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Therapeutic potential of GHSR-1A antagonism in alcohol dependence, a review

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ABSTRACT

Growth hormone secretagogue receptor type 1A (GHSR-1A) is a functional receptor of orexigenic peptide ghrelin and is highly expressed in mesolimbic dopaminergic systems that regulate incentive value of artificial reward in substance abuse. Interestingly, GHSR-1A has also shown ligand-independent constitutive activity. Alcohol use disorder (AUD) is one of the growing concerns worldwide as it involves complex neuro-psycho-endocrinological interactions. Positive correlation of acylated ghrelin and alcohol-induced human brain response in the right and left ventral striatum are evident. In the last decade, the beneficial effects of ghrelin receptor (GHSR-1A) antagonism to suppress artificial reward circuitries and induce self-control for alcohol consumption have drawn significant attention from researchers. In this updated review, we summarize the available recent preclinical, clinical, and experimental data to discuss functional, molecular actions of central ghrelin-GHSR-1A signaling in different craving levels for alcohol as well as to promote "GHSR-1A antagonism" as one of the potential therapies in early abstinence.

1. Introduction

The growth hormone secretagogue receptor (GHSR) is a 366 aa long 7 trans-membrane GPCR which was first identified in 1996 [1] and since then, it's differential physiological functions are of great interest in pharmacology [2]. GHSRs, which have two isoforms, GHSR-1A and GHSR-1B [3], GHSR-1A mRNA expression is found on various neurons including the ventral tegmental area (VTA) [4,5]. Ghrelin, 28 a long gastrointestinal peptide is a natural ligand of GHSR-1A, whereas GHSR-1B, is believed to be mostly non-functional [6]. GHSR-1A mRNA is expressed in the brain and controls the hedonic and incentive aspects of some stimuli. Even ligand-independent [7] constitutive activity [8] of this receptor is evident but ~50% of its capacity is attenuated in the absence of the agonist, ghrelin [7]. In plasma, ghrelin is also found in unacylated as well as acylated form; however, unacylated ghrelin (UAG) does not act on the GHSR-1A [9]. Ghrelin O-acyltransferase (GOAT) enzymes act as a "master switch" for the ghrelin system, acylating it into its "active" form [10]. Ghrelin receptor GHS-R1A is abundantly expressed in the brain, particularly in the hypothalamus (arcuate (Arc) and the ventromedial (VMH) nuclei) and pituitary gland [11–13]. Thus, ghrelin-mediated direct actions in different neurological circuitry can be well defined.

Alcohol use disorder (AUD) is a major public health crisis worldwide and a burden on healthcare in the form of global death of 3.3 million yearly [14–16]. Uncontrolled, compulsive alcohol drinking contributes to several physical and psychiatric disorders [17–19]. Multiple psychological, genetic, and/or environmental factors contribute to the development and progression of AUD [20–23]. Alcohol drinking induces mild euphoria, mood disorders and disrupts cognitive function in people who are not yet tolerant [24–26]. AUD is linked to several diseases including cancer, heart disease, chronic obstructive pulmonary disease, dementia, and Alzheimer's disease that affect the quality of life [27–31]. Despite considerable progress to understand brain circuitry or pathological changes in social and/or compulsive drinkers, challenges remain in the pharmacological treatment of addiction [32–36]. Recovering addicts also face significant cognitive deficits and are even more vulnerable to relapse [37–39].

Recently, there has been a growing interest in understanding the role of different endocrine pathways and their cross-talk with the brain to develop novel therapeutic targets for addictive behaviors [40–42] as

