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Gut-brain axis and addictive disorders: A review with focus on alcohol and drugs of abuse

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ABSTRACT

Due to the limited efficacy of existing medications for addictive disorders including alcohol use disorder (AUD), the need for additional medications is substantial. Potential new medications for addiction can be identified through investigation of the neurochemical substrates mediating the ability of drugs of abuse such as alcohol to activate the mesolimbic dopamine system. Interestingly, recent studies implicate neuropeptides of the gut-brain axis as modulators of reward and addiction processes. The present review therefore summarizes the current studies investigating the ability of the gut-brain peptides ghrelin, glucagon-like peptide-1 (GLP-1), amylin and neuromedin U (NMU) to modulate alcohol- and drug-related behaviors in rodents and humans. Extensive literature demonstrates that ghrelin, the only known orexigenic neuropeptide to date, enhances reward as well as the intake of alcohol, and other drugs of abuse, while ghrelin receptor antagonism has the opposite effects. On the other hand, the anorexigenic peptides GLP-1, amylin and NMU independently inhibits reward from alcohol and drugs of abuse in rodents. Collectively, these rodent and human studies imply that central ghrelin, GLP-1, amylin and NMU signaling may contribute to addiction processes. Therefore, the need for randomized clinical trials investigating the effects of agents targeting these aforementioned systems on drug/alcohol use is substantial.

Contents

1. Introduction

Alcohol addiction affects approximately 4% of the population over the age of 15 and contributes significantly to the global burden of diseases by causing substantial morbidity and early mortality (Rehm et al., 2009). However, only four medications are used for the treatment of alcohol addiction in Europe and/or the United States. Reports display a robust reduction in alcohol intake following treatment with disulfiram (an aldehydedehydrogenase inhibitor), naltrexone (an opioid receptor antagonist), acamprosate (various targets affected) and nalmefene (an opioid receptor modulator) (Jonas et al., 2014; Maisel, Blodgett,

Abbreviations: AUD, Alcohol use disorder; CPP, Conditioned place preference; Ex4, Exendin-4; GHSR-1A, Growth hormone secretagogue receptor; GLP-1, Glucagon-like peptide-1; LDTg, Laterodorsal tegmental area; NAc, Nucleus accumbens; nAChR, Nicotinic acetylcholine receptors; NMU, Neuromedin U; NMUR2, NMU receptor 2; NTS, Nucleus tractus solitarius; sCT, Salmon calcitonin; VTA, Ventral tegmental area.

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Wilbourne, Humphreys, & Finney, 2013; Serecigni, 2015). However, the outcomes of these medications vary and the majority of patients with alcohol use disorder (AUD) remain untreated (Heilig & Egli, 2006). In addition to AUD, addiction to other drugs of abuse negatively impacts to the global burden of diseases and the number of available pharmacotherapies targeting drug dependences is limited. There is therefore a substantial need for new medications that can be used to treat addictive disorders.

Dopamine neurons in the ventral tegmental area (VTA) projecting to nucleus accumbens (NAc) are denominated the mesolimbic dopamine system (for review see (Jayaram-Lindström, Ericson, Steensland, & Jerlhag, 2016)). As reviewed elsewhere extensive research collectively shows that the reinforcing effects of drugs of abuse and natural rewards are mediated by increased dopamine release in the NAc and that this increase contribute the incentive salience of motivated behaviors (Berridge & Robinson, 1998; Koob & Volkow, 2016; Wang, Volkow, Thanos, & Fowler, 2004). Cholinergic afferent projections from the laterodorsal tegmental area (LDTg) onto the VTA-dopamine neurons (for review see (Larsson & Engel, 2004)), i.e. the cholinergic-dopaminergic circuitry, may also participate in reinforcement as it is activated by both addictive drugs and non-drug rewards (Di Chiara & Imperato, 1986; Engel et al., 1988; Larsson, Edstrom, Svensson, Soderpalm, & Engel, 2005; Larsson & Engel, 2004; Soderpalm & Ericson, 2013; Weiss, Lorang, Bloom, & Koob, 1993; Wise & Rompre, 1989). This is exemplified by a study demonstrating that alcohol intake in high alcohol-consuming rats causes a concomitant and time-locked increase in acetylcholine levels in the VTA and dopamine levels in the NAc shell (Larsson et al., 2005). Moreover, a role of this acetylcholine-dopamine circuitry for reward-related behaviors and addiction processes has been implied (Larsson et al., 2005; Larsson & Engel, 2004; Lodge & Grace, 2006).

Due to studies reporting a co-morbidity between addiction and binge eating (for studies and reviews see e.g. (Bulik, Sullivan, Carter, & Joyce, 1997; Kaye et al., 1996; Wolfe & Maisto, 2000) and that appetite regulatory peptides are expressed throughout reward-related areas (Morganstern, Barson, & Leibowitz, 2011; Thiele et al., 2004), collectively outlined the possibility that modulation of food and drug consumption share overlapping neurobiological substrates. The possibility that endocrine signals play a role in reward regulation was less studied at this time and this gap in knowledge intrigued to the unraveling thereof.

As extensively reviewed previously, appetite regulation is complex and involves various neuropeptides (see e.g. (Egecioglu et al., 2010; Fulton, 2010; Zheng, Lenard, Shin, & Berthoud, 2009)). This includes for instance neuropeptides produced by the gastrointestinal tract, e.g. peptide YY, ghrelin, neuromedin U (NMU) and glucagon-like peptide-1 (GLP-1), the adipose tissue such as leptin and interleukin-6, the pancreatic β-cells e.g. amylin and insulin, as well as the brain e.g. galanin and neuropeptide Y. Several of these peptides have been attributed multiple processes and have during later years received attention as regulators of reinforcement. Two of these neuropeptides that have been studied extensively are ghrelin and GLP-1 and thus, the present review will cover their involvement in alcohol- and drug-related behaviors. In addition, the present knowledge of the ability of amylin and NMU to modulate reinforcement will be described.

2. Ghrelin

The 28-amino acid peptide ghrelin is produced and secreted from the stomach and other peripheral tissues (Kojima et al., 1999). Circulating ghrelin is enhanced following hunger (Cummings et al., 2001; Cummings, Frayo, Marmonier, Aubert, & Chapelot, 2004). Ghrelin containing neurons and ghrelin mRNA is detected in the brain, raising the possibly that ghrelin is produced in parts of the brain (Cowley et al., 2003; Lu et al., 2002; Mondal et al., 2005). Ghrelin has been ascribed numerous feeding-related functions, from an increase in food intake and appetite (Egecioglu et al., 2010; Wren et al., 2001; Wren et al., 2001; Wren et al., 2000) to an initiation of meal (Cummings et al., 2001) as well as an enhanced adiposity (Theander-Carrillo et al., 2006; Tschop, Smiley, & Heiman, 2000). The involvement of ghrelin in these key energy balance phenotypes outlined the possibility that "ghrelin receptors" (i.e. growth hormone secretagogue receptor (GHSR-1A)) could constitute a treatment target for obesity. In addition to energy balance modulation, ghrelin has been implied in a myriad of other different functions such as stimulation of growth hormone production (Kojima et al., 1999), enhanced prolactin secretion, induction of sleep and stimulation of gastric motility (for review see (Masuda et al., 2000; van der Lely, Tschop, Heiman, & Ghigo, 2004). These additional physiological effects of ghrelin, may suggest that ghrelin signaling is less appealing as a treatment target due to possible side effects including constipation, disrupted sleep pattern and reduced growth hormone and prolactin production.

2.1. Ghrelin activates the cholinergic-dopaminergic circuitry

The existing literature display an expression of GHSR-1A along the cholinergic-dopaminergic circuitry (Guan et al., 1997; Landgren et al., 2011; Zigman, Jones, Lee, Saper, & Elmquist, 2006), indicating that ghrelin modulates reward-related behaviors. A first indication thereof are the findings demonstrating that ghrelin administration into the third ventricle causes an accumbal dopamine release as well as a locomotor stimulation in mice (Jerlhag et al., 2006). The ability of ghrelin to cause release of dopamine in the striatum was later verified (Palotai et al., 2013a). Repeated occurrence of an addictive drug can promoted an aforementioned response and this is referred to locomotor sensitization (for review see (Sanchis-Segura & Spanagel, 2006)). This phenomenon has been suggested to play an important part of addiction processes (Berridge & Robinson, 1998; Robinson & Berridge, 1993; Robinson & Kolb, 2004) as it in rodents causes an increase in progressive ratio schedules as well as enhances drug seeking behavior (Cardinal & Everitt, 2004; Shaham & Hope, 2005; Vezina, 2004). The findings that sub-chronic systemic ghrelin treatment causes locomotor sensitization in mice, may therefore support that ghrelin activates the mesolimbic dopamine system and modulates reward (Suchankova, Engel, & Jerlhag, 2016). However, addiction can also be promoted through sensitization-independent neuroplastic changes (for review see e.g. (Kalivas, 2005; Koob & Le Moal, 2005) and the possible relevance of drug-induced behavioral sensitization in humans is still unclear (Sax & Strakowski, 2001). Therefore the significance and interpretation of sensitization data should be taken with consideration.

