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Research Article

THE ROLE OF GLP-1 RECEPTOR AGONIST IN MODULATING ALCOHOL INTAKE: INSIDES FROM SEMAGLUTIDE THERAPY

Dr. Mekala Anusha^{1*}, Padakantinaga Harshitha², Banda jashwanth³, Vaddera Prashanthi⁴

¹Assistant professor, department of pharmacy practice, Maisammaguda, Dhulapally, Secunderabad, 500100

²Pharm-D 4th year malla reddy college of pharmacy, Maisammaguda, Dhulapally, Secundrabad, 500100

³Pharm-D 4th year malla reddy college of pharmacy, Maisammaguda, Dhulapally, Secundrabad, 500100

⁴Pharm-D 4th year malla reddy college of pharmacy, Maisammaguda, Dhulapally, Secundrabad, 500100

* Author for Correspondence: Dr. Mekala Anusha

Email: Anushayadav@gmail.com

	Abstract
Published on: 29 Oct 2025	Recently, there has been evidence that semaglutide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for type 2 diabetes and obesity, may help lower alcohol intake and cravings. Modification of several neurobiological systems that control reward, motivation, and stress reactions is the pharmacological basis for this effect. By inhibiting mesolimbic dopamine signalling, central GLP-1 receptor activation, specifically in the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex, amygdala, and hypothalamus, reduces the reinforcing effects of alcohol. Additionally, semaglutide increases satiety and decreases the motivational salience of alcohol cues by activating the gut–brain axis through vagal afferents. GLP-1R stimulation may also lessen neuroinflammatory processes linked to long-term alcohol exposure and restore normalcy to the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Semaglutide and related GLP-1R agonists may be promising pharmacotherapeutic candidates for alcohol use disorder (AUD) because these mechanisms work together to suppress alcohol reward, craving, and stress-induced relapse.
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Keywords: Glucagon-like peptide-1 receptor agonist (GLP-1RA), Ventral tegmental area (VTA), Nucleus Accumbens (NAc), Alcohol Use Disorder (AUD), Stress-Induced Relapse, Hypothalamic-Pituitary-Adrenal (HPA).	

1. INTRODUCTION

GLP-1:

Proglucagon is broken down by enzymes to produce the peptide hormone GLP-1. This substance is produced by neurons in the solitary tract nucleus, α -cells in the pancreatic islet, and L-cells in the intestinal mucosa. Enteroendocrine L-cells in the colon, ileum, and distal jejunum release the endocrine hormone GLP-1 in response to neuroendocrine stimulation and dietary intake. It starts with the pre-proglucagon precursor, which is then processed by enzymes in intestinal L-cells to produce derivatives of GLP-1(1-37) and GLP-1(7-36) amide or GLP-1(7-37) peptide. The incretin hormone GLP-1 is essential for the careful regulation of blood glucose levels in humans. However, under normal physiological conditions, its duration of action is rather brief, lasting only one to two minutes within the circulatory system. The biological efficacy of GLP-1 is then lost as a result of enzymatic degradation that is aided by dipeptidyl peptidase IV (DPP-4).

Brain GLP-1 synthesis:

Pre-proglucagon expression is present in the brainstem and solitary tract nucleus (NTS). Similar to L-cell processing, post-translational processing of proglucagon results in GLP-1 with approximately equimolecular levels of glicentin and oxyntomodulin. Neuronal cell bodies in the brainstem's caudal region of the NTS synthesize GLP-1 (7-36)-amide. Within the fourth ventricle, the caudal region is bounded by a nucleus. The area postrema (AP) and the dorsal motor nucleus of the vagus (DMNX) are components of the dorsal vagal complex (DVC), which is where the NTS is situated. The vagal nerves that innervate the gastro-duodenal tract provide visceral sensory inputs to this complex. Pre-proglucagon-expressing cells are not restricted to a group of neurons in the caudal region of the NTS. Additionally, it is present in a few neurons that branch off laterally from the NTS and enter the medulla's A1 area via the dorsal reticular area.

Brain GLP-1 receptors:

Human and rat brain GLP-1 receptor cDNA has been cloned and sequenced. The amino acid sequences inferred are identical to those in the islets of the pancreas. More specifically, both receptors exhibit 90% amino acid sequence homology and have a length of 463 amino acids [44–46]. The receptor is one of seven transmembrane-spanning G-protein-coupled receptors that make up the class B family. This receptor is connected to the activation of protein kinase A (PKA) and the adenylate cyclase system. Nevertheless, it has been demonstrated that the receptor can also trigger the pancreatic β -cells' phospholipase C pathway, which results in the stimulation of protein kinases C (PKC). Labelled cells have been found throughout the entire brain in both humans and rodents through in situ hybridization with GLP-1 receptor mRNA and binding studies using radiolabelled GLP-1. These investigations have also revealed that the brainstem and hypothalamus contain a large number of neurons that express the GLP-1 receptor. These two regions of the brain are involved in autonomous functions and the central regulation of energy homeostasis. The arcuate nucleus, paraventricular nucleus, dorsomedial nucleus, and supraoptic nucleus are the main locations of the receptor in the hypothalamus. It is also present in the DVC, particularly in the postrema area and the NTS. Additionally, the circumventricular organs, including the postrema and sub-fornical organ, contain GLP-1 binding sites. Both peripheral GLP-1 of intestinal origin and GLP-1 produced in the nervous system may target these final two sites.

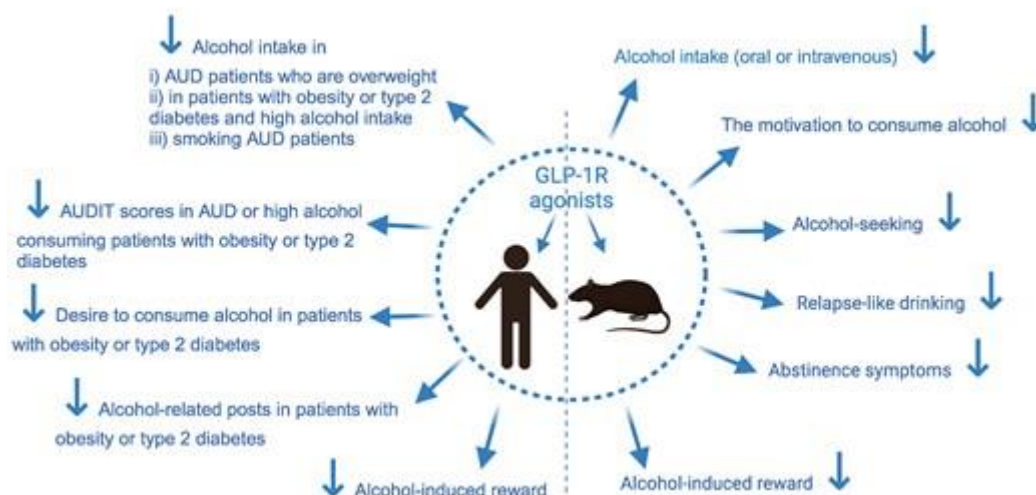


FIG-1

Diagrammatic representation of preclinical and clinical research. An overview of the effects of GLP-1 receptor (GLP-1R) agonists on alcohol-related reactions in humans (left) and animals (right). Alcohol Use Disorders Identification Test (AUDIT); AUD, alcohol use disorder; decline.