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hormones interfere with reward-based and relief-based binge drinking. Ghrelin (28 aa) seems to be an important link concerning addictive behaviors [43,44]. Being an orexigenic peptide, ghrelin appears to be a major player in hunger signal [45] and is thought to be augmenting the rewarding properties of food via the mesolimbic dopaminergic pathways [46,47]. Functional imaging studies on humans suggest that ghrelin can increase the activity of different brain areas involved with food-reward processing [48]. Interestingly, hunger and craving in addiction have been described to have similar psychological qualities [49,50]. Exogenous administration of ghrelin peptide in the third ventricle of brain VTA induces extracellular dopamine in the nucleus accumbens (NAc) which can be reversed by pharmacological GHSR-1A blockers treatment in the same region in combination [47,51–55]. The above effects are probably mediated by cholinergic neuronal input from the laterodorsal-tegmental nucleus (LTDg) to the VTA [53,56,57]. Chronic administration of ghrelin induces conditioned place preference (CPP) [47] as well as mesolimbic reward system too [58]. Collectively, ghrelin's role in both stress and reward pathways indicates strongly its potential role in addiction, linked to positive reinforcement (reward) and negative reinforcement (stress relief) mechanisms [21,59,60].

In this review, we have discussed recent progress as well as knowledge gaps in preclinical and clinical studies of the belly to brain nexus regulated by the ghrelin-GHSR-1A system promoting binge alcohol drinking. We also highlight pharmacokinetic evidence to promote "ghrelin-receptors GHSR-1A suppression" as potential future therapy of AUDs at different levels.

2. Elephant in the room: 'ghrelin-GHSR1A system' and alcohol dependence

For decades, there are direct as well as indirect evidence that indicates an association between the ghrelin-GHSR-1A system and alcoholism. Alcohol administration affects plasma ghrelin and vice versa. Exogenous ghrelin administration alters alcohol consumptions in alcohol-dependent animal models. The shreds of evidence of ghrelin as one of the key regulators of 'alcohol cravings' from three different facets have been summarised here as follows:

2.1. Experimental pieces of evidence in animal models

Ghrelin-GHSR-1A signaling is important in increased "cravings" or motivation to consume alcohol in animals [61–63]. But the effect of acute ethanol exposure on plasma levels of ghrelin in few adult rodent studies showed conflicting findings [64,65]. Several experiments have been done to decipher the nexus of ghrelin and alcohol addiction and/or withdrawal in different animal models. Intracerebroventricular (ICV) injection of ghrelin, increased alcohol intake but ghrelin in combination with GHS-R1A antagonists led to a significant decrease in alcohol consumption in a 2-bottle (water/alcohol) free choice limited access paradigm in 9 weeks old mice [66]. Ghrelin-induced alcohol consumption in rodents is evident [66,67] by activating ghrelinergic, dopaminergic & serotonergic neurons [64]. In contrast, though the peripheral administration of ghrelin did not show any effect on alcohol consumption [68,69], ethanol affects total and acylated ghrelin levels in peripheral blood in rats with alcohol dependence independent of administration route or gender [65,70]. These divergent results may be due to different experimental setups (long-term or short-term study) or by different stages of alcohol dependence. Alcohol-induced dopamine release in the NAc has been attenuated in ghrelin-knockout mice [62,71,72]. Acyl ghrelin acts via a G-protein coupled receptor (GPCR) called GHSR-1A [73] and this GHSR-1A gene expression in the NAc, VTA, amygdala, prefrontal cortex, and hippocampus is significantly increased in rats who are high alcohol-consuming (Alko, Alcohol strain) as compared to low alcohol-consuming strains (Alko, Non-alcohol) [65,74]. After alcohol exposure, high-alcohol-consuming rats showed lower plasma ghrelin than that of low alcohol-consuming group [74]. Alcohol misuse after Roux-en-Y gastric bypass (RYGB) surgery in rats is due to dopamine firing in VTA by dampened GHSR activity, thus affecting midbrain ghrelin signaling [75]. Importantly, only central ghrelin signaling but not peripherally circulating ghrelin level is important for alcohol-reward [68]. Thus, the central ghrelin system may be a potential target to treat alcohol dependence in the future as GHSR-1A suppression reduces alcohol consumption in rats [76,77].