The VTA, known to express GHSR-1A on dopaminergic neurons (Abizaid et al., 2006), was initially identified as an area of importance for 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 (Abizaid et al., 2006) as well as enhances accumbal dopamine release and causes hyperactivity in mice (Jerlhag, Egecioglu, Dickson, Svensson, & Engel, 2007). A subsequent study corroborates the importance of ghrelin singling in VTA for reward regulation since local infusion of ghrelin into the VTA conditions a place preference in mice (Schuette, Gray, & Currie, 2013). In the VTA, glutamatergic NMDA receptors appear to be important for ghrelin's ability to activate the mesolimbic dopamine system as local VTA infusion of an NMDA receptor antagonist, AP5, attenuates the ability of ghrelin to cause a locomotor stimulation as well as to release accumbal dopamine (Jerlhag, Egecioglu, Dickson, & Engel, 2011; Jerlhag, Egecioglu, Dickson, Svensson, & Engel, 2008).

Further studies have thereafter established a role for LDTg as a mediator for ghrelin's behavioral effects. Initial studies show that ghrelin into the LDTg, where GHSR-1A are expressed on cholinergic neurons (Dickson et al., 2010), stimulates the locomotor activity and causes an accumbal dopamine release in mice (Jerlhag et al., 2007). Compelling evidence further imply that ghrelin stimulates the cholinergic-dopaminergic circuitry, as the ability of central ghrelin to activate the mesolimbic dopamine system is mediated via VTA nicotinic acetylcholine receptors (nAChR) (Jerlhag, Egecioglu, et al., 2006), specifically the α3β2, β3 and α6 subtypes (Jerlhag et al., 2008). A more direct association of this link is provided by data showing that LDTg-ghrelin concomitantly enhances VTA-acetylcholine and NAc-dopamine via nAChR dependent mechanisms (Jerlhag, Janson, Waters, & Engel, 2012). Collectively, these data imply that ghrelin, from the periphery or brain, acts via local mechanisms within both the VTA and LDTg to stimulate the cholinergic-dopaminergic circuitry. Albeit the physiological relevance of this activation should be investigated it might be suggest that ghrelin increases the incentive salience of motivated behaviors since the acetylcholine-dopamine circuitry mandates motivational behaviors (see e.g. (Koob, 1992; Robinson & Berridge, 1993; Wise, 1987)).

Studies have shown that circulating ghrelin penetrates the blood brain barrier (Banks, Tschop, Robinson, & Heiman, 2002), that systemic ghrelin administration causes accumbal dopamine release, locomotor stimulation and conditions a place preference via VTA-GHSR-1A in mice (Jerlhag, 2008; Quarta et al., 2009) and that a peripheral ghrelin injection induces a concomitant release of VTA-acetylcholine and NAc-dopamine (Jerlhag et al., 2012), indicating that ghrelin from the periphery may target reward related brain areas to activate the mesolimbic dopamine system and modulate motivated behaviors. In agreement are the imaging data demonstrating that systemic ghrelin enhances the response in reward-related areas such as NAc to visual food as shown healthy volunteers (Malik, McGlone, Bedrossian, & Dagher, 2008) as well as activates a neuronal network of VTA, NAc and lateral hypothalamus in rats (Wellman et al., 2012). Despite these initial studies, the ability of circulating ghrelin to have direct effects on areas of the mesolimbic dopamine system is debated. Indeed, studies have revealed that peripheral ghrelin administration might not reach deeper brain areas other than hypothalamus (Furness et al., 2011; Grouselle et al., 2008; Pirnik et al., 2011; Sakata et al., 2009; Schaeffer et al., 2013). It should therefore be considered that peripheral ghrelin may via indirect mechanisms originating in the hypothalamus, such as orexin containing neurons projecting to reward related areas, may contribute to the ability of systemic ghrelin to activate the mesolimbic dopamine system. In addition, the possibility that ghrelin produced centrally may influence reward-related behaviors should be evaluated.

2.2. Ghrelin and alcohol mediated behaviors in rodents

Evidence has revealed similarities in the mechanisms regulating the ability of ghrelin as well as alcohol to activate the mesolimbic dopamine system. Indeed, nAChR, of the α3β2, β3 and α6 subtypes, modulates the ability of either substance to cause a locomotor stimulation and to release dopamine in NAc shell in rodents (Jerlhag et al., 2008; Larsson, Jerlhag, Svensson, Soderpalm, & Engel, 2004; Larsson, Svensson, Soderpalm, & Engel, 2002; Lof et al., 2007; Steensland, Simms, Holgate, Richards, & Bartlett, 2007). It is therefore intriguing that both preclinical and clinical studies reviewed herein, demonstrate a close association between alcohol and ghrelin signaling.

The first study highlighting the alcohol-ghrelin link shows that genetic or pharmacological (JMV2959 or BIM28163) suppression of the GHSR-1A function prevents the ability of alcohol to activate the mesolimbic dopamine system as measured by locomotor stimulation, accumbal dopamine release and conditioned place preference (CPP) in mice (Jerlhag et al., 2009). This initial study was verified in two studies in ghrelin knockout mice displaying that these mice do not respond to alcohol by increasing accumbal dopamine release, condition a place preference or enhance locomotor activity (Bahi et al., 2013; Jerlhag, Landgren, Egecioglu, Dickson, & Engel, 2011). The findings that subchronic treatment with the GHSR-1A antagonist JMV2959 attenuates the alcohol-induced locomotor stimulation in mice (Suchankova, Engel, & Jerlhag, 2016), supports the emerging importance of GHSR-1A for alcohol-induced reward.

These initial studies proposing the involvement of ghrelin-signaling in alcohol reward processes outline the possibility of a role in various other alcohol-mediated behaviors. As expected, acute peripheral (JMV2959) or central (BIM28163) GHSR-1A antagonist treatment reduces alcohol intake not only in mice consuming alcohol for 12 weeks (Jerlhag et al., 2009), but also in high alcohol-consuming outbred and genetically-modified rats (Landgren et al., 2012). On the same note, peripheral administration of the GHSR-1A antagonists JMV2959 or [DLys3]-GHRP-6 (DLys) reduce alcohol intake in mice (Bahi et al., 2013; Gomez et al., 2015), rats (Gomez et al., 2015; Gomez & Ryabinin, 2014; Kaur & Ryabinin, 2010) and prairie voles (Stevenson et al., 2015) exposed to alcohol only for a shorter period of time. Interestingly, the ability of the GHSR-1A antagonist to reduce alcohol intake is more pronounced over time (Suchankova, Steensland, Fredriksson, Engel, & Jerlhag, 2013), implying that the sensitivity of the ghrelin system increases with enhanced duration of alcohol exposure.

AUD patients in withdrawal commonly relapse to enhanced alcohol intake partly due to cravings and this relapse is considered a contribution to the disease severity. In rats, this is studied with the alcohol deprivation model where rats are introduced to alcohol following a period of abstinence (Spanagel, 2000). It is therefore of clinical interest that acute GHSR-1A antagonist treatment (JMV2959) prevents relapse drinking in the alcohol deprivation model (Suchankova, Steensland, et al., 2013). It should however be mentioned that relapse is contributed by various factors including avoidance of withdrawal symptoms. However, the ability of GHSR-1A antagonists to reverse these behaviors have to date not been studied. Of further clinical interest is that repeated treatment with the GHSR-1A antagonist JMV2959 decreases alcohol consumption without inducing tolerance or rebound increase in alcohol intake after treatment termination (Suchankova, Steensland, et al., 2013). It should however be mentioned that in a paradigm where rats have been exposed to alcohol for a short period of time, the GHSR-1A antagonist [DLys3]-GHRP-6 (DLys) induces tolerance in its ability to reduce alcohol intake (Gomez & Ryabinin, 2014). Whether the discrepancy in tolerance outcome depends on the prior time of alcohol exposure or selectivity of the two GHSR-1A antagonists used is not known. In addition to relapse drinking, another important characteristic in the human AUD population is the motivation to consume alcohol. Of relevance are therefore the studies reporting a reduction in operant self-administration of alcohol following pharmacological suppression of the GHSR-1A by either JMV2959 or [DLys3]-GHRP-6 (DLys) (Gomez et al., 2015; Landgren et al., 2012). Collectively, these data show that GHSR-1A antagonism suppresses various alcohol-related drinking paradigms and that ghrelin signaling participates in AUD processes.