GLP-1R:

More recent clinical research has shown an impact on alcohol consumption in humans, even though these preclinical studies have identified that GLP-1R activation regulates several elements of the AUD cycle. In a small, early pilot study, patients with type 2 diabetes who self-reported consuming less alcohol following liraglutide treatment showed the first association between GLP-1R and alcohol. A human genetic study offered additional support, showing that single nucleotide polymorphisms (SNPs) of the GLP-1R genes were linked to the diagnosis of AUD in two distinct population cohorts of AUD patients who were of normal weight. Additionally, SNPs of the GLP-1R genes were found to positively correlate with intravenous self-administration of alcohol and breath alcohol concentrations in individuals who consume alcohol. Given that polymorphisms of the GLP-1R gene were linked to Alcohol Use Disorders Identification Test (AUDIT) scores, others subsequently confirmed these human genetic findings in a population of regular-weight people with low- and high-risk alcohol consumption. Since GLP-1R expression in the hippocampus was higher in AUD patients than in controls, this region of the brain was one of interest for the relationship between GLP-1R and alcohol. Additionally, SNPs in the GLP-1R genes were linked to the right globus pallidus blood oxygen level-dependent response to monetary reward in alcohol-consuming individuals. Daily injections of exenatide reduced alcohol intake in overweight patients with AUD, an effect not seen in people of normal weight, according to a randomized clinical trial, which offered more proof of the relationship between GLP-1 and alcohol. Similarly, a randomized clinical trial evaluated the efficacy of dulaglutide in lowering alcohol consumption in smoking AUD patients who were mostly obese but ranged in weight. In this study, dulaglutide treatment for 12 weeks reduced alcohol intake; this effect was obtained regardless of body weight, baseline alcohol consumption, or smoking status. A nationwide cohort study examining the risk of alcohol-related events in patients prescribed GLP-1-based therapies also discovered the interaction between GLP-1R and alcohol. According to this register-based study, GLP-1R agonists reduced alcohol-related events more than DPP-IV inhibitors did. This study did not, however, report the effect on weight, which included both type 2 diabetics and obese people. Additionally, a social media study that examined anonymous online reports showed that people receiving GLP-1R agonist treatment self-report lower rates of alcohol consumption, interest in alcohol, and desire to consume alcohol, even when they do not report their weight. Similarly, semaglutide decreased alcohol-related posts—such as expressions of desire, craving, and negative effects—among overweight people and people with type 2 diabetes who drink a lot of alcohol, according to machine learning analysis of social media posts. The ability of semaglutide to lessen the stimulatory and sedative effects of alcohol may be the reason for the observed decrease in alcohol intake in these obese patients who consume large amounts of alcohol. Semaglutide reduced the AUDIT scores in a small sample of overweight patients with AUD comorbidity. Although the majority of these studies show that GLP-1R agonists significantly lower alcohol consumption in overweight AUD patients,

little is known about how these drugs affect people of normal weight. Therefore, randomized clinical trials should compare how these GLP-1R agonists affect alcohol intake in people who are regular weight versus those who are obese. Furthermore, since animals of normal weight and primarily overweight humans have been studied, there are some differences in the preclinical and clinical work that has been done thus far. Therefore, it is debatable whether more preclinical research involving overweight animals is necessary. It is still too early to draw firm conclusions about which patient groups might respond best because these preclinical and clinical studies are still in their early stages. However, a subgroup of patients with obesity and AUD comorbidities may be more susceptible to the effects of appetite-regulatory peptides, which are known to control feeding and alcohol intake, than other subtypes.

Although the effect of high endogenous GLP-1 levels on alcohol consumption has not been investigated, one study found that GLP-1 levels are comparable in AUD patients and controls, and that intravenous and oral alcohol consumption lowers serum GLP-1 levels. Furthermore, regardless of body weight, alcohol consumption decreased the levels of GLP-1 in the blood in a placebo-controlled crossover study involving females. In conclusion, these human studies show that GLP-1R agonists lower alcohol consumption and alcohol-related incidents in people who abuse alcohol excessively or have an alcohol dependence. Although the majority of these studies show an effect in people with type 2 diabetes or who are overweight, it is still unclear how weight affects treatment response. Although GLP-1R activation results in a decrease in alcohol consumption, the precise neural circuits and mechanisms causing this effect in humans—as well as in rodents—remain unclear.

Effects of semaglutide alcohol consumption, either acutely or repeatedly, in male and female rats:

We investigated semaglutide's potential to lower alcohol consumption in male and female rats since high alcohol consumption over an extended period of time is crucial for the development of AUD. For three 24-hour sessions per week (Monday, Wednesday, and Friday), individually housed male or female rats could select between one alcohol (20%) bottle and one water bottle; on the other days, they could choose between two water bottles. This intermittent access model was employed in all alcohol drinking experiments. When the lights were switched off, the bottles were replaced. This model, which has been suggested to represent various aspects of alcohol abuse, shows how alcohol consumption rises to high, stable levels without the use of sucrose fading or coerced procedures. This model's predictive validity has been proposed because acamprosate, an anti-AUD drug, lowers alcohol consumption in this model but not in continuous access models. Our research does not support the alcohol deprivation effect that some have reported in this model. In this model, we track the rats' body weight, food, water, and alcohol intake during the experiments, as well as the amount of alcohol they drank eight to ten weeks prior to the start of treatment (baseline drinking). In every experiment, rats that were subsequently given either vehicle treatment or semaglutide had comparable baseline alcohol consumption. In order to match the vehicle-treated group with the semaglutide-treated group based on similar pre-treatment drinking behavior, the experimental rats were stratified based on baseline alcohol intake. For every experiment, semaglutide or vehicle treatment groups were utilized. Leaking bottles were the predetermined exclusion criterion:

Male (n = 24) or female (n = 24) rats were given either vehicle or semaglutide (0.026 mg/kg, sc) 60 minutes before alcohol exposure in order to examine the acute effects of semaglutide on alcohol intake. To find the lowest effective dose for lowering alcohol consumption, semaglutide was given once a week (on Mondays) for three weeks in a row. The dose-dependent impact of semaglutide on alcohol consumption was investigated in later studies. Consequently, a slightly higher dose of semaglutide (0.052 mg/kg) or vehicle was injected into male (n = 24) or female (n = 24) rats once a week (Mondays) 60 minutes before alcohol exposure.

