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Role of the ghrelin system in alcohol use disorder and alcohol-associated liver disease: A narrative review

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Abstract

Unhealthy alcohol consumption is a global health problem. Individual and public health, and socioeconomic consequences are attributable to harmful alcohol use. Epidemiological studies have shown that alcohol use disorder (AUD) and alcohol-associated liver disease (ALD) are the top two pathologies among alcohol-related diseases. Consistent with the major role that the liver plays in alcohol metabolism, uncontrolled drinking may cause significant damage to the liver. This damage is initiated with excessive fat accumulation in the liver, which can further progress to advanced liver disease. The only effective therapeutic strategies currently available for ALD are alcohol abstinence or liver transplantation. Any molecule with dual pronged effects at the central and peripheral organs controlling addictive behaviors and associated metabolic pathways could be a promising therapeutic target to treat AUD and ALD. Ghrelin, a hormone primarily derived from the stomach, has such properties and regulates both behavioral and metabolic functions. In this review, we highlight recent advances in understanding the peripheral and central functions of the ghrelin system and its role in AUD and ALD pathogenesis. We first discuss the correlation between blood ghrelin concentrations and alcohol use or abstinence. Next, we discuss the role of ghrelin in alcohol-seeking behaviors, and finally its role in development of fatty liver by metabolic regulations and organ-crosstalk. We propose that understanding the ghrelin system may open an innovative avenue for improved treatments for AUD and associated medical consequences, including ALD.

Keywords

Ghrelin; Gut-brain axis; Alcohol; Alcohol use disorder; Alcohol-associated liver disease

Introduction:

Excessive alcohol use is a serious health concern in the US and worldwide that inflicts significant social and economic burden on individuals and society at large (Axley et al., 2019). According to the World Health Organization (WHO), 43% of the global population were current alcohol drinkers in 2016, and alcohol use resulted in ~3 million deaths and 132.6 million disability-adjusted life years in 2016 (Axley et al., 2019). In addition to alcohol-related mental illnesses, chronic excessive alcohol use can lead to liver disease, cancers, and increased transmission of infectious diseases, (Rehm et al., 2017, Scott-Sheldon et al., 2016), which highlights some of the harmful effects of excessive alcohol use.

Chronic, heavy alcohol consumption disrupts normal organ function in virtually every tissue of the body, but the liver typically sustains the greatest damage (Axley et al., 2019). This is primarily because the liver is the first organ exposed to alcohol absorbed in the gastrointestinal tract via the portal circulation and secondly, because the liver is the principal site of alcohol metabolism (Zakhari and Li, 2007). Indeed, approximately half of global liver cirrhosis cases are attributed to excessive alcohol use (Mellinger, 2019). Ninety percent of individuals with excessive alcohol use develop fatty liver (steatosis), characterized by accumulation of lipids in hepatocytes (Ohashi et al., 2018). About 20–40% of current drinkers with continued excessive alcohol use develop alcohol-associated steatohepatitis (ASH). ASH is characterized by fatty liver, inflammation, and lobular fibrosis. Repeated

episodes of ASH with continued drinking can lead to advanced liver diseases, including fibrosis/cirrhosis and hepatocellular carcinoma (Lieber, 2004, Ohashi et al., 2018, Leggio and Lee, 2017). Moreover, the rapidly growing prevalence of obesity exacerbates the progression of liver damage in individuals with ALD (Alkhouri et al., 2022). The effective therapeutic strategies currently available for ALD are abstinence or liver transplantation (Ohashi et al., 2018). Thus, abstinence is a vital therapeutic goal for patients with ALD, as it can improve outcomes at nearly all stages of the disease and is particularly important pre- and post-liver transplantation (Mathurin and Lucey, 2020, Shawcross and O'Grady, 2010, Wackernah et al., 2014). Despite this, abstinence can be challenging to achieve in patients where chronic excessive alcohol use occurs as a result of alcohol use disorder (AUD).