In addition to patients with AUD, GHSR-1A antagonists may be valuable pharmacological tools to decrease excessive alcohol drinking in obese patients following gastric bypass. In support for such a contention is the data reporting that GHSR-1A antagonism profoundly reduces alcohol intake in obese rats following either vertical sleeve gastrostomy or Roux-en-Y Gastric bypass (Hajnal et al., 2012; Orellana, Jamis, Horvath, & Hajnal, 2018). Moreover, the ability of ghrelin to set the tone of VTA-dopamine neurons is diminished in Roux-en-Y Gastric bypass rats consuming elevated levels of alcohol, indicating a possible ghrelin-dependent mechanism for the misuse of alcohol following this operation (Orellana et al., 2018). Albeit an intriguing line of research, this falls out of the scope of the present review and is addressed in detail elsewhere (Blackburn, Hajnal, & Leggio, 2017).

Albeit of less importance for AUD processes, acute alcohol injection in mice reduces the plasma levels of ghrelin (Yoshimoto et al., 2017). Of more relevance for AUD processes are the data demonstrating that ghrelin in the plasma is lower in high than low alcohol-consuming rats (Szulc et al., 2013). However, these data were not corroborated by another rat study (Landgren et al., 2012). However, as mentioned previously the role of circulating ghrelin for behaviors driven by the central nervous system, such as AUD, is debated as the passage into the brain might be limited (Furness et al., 2011; Grouselle et al., 2008; Pirnik et al., 2011; Sakata et al., 2009; Schaeffer et al., 2013). Supportively, peripheral ghrelin administration has no significant effect on alcohol intake in mice (Lyons, Lowery, Sparta, & Thiele, 2008) and neutralization of active acylated ghrelin in the periphery by NOX-B11-2 has no effect on either alcohol-induced reward or alcohol intake in rodents (Jerlhag, Ivanoff, Vater, & Engel, 2013). Taken together with the possibility that ghrelin might be produced centrally (Cowley et al., 2003; Lu et al., 2002; Mondal et al., 2005) a role of ghrelin proceed in the brain, rather in the periphery, for AUD processed should be considered.

Despite these initial intriguing studies showing a link between ghrelin and alcohol-mediated behaviors, the neurocircuits mediating these behavioral effects have only been partly elucidated. Involvement of the cholinergic-dopaminergic circuitry in the interaction between ghrelin and alcohol has been suggested, as local infusion of ghrelin into either the VTA or LDTg enhanced alcohol consumption in alcohol drinking mice (Jerlhag et al., 2009). In further support of a VTA ghrelin signaling in alcohol-mediated behaviors are the expression data demonstrating that the ventral tegmental mRNA GHSR-1A levels are lower in high- compared to low-alcohol consuming rats (Suchankova, Steensland, et al., 2013). Given that VTA projects to various areas in the brain, downstream targets of the VTA could also be potential targets modulating the link between ghrelin and alcohol-mediated behaviors. One such area might be the perioculomotor urocortin-containing neurons of the Edinger-Westphal nucleus. Indeed, this area contains high expression of GHSR-1A (Zigman et al., 2006) and the activity of this area is inhibited by tonic activity of dopamine neurons of the VTA (Ryabinin, Cocking, & Kaur, 2013). Indeed, the GHSR-1A antagonist [DLys3]-GHRP-6 (DLys) prevents the ability of peripheral injection of alcohol to increase c-Fos of the perioculomotor urocortin-containing neurons of the Edinger-Westphal nucleus (Kaur & Ryabinin, 2010). Another area of interest may be amygdala, known to express GHSR-1A (Cruz, Herman, Cote, Ryabinin, & Roberto, 2013; Landgren, Engel, et al., 2011), since it was recently revealed that ghrelin increases the inhibitory GABAergic transmission in this area in both naive and alcohol-dependent rats (Cruz et al., 2013; Yoshimoto et al., 2017). With regards to amygdala, ghrelin regulates other behaviors, including anxiety, via increased serotonergic signaling in mice (Hansson et al., 2014). Moreover, ghrelin influences memory formation via hippocampal GHSR-1A (Diano et al., 2006), suggesting its possible involvement in the habit formation of AUD. Another area of interest in the ghrelin-alcohol link is the lateral hypothalamus, since it has been shown that acute alcohol administration to rats exposed to alcohol, either long- or short-term, causes a robust increase in ghrelin accompanied by dopamine release in this area (Yoshimoto et al., 2017). Collectively, these data indicate that several possible networks may be of crucial importance in the ghrelin-AUD link rendering it an interesting target for further studies.

2.3. Ghrelin and addictive drugs in rodents

As ghrelin is an orexigenic peptide and that alcohol contains calories, the link between ghrelin and alcohol-mediated behaviors could also be tentatively explained by caloric influence rather than reward modulation. However, this appears less likely since ghrelin signaling modulates various behavioral responses of drugs of abuse without any caloric component such as cocaine, amphetamine, nicotine and morphine.

The first indirect support for the association between ghrelin and the behavioral responses to addictive drugs is provided by the findings that food restriction, which enhances circulating ghrelin (Gualillo et al., 2002), increases the intake of amphetamine as well as cocaine in rats (Carroll, France, & Meisch, 1979). Initial studies suggest a direct link between ghrelin and the behavioral response of addictive drugs since peripheral ghrelin administration strengthens the cocaine-induced locomotor sensitization (Wellman, Davis, & Nation, 2005) as well as CPP (Davis, Wellman, & Clifford, 2007). The data demonstrating a positive association between cocaine seeking behaviors and enhanced ghrelin levels in rats (Tessari et al., 2007) provides additional support. Further rodent studies reveal that pharmacological suppression of GHSR-1A by JMV2959 attenuates cocaine- as well as amphetamine-induced locomotor stimulation, accumbal dopamine release and CPP (Jerlhag, Egecioglu, Dickson, & Engel, 2010). Moreover, genetic or pharmacological (JMV2959) suppression of GHSR-1A decreases both the acute and the sensitization effect of cocaine on locomotor activity (Abizaid et al., 2011; Clifford et al., 2012). Additional evidence for a link between ghrelin signaling and behavioral responses induced by addictive drugs is provided by the fact that sub-chronic pre-treatment of a GHSR-1A antagonist JMV2959 attenuates the ability of acute administration of amphetamine to stimulate locomotor activity in mice, without changing the expression of the GHSR-1A gene in the VTA or the NAc (Suchankova, Engel, & Jerlhag, 2016). Only one study has to date examined the site of action for the overlap between ghrelin and psychostimulant drugs, where it was shown that local administration of ghrelin into the VTA potentiates cocaine-induced CPP in rats (Schuette et al., 2013).

Additional behavioral studies in rodents reveal that pharmacological suppression of the GHSR-1A by JMV2959 prevents the nicotine-induced locomotor sensitization (Wellman et al., 2011), as well as locomotor stimulation, dopamine release and CPP in rodents (Jerlhag & Engel, 2011). Moreover, ghrelin enhances nicotine-induced dopamine release in the striatum, and this potentiation possibly involves nAChR expressed on cholinergic interneurons in the NAc (Palotai et al., 2013a). When it comes to morphine, studies show that the GHSR-1A antagonist JMV2959 prevents the morphine induced locomotor stimulation, CPP and locomotor sensitization, as well as attenuates morphine's ability to increase endocannabinoids and dopamine in the NAc (Engel, Nylander, & Jerlhag, 2015; Jerabek et al., 2017; Sustkova-Fiserova, Jerabek, Havlickova, Kacer, & Krsiak, 2014; Sustkova-Fiserova, Jerabek, Havlickova, Syslova, & Kacer, 2016). It has also been demonstrated that JMV2959 decreases the consumption saccharine, which is considered a non-caloric rewarding substance (Landgren et al., 2011). When taken these data together it might be implied that ghrelin signaling modulates the ability of addictive drugs to activate the mesolimbic dopamine system in rodents.

