:e71284. doi:10.1371/journal.pone.0071284

Szulc M, Mikolajczak PL, Geppert B, Wachowiak R, Dyr W, Bobkiewicz-Kozlowska T (2013) Ethanol affects acylated and total ghrelin levels in peripheral blood of alcohol-dependent rats. Addict Biol 18:689–701. doi:10.1111/adb.12025

Tanda G, Di Chiara G (1998) A dopamine-mu1 opioid link in the rat ventral tegmentum shared by palatable food (Fonzies) and non-psychostimulant drugs of abuse. Eur J Neurosci 10:1179–1187

Tessari M, Catalano A, Pellitteri M, Di Francesco C, Marini F, Gerrard PA, Heidbreder CA, Melotto S (2007) Correlation between serum ghrelin levels and cocaine-seeking behaviour triggered by cocaine-associated conditioned stimuli in rats. Addict Biol 12:22–29. doi:10.1111/j.1369-1600.2007.00052.x

Thompson NM, Gill DA, Davies R, Loveridge N, Houston PA, Robinson IC, Wells T (2004) Ghrelin and des-octanoyl ghrelin promote adipogenesis directly in vivo by a mechanism independent of the type 1a growth hormone secretagogue receptor. Endocrinology 145:234–242. doi:10.1210/en.2003-0899

Tomoda K, Kubo K, Nishii Y, Yamamoto Y, Yoshikawa M, Kimura H (2012) Changes of ghrelin and leptin levels in plasma by cigarette smoke in rats. J Toxicol Sci 37:131–138

Toshinai K, Mondal MS, Nakazato M, Date Y, Murakami N, Kojima M, Kangawa K, Matsukura S (2001) Upregulation of Ghrelin expression in the stomach upon fasting, insulin-induced hypoglycemia, and leptin administration. Biochem Biophys Res Commun 281:1220–1225. doi:10.1006/bbrc.2001.4518

Toshinai K, Yamaguchi H, Sun Y, Smith RG, Yamanaka A, Sakurai T, Date Y, Mondal MS, Shimbara T, Kawagoe T, Murakami N, Miyazato M, Kangawa K, Nakazato M (2006) Des-acyl ghrelin induces food intake by a mechanism independent of the growth hormone secretagogue receptor. Endocrinology 147:2306–2314. doi:10.1210/en.2005-1357

Tschop M, Smiley DL, Heiman ML (2000) Ghrelin induces adiposity in rodents. Nature 407:908–913. doi:10.1038/35038090

Tschop M, Wawarta R, Riepl RL, Friedrich S, Bidlingmaier M, Landgraf R, Folwaczny C (2001) Post-prandial decrease of circulating human ghrelin levels. J Endocrinol Investig 24:RC19–RC21

Tucci SA, Rogers EK, Korbonits M, Kirkham TC (2004) The cannabinoid CB1 receptor antagonist SR141716 blocks the orexigenic effects of intrahypothalamic ghrelin. Br J Pharmacol 143:520–523. doi:10.1038/sj.bjp.0705968

Urstadt KR, Coop SH, Banuelos BD, Stanley BG (2013a) Behaviorally specific versus non-specific suppression of accumbens shell-mediated feeding by ipsilateral versus bilateral inhibition of the lateral hypothalamus. Behav Brain Res 257:230–241. doi:10.1016/j.bbr.2013.09.048

Urstadt KR, Kally P, Zaidi SF, Stanley BG (2013b) Ipsilateral feeding-specific circuits between the nucleus accumbens shell and the lateral hypothalamus: regulation by glutamate and GABA receptor subtypes. Neuropharmacology 67:176–182. doi:10.1016/j.neuropharm.2012.10.027

van der Lely AJ, Tschop M, Heiman ML, Ghigo E (2004) Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. Endocr Rev 25:426–457. doi:10.1210/er.2002-0029

Volkow ND, Fowler JS, Wang GJ (2003a) The addicted human brain: insights from imaging studies. J Clin Invest 111:1444–1451. doi:10.1172/JCI18533

Volkow ND, Wang GJ, Maynard L, Jayne M, Fowler JS, Zhu W, Logan J, Gatley SJ, Ding YS, Wong C, Pappas N (2003b) Brain dopamine is associated with eating behaviors in humans. Int J Eat Disord 33:136–142. doi:10.1002/eat.10118

Wellman PJ, Davis KW, Nation JR (2005) Augmentation of cocaine hyperactivity in rats by systemic ghrelin. Regul Pept 125:151–154. doi:10.1016/j.regpep.2004.08.013

Wellman PJ, Hollas CN, Elliott AE (2008) Systemic ghrelin sensitizes cocaine-induced hyperlocomotion in rats. Regul Pept 146:33–37. doi:10.1016/j.regpep.2007.07.007

Wellman PJ, Clifford PS, Rodriguez J, Hughes S, Eitan S, Brunel L, Fehrentz JA, Martinez J (2011) Pharmacologic antagonism of ghrelin receptors attenuates development of nicotine induced locomotor sensitization in rats. Regul Pept 172:77–80. doi:10.1016/j.regpep.2011.08.014

Wisse BE, Frayo RS, Schwartz MW, Cummings DE (2001) Reversal of cancer anorexia by blockade of central melanocortin receptors in rats. Endocrinology 142:3292–3301

Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, Dhillo WS, Ghatei MA, Bloom SR (2001) Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab 86:5992

Wurst FM, Graf I, Ehrenthal HD, Klein S, Backhaus J, Blank S, Graf M, Pridzun L, Wiesbeck GA, Junghanns K (2007) Gender differences for ghrelin levels in alcohol-dependent patients and differences between alcoholics and healthy controls. Alcohol Clin Exp Res 31:2006–2011. doi:10.1111/j.1530-0277.2007.00527.x

Yeomans MR, Gray RW (1997) Effects of naltrexone on food intake and changes in subjective appetite during eating: evidence for opioid involvement in the appetizer effect. Physiol Behav 62:15–21

Yoon SJ, Pae CU, Lee H, Choi B, Kim TS, Lyoo IK, Kwon DH, Kim DJ (2005) Ghrelin precursor gene polymorphism and methamphetamine dependence in the Korean population. Neurosci Res 53:391–395. doi:10.1016/j.neures.2005.08.013

Zigman JM, Elmquist JK (2003) Minireview: from anorexia to obesity—the yin and yang of body weight control. Endocrinology 144:3749–3756. doi:10.1210/en.2003-0241

Zigman JM, Jones JE, Lee CE, Saper CB, Elmquist JK (2006) Expression of ghrelin receptor mRNA in the rat and the mouse brain. J Comp Neurol 494:528–548. doi:10.1002/cne.20823

Zimmermann U, Buchmann A, Steffin B, Dieterle C, Uhr M (2006) Alcohol administration acutely inhibits ghrelin secretion in an experiment involving psychosocial stress. Addict Biol 12:17–21