AUD is a medical condition characterized by loss of control over alcohol consumption despite adverse social, occupational, and/or health consequences (Leggio and Lee, 2017). In addition to liver toxicity, chronic alcohol use and AUD are accompanied by changes in the brain, motivational behavior, and negative emotional states when alcohol is not used (Leggio and Lee, 2017). These changes ultimately reinforce excessive alcohol consumption and make total abstinence from alcohol difficult to achieve for patients with AUD. Given that alcohol abstinence is important for the improvement of ALD outcomes, AUD treatment becomes a necessary component of ALD management to prevent continued liver damage and disease progression. Moreover, AUD treatment is a critical factor in lowering pre- and post- transplantation relapse rates (Arab et al., 2022). Therefore, understanding the common pathophysiological mechanisms related to AUD and ALD is crucial for developing dual treatment approaches for AUD and ALD. Considering that recent epidemiological data suggest an increase in the prevalence of AUD, alcohol-associated cirrhosis, and liver transplantations in many countries, including the USA (Lee et al., 2019), there is critical need for therapeutic strategies that address both AUD and ALD.

Accumulating evidence demonstrates that gut-derived hormones often play a role in communications between peripheral organs and the brain (Czerwinska et al., 2021). There is a growing interest in understanding the role of gut-derived peptides in organ crosstalk as well as in the development of psychological and metabolic diseases, including AUD and ALD (Vadnie et al., 2014). One such hormone of interest is ghrelin, a gut-derived peptide hormone that exerts regulatory effects on both the central nervous system and peripheral organs. Ghrelin is an acylated 28-amino-acid peptide that is mainly secreted from the stomach, but is also expressed in the intestine, pancreas, kidney, adipose tissue and brain (Ariyasu et al., 2001). The ghrelin gene (*GHRL*) produces a ghrelin-obestatin preproprotein, which is cleaved/converted to proghrelin. Proghrelin undergoes acylation by ghrelin-O-acyltransferase (GOAT) and is then cleaved to its active form, acyl-ghrelin/ acylated ghrelin (here referred to as ghrelin) (Muller et al., 2015). Notably, des-acyl ghrelin (DAG; also referred to as unacylated ghrelin) can also be formed. DAG is devoid of action at the ghrelin receptor but may play a distinct role in metabolic regulation (Asakawa et al., 2005, Fernandez et al., 2016). The specific receptor for ghrelin is the growth hormone secretagogue receptor (GHSR1a) a G-protein-coupled receptor (GPCR) expressed both centrally and peripherally that mediates the metabolic and neurobehavioral effects of ghrelin (Muller et al., 2015). Through GHSR1a, ghrelin modulates a wide range of physiological functions, such as glucose homeostasis (Lin et al., 2019, Mani et al., 2019b, Sovetkina et

al., 2020), lipid metabolism (Barazzoni et al., 2005, Li et al., 2014), inflammation (Baatar et al., 2011), and apoptotic cell death (Bonfili et al., 2013), which makes it of interest in identifying new ALD therapies. Moreover, ghrelin has been shown to play a role in the rewarding effects of food, alcohol, and other addictive drugs, demonstrating an effect on centrally mediated consummatory behaviors (Al Massadi et al., 2019, Zallar et al., 2017). Significant evidence suggests that targeting the ghrelin system is a viable therapeutic strategy for AUD (Farokhnia et al., 2019). Thus, current knowledge of ghrelin's central and peripheral actions suggests that the ghrelin system is a promising target for novel therapies that address both ALD and AUD.

In this review, we discuss recent advances in understanding the peripheral and central functions of the ghrelin system in AUD and ALD (Fig.1), obtained from studies conducted in humans and experimental animals.

a) Alcohol consumption and blood ghrelin concentration

There are only a few experimental studies which explore the relationship between alcohol intake and serum/plasma ghrelin concentrations in humans and rodents. Studies conducted in male Wistar rats fed the Lieber-DeCarli ethanol-containing liquid diet (6.7% v/v or 36% calories) for 6 weeks showed a significant increase in serum ghrelin concentrations (acylated ghrelin), as well as ghrelin and GOAT gene expression in stomach, compared to their isocaloric control liquid diet-fed rats (Rasineni et al., 2019a, Rasineni et al., 2019b). Further, mice administered ethanol (20% ethanol in water) for 10 days showed an increase of both serum acylated and des-acylated ghrelin (Godlewski et al., 2019).