2.4. Associations of ghrelin, alcohol and drugs of abuse in human genetic and clinical studies

Albeit this preclinical literature pinpoints the relevance of ghrelin signaling in the behavioral responses from various addictive drugs, clinical relevance was initially provided by human genetic studies as well as plasma-association studies.

Providing the heredity component underlying AUD, the human genetic findings revealing associations between ghrelin-related genes and alcohol/AUD are of great interest. Indeed, a single nucleotide polymorphism in the GHSR-1A gene is associated with high alcohol consumption in Spanish individuals (Landgren et al., 2008) and higher alcohol use disorder identification test scores as well as smoking in a Finnish population based cohort (Suchankova et al., 2016). A Swedish cohort with alcohol dependent females identifies association between haplotypes of either the preproghrelin or GHSR-1A gene and paternal alcohol dependence or type II alcohol dependence (Landgren et al., 2010). Furthermore, personality traits of decreased self-directedness and alterations in self-transcendence in patients with AUD were associated with polymorphisms of the ghrelin signaling system (Landgren et al., 2011). In a more recent study, preliminary findings of a case-control study show a trend of association between a single nucleotide polymorphism in the preproghrelin gene and AUD diagnosis (Suchankova et al., 2017). In addition, this genotype was associated with lower average drinks per days, fewer heavy drinking days as well as reduced subjective response to alcohol in the intravenous self-administration paradigm in AUD patients (Suchankova et al., 2017). Regarding other addictive drugs, two genetic studies have so far associated a link between ghrelin-related genes and drug use. Indeed, a single nucleotide polymorphism in the GHSR-1A gene is associated with smoking, as well as with amphetamine dependence (Landgren et al., 2010; Suchankova, Jerlhag et al., 2013). Albeit human genetic studies of this kind include various limitations, these data may collectively indicate that ghrelin-related genotypes contribute to the risk of developing addictions.

With regards to plasma-ghrelin studies, these provide data of altered plasma levels of ghrelin, total or active, in patients at different stages of AUD. Initial studies in healthy volunteers report that the plasma levels of ghrelin decreases following food ingestion (Tschop et al., 2001) as well as acute oral alcohol consumption (Calissendorff, Danielsson, Brismar, & Rojdmark, 2005, 2006; Zimmermann, Buchmann, Steffin, Dieterle, & Uhr, 2007). The possibility that this reduction in circulating ghrelin levels is due to the caloric content of alcohol should be considered. However, these data are is not associated with alcohol's ability to increase appetite (Calissendorff, Gustafsson, Holst, Brismar, & Rojdmark, 2012). More specifically, reduction of acylated ghrelin by acute oral alcohol consumption has also been confirmed in social drinkers (Ralevski et al., 2017). The possibility should be considered that alcohol acts directly in the stomach by preventing ghrelin secretion in social drinkers, since acute intravenous administration of alcohol has no effect on circulating ghrelin, but suppresses the fasting-induced ghrelin elevation (Leggio, Schwandt, Oot, Dias, & Ramchandani, 2013). However, these data may be of less relevance for AUD processes since they report only the effects on plasma levels of ghrelin following acute rather than chronic alcohol consumption.

In studies investigating the plasma levels of ghrelin in patients with AUD, the results depend on the stage of drinking as well as withdrawal. Indeed, active drinking in AUD patients decreases both circulating ghrelin levels and ghrelin production (Addolorato et al., 2006; Badaoui et al., 2008; Kraus et al., 2005). In social drinkers, elevated fasting plasma levels of ghrelin are associated with more intense and longer subjective effects of alcohol (Ralevski et al., 2017), indicating that the response to alcohol depends on circulating ghrelin. Several studies in abstaining alcoholics show that ghrelin levels are increased in both males (Kim et al., 2005; Kraus et al., 2005) and females (Wurst et al., 2007). In these abstained AUD patients, elevated ghrelin levels are positively associated with craving for alcohol (Addolorato et al., 2006; Wurst et al., 2007) and baseline ghrelin levels correlate with self-reported craving scores (Leggio et al., 2012). These studies investigate total ghrelin levels, but advances in analysis tools today allow investigations of ghrelin's active form. Indeed, active ghrelin levels are increased during early abstinence and are associated with craving scores for alcohol (Koopmann et al., 2012). In a study showing a direct relationship between fasting ghrelin and personality traits, social drinkers with elevated ghrelin levels are more sensitive to reward and more impulsive due to reduced self-control (Ralevski et al., 2018). This adds to the human genetic study mentioned above, showing associations between polymorphisms in the pre-pro-ghrelin gene, possibly causing lower ghrelin levels, decreased average number of drinks and lower response to alcohol (Suchankova et al., 2017). Collectively, this suggests that elevated ghrelin contributes to the pathophysiology of AUD, possibly via mechanisms involving a higher reward response and less self-control.

More recent published human laboratory studies provide more gain-in-knowledge compared to the previous studies measuring endogenous ghrelin. As shown by two reports from heavy-drinking patients with AUD, intravenous infusion of ghrelin, in high doses, potentiates alcohol craving (Leggio et al., 2014), increases the number of intravenous self-administration of alcohol and reduces the time to first alcohol drink (Farokhnia et al., 2018). In this bar setting, ghrelin infusion did not affect the urge to drink juice or crave food (Leggio et al., 2014) nor did the GHSR-1A inverse agonist, PF-5190457, alter the craving for food (Lee et al., 2018). Therefore it has been implied that elevated circulated ghrelin may have a selective effect on alcohol craving and alcohol consumption in humans with AUD. It has also been shown that intravenous administration of ghrelin, but not an inverse GHSR-1A agonist, reduced alcohol hangover after intravenous self-administration of alcohol (Farokhnia et al., 2018). Although the mechanisms of action still need to be explored and mapped in detail, one study has reported that in the presence of cues, intravenous administration of ghrelin increases alcohol-related signals in the amygdala in heavy drinking alcohol-dependent individuals (Farokhnia et al., 2018). This link between alcohol, cues and amygdala are in line with increasing but complex work on ghrelin/stress (for review see (Morris, Voon, & Leggio, 2018)). The first translational evidence of the clinical use of GHSR-1A-related compounds in patients with AUD is provided by data from heavy drinkers. In this single-blinded placebo controlled, within-subject study, a GHSR-1A inverse agonist reduced alcohol craving during a cue reactivity test (Lee et al., 2018). It should also be mentioned that this study primarily was designed to assess safety/tolerability and demonstrate that all adverse events were mild or moderate and did not require discontinuation or dose reductions (Lee et al., 2018).

Only one study has investigated the acute effects of intravenous cocaine administration on the plasma levels of ghrelin, displaying no effect on this gut-brain peptide (Bouhlal et al., 2017). Regarding smoking data show that smoking cessation reduces ghrelin levels in abstaining smokers (Lee et al., 2006). However, baseline ghrelin levels are higher in ad libitum smoking patients and this predicts subsequent increase risk to relapse (Al'Absi, Lemieux, & Nakajima, 2014). On the other hand, the data for the effects of nicotine on the plasma levels of ghrelin are inconclusive since i) smoking decreases total ghrelin in naïve, but not habitual smokers (Kokkinos et al., 2007) ii) smoking elevates plasma concentrations of acylated ghrelin, but not total ghrelin in smokers (Koopmann et al., 2015) and iii) controlled delivery of nicotine to habitual smokers does not change total ghrelin levels (Pilhatsch et al., 2014). There is to date only one study with acylated ghrelin, showing that these levels are higher in smokers than in non-smokers, and that lower ghrelin levels are correlated to the severity of nicotine dependence (Koopmann et al., 2015). A more recent study demonstrates that relapsing smokers, but not abstaining smokers or non-smokers, display a decline in ghrelin over the initial 48 h of abstinence (Lemieux & Al'Absi, 2018). However, this was not confirmed in a study that showed that there was no correlation between ghrelin and smoking abstinence (Mutschler et al., 2012). The possibility that ghrelin may be a predictor of relapse-behavior should be considered, however this claim needs to be investigated in more detail.