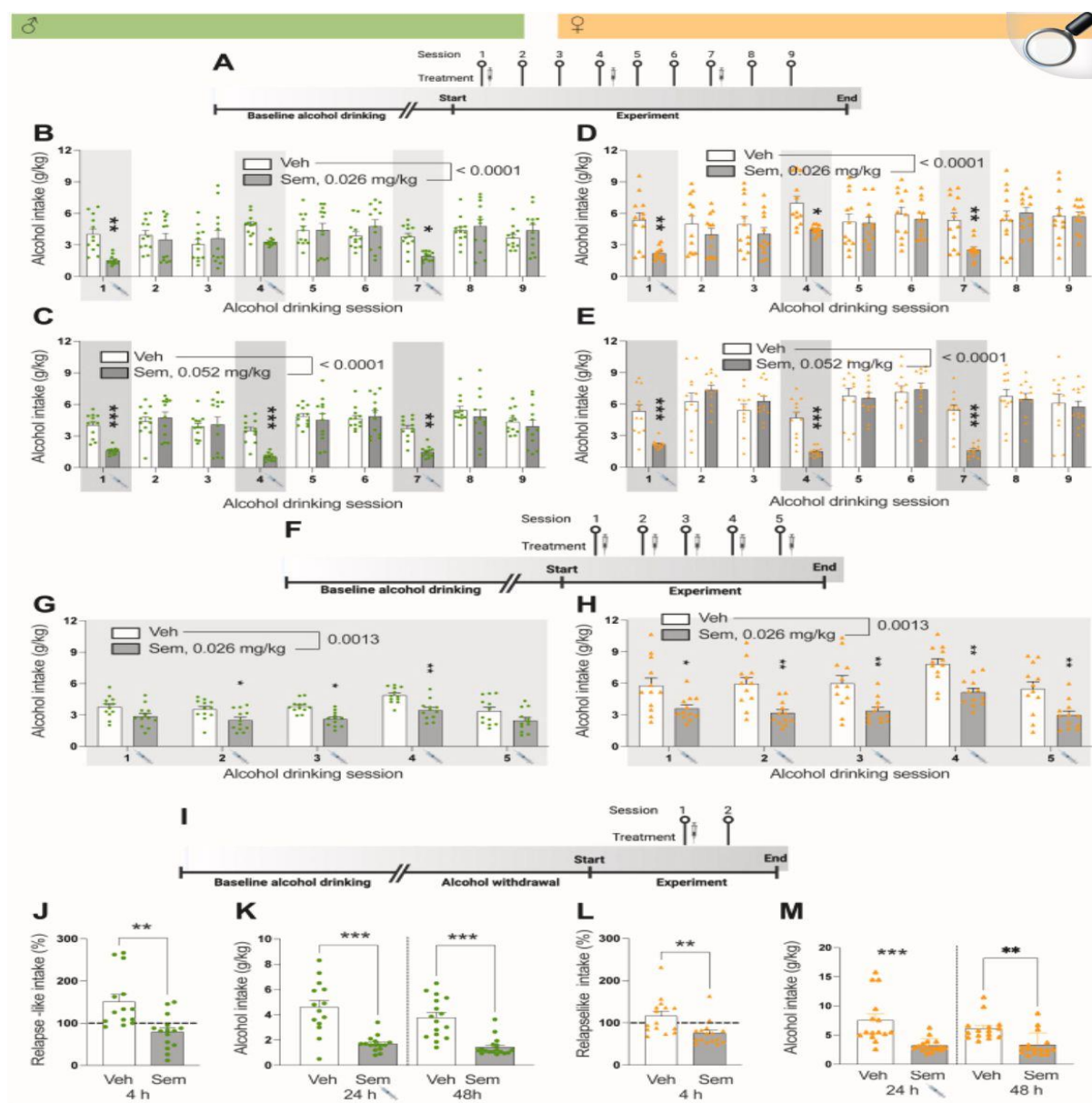


FIG-2

In both male and female rats, semaglutide treatment reduces alcohol consumption and stops relapse drinking: (A) Diagrammatic representation of the alcohol consumption experiment, where three alcohol consumption sessions (S1, S4, S7) involved acute injections of semaglutide.

(B) Semaglutide (0.026 mg/kg, $n = 12$) decreases alcohol consumption in male rats when compared to vehicle ($n = 12$); this decrease is particularly noticeable during alcohol drinking sessions 1 and 7.

(C) Additionally demonstrated in males, semaglutide (0.052 mg/kg, $n = 12$) reduces alcohol consumption at each treatment session when compared to vehicle ($n = 12$). Similarly, both semaglutide doses.

(D) 0.026 mg/kg ($n = 12$).

(E) 0.052 mg/kg ($n = 12$), decrease alcohol consumption at each treatment session in female rats when compared to vehicle ($n = 12$ in each test).

(F) Diagrammatic representation of the alcohol consumption experiment, in which five subsequent alcohol consumption sessions (S1, S2, S3, S4, S5) involved repeated injections of semaglutide.

(G) In this design, male rats treated with repeated semaglutide (0.026 mg/kg, $n = 12$) consume less alcohol than those treated with a vehicle ($n = 12$).

(H) Additionally, repeated semaglutide treatment (0.026 mg/kg, $n = 12$) reduced alcohol consumption in female rats compared to vehicle ($n = 12$). For men, this decrease is noticeable at drinking sessions two, three, and four; for women, it is noticeable at every session.

(I) Diagrammatic representation of the alcohol consumption experiment, which examined the impact of semaglutide on relapse-like drinking following alcohol withdrawal.

The rats were injected with semaglutide 60 minutes before they were exposed to alcohol, and they then drank it for 48 hours.

(J) Semaglutide lowers the percentage increase in alcohol consumption from baseline (dotted line). In particular, in male rats, alcohol withdrawal causes relapse drinking ($t(13) = 3.29$, $P = 0.0059$, paired t-test, $n = 14$), and semaglutide prevents relapse-like drinking ($t(14) = 2.67$, $P = 0.0187$, paired t-test, $n = 15$).

(K) Semaglutide also reduces alcohol consumption 24 and 48 hours after therapy.

(L) Semaglutide lowers the percentage increase in alcohol consumption from baseline in female rats (dotted line). In female rats, alcohol withdrawal tends to result in relapse-like drinking ($t(14) = 1.18$, $P = 0.1287$, paired t-test, $n = 14$), but semaglutide treatment prevented this ($t(15) = 4.65$, $P = 0.0003$, paired t-test, $n = 16$).

(M) The decreased alcohol consumption is also noticeable 24 and 48 hours following semaglutide therapy. The figure displays the overall treatment effect (G–H) and overall interaction effect (B–E) from a two-way ANOVA with repeated measures. A paired t-test was used to analyse J–K data, and an unpaired t-test was used to analyse K–L data. There was no replication of the experiments. Significant data are indicated by * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$. Data are displayed as mean $\pm$ SEM. The injection time is indicated by the syringe.