In agreement with these rodent data, large population-based studies found higher serum total ghrelin (acylated and des-acylated ghrelin) among alcohol drinkers than non-drinkers (Farokhnia et al., 2021), and that alcohol consumption was positively associated with serum total ghrelin in alcohol drinkers (Wittekind et al., 2018). In addition, patients with alcohol-associated cirrhosis and chronic alcohol dependence showed higher plasma ghrelin than healthy volunteers (Goodyear et al., 2010, Kim et al., 2005, Kraus et al., 2005). Interestingly, studies conducted in patients with AUD showed that abstainers have higher blood ghrelin compared to current drinkers (Kim et al., 2005, Kim et al., 2013, Koopmann et al., 2012, Kraus et al., 2005, Leggio et al., 2012). Further, acute alcohol administration to both healthy volunteers and rodents reduces plasma ghrelin (Calissendorff et al., 2005, Calissendorff et al., 2006, Leggio et al., 2013, Ralevski et al., 2017, Zimmermann et al., 2007). In contrast to former hypotheses, recent data suggests that this suppressive effect of acute alcohol on ghrelin does not occur through direct action of alcohol on ghrelin-secreting gastric mucosal cells or in proportion to the caloric value of alcohol administered (Deschaine et al., 2021). These data demonstrate that alcohol has an acute suppressive effect on ghrelin secretion, and that this effect likely occurs through an indirect mechanism separate from the effects of alcohol metabolism on energy homeostasis.

Overall, the reports on the effects of alcohol on blood ghrelin concentrations are mixed, mainly because of differences between acute *vs* chronic exposure to alcohol, but also because of differences in, for example, the dose, duration, mode of alcohol administration, and the time of ghrelin measurement post-alcohol intake. When different effects of

acute *vs* chronic alcohol consumption on ghrelin concentration are considered, side-by side, the following hypothesis may explain their relationship. With prolonged, harmful alcohol consumption, the acute alcohol-induced suppression of ghrelin secretion may lead to compensatory physiological changes that promote a rebound increase in circulating ghrelin concentrations. This hypothesized mechanism may explain why increased ghrelin concentrations are observed in chronic alcohol drinkers compared to non-drinkers and during alcohol abstinence *vs* chronic alcohol drinkers. However, additional controlled animal and human studies are needed to confirm this hypothesis and obtain more conclusive information on changes in peripheral ghrelin concentrations following acute *vs* chronic and continuous *vs* intermittent alcohol consumption in fed *vs* fasted conditions. Nevertheless, consistent observations of increased ghrelin concentrations following prolonged alcohol consumption, while reduction in ghrelin concentrations following acute alcohol intake, are reported. Moreover, serum ghrelin is increased in patients with alcohol-associated cirrhosis and in abstinent patients with AUD, suggesting that upregulation of ghrelin secretion may be a pathophysiological component or consequence of chronic alcohol consumption that can be therapeutically leveraged.

b) Ghrelin and alcohol-mediated behavior: Clinical and experimental studies

Ghrelin is traditionally known to stimulate hunger and meal initiation through a GHSR1a-stimulated complex network of neuronal circuits (Muller et al., 2015), although its effects are complex and not fully understood (Deschaine and Leggio, 2022). GHSR1a is expressed in reward-related brain areas, including the ventral tegmental area (VTA) and nucleus accumbens (NAc) (Zigman et al., 2006, Shevchouk et al., 2021, Suchankova et al., 2016a), suggesting that ghrelin may regulate reward processing. Growing evidence from preclinical experiments and human studies shows that ghrelin is also involved in alcohol craving and alcohol consumption (Deschaine and Leggio, 2022, Farokhnia et al., 2019, Shevchouk et al., 2021). These findings indicate that increased circulating ghrelin following chronic alcohol consumption may in turn increase alcohol craving and consumption and lead to more severe AUD and/or ALD. Below we review the literature describing the relationship between ghrelin and alcohol craving and consumption.