3. GLP-1

L-cells of the intestines have been shown to produce and secret GLP-1 (Novak, Wilks, Buell, & McEwen, 1987) in response to nutrient ingestion (Brubaker & Anini, 2003). Besides peripheral production, GLP-1 production has been identified in the nucleus tractus solitarius (NTS) neurons of the hindbrain (Alvarez, Roncero, Chowen, Thorens, & Blazquez, 1996). GLP-1 is an important regulator of feeding behaviors as central as well as peripheral administration of GLP-1 analogues such as Exendin4 (Ex4) reduces food intake (Hayes, Skibicka, & Grill, 2008; Langhans, 2000; Naslund, Schmidt, & Hellstrom, 2005; Tang-Christensen et al., 1996; Turton et al., 1996) as well as sucrose and high fat diet intake (Alhadeff, Rupprecht, & Hayes, 2012; Mietlicki-Baase et al., 2013; Wang et al., 2015). This intake reduction is accompanied by a decrease in body weight, which led to the approval of GLP-1 analogues for the treatment of obesity in humans (for review see e.g. (Srivastava & Apovian, 2018)). In addition to obesity, GLP-1 analogues have been approved for the treatment of type II diabetes as the incretin peptide GLP-1 (Kreymann, Williams, Ghatei, & Bloom, 1987) regulates glucose-dependent insulin secretion (Holst & Seino, 2009), gastric emptying and glucagon secretion (Gutniak, Orskov, Holst, Ahren, & Efendic, 1992; Matsuyama et al., 1988). GLP-1 receptors in areas of the hypothalamus as well as NTS were initially associated with the ability of GLP-1 to reduce food intake (Hayes et al., 2008; Hayes, Bradley, & Grill, 2009; Shughrue, Lane, & Merchenthaler, 1996).

3.1. Preclinical studies of GLP-1 and alcohol mediated behaviors

Despite the intriguing findings that GLP-1 receptors are expressed throughout the mesolimbic dopamine system (Merchenthaler, Lane, & Shughrue, 1999) and that GLP-1 containing neurons project directly to the VTA and NAc (Alhadeff et al., 2012), the importance of GLP-1 in animal models of alcohol dependence had not been explored until the first publication in 2012 (Egecioglu et al., 2013).

This study ascribes a role of GLP-1 as a modulator of alcohol-mediated behaviors, since it demonstrates that systemic administration of the GLP-1 receptor agonist Ex4 prevents alcohol-induced locomotor stimulation and release of dopamine in the NAc shell as well as attenuates both the rewarding properties of alcohol and the memory of alcohol reward in two separate CPP paradigms in mice (Egecioglu, Steensland, et al., 2013). The ability of Ex4 to antagonize the expression of alcohol-induced CPP and to reduce alcohol intake was corroborated by a follow-up study in 2013 (Shirazi, Dickson, & Skibicka, 2013). Besides this, stimulation of GLP-1 receptors by Ex4 was demonstrated to decrease various alcohol consummatory behaviors such as alcohol intake in the intermittent access two-bottle-choice model and alcohol seeking in the progressive ratio test in the operant self-administration model (Egecioglu, Steensland, et al., 2013). In support for a role of GLP-1 in relapse drinking are the mice data showing that Ex4 prevents the deprivation-induced increase in alcohol intake in socially housed mice (Thomsen et al., 2017). However, there are clinical limitations of Ex4, since in humans it needs to be administered twice daily due to its rapid degradation (Deacon, Johnsen, & Holst, 1995). Thus, other GLP-1 receptor agonists with longer half-life in plasma may provide a clinical advantage. One such candidate is liraglutide, which is administered once daily due to protracted and maintained biological activity (for review see (Holst, 2004)). Liraglutide has been shown to have advantageous effects on various alcohol-mediated behaviors, as shown by two preclinical studies of AUD. Indeed, acute systemic administration of a low dose of liraglutide blocks alcohol-induced accumbal dopamine release as well as reward in the CPP model, decreases alcohol consumption and prevents relapse drinking in the alcohol deprivation model in rodents (Vallof et al., 2016). In addition, liraglutide normalizes anxiety behaviors caused by alcohol abstinence (Sharma, Pise, Sharma, & Shukla, 2015b). Of clinical interest are also the findings that repeated administration of low liraglutide doses reduces alcohol consumption in outbred rats as well as decreases the motivation to obtain alcohol in the operant self-administration paradigm in rats selectively bred to be alcohol-preferring (Vallof et al., 2016).

Albeit these first publications demonstrate that GLP-1 analogues modulates the ability of alcohol to activate the mesolimbic dopamine system as well as reduces the overall consumption of alcohol, additional reports demonstrate that activation of GLP-1 receptors alters drinking patterns. Thus, the ability of Ex4 to decrease alcohol intake was attributed to the fact that this agonist protracted latency to the first drink as well as decreased the number of drinking bouts (Thomsen et al., 2017). In addition, yet another GLP-1 receptor agonist, AC3174, decreases the escalated drinking exhibited by alcohol dependent mice (Suchankova et al., 2015). Of further interest is the data showing that the effect of different GLP-1 receptor agonists persists after termination of the treatment. Indeed, the ability of AC3174 to reduce alcohol intake only returns to baseline drinking following the second washout cycle (Suchankova et al., 2015) and the ability of liraglutide to decrease operant self-administration of alcohol persist for three additional non-treatment days without returning to baseline of self-administration of alcohol (Vallof et al., 2016). Albeit additional studies are warranted, these two reports suggest that the effects of GLP-1 receptor activation may manifest after chronic treatment.

The results of two separate CPP tests investigating memory consolidation of alcohol reward (Sanchis-Segura & Spanagel, 2006) show that Ex4, but not liraglutide, treatment on the post-conditioning day prevents alcohol-induced CPP (Egecioglu, Steensland, et al., 2013; Vallof et al., 2016). These data provide an indication of a discrepancy in behavioral effects between different GLP-1 analogues, which possibly may be due to their different ability to penetrate and activate various brain areas. In support for such a contention are the data demonstrating that systemic administration of liraglutide accesses the hypothalamus and brainstem, whereas peripheral Ex4 injection has less direct effect on GLP-1 expressing neurons in the NTS, but rather activates regions of the brain corresponding to those innervated by GLP-1 afferents (Gu et al., 2013; Salinas et al., 2018). The lack of effect of liraglutide on the memory of alcohol-CPP may also be due to that liraglutide rather enhances than prevents, memory formation, synaptic plasticity and hippocampal neuroprotection in a mouse model of Alzheimer's disease (Holscher, 2014).

Albeit these studies provide evidence that stimulation of GLP-1 receptors prevents various alcohol-mediated behaviors, they do not investigate the role of circulating GLP-1 for AUD development. An first indication of a a link between endogenously released GLP-1 and alcohol-mediated behaviors are provided the findings demonstrating that blockade of GLP-1 receptors, following systemic or intra-VTA administration of exendin-9-39, results in an increased alcohol intake (Shirazi et al., 2013). On the same note, pharmacological suppression of dipeptidyl-peptidase IV, the enzyme responsible for degradation of endogenous GLP-1, attenuates anxiety induced by alcohol withdrawal (Sharma, Pise, Sharma, & Shukla, 2015a). Providing that anxiety during alcohol abstinence contributes to relapse of alcohol drinking (Roelofs, 1985; Samson & Harris, 1992), these data link higher circulating GLP-1 levels to a decreased risk of relapse drinking.

Due to the peripheral administration route in the aforementioned publications, the neurocircuits implied in the interaction between alcohol and GLP-1 cannot be evaluated. This gap in knowledge represents an opportunity to explore the role of central GLP-1 receptors for development of AUD. The findings that both Ex4 and liralgutide cross the blood brain barrier (Hunter & Holscher, 2012; Kastin & Akerstrom, 2003), along with the presence of GLP-1 signaling within the cholinergic-dopaminergic circuitry (Alhadeff et al., 2012; Alvarez et al., 1996; Merchenthaler et al., 1999), which is associated with AUD pathophysiology, contribute to the hypothesis that GLP-1 receptors in reward-related areas such as the NAc, VTA and LDTg may be involved. This is substantiated by the findings that Ex4 reduces alcohol intake in peripheral, but not central GLP-1 receptor knockout mice indicating that central but not peripheral GLP-1 receptors are essential for the consumption of alcohol (Sirohi, Schurdak, Seeley, Benoit, & Davis, 2016) and data showing that GLP-1 receptors in the NAc shell (Alhadeff et al., 2012) as well as posterior part of the VTA (Alhadeff et al., 2012; Mietlicki-Baase, Ortinski, et al., 2013; Wang et al., 2015) are attributed an important role in non-drug rewards. It should be mentioned that high doses of GLP-1 or Ex4 into the posterior VTA reduces alcohol intake in rats (Shirazi et al., 2013). However, since high doses of Ex4 may have unselective receptor effects (Barrera, D'Alessio, Drucker, Woods, & Seeley, 2009; Malendowicz et al., 2003; Sonne, Engstrom, & Treiman, 2008) as well as effects on gross behaviors (Egecioglu, Steensland, et al., 2013) this initial study should be replicated with lower Ex4 doses.