2.2. Clinical evidence in patients

Alcohol consumption is positively correlated to serum ghrelin level in population-based large samples [78–81]. Ghrelin levels are decreased in AUD patients drinking alcohol regularly and significantly increased during withdrawal [82,83]. A moderate oral dose of alcohol with other substances resulted in a significant reduction of fasting total as well as acyl ghrelin [84–86]. Intravenous administration of alcohol in social drinkers showed blunting in a fasting-induced increase of plasma acyl ghrelin [87]. Intravenous ghrelin administration is involved in cue-induced alcohol cravings in patients [88–90]. In heavy drinkers, increased aldosterone and cortisol may affect the ghrelin system as well as alcohol cravings [91]. Fasting-ghrelin levels were increased significantly in 47 individuals following at least 30-day-long abstinence with chronic alcoholism compared to 50 control subjects [92]. Similarly, AUD patients showed higher fasting-ghrelin levels at early abstainers (who had their last drink 1–3 days beforehand) than that of active drinkers and fasting-ghrelin mediated craving scores are described [82]. Gender differences have been observed in ghrelin levels in AUD patients, females have significantly higher ghrelin than males in alcohol-dependent abstinent patients [93]. These data suggest the role of ghrelin in a relapse of addiction during withdrawal. On one hand, ghrelin affects alcohol cravings but on the other hand, alcohol also affects ghrelin signaling via a local effect on the stomach mucosa [81,94]. Besides this, the systemic effect was also observed in a study involving 44 non-smoker social drinkers, where intravenous alcohol administration blunted fasting-induced excessive ghrelin levels [81]. Similarly, male patients with alcohol dependence and who have consumed alcohol in the last 24 h have been shown lower fasting-ghrelin levels compared to those in controls [84]. In another study, different craving scales were explored in terms of ghrelin levels in 61 AUD patients and it was hypothesized that only acetylated ghrelin (not total ghrelin) is involved in reward-associated craving in early abstinence of alcohol-dependent males, and antagonizing GHSR-1A in VTA can be a novel pharmacological target in future to resist craving and relapse [95].

However, literature is inconsistent as to whether levels of plasma ghrelin are altered in alcohol-dependent individuals and abstinence, compared to placebo-controls [79,82,92,95–97]and more studies are required with a large sample size. Ghrelin remains inactivated as well as inactivated forms [98]. While some studies measured the changes in total ghrelin, others measured only acyl-ghrelin [99], which aggravated the contradiction [44,100].

2.3. Genetic markers associated ghrelin and alcoholism

There is also genetic evidence showing a significant association between ghrelin and alcoholism [80,101,102]. A single-nucleotide polymorphism (SNP) rs2232165 of the GHSR-1A gene has been identified which is positively associated with heavy alcohol consumption in a Spanish individual (moderate or heavy alcohol drinkers and abstainers) [101]. Six tag SNPs in the GHRL (rs3491141, rs696217, rs4684677, rs42451, rs35680, and rs26802) and four SNPs in the GHSR (rs495225, rs2232165, rs2948694, and rs572169) were genotyped in 113 Swedish females and GHRL haplotype has shown to be associated with alcohol dependence and paternal heritability of the same [103]. There are some conflicting results related to Leu72Met polymorphism [80,102]. A Leu72Met haplotype associated with paternal alcohol dependence (self-reported) was observed [103]. In contrast, the Arg51Gln and Leu72Met

ghrelin gene polymorphism in alcohol-dependent individuals were not statistically significant [80]. But later, Leu72Leu genotype was found to be associated with increased risk of excessive alcohol consumption and later AUD [102]. Studies with a much larger sample size are required to infer the relationship between genetic polymorphism of ghrelin gene and alcohol dependence as well as a failed abstinence. Still, available data suggest some correlation of ghrelin to alcoholism.

