Nutr Cur 2024; 03(Special 1): e147
DOI: 10.57625/nec.2024.54

Neuroendocrine pathways in alcohol use disorder: opportunities to develop biomarkers for alcohol craving?

Massimo A. Koffler[1,2], Lorenzo Leggio[3-6].

[1]MiraCosta College, Oceanside, CA, USA;

[2]Bunker Hill Community College, Boston, MA, USA;

[3]Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, Translational Addiction Medicine Branch, National Institute on Drug Abuse Intramural Research Program and National Institute on Alcohol Abuse and Alcoholism Division of Intramural Clinical and Biological Research, National Institutes of Health; Baltimore and Bethesda, MD, USA;

[4]Department of Behavioral and Social Sciences, Center for Alcohol and Addiction Studies, Brown University, Providence, RI, USA;

[5]Division of Addiction Medicine, Department of Medicine, School of Medicine, Johns Hopkins University; Baltimore, MD, USA;

[6]Department of Neuroscience, Georgetown University Medical Center; Washington DC, USA.

Corresponding Author: Lorenzo Leggio, MD, Ph.D; e-mail: lorenzo.leggio@nih.gov

ABSTRACT

Recent research developments in the alcohol use disorder (AUD) field have prompted researchers to invest in novel approaches to evaluate alcohol craving. Neuroendocrine pathways portray activity within the central nervous system (CNS) with potential biomarkers that can be collected safely at the peripheral level. Traditionally, one of the most studied neuroendocrine systems, especially when applied to treating AUD, is the hypothalamus-pituitary-adrenocortical (HPA) axis; however, recently, there has been interest in the gut-liver-brain axis as appetite-related neuroendocrine pathways may affect alcohol craving. This narrative review reports on both preclinical and clinical studies to evaluate ghrelin and insulin as hormonal biomarkers to quantify craving and the recent research on glucagon-like-peptide 1 (GLP-1) receptor agonists, regarding them as potential treatment options for people with AUD. Collecting and measuring those hormones may offer the opportunity to investigate novel ways to investigate alcohol cravings. Those analytical measures could provide clinicians with novel critical information regarding the severity of a patient's condition and, thus, be able to provide their patients with more personalized and effective treatments.

KEYWORDS

ALCOHOL USE DISORDER
CRAVING
NEUROENDOCRINE
GHRELIN
GLP-1

ALCOHOL CRAVING AND THE CHALLENGES OF MEASURING IT

The scientific community has made great strides in recent years, defining craving in the *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10) as "a strong desire or sense of compulsion to take the substance [alcohol]" and including craving as part of the criterion for diagnosing Alcohol Use Disorder (AUD) in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[1]. These developments have prompted researchers to invest in more concrete ways to quantify craving, including methodologies aimed at improving retrospective assessments of craving. Examples include assessing craving in real time in human laboratory settings (such as alcohol cue-reactivity procedures conducted in bar-like settings) and assessing craving in real-time and in the real-world via ecological momentary assessment techniques.

Craving, in the context of alcohol and other substance use disorders (AUD and SUD), historically has been incredibly difficult to quantify for various reasons. It did not have a universally agreed upon definition within the scientific community, meaning researchers noted different characteristics when discussing it as a *qualitative* result. For example, craving has been described by some as "desire and urge", while others have defined it as only the "desire" to experience the effects of a drug, while using the term "urge" to describe the behavioral intention to use the drug[2].

Craving, reported as a *quantitative* result, is also commonly measured in a self-reported manner, which is challenging as it leads to subjective results, and patients may over exaggerate or deny experiencing it. Furthermore, in the research setting for AUD, the most common and well- regarded self-reported quantifiers of craving, such as the Obsessive Compulsive Drinking Scale (OCDS) and the Penn Alcohol Craving Scale (PACS)[3], are retrospective measures. This means that, rather than describing their symptoms as they come, patients are asked to reflect on symptoms they felt in the days or weeks prior, which they may forget, misremember, or perceive differently based on unrelated life factors (recall bias).

A real-time measure of craving is the Visual Analog Score (VAS), a unidimensional Likert scale measure of craving intensity; however, this measure has reported inconsistent predictive results over time[4], and it should be supported with other assessments that include psychometric and physiological values[5]. From a translational perspective, the lack of quantitative instruments and the temporal aspect of data collection, also have made operationalizing valid and reliable preclinical models to predict human craving especially challenging6. Cravings in animal studies are exclusively measured using quantitative measurements, and data are collected with instruments that report real-time states[7].

Alcohol Craving Questionnaire (ACQ)[8] measures craving during laboratory procedures. It was developed to assess craving in real-time[9], and it has been validated for application in the alcohol cue reactivity paradigm[10] Furthermore, the ACQ subscale measures compulsivity, expectancy, purposefulness and emotionality[11], providing an index of degree of acute craving, which can be associated with the Obsessive-Compulsive Drinking Scale (OCDS)[5] collected retrospectively.