Acute semaglutide treatment's effects on male and female rats' relapse-like drinking:

A key factor in the diagnosis of alcohol use disorder (AUD) is the incapacity of patients to abstain from alcohol during abstinence, which includes alcohol cravings. Male rats' relapse-like drinking can be modeled using the alcohol deprivation model. Further rats of both sexes were used to test the hypothesis that semaglutide inhibits relapse-like drinking in the alcohol deprivation model. Male ($n = 33$) or female ($n = 31$) rats were denied alcohol for nine days following eight weeks of sporadic access. The rats were given either vehicle or semaglutide (0.026 mg/kg, sc) 60 minutes before alcohol was reintroduced. After that, alcohol was continuously reintroduced for 48 hours (Monday through Tuesday). Following the reintroduction of alcohol, their alcohol consumption was measured at 4 (0–4) hours, 24 (0–24) hours, and 48 (24–48) hours. The percentage change from baseline alcohol consumption is the definition of relapse-like drinking. The vehicle and semaglutide-treated rats' baseline and reintroduction intakes were also compared.

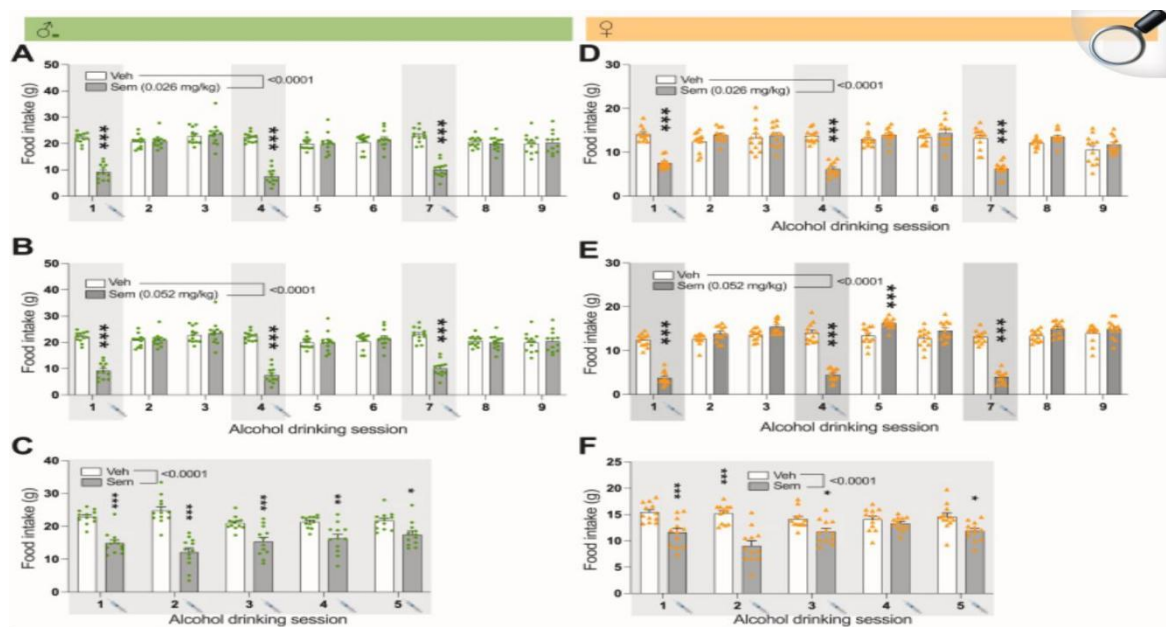


FIG-3

Acute semaglutide treatment's effects on alcohol's mesolimbic dopamine system activation in male mice:

In NAcS, alcohol stimulates the mesolimbic dopamine system, which results in dopamine release and locomotor stimulation. In humans, alcohol responses are possibly linked to reward. Therefore, semaglutide's ability to suppress dopamine release and alcohol-induced locomotor stimulation in NAcS was investigated in male mice. As previously mentioned, six open field boxes (42 × 42 × 20 cm; Med Associates Inc.; Georgia, Vermont, USA) were used to record the 1-hour locomotor activity (distance travelled).^{15,36} Two distinct levels of 16 × 16 infrared beams were used to measure activity. The mice used in this experiment were housed in groups. To guarantee that every treatment was represented in every cage, the male mice were assigned to treatment groups using a cage-stratified approach. Additionally, a box-stratified approach was used to assign distinct treatments to every open field box that was utilized. Vehicle-vehicle, vehicle-alcohol, semaglutide-vehicle, and semaglutide-alcohol were the treatment groups utilized. The vehicle-vehicle and semaglutide-vehicle treatments were given to 12 male mice.

Since alcohol causes a greater response variation, 18 male mice were divided into two groups: vehicle-alcohol and semaglutide-alcohol. Semaglutide (0.026 mg/kg) or a vehicle were injected into 60 male mice for this experiment. After that, they were given sixty minutes to get used to the open field boxes, which are sound-isolated, ventilated, and dimly lit (3 lux). The distance the male mice travelled in the open field boxes was then measured after they were given either a vehicle or alcohol (1.75 g/kg). Average velocity, vertical counts, and stereotypic counts were also noted. Male aggressive behaviour within the cage was a pre-established exclusion criterion because it adversely affects typical behaviour.

Next, in freely moving male mice, semaglutide's capacity to reduce alcohol-induced dopamine release in NAcS was assessed. Initially, a probe was surgically inserted unilaterally into the NAcS of 40 male mice. Isoflurane Baxter (given by a Univentor 400 Anaesthesia Unit from Univentor Ltd, Zeitun, Malta) was used to put the mice to sleep. After that, they were set up in a stereotaxic frame with a heating pad (David Kopf Instruments, Tujunga, CA, USA). Xylocaine Adrenaline (5 µg/ml; Pfizer Inc, New York, NY, USA) was applied locally to relieve pain, and Caprofen (5 mg/kg; Astra Zeneca, Gothenburg, Sweden) was injected subcutaneously. In order to prepare the surgical site, the skull bone was exposed, and a hole was drilled for the probe at coordinates of 1.3 mm anterior, ±0.5 mm lateral to midline, and -4.6 mm ventral. Additionally, a hole was drilled for an anchoring screw. The probe was inserted unilaterally, alternating between the brain's left and right hemispheres. The mice were kept apart for two days of recuperation after the procedure. Following that, in vivo micro-dialysis was carried out using the vehicle-vehicle, vehicle-alcohol, semaglutide-vehicle, and semaglutide-alcohol treatment groups (n = 56). To guarantee that every treatment was tested in every micro-dialysis setup (six at each time), mice were assigned to treatment groups. Loss of implantation, misplaced probes, and technical issues during micro-dialysis were pre-established exclusion criteria.