3. Relevance of GHSR-1A signaling in 'alcohol cravings

The GHSR-1A gene is expressed in all 3 components of the dorsal vagal complex [104–106], hippocampus, amygdala [107], CeA [108], nucleus accumbens, and prefrontal cortex [74,109]. Interestingly, ghrelin has an impact on higher cognitive functions, such as learning and/or memory in rodents [110–112]. However, accessibility of circulating ghrelin to the brain through the blood-brain barrier seems to be limited to specific brain regions [113–115]. The main targets of ghrelin include circumventricular organs such as the area postrema, where it can diffuse freely through fenestrated capillaries [116,117]. Though ghrelin concentration in cerebrospinal fluid (CSF) is approximately 1000-fold lower than plasma ghrelin levels in mammals [118,119], it can reach brain areas via CSF, crossing the blood–CSF barrier in choroid plexus, and/or the hypothalamic tanycytes [120,121]. GHSR-1A constitutive signaling also has been reported in ligand-independent manner [122–125] and such constitutive activity of GHSR-1A has shown to strongly impact the neuronal activity too [2,126]. Additionally, GHSR-1A being a GPCR can heterodimerize with other GPCRs, including melanocortin 3 receptor, serotonin 2C receptor, somatostatin 5 receptor, and the dopamine D1 and D2 receptors [127–129] and thus play several neurological functions independently without ghrelin binding. Despite decades of investigations, the evidence of ghrelin production in the brain has been inconsistent and a matter of conjecture. Ghrelin and dopamine receptors both are GPCRs and co-expressed in several regions of the brain, including the ventral tegmental area (VTA) [130,131]. Heterodimerization of GHSR with both D1 &/or D2 receptors with disulfide bridge is evident [2,125,132]. When both the receptors are stimulated, cAMP accumulation is observed unlike the situation when GHSRs alone are activated causing no change in cAMP levels [127,133]. Coadministration of exogenous ghrelin and dopamine induces cAMP signaling in HEK293 cells indicating ghrelin and dopamine crosstalk [127]. D2-GHSR-1A dimer receptor-induced Ca^{2+} mobilization from the endoplasmic reticulum occurs via IP3 receptors [132,134]. Interestingly, when the GHSR-1A receptor is activated alone (without dopamine receptor dimerization), cAMP signaling is not activated but Ca^{2+} accumulation is evident [127,135]. The synergy between D1R and GHSR-1A is due to switching from $G\alpha_{q/11}$ to $G\alpha_{i/o}$ coupling in GHSR-1A [133,136]. Ghrelin induces dopaminergic (DA) firing via voltage-gated potassium channels KV7, which are inhibited by the Gq-PLC-IP3 pathway [137].

Thus, in addition to VTA-NAc mesolimbic pathway induction, ghrelin also enhances alcohol-activated dopaminergic circuitry of reward [138,139]. This artificial reward mediates the transition from 'liking' to 'craving' with or without simultaneous enjoyment [140–142].

4. Amplification of artificial reward of alcohol by ghrelin-GHSR-1A system

Now the question is can ghrelin-GHSR-1A signaling amplify alcohol reward? Compulsive alcohol drinking and dependence involve central nicotinic acetylcholine receptor (nAChR), especially the α3β2* subtype located in the VTA [143–148]. Interestingly, ghrelin and alcohol partly share a common dopaminergic reward link, via α3β2*, β3, and/or α6 subtypes of the nicotinic acetylcholine receptor (nAChR) that induce alcohol reinforcement ([143,144,149]. The brain-reward pathway is connected to special areas of the brain that control behavior and memory. It begins in the ventral tegmental area (VTA), a complex midbrain structure composed of dopaminergic and GABAergic neurons which are important to induce a hedonic feeling or pleasure by ghrelin [150]. When the brain begins to make links between some activity and pleasure, the crucial brain-reward circuitry is activated [151]. Ghrelin can significantly modulate GABAergic neuron transmission in the nucleus of the amygdala in association with ethanol actions in rats [108]. Ethanol can activate neurons in VTA in vivo [152–154] as well as in vitro [155–157]. Exogenous ghrelin administration in rodent-brain causes an induced dopamine release in the accumbal nucleus as well as the striatum [53,158,159]. This ghrelin-mediated reward-motivation is activated by its GHSR-1A receptor via cholinergic-dopaminergic circuitry [52,160–162].