Albeit the existing literature indicates that GLP-1 receptor activation reduced various alcohol-mediated behaviors via attenuated alcohol reinforcement, other tentative explanations should be considered to drive this effect. One of these should be malaise and nausea since both human and rodent studies report these aversive effects following treatment with various GLP-1 analogues. Indeed, Ex4 induces a condition taste aversion at a similar dose range as used in the present studies (Kanoski, Rupprecht, Fortin, De Jonghe, & Hayes, 2012). However, neither a low dose of Ex4 nor liraglutide have in these alcohol-related publications an effect on water intake nor on conditioned taste aversion, which has been suggested to correlate to conditioned taste aversion (Cagniard & Murphy, 2012). Moreover, in rodents' only higher doses of liralgutide than used in the alcohol studies induces aversion (Kanoski et al., 2012). Moreover, GLP-1 receptors in areas of importance for reward such as the VTA and NAc are not involved in a taste aversion in rats (Alhadeff et al., 2012; Dickson et al., 2012).

3.2. GLP-1 and addictive drugs in rodents

Providing that other drugs of abuse than alcohol activate the mesolimbic dopamine system (Dichiara & Imperato, 1988; Engel & Jerlhag, 2014) the possibility that GLP-1 signaling regulates the ability of other addictive drugs to stimulate this circuitry should be considered. This was initially verified in a publication demonstrating that a high dose of Ex4, that affects baseline locomotor activity but not anxiety, attenuates amphetamine-induced locomotor stimulation in mice (Erreger et al., 2012). In agreement are the mice data showing that high doses of Ex4 prevent cocaine-induced reward in the CPP model (Graham, Erreger, Galli, & Stanwood, 2013). These studies were corroborated and extended by additional rodent studies, showing that activation of GLP-1 receptors by low doses of Ex4 i) attenuates the ability of amphetamine and cocaine to cause a locomotor stimulation, to release accumbal dopamine and to express a CPP (Egecioglu, Engel, & Jerlhag, 2013b; Sorensen et al., 2015), ii) decreases cocaine self-administration (Sorensen et al., 2015) as well as iii) suppresses the ability of intravenous cocaine administration to increase phasic dopamine release in NAc core, but not shell (Fortin & Roitman, 2017). Moreover, systemic fluoro-Ex4 administration, at a subthreshold dose for producing malaise, reduces the number of active lever presses for cocaine (Hernandez, O'Donovan, Ortinski, & Schmidt, 2017) as well as attenuates the cocaine priming induced reinstatement of drug-seeking (Hernandez et al., 2018).

Attempts have been made to define the neurochemical mechanisms and brain areas modulating the effects of GLP-1 analogues on drug reinforcement. An initial study shows, by using central GLP-1 knockout mice treated with Ex4 systemically, that central rather than peripheral GLP-1 receptors are essential for the amphetamine-induced CPP (Sirohi et al., 2016). On the contrary, the same study defines that both central and peripheral GLP-1 receptors are crucial for the anorexigenic properties of GLP-1 (Sirohi et al., 2016). This indicates that there are differences in mechanism through which GLP-1 modulates food intake and drug mediated behaviors. The first study converging on the specific GLP-1 dependent neuroanatomical target that ultimately decreases cocaine-related behaviors identified NAc as an important area. Indeed, systemic treatment with Ex4 attenuates the ability of cocaine to increase the expression of *c-Fos*, which is an indicator of neuronal activation, in striatum (Sorensen et al., 2015). A functional role of GLP-1 receptors in NAc in drug related behaviors were later verified in experiments demonstrating that systemic administration of fluro-Ex4 penetrates the brain and localizes with neurons as well as astrocytes in the NAc and that Ex4 increases the action potential in NAc in cocaine exposed rats (Hernandez et al., 2017). The findings that local infusion of Ex4 into the NAc reduces cocaine self-administration (Hernandez et al., 2017), provides additional support for a NAc-GLP-1 link. Contrarily, Ex4 into NAc does not alter the consumption of either sucrose (Alhadeff et al., 2012; Hernandez et al., 2017) or chow (Alhadeff et al., 2012; Dossat, Lilly, Kay, & Williams, 2011), indicating that accumbal GLP-1 receptors modulate cocaine, but not sucrose, self-administration. In addition to NAc, the posterior part of the VTA has been suggested as an important brain area for the ability of GLP-1 to modulate cocaine related behaviors. Local infusion of Ex4 into the posterior VTA dose-dependently reduces both the number of lever presses for cocaine as well as the breakpoint for cocaine (Schmidt et al., 2016) and attenuates the cocaine priming induced reinstatement of cocaine seeking in rats (Hernandez et al., 2018) in the operant self-administration model. A role of posterior VTA is further substantiated by that findings that AAV-shRNA, which selectively provides a VTA-GLP-1 receptor knockout model, increases the breakpoint for cocaine as well as enhances the number of cocaine infusions in the progressive ratio test in rats (Schmidt et al., 2016). Additional support is provided by the data demonstrating that blockade of GLP-1 receptors in the VTA by exendin-9-39 prevents the ability of systemic fluoro-Ex4 to attenuate cocaine-seeking (Hernandez et al., 2018). As for NAc, GLP-1 signaling in the posterior VTA does not affect sucrose self-administration (Schmidt et al., 2016), On the contrary, GLP-1 receptors in the posterior part of the VTA have also been ascribed a modulatory role of non-drug behaviors including chow and high fat diet consumption as well as body weight regulation (Alhadeff et al., 2012; Mietlicki-Baase, Ortinski, et al., 2013; Wang et al., 2015). GLP-1 receptors outside of, but highly interconnected with, the mesolimbic dopamine system may be linked to drug reinforcement. Indeed, activation of GLP-1 receptors in the NTS, known to project to the NAc, VTA and LDTg, reduces cocaine self-administration (Schmidt et al., 2016). A role of GLP-1 receptors for cocaine related behaviors are substantiated by the recent data showing that cocaine self-administration reduced the expression of preproglucagon (known to contain GLP-1) mRNA in the NTS (Hernandez et al., 2018). Moreover, genetic ablation of GLP-1 receptors in the lateral septum causes a suppression of cocaine-induced locomotor stimulation and CPP, due to an increased excitability of GLP-1 containing neurons in lateral septum (Harasta et al., 2015). Albeit indirect support GLP-1 receptors in this area are the data demonstrating that systemic Ex4 attenuated dopamine release in the lateral septum which follows acute administration of cocaine (Reddy et al., 2016). The ex vivo findings that acute GLP-1 receptor activation selectively decreases the levels of arachidonic acid and enhances the expression of the dopamine transporter in the lateral septum provide tentative neurochemical mechanisms that might to some extent contribute to the regulation of behaviors induced by acute cocaine (Reddy et al., 2016). In conclusion these data indicate that different subpopulations of GLP-1 receptors modulate various behaviors.

In addition to the psychostimulant drugs described above a few studies have shown that GLP-1 signaling regulates the ability of nicotine to activate the mesolimbic dopamine system. Indeed, systemic administration of Ex4 prevents the nicotine induced locomotor stimulation, release of NAc-dopamine and memory consolidation of nicotine reward in the CPP paradigm, as well as attenuates the nicotine-induced expression of locomotor sensitization in mice (Egecioglu, Engel, & Jerlhag, 2013a). In further support of GLP-1 modulation of nicotine related behaviors are the data showing that pharmacological activation of GLP-1 receptors (Ex4) as well as inhibition of GLP-1 degradation (dipeptidyl-peptidase IV inhibitor, sitagliptin) reduces the intake of nicotine in mice (Tuesta et al., 2017). Conversely, this study also report genetic suppression of the GLP-1 receptors increases the infusion of nicotine compared to wild type mice (Tuesta et al., 2017). The findings that activation of GLP-1 receptors within the medial habenular - interpeduncular nucleus circuitry abolishes nicotine reward as well as enhances nicotine avoidance (Tuesta et al., 2017) supports the clinical interest of GLP-1 receptor agonists for treatment of nicotine dependence since nicotine use in humans is regulated by the rewarding response to nicotine as well as avoidance of nicotine aversion (for review see (Fowler & Kenny, 2014)). Albeit activation of GLP-1 receptors of the medial habenular - interpeduncular nucleus pathway reduces the intake of nicotine as well as promotes nicotine avoidance, it's today unknown weather this circuitry modulates reward from other addictive drugs such as alcohol.