A micro-perfusion pump (U-864 Syringe Pump: AgnThj AB) with a perfusion rate of 1.6 µl/min was attached to the probe on test day, and the mice were acclimated for two hours. Following the collection of three baseline samples, the mice received injections of semaglutide (0.026 mg/kg) or vehicle, and then alcohol (1.75 g/kg) or vehicle. After that, samples were taken every 20 minutes for three more hours, enabling the tracking of treatment results in mice that were free to move around. A two-dimensional high-performance liquid chromatography and electrochemical detection (HPLC-EC) system was used in accordance with a modified protocol to measure the levels of dopamine, noradrenaline, serotonin, L-DOPA, and their metabolites (HVA, DOPAC, 3-MT, NM, and 5-HIAA). Only mice with the proper placements were included in the analysis after the probe's location was confirmed using a microtome. In addition to comparing the treatment's impact on dopamine release to baseline, the area under the curve (AUC) result was examined. Since memory of the alcohol reward plays a significant role in the AUD process, the effect of semaglutide on this was investigated using the previously described memory of CPP (Mcpp) test. In short, in low light (3 lux), a two-chambered CPP device with unique tactile and visual cues was utilized. Pre-conditioning (day 1), conditioning (days 2–5), and post-conditioning (day 6) make up the paradigm. Each session lasts 20 minutes. Alcohol was conditioned to the least preferred side during pre-conditioning as part of a biased design. In a balanced design, the injections were switched between morning and afternoon. The mice were conditioned to alcohol (1.75 g/kg) for four days following the pre-test, in which the group of male mice (n = 16) were given a vehicle injection and allowed to explore the entire CPP arena. Following the post-test, the mice received either a vehicle injection or semaglutide

(0.026 mg/kg), and the male mice were once again permitted to explore the entire CPP arena. Mice were assigned to either alcohol-vehicle or alcohol-semaglutide treatments. The mice were divided into treatment groups according to their initial preference for one side and the time of day (morning or afternoon) that the alcohol conditioning took place. Extra control In order to rule out the possibility that semaglutide directly affects Mcpp, Mcpp tests were performed on 16 additional male mice. It was not possible to test conditioned approach behaviour (i.e., reflection of reward) due to the lengthy half-life of semaglutide and the design of CPP for alcohol. CPP is calculated by deducting the amount of time spent in the alcohol-conditioned chamber between the pre-conditioning and post-conditioning phases, then dividing the result by the total amount of time spent in the CPP apparatus. A predetermined exclusion criterion is to jump out of the CPP apparatus.

Semaglutide's effects on ex vivo dopamine metabolite levels in Nac in male and female rats that consume alcohol:

The ex vivo levels of monoamines and their metabolites were assessed in NacS and NacC of alcohol-drinking male and female rats treated with semaglutide in order to further investigate the potential of semaglutide and alcohol to improve dopamine metabolism in Nac. Ex vivo HPLC measures neurotransmission in a single area at a single time point following termination, whereas in vivo micro-dialysis evaluates the release of dopamine metabolites in freely moving male mice over time. As a result, the ex vivo data should be viewed as a supplement to the in vivo data, which offers more details. Therefore, the alcohol-drinking rats were sacrificed after receiving vehicle or semaglutide (0.026 mg/kg) treatments five times. The brains of the rats were then collected, punched out, and stored at -80 °C. An established HPLC-EC method was used to measure the ex vivo levels of monoamines (dopamine, noradrenaline, serotonin), the dopamine precursor (L-DOPA), and metabolites (DOPAC, HVA, 3-MT, 5-HIAA). Additionally, the ex vivo levels of these neurotransmitters were examined in the VTA, latero-dorsal tegmental nucleus, paraventricular thalamus, and lateral septum to obtain insight into neurotransmission in other reward-related regions that regulate alcohol responses. Sample contamination was the pre-established exclusion criterion.

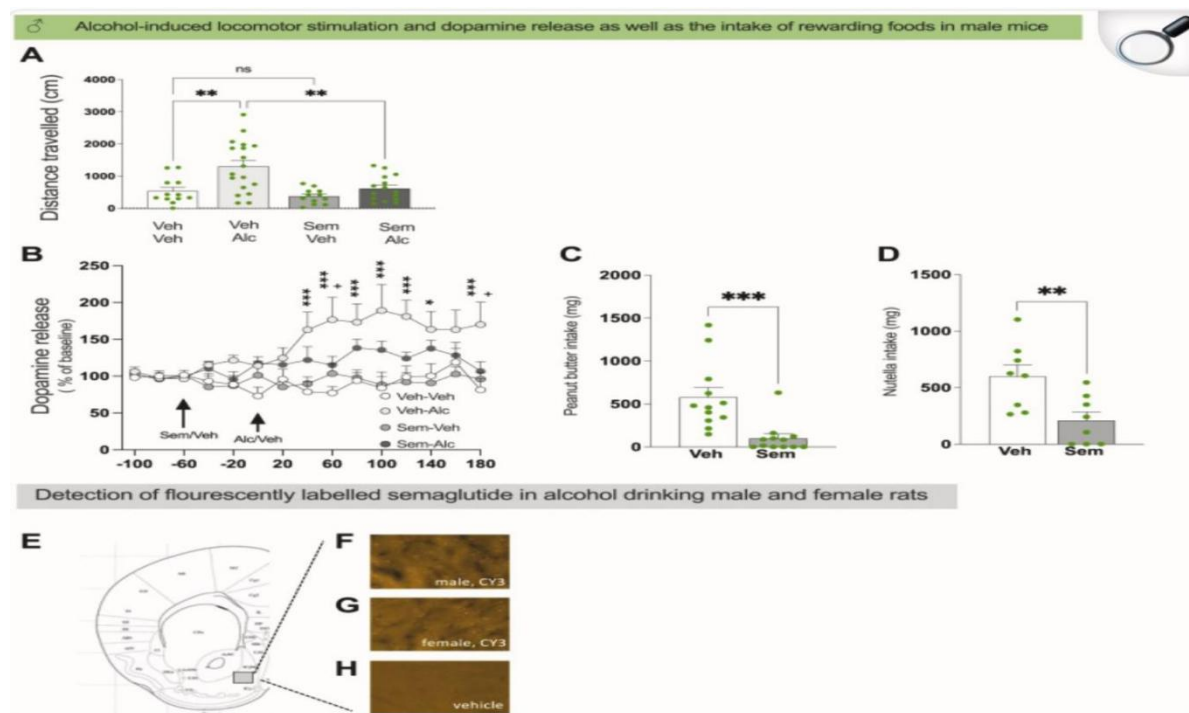


FIG-4

Semaglutide treatment's effects on dopamine-driven behaviors in male and female rats who have never had alcohol:

Semaglutide's impact on dopamine-driven behaviours such as exploration and novelty-seeking was examined in alcohol-naïve male (n = 20) and female (n = 20) group-housed rats in order to further investigate the possibility

that it influences dopaminergic neurotransmission. To guarantee equitable distribution, rats were divided into two treatment groups: vehicle and semaglutide. After injecting semaglutide (0.026 mg/kg) or a vehicle, the rats were put in the middle of open field boxes (42 × 42 × 20 cm; Med Associates Inc.) that are dimly lit (3 lux) and sound-isolated after 60 minutes. After exploring the arena for sixty minutes, they were quickly taken out, and a new object (a 3 × 3 × 3 cm Lego piece) was put in the middle of the arena. The rats then spent two more minutes investigating the item and arena. Observer XT software (Noldus, Wageningen, Netherlands) was used to analyze the time spent in the inner/novel zone (15 × 15 cm), corners, and zone entries for both tests. The person in charge of scoring had to have an intra- and inter-individual scoring reliability of at least 90% in order to avoid treatment bias. Intra-cage aggressive behavior was a predetermined exclusion criterion because it adversely affects typical behavior.