Ghrelin and alcohol craving: Systemic or central administration of ghrelin increases alcohol consumption in rodents (Jerlhag et al., 2009). Genetic knock-out or pharmacological blockage of the ghrelin system reduces alcohol consumption (Jerlhag et al., 2009, Suchankova et al., 2016b, Zallar et al., 2019, Godlewski et al., 2019). Moreover, suppression of either GHSR1a (genetic or pharmacological) or ghrelin production (genetic) suppresses conditioned place preference (CPP) for alcohol (Bahi et al., 2013, Jerlhag et al., 2009, Jerlhag et al., 2011). Indeed, acute treatment with a GHSR1a antagonist reduces alcohol intake in rodents (Bahi et al., 2013, Gomez et al., 2015, Gomez and Ryabinin, 2014, Jerlhag et al., 2009, Kaur and Ryabinin, 2010, Landgren et al., 2012, Stevenson et al., 2015). Besides regular alcohol intake, GHSR1a antagonism decreases operant self-administration of alcohol (Gomez et al., 2015, Landgren et al., 2012). Following abstinence from alcohol, pharmacological suppression of GHSR1a prevents relapse in male rats (Suchankova et al., 2013b, Jerlhag et al., 2009).

In clinical studies, peripheral endogenous ghrelin is positively correlated with alcohol craving, subjective response to alcohol, and brain activity in response to alcohol (Bach et al., 2019, Koopmann et al., 2019, Leggio et al., 2012). In a randomized, between-subject, double-blind, placebo-controlled, human laboratory study, intravenous (IV) ghrelin administration significantly increased cue-induced craving for alcohol in a bar-like laboratory, with no significant effect on craving for juice (used as a non-alcoholic appetitive control) (Leggio et al., 2014). In a subsequent study, the potential role of ghrelin administration in influencing motivation to self-administer alcohol and/or brain functional activity during reward anticipation was investigated in a randomized, crossover, double-blind, placebo-controlled human laboratory study with IV ghrelin. This study revealed that IV ghrelin infusion motivates participants to self-administer more alcohol and increases amygdala activity during alcohol reward anticipation (Farokhnia et al., 2018).

Sites and mode of ghrelin action: While the impact of ghrelin on alcohol-related behaviors has been widely explored, the brain circuits responsible for this interaction remain to be fully mapped. Some of the brain regions expressing GHSR1a have been identified as potentials sites of action for ghrelin to modulate alcohol-related behaviors (Cruz et al., 2013, Landgren et al., 2011, Zigman et al., 2006). One of these is the VTA, an important site for reinforcement, as its dopaminergic neurons project to the NAc shell. Indeed, local infusion of ghrelin into the VTA increases alcohol intake in male mice (Jerlhag et al., 2009), and GHSR1a antagonism reduces the ability of alcohol to cause somatodendritic dopamine release in this area (Edvardsson et al., 2021). Another implicated brain region is the amygdala, as ghrelin administration to alcohol-dependent male rats enhances the GABA levels in this area (Cruz et al., 2013, Yoshimoto et al., 2017). Additionally, findings that alcohol elevates both c-fos in the Edinger-Westphal nucleus (Kaur and Ryabinin, 2010) and both acyl- and des-acyl ghrelin within the lateral hypothalamus (Yoshimoto et al., 2017), combined with findings that local ghrelin infusion into the laterodorsal tegmental area (LDT) increases alcohol intake (Jerlhag et al., 2009), indicate that areas outside of the mesolimbic dopamine system are of importance for the ghrelin-alcohol link.

The influence of ghrelin signaling on brain regions involved in reward processing and memory have been examined in a few human functional magnetic resonance imaging (fMRI) studies by assessing the effects of acute exogenous ghrelin administration on the blood oxygen level dependent (BOLD) signal. In the fed state (when endogenous plasma ghrelin is reduced), in healthy adults without obesity, IV or subcutaneous (SC) ghrelin administration increased BOLD signal during viewing of food pictures in areas implicated in reward processing, such as the orbitofrontal cortex (OFC) and hippocampus (mimicking the effects of fasting where there is endogenous hyperghrelinemia), and amygdala, anterior insula and striatum, and increased appeal rating of high-energy food pictures (Goldstone et al., 2014, Malik et al., 2008). Note that, SC ghrelin administration had no effect on BOLD signal in primary auditory, motor, or visual cortices during control auditory, motor or visual tasks, respectively, suggesting a lack of non-specific effects of ghrelin on neurovascular coupling (Goldstone et al., 2014).