3.3. GLP-1, alcohol and addictive drugs in human studies

To date, there is a limited number of studies addressing the link between GLP-1 and the use of alcohol or addictive drugs in humans. In a small, preliminary report from 2011 it was demonstrated that the GLP-1 receptor agonist, liraglutide, decreases the consumption of alcohol in individuals with diabetes mellitus type 2 (Kalra, 2011). A human genetic study thereafter reveals association between polymorphisms in the GLP-1 receptor gene and alcohol dependence, and this correlation is evident in both Caucasians and Afro Americans (Suchankova et al., 2015). Subsequent analysis of an additional independent cohort also demonstrates this association, providing a replication of the initial findings (Suchankova et al., 2015). An additional experiment, examining intravenous-self administration of alcohol in social drinkers, displays that a GLP-1 receptor genotype is associated with enhanced intravenous infusion of alcohol and increased measurement of breath alcohol (Suchankova et al., 2015). Finally, notification of outcome for high monetary reward in individuals with the GLP-1 receptor genotype causes a higher BOLD response in the right globus pallidus (Suchankova et al., 2015). The third human study providing a link between GLP-1 and drug-related behaviors, firstly shows that intravenous cocaine infusion causes a significant reduction in plasma levels of GLP-1 (Bouhlal et al., 2017) and secondly that the GLP-1 levels are associated with the subjective experience in cocaine namely increased heart rate, enhanced feeling of high and elevated respiratory rate (Bouhlal et al., 2017).

4. Other appetite regulatory peptides

In addition to the gut-brain peptides ghrelin and GLP-1, other appetite regulatory substances namely amylin and NMU have been attributed a modulatory role for alcohol/drug related behaviors in rodents.

4.1. Amylin and alcohol mediated behaviors

Pancreatic β-cells co-secrete amylin with insulin and the physiological role of this 37 amino acid peptide includes insulin secretion reduction, decrease of gastric emptying as well glucagon secretion (Hay, Chen, Lutz, Parkes, & Roth, 2015; Westermark, Andersson, & Westermark, 2011). However growing evidence imply that amylin is expressed in the brain. For instance in situ hybridization studies in lactating rats demonstrate the expression of amylin mRNA in the medial preoptic nucleus, the medial preoptic area, and the central part of the bed nucleus of the stria terminalis (Dobolyi, 2009). Moreover, in mice the islet amyloid polypeptide (precursor to amylin) is expressed in neurons in the lateral hypothalamus, arcuate nucleus, medial preoptic area, area postrema, and nucleus tractus solitarius (Li, Kelly, Heiman, Greengard, & Friedman, 2015). It should therefore be considered that amylin produced and released in the brain, may have physiological roles which are independent of amylin released peripherally. Amylin as well as salmon calcitonin (sCT), an amylin analogue and amylin receptor agonist, have also been attributed anorexigenic properties since they reduce food intake as well as induce satiation (Lutz, 2010; Lutz et al., 1998; Lutz, Geary, Szabady, Del Prete, & Scharrer, 1995; Lutz & Meyer, 2015; Lutz, Tschudy, Rushing, & Scharrer, 2000; Mack et al., 2007; Reidelberger et al., 2004). These anorexigenic effects have been suggested to involve amylin signaling in areas such as the area postrema and NTS (Braegger, Asarian, Dahl, Lutz, & Boyle, 2014; Lutz et al., 1998; Mollet, Gilg, Riediger, & Lutz, 2004; Potes & Lutz, 2010). Of interest for reward and addiction processes are the recent studies demonstrating that amylin receptors are present in the NAc, VTA and LDTg (Baisley & Baldo, 2014; Mietlicki-Baase et al., 2013; Mietlicki-Baase et al., 2015; Reiner et al., 2017) and that amylin signaling in these areas contributes to its anorexigenic properties (Mietlicki-Baase et al., 2015; Mietlicki-Baase, Rupprecht, et al., 2013). The first link between amylin and reward related behaviors is provided by a recent study showing that sCT attenuates the ability of alcohol to activate the mesolimbic dopamine system as measured by locomotor stimulation and accumbal dopamine release as well as reduces alcohol intake in high alcohol consuming rats (Kalafateli, Vallof, & Jerlhag, 2018). In addition, this amylin receptor agonist prevents alcohol-induced CPP, after both a single and a repeated alcohol injection of the sCT (Kalafateli et al., 2018), indicating that amylin regulates both expression of reward-associated as well as memory-dependent CPP in mice. On an interesting note are the findings that alcohol-preferring compared to non alcohol-preferring rats display lower levels of the calcitonin-gene related peptide in the hippocampus and frontal cortex (Ehlers et al., 1999) and that some forebrain regions of high alcohol-drinking rats have fewer calcitonin-gene related peptide receptor-binding sites (Hwang, Kunkler, Lumeng, & Li, 1995). A role of amylin singling in drug related behaviors are provided by a study demonstrating that sCT blocks amphetamine-induced locomotor stimulation in rats (Twery, Kirkpatrick, Lewis, Mailman, & Cooper, 1986).

The rodent findings that sCT neither have an effect on the blood alcohol concentrations, the levels of corticosterone in plasma or the intake of peanut butter (Kalafateli et al., 2018), indicate that the ability of sCT to attenuate alcohol-mediated behaviors is independent of changes in metabolism, stress responses and calories respectively. Furthermore, nausea or aversion is less likely to explain the effects of sCT on alcohol intake since neither sCT into the VTA (Mietlicki-Baase, Rupprecht, et al., 2013) nor intraperitoneal injection of amylin (Mack et al., 2007) influences kaolin intake.

Albeit this initial report did not provide any downstream mechanisms for the alcohol-amylin link, the study reporting that peripherally administered sCT decreases VTA-evoked phasic dopamine release in the NAc (Whiting, McCutcheon, Boyle, Roitman, & Lutz, 2017), provides a tentative VTA-dependent mechanism. The link between amylin-VTA and reward is further supported by the findings that local infusion of sCT into the VTA reduces intake of fat, sucrose as well as a non-nutritive sweetener (Mietlicki-Baase et al., 2017). Further evidence for a tentative VTA-dependent mechanism are the findings that amylin receptor activation in the VTA attenuates food-evoked phasic dopamine release in the NAc (Mietlicki-Baase et al., 2015).

Only one human study provides support for a correlation between amylin and addiction processes so far. This study demonstrates that intravenous cocaine infusion causes a tendency in amylin levels reduction in the plasma and offers association between plasma amylin and the subjective response to cocaine such as heart rate and anxiousness (Bouhlal et al., 2017).

4.2. NMU and addiction

The highly conserved neuropeptide NMU modulates a myriad of different functions, where most reports reflect its ability to reduce food intake as well as appetite (for review see (Hanada et al., 2004; Martinez & O'Driscoll, 2015)). Studies aiming at identifying the neurocircuits underlying these anorexigenic properties have revealed that NMU receptor 2 (NMUR2) located in the arcuate nucleus, paraventricular nucleus and dorsal raphe nucleus are essential for the food intake reduction by NMU (Howard et al., 2000; Ida et al., 2005; McCue, Kasper, & Hommel, 2017). The findings that NMUR2 are expressed in the VTA and presynaptically on GABAergic neurons in the NAc (Gartlon et al., 2004; Kasper et al., 2016; Maderdrut, Lazar, Kozicz, & Merchenthaler, 1996; McCue et al., 2017) and that the highest levels of NMU are displayed in the NAc (Domin, Ghatei, Chohan, & Bloom, 1987) collectively imply that NMU may participate in reward and addiction processes.