Fluorescently labelled semaglutide was found in the NAcS of male and female rats that drank alcohol:

We speculate that fluorescently labelled semaglutide is present and may have local effects in NAcS because it increases dopamine metabolism when alcohol is on board. To test whether CY3-semaglutide could reach NAcS, male (n = 2) and female (n = 2) rats received acute injections of either CY3-semaglutide or vehicle after 10 weeks of alcohol consumption. After the rats were perfused for 60 minutes, their brains were removed, post-fixed, cut into 40 µmNac sections, and stored as previously mentioned. After being cleaned with TBS (Tris-buffered saline), the brain sections were placed on coverslips and adhesion glass slides (Super-Frost Plus TM, Thermo-Fisher Scientific, Waltham, MA, USA) with a few drops of mounting medium (Pro-Long TM Gold Antifade, Life Technologies Europe BV). CY3-semaglutide was imaged using the ZEN microscope software and a ZEISS Axio observer Z1 with a 20× objective. Because blood in slices makes them difficult to see under a microscope, it was used as a predetermined exclusion criterion.

Semaglutide treatment's effects on cAMP in alcohol-naïve male mice's NAc:

Semaglutide did not alter dopamine, DOPAC, or HVA in and of itself, although in vivo micro-dialysis studies in male mice showed that semaglutide and alcohol increased dopamine metabolism. Therefore, we hypothesize that when semaglutide is injected alone, NAc neurons are not activated. This was investigated by measuring the impact of semaglutide (0.026 mg/kg) on cAMP, a crucial GLP-1R downstream signaling molecule, in the NAc. cAMP was measured in regions projecting to NAc (amygdala, VTA, or nucleus tractus solitarius (NTS)) in order to investigate additional potential areas targeted by semaglutide. Male mice in the alcohol-naïve group (n = 14) were given either vehicle or semaglutide, sacrificed after 60 minutes, and the brain regions listed above were punched out and stored at -80 °C until further ELISA analysis, as directed by the manufacturer. To guarantee equitable distribution, mice were divided into two treatment groups: vehicle and semaglutide. The predetermined exclusion criterion was sample contamination.

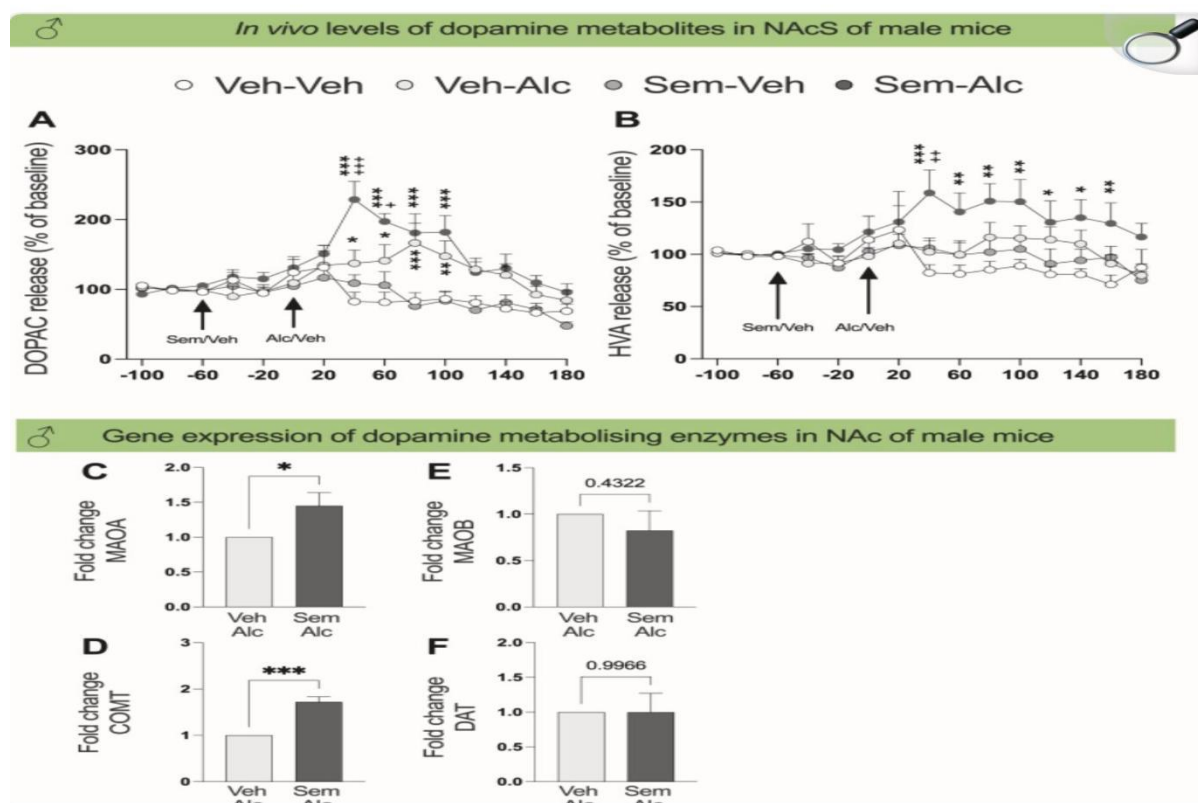


FIG-5

. Acute semaglutide treatment's effects on locomotor activity and anxiety-like behaviours in male and female rats who have never had alcohol:

The semaglutide-induced decrease in alcohol consumption may be confounded by activity and anxiety, which has been investigated in locomotor activity and elevated plus maze (EPM) studies. Alcohol-naïve male ($n = 20$) and female ($n = 20$) rats were given semaglutide (0.026 mg/kg) or vehicle injections after 30 minutes of acclimation to the open field boxes ($42 \times 42 \times 20$ cm, Med Associates Inc.) that are ventilated and dimly lit (3 lux). The rats' 60-minute activity was then recorded. Analysis was done on the distance covered, vertical counts, zone entries, and time spent in the inner zone. Alcohol in male ($n = 20$) and female ($n = 20$) rats were injected with either vehicle or semaglutide (0.026 mg/kg) and positioned in the centers of the EPM, that has open arms raised 70 cm above the floor and closed walls that are 40 cm high. Observer XT software (Noldus, Wageningen, Netherlands) was used to analyse time in the open and closed arms and central zones. The following treatment groups—semaglutide and vehicle—were used for both tests in order to guarantee equal distribution of the rats. Intra-cage aggressive behaviour was a pre-established exclusion criterion because it adversely affects typical behaviour.