In fed, adults without obesity, but with alcohol dependence, IV ghrelin administration decreased BOLD signal during anticipation of delayed food reward in the medial OFC

and increased BOLD signal in the NAc; increased BOLD signal in the amygdala during anticipation of an IV alcohol administration was also observed (Farokhnia et al., 2018). Additionally, IV ghrelin administration decreased the latency to initiate self-administration of IV alcohol (Farokhnia et al., 2018). In detoxified patients with alcohol dependence (21 days of controlled alcohol abstinence), an fMRI study found that alcohol cue-induced brain activity in a network of brain clusters, including the bilateral ventral striatum, showed a significant positive association with plasma acylated ghrelin (Koopmann et al., 2019).

Furthermore, the association between plasma acylated ghrelin and alcohol craving was mediated by a cue-induced brain response in the ventral striatum and mesolimbic pathway (Koopmann et al., 2019)

Des-acyl ghrelin: Although acyl-ghrelin modulates alcohol-related behaviors in rodents, the effects of DAG are not yet clear. DAG is the major circulating form of ghrelin and was initially thought to be inactive because it does not bind to GHSR1a at physiologically relevant concentrations. However, new findings reveal various physiological properties of DAG. Some studies showed that DAG inhibits ghrelin-enhanced food intake (Fernandez et al., 2016) and decreases feeding (Asakawa et al., 2005) in rodents. In addition, DAG decreases gastric emptying (Asakawa et al., 2005) and regulates body temperature, glucose homeostasis, and lipid metabolism (Heppner et al., 2014) in rodents. Nevertheless, recent human studies reported that only plasma acylated ghrelin is associated with alcohol craving (Koopmann et al., 2012, Koopmann et al., 2019, Sha et al., 2021). This was also confirmed by fMRI studies which documented that only acylated ghrelin, and not DAG, positively correlate with BOLD signal in the brain to alcohol cues (Bach et al., 2019, Koopmann et al., 2019).

Preliminary human work on ghrelin receptor blockade in AUD: Given the role of ghrelin in increasing alcohol craving and intake, and that GHSR1a antagonists reduce alcohol intake and alcohol preference in preclinical studies (Jerlhag et al., 2009, Kaur and Ryabinin, 2010, Stevenson et al., 2016, Landgren et al., 2012), blocking the ghrelin system is under clinical investigation as a potential pharmacotherapeutic approach for AUD.

PF-5190457 is a ghrelin receptor inverse agonist, which can inhibit GHSR1a constitutive activity, as well as ghrelin mediated activity. In rodents and humans (heavy drinking individuals), PF-5190457, combined with alcohol, was shown to be safe and no alcohol-drug interactions were detected (Lee et al., 2020b). Furthermore, in a preliminary alcohol/food cue-reactivity session, PF-5190457, compared to placebo, reduced cue-induced alcohol craving and attention to alcohol cues, as well as cue-induced food craving, in a bar-like laboratory (Lee et al., 2020b). In addition, despite reducing ghrelin mediated alcohol craving, PF-5190457 did not significantly affect the serum concentrations of appetitive/metabolic and stress-related hormones or inflammatory markers, confirming the safety profile of this compound, especially when co-administered with alcohol (Farokhnia et al., 2020, Lee et al., 2020b, Lee et al., 2020a).

In summary, a significant body of literature demonstrates that stimulating the ghrelin system increases, while blocking the ghrelin system decreases, alcohol craving and consumption.