Ghrelin treatment in sub-chronic levels causes locomotor sensitization in mice, which supports that ghrelin activates the mesolimbic dopamine system and modulates reward [100,163–165]. T Glutamatergic NMDA receptors mediated postsynaptic current is induced by ghrelin's mesolimbic dopamine system [166–168] and NMDA receptor antagonist, AP5, attenuates ghrelin mediated locomotor stimulation as well as release accumbal dopamine [165,169]. Further studies have established a role for the laterodorsal tegmental area (LDTg) as another mediator for ghrelin's behavioral effects [160,170], stimulates the locomotor activity, and causes an accumbal dopamine release in mice [72,171]. LDTg-ghrelin enhances VTA-acetylcholine as well as NAc-dopamine concomitantly via nAChR dependent mechanisms, LDTg-ghrelin concomitantly enhances VTA-acetylcholine and NAc-dopamine via nAChR dependent mechanisms [172–174].

Studies have shown that circulating ghrelin penetrates the blood-brain barrier [175,176]. It was demonstrated that systemic ghrelin administration causes accumbal dopamine release, locomotor stimulation, and conditions a place preference via VTA-GHSR-1A in mice [173,177]. The VTA, known to express GHSR-1A on dopaminergic neurons [164,178], is an important area of ghrelin's ability to activate the mesolimbic dopamine system. Accordingly, local infusion of ghrelin into the VTA increases the dopamine turnover in NAc in rats [52] along with enhancement of accumbal dopamine release. This causes hyperactivity in mice which are reversed by ghrelin receptor antagonisms [66,72,172,179]. Ghrelin also activates a neuronal network of VTA, NAc, and lateral hypothalamus in rats [180]. GHSR-1A forms a heteromeric complex with dopamine-2 (D2) receptors in the hypothalamus in mice [128]. Similarly, dopamine-1 (D1) receptors and GHSR-1A are co-expressed in the hippocampus, VTA, substantia nigra, and other cortical regions [181]. Antagonism of D1 receptors can attenuate ghrelin-enhanced food reward. These results proved direct evidence of ghrelin-mediated dopaminergic reward as D1 receptor activation is a kind of 'direct pathway' in reward-related incentive [182–184]. A schematic diagram showing the neuro-psycho-endocrinological connections like a 'craving cycle' of artificial reward by ghrelin has been depicted in Fig. 1.

5. GHSR-1A blocking, a new hope to combat AUD

After the discovery of ghrelin in 1999, its role in obesity and metabolism was established and since then active ghrelin receptor GHSR-1A antagonism or inverse agonism has been in scientific arguments [66,185]. As the ghrelin system is one of the key regulators of alcohol-seeking behavior and uncontrolled binge drinking, targeting ghrelin receptors as a potential pharmacological treatment was suggested by scientists [186,187]. Interestingly, a growing body of literature is showing that acute pharmacological or genetic knockout of GHSR-1A significantly attenuates alcohol preference, compulsive-seeking behavior, and consumption and attenuates dopamine release in NAc of the brain [62,76,77,188–193].

GHSR-1A antagonist, JMV2959 treatment significantly reduced the operant self-administration of alcohol in alcohol two-bottle choice drinking paradigm (preference to the bottle of alcohol over water) in alcohol-preferring rats [76]. Similar results were found in C57BL/6