In male and female alcohol-drinking rats, semaglutide treatment stops alcohol consumption after withdrawal:

The incapacity of AUD patients to abstain from alcohol consumption is a crucial trait that must be addressed in treatment. Thus, alcohol-exposed rats of both sexes were used to test semaglutide's capacity to stop relapse-like drinking in the alcohol deprivation model. Male withdrawal caused relapse drinking ($t(13) = 3.29$, $P = 0.0059$, $n = 14$; paired t-test), and semaglutide prevented this relapse-like drinking ($t(14) = 2.67$, $P = 0.0187$, $n = 15$; paired t-test). In particular, semaglutide decreased the percentage increase in alcohol consumption from baseline ($t(27) = 3.66$, $P = 0.0011$; unpaired t-test). Additionally, male rats given semaglutide consumed less alcohol at 24 ($t(27) = 5.09$, $P < 0.0001$, unpaired t-test) and 48 ($t(27) = 5.03$, $P < 0.0001$, unpaired t-test) hours following

treatment. Semaglutide increased water and total fluid intake, decreased alcohol preference and food intake, and decreased body weight change in males in this alcohol deprivation experiment. Due to leaking bottles, two male rats treated with semaglutide and two vehicle rats were eliminated. Alcohol withdrawal in female rats was associated with a tendency toward relapse-like drinking ($t(14) = 1.18$, $P = 0.1287$, $n = 14$, paired t-test), but this trend disappeared following semaglutide treatment ($t(15) = 4.65$, $P = 0.0003$, $n = 16$; paired t-test) (data not shown). Additionally, semaglutide decreased the percentage increase in alcohol consumption from baseline ($t(29) = 3.14$, $P = 0.0039$, unpaired t-test). Similarly, 24 ($t(29) = 3.99$, $P = 0.0004$) and 48 ($t(29) = 3.79$, $P = 0.0007$) hours after treatment, semaglutide reduced alcohol consumption (Fig. 1M; unpaired t-test). Additionally, semaglutide reduced food and alcohol preferences in females while increasing water and overall intake while reducing changes in body weight. Due to leaking bottles, one vehicle-treated female rat was eliminated.

In both male and female alcohol-drinking rats, semaglutide reduces food intake:

In both male and female rats, acute or repeated semaglutide treatment reduced food intake at both doses. Semaglutide (0.026 mg/kg) had an overall effect on food intake in males (time, $F(8,176) = 33.75$, $P < 0.0001$; treatment, $F(1,22) = 24.45$, $P < 0.0001$; interaction, $F(8,176) = 52.38$, $P < 0.0001$; two-way ANOVA, with repeated measures). In particular, this decline was noticeable at every alcohol consumption session ($P < 0.001$; Tukey's posthoc test). Additionally, it was clear that 0.052 mg/kg of semaglutide had an overall effect on food intake in males (time, $F(8,176) = 85.12$, $P < 0.0001$; treatment, $F(1,22) = 50.40$, $P < 0.0001$; interaction, $F(8,176) = 84.29$, $P < 0.0001$; two-way ANOVA, with repeated measures). Every alcohol consumption session showed this decrease ($P < 0.001$; Tukey's posthoc test). Furthermore, a two-way ANOVA with repeated measures revealed that repeated treatment with semaglutide (0.026 mg/kg) had an overall treatment effect ($F(1,22) = 41.03$, $P < 0.0001$), an interaction effect ($F(4,88) = 11.59$, $P < 0.0001$), but not a time effect ($F(4,88) = 1.15$, $P = 0.3391$). Each treatment session showed a decrease in food intake ($P < 0.05$, S5; $P < 0.01$, S4; $P < 0.0001$, S1, S2, S3 Tukey's posthoc test).

Semaglutide and alcohol's effects on neurotransmission and gene expression in different parts of the brain:

In order to investigate the potential for semaglutide to modify neurotransmission in other brain regions, additional data from the aforementioned experiments were collected and analyzed ($n = 5-7$, samples excluded due to pre-set exclusion criteria). The effects of i) on monoaminergic neurotransmission in NAcS and NAcC of male and female rats that consume alcohol are summarized in the supplemental material. ii) semaglutide and alcohol treatment on gene expression in the VTA of male mice; iii) semaglutide treatment on ex vivo neurotransmission in the VTA of male and female alcohol-drinking rats; and iv) monoaminergic neurotransmission in the paraventricular thalamus, lateral septum, and latero-dorsal tegmental area of alcohol-drinking male and female rats. The VTA of male mice and rats was identified as one region of interest from these extra analyses. The trials were not repeated. Semaglutide administration alone had no effect on the neurotransmission in NAc in male mice, according to the in vivo micro-dialysis experiment. Therefore, we hypothesized that when administered alone, semaglutide does not activate neurons in NAc. Semaglutide also tended to raise cAMP in the amygdala without changing cAMP in the VTA or NTS, but it had no effect on cAMP in the NAc of male mice. The pre-established exclusion criterion eliminated three samples. The trials were not repeated.

Semaglutide affects alcohol-naïve female rats' anxiety-like behaviours:

The effects of semaglutide on activity and anxiety-like behaviours were examined because these behaviours may be confounding factors for semaglutide's ability to lower alcohol consumption. Semaglutide increased average velocity, vertical counts, and distance traveled in males and increased time in the inner zone in females in a locomotor activity test in alcohol-naïve rats with comparable activity during habituation. In an EPM test, semaglutide reduced time in the center and increased time in closed arms in female rats, but it had no effect on anxiety-like behaviours in male rats. Experiments were not repeated, and no animals were eliminated based on predetermined exclusion criteria.

Semaglutide increases dopamine-driven behaviours in alcohol-naïve male and female rats and affects the dopamine metabolism in NAc of alcohol-drinking male and female rats:

Ex vivo levels of dopamine and its metabolites were measured in NAc in alcohol-drinking male and female rats treated with semaglutide in order to validate the increased dopamine metabolism seen in male mice. Semaglutide increased ex vivo dopaminergic neurotransmission in both male and female alcohol-drinking rats' NAcS and NAcC. Semaglutide's capacity to affect dopamine signalling was demonstrated by testing its effects on dopamine-driven behaviours. Semaglutide was found to enhance exploration and novelty-seeking in alcohol-naïve rats of both sexes. The experiments were not repeated, and no animals were eliminated based on predetermined exclusion criteria (n = 10 per treatment group).

Male and female rats that consume alcohol have fluorescently labelled semaglutide in their NAcS:

The potential for CY3-semaglutide to reach NAcS following systemic administration was examined in alcohol-drinking male and female rats since semaglutide reduces dopamine release in NAcS by alcohol. A CY3-semaglutide signal was found in NAcS during this experiment, but no CY3-semaglutide signal was found following vehicle injection.