Although the mechanism(s) and potential brain regions involved in the effect of ghrelin on alcohol craving and consumption, as well as the role of DAG in this relationship, have yet to be fully elucidated, the evidence thus far suggests that inhibiting the ghrelin system can be a potential therapeutic strategy for AUD. Considered together, observations of (i) an association between chronic alcohol consumption and increased circulating ghrelin, and (ii) a positive association between ghrelin and alcohol craving and consumption, suggest the presence of a pathological positive feedback loop, where chronic alcohol increases ghrelin secretion which, in turn, further promotes alcohol consumption and together lead to increased AUD and/or ALD severity. Inhibiting the ghrelin system may therefore halt this harmful cycle.

c) Ghrelin in development of ALD

Liver and adipose tissue play a prominent role in glucose and fatty acid metabolism. Liver-adipose crosstalk and energy homeostasis is regulated by peptide hormones, such as ghrelin, insulin, and adiponectin secreted by the gut, pancreas, and adipose tissue, respectively. From clinical and experimental studies, it is well known that ghrelin reduces insulin secretion by suppressing intracellular Ca^{2+} levels in pancreatic β cells (Broglio et al., 2001, Dezaki et al., 2004, Dezaki et al., 2008). An inverse relationship between plasma ghrelin and insulin concentrations were reported in alcohol-fed rats (Rasineni et al., 2019b). Further studies revealed that an alcohol-induced increase in serum ghrelin impaired insulin secretion from pancreatic β-cells (Rasineni et al., 2019b, Rasineni et al., 2019a). Since insulin promotes export of lipoproteins from the liver and facilitates fat storage in adipose tissue (Saltiel and Kahn, 2001), suppression of circulating insulin by ethanol-induced ghrelin increases results in increased adipose lipolysis. The consequent rise in circulating fatty acids level and their enhanced hepatic uptake and esterification, leads to the development of alcohol-associated steatosis (Kang et al., 2007, Wei et al., 2013). Treatment of chronic alcohol-fed rats with the GHSR1a antagonist, [D-Lys-3] GHRP-6, increased serum insulin and by reduced circulating free fatty acids attenuated hepatic steatosis (Rasineni et al., 2019a). These results highlight the important role of ghrelin in modulating the pancreas-adipose-liver axis to promote the development of ALD. Since gene knockout of either *GHRL* or *GHSR* or inhibition of GOAT reduces the incidence of hepatic steatosis of diverse etiology (Li et al., 2014, Wortley et al., 2005, Zhang et al., 2018), underscores the importance of ghrelin in regulating hepatic lipid metabolism.

Ghrelin also directly promotes fat accumulation in hepatocytes by increasing fatty acid transport as well as *de novo* fatty acid synthesis and esterification (Barazzoni et al., 2005, Li et al., 2014, Rasineni et al., 2019a). *In vitro* studies conducted on isolated hepatocytes revealed that ghrelin promotes lipid accumulation via a similar mechanism as alcohol (Rasineni et al., 2019b). In support of these results, ghrelin directly increases lipogenesis in hepatocytes by activating the mammalian target of rapamycin (mTOR) and peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway (Li et al., 2014). Additionally, several other *in vivo* studies reported that ghrelin infusion increased hepatic lipid accumulation by elevating levels of fatty acid synthase enzymes (acetyl coenzyme A carboxylase, stearoyl-CoA desaturase-1) and decreasing fatty acid oxidation

enzymes (carnitine palmitoyl transferase and PPARγ) (Dallak, 2018, Sangiao-Alvarellos et al., 2009).

In addition to its indirectly affecting adipose tissue via decreasing pancreatic insulin, ghrelin can directly alter adipose tissue metabolism. Ghrelin inhibits adipocyte differentiation/maturation, as well as increases lipolysis and release of free fatty acid from differentiated adipocytes in *in vitro* (Rasineni et al., 2020, Salmeron et al., 2015, Zhang et al., 2004, Miao et al., 2019). These studies were corroborated by *in vivo* studies, showing that ghrelin infusion reduces peripheral insulin sensitivity and increases lipolysis in adipose and muscle tissue (Vestergaard et al., 2008a, Vestergaard et al., 2008b, Theander-Carrillo et al., 2006). In addition, ghrelin decreases secretion of adiponectin (Rasineni et al., 2020, Ott et al., 2002), a hormone that protects liver from fat accumulation by increasing hepatic lipid oxidation (You et al., 2005). Indeed, clinical and experimental studies showed that chronic ethanol treatment/intake is associated with low serum adiponectin (Chen et al., 2007, Jung et al., 2013, Nishise et al., 2010). That this decrease with alcohol administration is likely a consequence of ghrelin increase was shown by the improved serum adiponectin in chronic alcohol-fed rats treated with the ghrelin receptor antagonist [D-Lys-3] GHRP-6 (Rasineni et al., 2020). In contrast to these studies, brain ghrelin infusion (for 8 days) increased visceral adipose tissue deposition in rats (Sangiao-Alvarellos et al., 2009), which may likely be due to increased food intake.