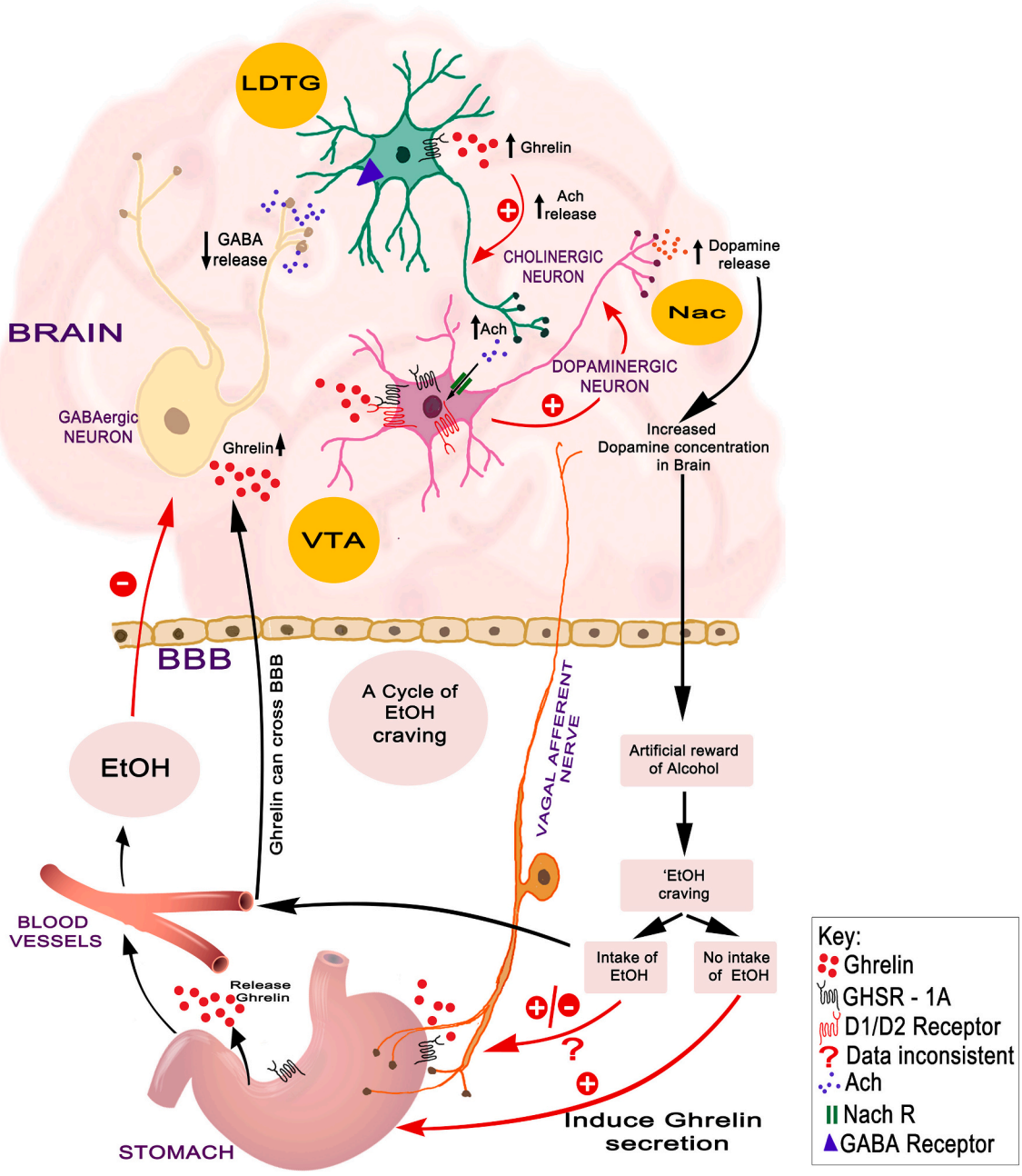

Fig. 1. A schematic representation of alcohol (EtOH) cravings by ghrelin-GHSR-1A pathway:
A) Ghrelin can cross blood brain barrier (BBB) and act through growth hormone secretagogue receptor 1A (GHSR-1A). Ghrelin may increase dopaminergic neuron activity directly binding to GHSR-1A on dopaminergic neurons in ventral tegmental area (VTA) and nucleus accumbens (NAc) and induce postsynaptic dopamine release.
B) Sometimes indirectly via activation of cholinergic neurons and Acetyl choline (ACh) secretion in LDTg, subsequently LDTg cholinergic neurons that release acetylcholine (ACh), Ach binds to nicotinic acetylcholine receptors (nAChR) on dopaminergic neurons in VTA and increase neuronal-activity and increase dopamine release in postsynaptic regions. Increased activation of dopamine D1 or D2 receptors in neurons by upregulated dopamine create artificial reward of alcohol.
C) Ghrelin can bind to GHSR-1A in stomach where there is connection of vagal nerves and thus through vagal nerve connection, passively ghrelin can induce dopaminergic reward in brain
Black arrows signified sequence of the pathways and red arrows are signified positive or negative feedback showing as ±, respectively.
Different regions of brain are just schematic (not positional) representation to understand the neuro-*endo*-psychological connections. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mice, where GHSR-1A antagonism suppressed both operant and self-administration of ethanol [71,194]. In a long-term study, a single administration of a GHSR-1A antagonist at VTA was able to reduce alcohol intake for 2 and 5 months with the effects being more pronounced after 5-month-long exposure [77]. Ten days treatment of the same could reduce alcohol intake following 8 months. Thus GHSR-1A blockers can be very helpful for AUD patients in abstinence [77]. JMV2959 was found to inhibit the mesolimbic dopamine system by attenuating dopamine release in alcohol abuse in the VTA and NAc region of the brain of rats [195]. Other than alcohol, JMV2959 has shown almost similar effects in nicotine and/or cocaine abuse in mice [45,179] and also reduces dopamine release in VTA Co-administration of a GHSR-

1A antagonist together with nicotine or cocaine on daily basis, prevents those substance-induced sensitizations in rats [196,197]. Very recently, GHSR-1A inverse agonist PF-5190457 treatment in heavy drinkers was found very promising results in a single-blind, placebo-controlled, within-subject human study as well as in rats, reducing alcohol cravings and found to be safe in human trials [198–202] Vertical sleeve gastrectomy (VSG) rats showed beneficial result with less alcohol consumption by GHSR-1A suppression than that of Roux-en-Y gastric bypass (RYGB) rats and thus VSG is thus preferred in AUD patients [203].