When alcohol is present, semaglutide increases dopamine metabolism in male NAc mice:

The possibility that semaglutide increases dopamine metabolism in NAc was investigated because semaglutide inhibited alcohol's ability to activate the mesolimbic dopamine system in male mice and because CY3-semaglutide was found in NAcS. Dopamine metabolite levels in NAc of semaglutide-treated male mice with alcohol on board were measured using in vivo microdialysis experiments (number of animals identical to above in vivo experiments, no replication of experiment). DOPAC levels in NAcS were affected overall in male mice given semaglutide and alcohol (treatment, $F(3,36) = 6.10$, $P = 0.0018$; time, $F(14,504) = 10.17$, $P < 0.0001$; interaction, $F(42,504) = 3.92$, $P < 0.0001$, two-way ANOVA with repeated measures). In comparison to the vehicle, alcohol raised DOPAC levels (40 minutes, $P = 0.0247$, 60 minutes, $P = 0.0120$, 80 minutes, $P = 0.0001$, 100 minutes, $P = 0.0089$; Tukey's posthoc test). Male mice treated with both semaglutide and alcohol also showed an increase (40 min, $P < 0.0001$; 60 min, $P < 0.0001$; 80 min, $P < 0.0001$; 100 min, $P < 0.0001$; 140 min, $P = 0.0247$; Tukey's posthoc test). Semaglutide and alcohol together increased DOPAC (40 min, $P < 0.0001$; 60 min, $P = 0.0308$; Tukey's posthoc test) in comparison to alcohol alone. HVA levels in NAcS of male mice treated with semaglutide and alcohol also showed an overall effect (treatment, $F(3,36) = 10.47$, $P = 0.0468$; time, $F(14,504) = 2.85$, $P = 0.0004$; interaction, $F(42,504) = 1.92$, $P = 0.0007$; two-way ANOVA with repeated measures). Semaglutide plus alcohol increased the HVA levels in NAcS compared to vehicle (40 min, $P < 0.0001$; 60 min, $P = 0.0040$; 80 min, $P = 0.0011$; 100 min, $P = 0.0026$; 120 min, $P = 0.0233$; 140 min, $P = 0.0107$; 160 min, $P = 0.0048$; Tukey's posthoc test). DOPAC and HVA were unaffected by semaglutide alone.

When alcohol is present, semaglutide increases dopamine metabolism in the nucleus accumbens:

According to the in vivo micro-dialysis experiment, male mice treated with semaglutide and alcohol had higher levels of (A) DOPAC and (B) HVA in the nucleus accumbens (NAc) shell than those treated with alcohol alone (n = 12 for vehicle-vehicle, n = 18 for vehicle-alcohol, n = 12 for semaglutide-vehicle, and n = 15 for semaglutide-alcohol; two-way ANOVA with repeated measures). These findings suggest that when alcohol is present, semaglutide improves dopamine metabolism. In support, male mice treated with both semaglutide and alcohol had higher NAc gene expression of (C) MAOA and (D) COMT but not (E) MAOB and (F) DAT (n = 5 for both treatment groups, unpaired t-test). The trials were not repeated. Significant results are shown as * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ when compared to vehicle treatment, and + $P < 0.05$, ++ $P < 0.01$, and +++ $P < 0.001$ when comparing alcohol treatment to the combination of semaglutide and alcohol. The data are displayed as mean $\pm$ SEM.

The expression of the enzymes that break down dopamine was measured in a different experiment involving male mice because a higher expression of these enzymes could account for the rise in dopamine metabolites. The NAc gene expression of MAOA ($t(8) = 2.38$, $P = 0.0447$, unpaired t-test) and COMT ($t(8) = 6.41$, $P = 0.0002$, unpaired t-test) increased in these experiments when semaglutide and alcohol were combined, but not MAOB ($t(8) = 0.83$, $P = 0.4322$, unpaired t-test) or DAT ($t(8) = 0.0002$, $P = 0.9966$, unpaired t-test). Experiments were not repeated, and no animals were eliminated based on predetermined exclusion criteria.

CONCLUSION

S.No	Experiment	Species	Sex	Rational	P value	Additional Outcome
1	Effects of semaglutide on alcohol intake for 8-10 weeks a. Acute, 0.026 mg/kg b. Acute, 0.052 mg/kg c. Repeated, 0.026 mg/kg.	Rat	Male Female	High intake over prolonged period of time is important for the manifestation of alcohol use disorder.	Reduced per day=4 Reduced per week=1 Reduced heavy drinking days=4.	Influence of semaglutide on food intake, alcohol preference, water and total fluid intake and body weight.
2	Effects of semaglutide on relapse-like drinking in the alcohol deprivation model.	Rat	Males Female	Abstinence to alcohol causes relapse-like drinking, a behaviour reflecting the inability to abstain from alcohol. This is an important aspect of alcohol use disorder.	Male- $P=0.0003$ Female- $P=0.0059$ Relapse- $P=0.0187$.	Influence of semaglutide on alcohol preference, water, total fluid and food intake as well as body weight.
3	Effects of semaglutide treatment on alcohol-induced locomotor stimulation.	Mice	Males	Alcohol causes a release of dopamine in NAcS in rodents and humans, an effect associated with an increase locomotor activity, thus reflecting the acute effects of alcohol.	$P \leq 0.05$	Effects on other locomotor activity parameters.
4	Effects of semaglutide treatment on alcohol-induced dopamine release in NAcS, in vivo.	Mice	Males	The ability of alcohol to enhance dopamine in NAcS is associated with the rewarding experience in man and is a risk factor for a	overall treatment effect ($F(3,28) = 19.14$, $(p < 0.0001)$) and a significant interaction effect ($F(42,392) = 4.960$, $(p < 0.0001)$	Effects of semaglutide together with alcohol on the release of dopamine metabolites CHVA, DOPAC: These additional data explore the possibility that

				later alcohol use disorder diagnosis.		semaglutide together with alcohol changes the metabolism of dopamine. This contributes to the identification of underlying molecular underpinnings. Effects on other monoaminergic neurotransmission in NAcS.
5	Effects of semaglutide treatment on alcohol-induced conditioned place preference.	Mice	Males	The memory of the Result section alcohol reward is an important aspect of the alcohol use disorder process, a behaviour that can be measured in the memory of conditioned place preference test.	$P < 0.0001$ to < 0.05 .	-
6	Effects of semaglutide treatment on the intake of rewarding foods.	Mice	Males	The possibility that semaglutide reduces other types of reward was further explored in feeding experiments, where intake of foods.	SC ROUTE- Total energy intake: $p < 0.0001$. Energy intake from high-fat, non-sweet foods: $p = 0.0184$. Implicit wanting for high-fat, non-sweet foods: $p = 0.0203$. Craving for savory foods: $p < 0.05$. ORAL ROUTE- Total daily energy intake: $p = 0.0001$. Energy intake from high-fat, sweet foods: $p = 0.0055$. Overall energy intake from high-fat foods: $p = 0.0026$. HIGHER-DOSE ORAL SEMAGLUTID	Effects of other feeding parameters at 4-h time point and at 2-h time point.

					E- Fewer cravings for sweet, dairy, starchy, and savory foods: $p < 0.05$.	
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