d) Future perspectives

Gene polymorphisms in ghrelin system—Several single nucleotide polymorphisms (SNPs) have been reported for *GHRL* and *GHSR* (Mora et al., 2015, Pabalan et al., 2014, Suchankova et al., 2013a). Several publications document an association of these SNPS with increased risk of alcohol and/or other substance abuse in humans (Suchankova et al., 2017, Landgren et al., 2010, Landgren et al., 2008, Suchankova et al., 2016b, Suchankova et al., 2013a). There is also clinical evidence showing that SNPs in the coding region of the *GHRL* are associated with differences in body mass index, fat mass, susceptibility to type 2 diabetes mellitus and development of chronic hepatitis B related liver cirrhosis (Mora et al., 2015, Ukkola et al., 2002, Choi et al., 2006, Bing et al., 2005, Zhang et al., 2015). However, future studies are required to examine whether there is a link between polymorphism in the ghrelin system and ALD pathogenesis.

Ghrelin receptor dimerization—Another relevant aspect is that GHSR1a can interact with other GPCRs, such as melanocortin-3 receptor, dopamine D1 and D2 receptors, serotonin 2C receptor, oxytocin receptor and prostanoid receptors (Price et al., 2021, Ringuet et al., 2021). The co-interaction may lead to decrease or increase in GHSR1a mediated signal transduction (Price et al., 2021, Xiao et al., 2020). Further investigation is warranted on whether such receptor-receptor interactions also exist in peripheral organs and tissues and the possible role of such interactions in modulating ALD pathogenesis.

Endogenous antagonist of ghrelin receptor—Liver-expressed antimicrobial peptide-2 (LEAP-2) is a recently discovered antimicrobial peptide predominantly expressed in the liver and gut. In addition to its antimicrobial role (Li et al., 2015, Townes et al.,

2009), LEAP-2 is an inverse agonist at GHSR1a, attenuating the effects of ghrelin on food intake and stimulation of growth hormone (Al-Massadi et al., 2018, Ge et al., 2018, Hagemann et al., 2022, Mani et al., 2019a). Interestingly, a recent study revealed that IV ghrelin administration in mice reduces plasma LEAP-2 and treatment of hepatocytes with ghrelin decreased LEAP-2 synthesis and secretion (Islam et al., 2020). Since ghrelin reduces the levels of LEAP-2 which has an important role in innate immunity via its antibacterial activity, it is likely that the increased ghrelin seen with alcohol consumption may (i) play a role in the development of hepatic steatosis (an early event in ALD pathogenesis) and (ii) promote ALD progression by increasing intestinal hyperpermeability and gut dysbiosis - crucial modulators of hepatic inflammation and fibrosis (Bajaj, 2019, Fairfield and Schnabl, 2021). Besides, the possibility that LEAP2 modulate addiction processes should also be evaluated in man and rodents.

Conclusions:

Emerging evidence documents a close, yet complex, interaction between the ghrelin system and alcohol-related outcomes (Fig.1). Consistent observations indicate that chronic alcohol consumption is associated with an increased in blood ghrelin concentrations in rodents, and clinical studies of patients with alcohol-associated cirrhosis report increased ghrelin levels, compared with healthy individuals. This increase in circulating ghrelin may drive an increase in alcohol consumption as preclinical and clinical experiments demonstrates that ghrelin stimulates alcohol-related behaviors, such as alcohol craving and consumption. These findings lead us to hypothesize a potentially unique therapeutic strategy for AUD where inhibiting the ghrelin system may reduce the effects of increasing circulating ghrelin on alcohol consumption. Indeed, preliminary studies in humans demonstrate that a ghrelin receptor inverse agonist/antagonist reduces cue-induced alcohol attention and craving, suggesting promising effects of ghrelin receptor antagonism on alcohol craving. The identified bi-directional relationship between alcohol consumption and circulating ghrelin concentrations is also of interest in the treatment of ALD. In addition to increasing alcohol consumption, ghrelin also increases ALD severity by (i) reducing insulin secretion from pancreatic β-cells and thereby stimulating adipose-derived fatty acid mobilization to ultimately contribute to hepatic steatosis; (ii) directly promoting fat accumulation in hepatocytes by increasing fatty acid transport, as well as *de novo* fatty acid synthesis and esterification; and (iii) reducing insulin sensitivity and impairing adipocyte differentiation and maturation consistent with an inflammatory state. Ghrelin system inhibition could therefore serve as a possible dual therapeutic strategy to decrease alcohol craving and consumption as well the effects of ghrelin on ALD pathogenesis.