In contrast, several studies showed no or little insignificant alteration of locomotor activity by pre-treatment of JMV2959 compared to vehicle treatment [196,197,] and no effect was observed on Ghsr gene expression neither in the VTA nor in the NAc following subchronic JMV2959 administration in mice [171]. Suchankova et al., thus hypothesized that sub-chronic JMV2959 treatment to attenuate the stimulatory effects of alcohol is not only due to an altered number of active GHSR-1A receptors [171] but the reduced ability of GHSR-1A to heterodimerize with dopamine D1 and D2 receptors [127,128], that decreases the constitutive activity of the GHSR-1A [204] as hedonic feelings inducer or reward-amplifier.

Either direct action as a GPCR or action via heterodimerization with D1 or D2 receptors, whatever the case is, GHSR-1A is very much related to alcohol consumption and alcohol cravings. GHSR-1A blockers are found to be safe in human clinical trials to [205]. Thus, blocking the ghrelin system is a new hope during pharmacological treatment of AUD patients, attenuating sensitivity of the mesolimbic dopamine system in alcohol abuse and reducing alcohol cravings.

6. Future perspectives

AUD is a matter of great concern worldwide and addressing the unmet medical needs related to different stages of alcohol addiction is the main problem of patients in early abstinence. Addiction is a complex manifestation where numerous molecular pathways act together and a multidisciplinary neuro-psycho-endocrinological approach is required to combat this. The search for novel treatments has largely been focused on finding pharmacological medications to control alcohol addiction and reduce relapse in reward-drinking and relief-drinking individuals. The ghrelin system being a reward amplifier generates alcohol cravings in different stages of drinkers and induces relapse in withdrawal. Ghrelin receptor GHSR-1A blocking showed promising results in laboratory animal models as well as clinical trials. Further work is warranted to shed light on different doses, treatment procedures and safety as GHSR-1A blockers are comprehensively a new hope in addiction biology.

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Credit authorship contribution statement

Both SG and SM have made substantial contributions to all of the following: (1) the conception and design of the manuscript, (2) drafting the article and revising it critically for important intellectual content, (3) final approval of the version to be submitted. Precisely, SG and AM conceived the idea and prepared the manuscript as well as figures. AM edited the draft manuscript, checked and arranged references. All the authors approved the final version of the manuscript.

Declaration of competing interest

We declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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