This is substantiated by a study showing that central infusion of NMU, at doses with no effect per se on reward-related parameters or gross behavior, attenuates the ability of alcohol to enhance locomotor activity, cause accumbal dopamine release and induce an expression of CPP in mice (Vallof, Ulenius, Egecioglu, Engel, & Jerlhag, 2016). Moreover, NMU into the third ventricle significantly reduces alcohol intake in high, but not low, alcohol-consuming rats in the intermittent access model (Vallof, Ulenius, et al., 2016). A role of NMU in AUD processes may be implied since the latter drinking paradigm is known to induce voluntary intake of high amounts of alcohol, as well as pharmacologically relevant blood alcohol concentrations (Simms et al., 2008). The possibility that NMU alters metabolism of alcohol appears less likely, since NMU administration did not alter blood alcohol concentrations in mice or in rats (Vallof, Ulenius, et al., 2016). The possibility that NMU contributes to the AUD pathophysiology is substantiated by findings from a genome-wide allelic association study demonstrating associations in polymorphisms in the *NMUR2* gene and AUD in humans (Lydall et al., 2011). In further support for an NMU-reward link is a preclinical study reporting that central infusion of NMU into the third ventricle prevents amphetamine-induced locomotor stimulation, accumbal dopamine release and expression of CPP (Vallof, Vestlund, Engel, & Jerlhag, 2016). Supportively, mice studies demonstrate that repeated NMU injections throughout the cocaine sensitization regimen, prevents cocaine-evoked hyperactivity and that knockdown of presynaptic *NMUR2* in NAc shell potentiates cocaine sensitization (Kasper et al., 2016). Albeit indirect, the findings that centrally administered NMU reduced the chocolate/coconut milk intake (Egecioglu et al., 2009) and that paraventricular *NMUR2* knockdown increased binge-eating behavior as well as preference for palatable high fat diet (Benzon et al., 2014), provide support for NMU's role in reward related processes. An area of interest for these behavioral effects may be NAc since local and bilateral NMU administration into the NAc attenuates amphetamine-induced locomotor stimulation (Vallof, Vestlund, et al., 2016).

5. General remarks

Given that the outcomes of available AUD medications vary (Heilig & Egli, 2006) and that the number of pharmacotherapies for addiction to other drugs is limited, new treatment strategies for addiction are warranted. In the present review the effects of ghrelin, GLP-1, amylin and NMU in relation to the mesolimbic dopamine system have been overviewed. The rational for this lies in the fact that rodent as well as human studies show that acute alcohol injection or consumption elevates dopamine in the NAc/ventral striatum and that dopamine in this area is involved in addiction processes (Blomqvist, Engel, Nissbrandt, & Soderpalm, 1993; Blomqvist, Ericson, Engel, & Soderpalm, 1997; Boileau et al., 2003; Di Chiara & Imperato, 1986; Doyon et al., 2003; Engel et al., 1988; Ericson, Blomqvist, Engel, & Soderpalm, 1998; Ericson, Molander, Lof, Engel, & Soderpalm, 2003; Imperato & Di Chiara, 1986; Jerlhag et al., 2009; Jerlhag, Grotli, Luthman, Svensson, & Engel, 2006; Larsson et al., 2002; Larsson et al., 2004; Larsson et al., 2005; Urban et al., 2010; Weiss et al., 1993). One way to identify novel treatment targets is to investigate the neurochemical substrates involved in reward and addiction processes by the preclinical methods described above (Edwards, Kenna, Swift, & Leggio, 2011). For instance, previous preclinical and clinical work shows that the partial nicotinic acetylcholine receptor agonist, varenicline, has beneficial effects on alcohol intake in both animal models and AUD patients (Ericson, Lof, Stomberg, & Soderpalm, 2009; Walther et al., 2015). It may therefore be implicated that GHSR-1A antagonists and/or agonists for the GLP-1, amylin or NMU receptors may consist novel targets for treatment of addiction disorders, such as AUD. It should however be emphasized that reward and addiction are not limited to the mesolimbic dopamine system, but rather involve various neurotransmitters and brain areas such as endogenous opioids (Engel et al., 1988; Ericson, Chau, Clarke, Adermark, & Soderpalm, 2011; Gilpin & Koob, 2008; Jarjour, Bai, & Gianoulakis, 2009; Koob, 2014; Koob & Volkow, 2016; Little, 1999; Pecina, 2008; Serecigni, 2015; Volkow, Wise, & Baler, 2017). However, the effects of these appetite regulatory peptides on behaviors related to these have yet not been studied.

6. Future directives and conclusions

Albeit the existing literature reviewed herein, collectively indicate that gut-brain peptides modulate reward related behaviors additional studies are warranted.

Initially, additional studies should further identify the brain areas that crucial for the link between these peptides and alcohol/drug related behaviors. When it comes to ghrelin, various studies have shown that the VTA, LDTg as well as Edinger-Westphal nucleus are important for ghrelin-related reward processes. However, other areas not yet studied may be of interest for ghrelin-mediated modulation of reward. One candidate in this regard is NAc since the expression of GHSR-1A in NAc has been identified (Landgren, Engel, et al., 2011) and ghrelin into NAc increases the intake of palatable food (Prieto-Garcia, Egecioglu, Studer, Westberg, & Jerlhag, 2015). Another area of is amygdala, as central ghrelin infusion causes release of dopamine in amygdala (Palotai et al., 2013b). The number of publications identifying the neurocircuits linking GLP-1 signaling to alcohol/drug reinforcement is limited. Initial studies should evaluate the effect of local administration of Ex4 into the VTA, NAc or LDTg on alcohol related behaviors since these areas have established roles in reward processes (Jerlhag & Engel, 2014; Larsson & Engel, 2004; Soderpalm & Ericson, 2013) and as GLP-1 signaling in these modulate cocaine reinforcement (Hernandez et al., 2017; Hernandez et al., 2018; Schmidt et al., 2016). In addition, the role of GLP-1 receptors in the NTS and lateral septum in AUD processes should be evaluated since they modulate cocaine related behaviors (Reddy et al., 2016; Schmidt et al., 2016,Hernandez, 2018 #6215,Harasta, 2015 #5940). Given that systemic administration of different GLP-1 receptor agonists, such as Ex4 and liraglutide, may activate different GLP-1 receptor populations in the brain (Gu et al., 2013; Salinas et al., 2018), additional studies are warranted where the behavioral response to various GLP-1 receptor agonists should be studied in more detail in upcoming investigations. As VTA, NAc and LDTg participate in food intake reduction induced by amylin (Baisley & Baldo, 2014; Mietlicki-Baase et al., 2015; Mietlicki-Baase, Rupprecht, et al., 2013; Reiner et al., 2017) and that accumbal NMUR2 modulates the amphetamine induced locomotor stimulation in mice (Vallof, Vestlund, et al., 2016), the role of amylin and NMU signaling in these aforementioned areas in regards to and alcohol-mediated behaviors should be evaluated. Albeit these gut-brain peptides mainly are produced and secreted in peripheral organs, studies have demonstrated that they may be produced centrally. Therefore the role of central versus peripheral production for reward related behaviors remains to be investigated.

One other research area that remains to be investigated is the underlying neurochemical substrates modulating the behavioral responses of these appetite regulatory peptides. Endogenous opioids may be of interest since the GHSR-1A antagonist JMV2959 increases the tissue levels of Met-enkephalin-Arg^{6}Phe^7 in VTA, dynorphin B in hippocampus and Leu-enkephalin-Arg^6 in striatum (Engel et al., 2015) and that two available treatments of AUD acts through this system. However, the effects of GLP-1, amylin and NMU administration on other neurotransmitter systems related to addiction should also be explored.

Albeit the clinical use of these gut-brain peptides for addictive disorders should be considered, several additional parameters has to be assessed before trying these in the clinical situation. First of all, the long-term treatment effects on the intake and self-administration of alcohol and drugs of abuse needs to be evaluated. Studies have also reported that the outcome of GLP-1 receptors stimulation on food intake varies in male and female rats (Lopez-Ferreras et al., 2018). Therefore, the possibility that treatment effects vary with gender should be evaluated. Given that these agents have beneficial effects on alcohol/addictive drugs as well as on food intake/body weight, the possibility that these agents have beneficial effect in a subset of addictive individuals, i.e. those with obesity or binge eating disorder, should be evaluated. It should also be reflected upon that the clinical used of these gut-brain peptides may come with unwanted side effects. For instance nausea, malaise, and vomiting has been reported from the use of clinically available GLP-1 analogues. Since a lower dose of these gut-brain peptides may produce less aversive effects studies should be set-up where the effect of combinations of GHSR-1A antagonists, GLP-1 receptor agonists, amylin and/or NMU analogues on reinforcement are tested. Combinational drug development should also be considered with regard to available AUD medications. For instance Ex4 together with naltrexone have additive feeding inhibitory effects (Liang, Bello, & Moran, 2013). Down the road, randomized clinical trials investigating the effects of the aforementioned or similar agents on alcohol/drug intake in patients with

AUD/drug dependence has to be conducted. Only then a final conclusion on the hypothesis that these gut-brain peptides could be used to treat addictive disorder can be made.

Conflict of interest statement

EJ has received financial support from the Novo Nordisk Foundation for another project. This does not alter the authors' adherence to any of the journal's policies on sharing data and materials.

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