Future studies are required to (i) conclusively catalog the relationship between serum/plasma ghrelin and varying degrees and types of alcohol consumption (i.e., acute *vs* chronic and intermittent *vs* continuous) with more carefully controlled studies; (ii) parse out the central and peripheral mechanisms by which ghrelin stimulates alcohol craving and consumption, (iii) understand the role of other components of the ghrelin system in AUD and ALD pathophysiology, such as DAG, LEAP-2, and GHSR1a heterodimers, and (iv) investigate the relationship between genetic variations in the ghrelin system and AUD and ALD pathogenesis. Altogether, the known interplay between alcohol, ghrelin, and ghrelin-

mediated organ crosstalk suggests that future research on the ghrelin system represents a viable target for dual treatment of AUD and ALD.

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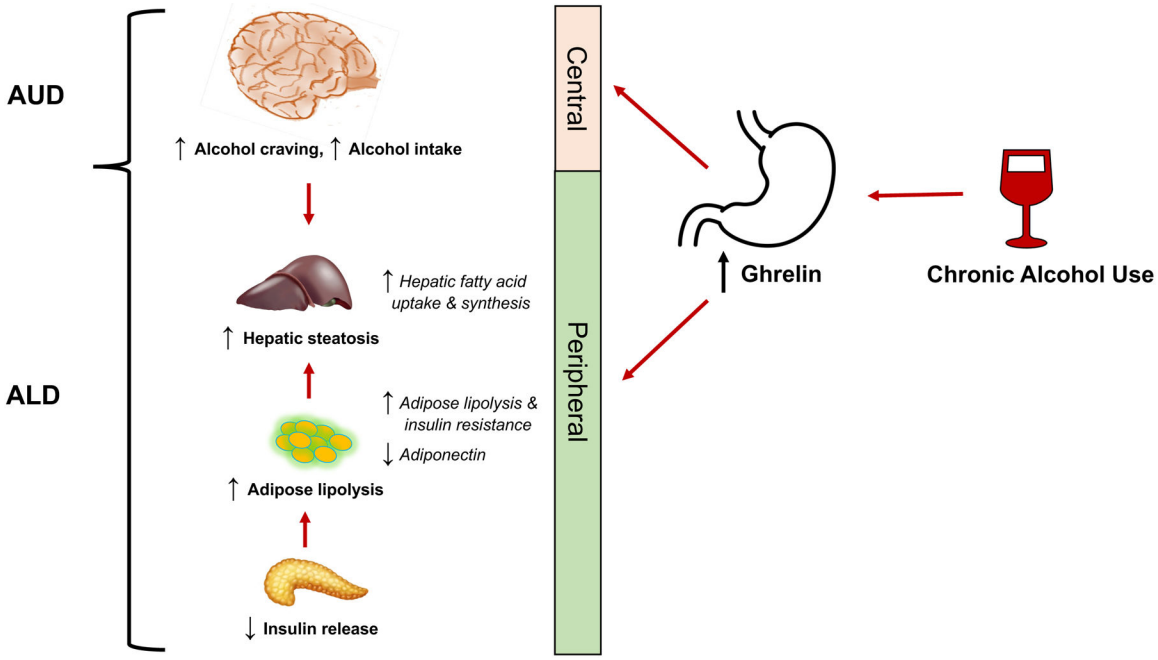

Figure 1:
Schematic of the potential role of the ghrelin system in alcohol use disorder (AUD) and alcohol-associated liver disease (ALD).