In the context of AUD human laboratory studies, researchers have utilized some of the conventional clinical biomarkers such as: gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and carbohydrate-deficient transferrin (CDT). Outside of traditional clinical laboratory tests, researchers also measure salsolinol, fatty acid ethyl esters (FAEE), and ethyl glucuronide (EtG). These biomarkers, however, mainly show the cytotoxic effects of alcohol on the body (e.g., in the liver, given that alcohol-associated liver disease is one of the most common alcohol-related organ damage), are not specific for AUD, and most at all they do not measure craving response. Recognizing that craving may result from an affective state, researchers have also utilized various imaging techniques to evaluate craving, such as facial electromyography to measure craving in real-time during a task[12]. As AUD is recognized as a brain disorder[13,14], measurement of craving has been done through imaging studies, which have been able to display the cue-induced activation of isolated brain structures. For example, using positron emission tomography (PET)[15] and functional magnetic resonance imaging (fMRI) during a cue-reactivity paradigm[16]. Recently, real-time fMRI has been utilized as an imaging modality used to examine craving-related behavior and targeting specific brain regions involved in alcohol craving[17].

These methods, however, have limitations and cannot always produce accurate results. When analyzing facial expressions with facial electromyography, individuals could make a variety of expressions due to factors that are entirely unrelated to the presented cue. Regarding imaging techniques, PET scans and fMRI are expensive, place subjects in a more synthetic environment, and merely show general activation in the brain (e.g., blood oxygen level dependent (BOLD) signal).

NEUROENDOCRINE PATHWAYS AND ALCOHOL CRAVING

Neuroendocrine pathways portray activity within the central nervous system (CNS) as the hormones may signal to the CNS (often by feedback loop), either directly or via the peripheral nervous system. Therefore, targeting specific hormonal biomarkers before, during, and after treatment would be an effective method of quantifying and analyzing cravings, especially considering that they can be collected safely at the peripheral level. Utilizing neurobiological markers to assess craving would be ideal since, theoretically, it would display neurobehavioral conditions that could be used to extrapolate the brain's discordance or homeostasis. Hormonal biomarkers are also more accessible and safer to acquire in human laboratory studies and can be collected both to assess real-time response and retrospective values. This is particularly valuable in human laboratory studies where the tools to access brain information are limited.

Traditionally, one of the most studied neuroendocrine systems, especially when applied to treating AUD, is the hypothalamus-pituitary-adrenocortical (HPA) axis[18]. For example, in a randomized clinical trial (RCT) of naltrexone with patients with AUD, an increase in plasma cortisol levels was associated with a lower intensity of craving for alcohol[19]. The HPA axis is highly conserved throughout mammalian phylogeny, which makes the factors, hormones, peptides, and neurotransmitters extremely valuable in translational research[20].

More recently, there has been interest in the gut-liver-brain axis as appetite-related neuroendocrine pathways may affect alcohol craving. Various studies, including randomized controlled trials (RCTs), have provided evidence that food-seeking behaviors and alcohol-seeking behaviors share similar neural pathways[21,22]. An example of a gut-liver-brain axis-related neuroendocrine pathway that has been studied in the context of craving for alcohol and AUD is ghrelin[23], a peptide secreted primarily in the stomach that stimulates appetite.

Preclinical studies have demonstrated that when ghrelin levels are increased by exogenous administration in either the brain (e.g., ventral tegmental area, VTA)[24] or peripherally[25], the cholinergic–dopaminergic reward link was activated in the same way alcohol activated it and dopamine concentrations increased. Conversely, the consumption of alcohol reduced ghrelin levels much more than the consumption of water[26]. Human laboratory studies found consistent results. One study in healthy volunteers revealed that acute alcohol consumption was able to lower the ghrelin level compared to water administration[26], demonstrating that alcohol may have an inhibitory action of ghrelin secretion and possible craving response. Similarly, in non-abstinent individuals with AUD, ghrelin levels were significantly lower compared to healthy controls[27] and raised significantly when these patients were abstinent[28].

Interestingly, using a retrospective measure of craving (OCDS), it was also discovered that plasma ghrelin levels were correlated with the increase of craving[27]. This bidirectional relationship established from these studies suggests that ghrelin levels within the rewarding circuitry may be related to the neurobiological response of craving. The first study that assessed alcohol craving in real-time using acute intravenous (IV) administration of ghrelin showed that it increased alcohol craving in individuals with AUD[29]. This study measured craving using the VAS, measured in real-time during a cue-reactivity procedure in a bar-laboratory setting to increase the saliency of the cues in a more naturalistic setting.

Ghrelin also interacts with several other hormones that could be exploited for measuring cravings. For example, in a secondary analysis of the same trial, exogenous IV ghrelin reduced leptin levels in individuals with AUD, and those changes were correlated with alcohol craving[30]. Importantly, those changes were specific only for leptin as other hormones that are secreted from adipocytes (i.e., resistin and visfatin) did not change craving response.

A follow-up study also assessed the role of insulin and alcohol craving after IV ghrelin administration[31]. Insulin is released by the pancreas and is responsible for regulating the quantity of glucose in the bloodstream. The relationship between insulin and AUD is still under active investigation. Alcohol is a drug with stimulant and sedative effects, but it is also high in kilojoules without delivering any nutritional benefit. The effects of alcohol consumption are therefore interlaced with the regulation of gluconeogenesis and insulin production, metabolism and release[32]. In this study, after IV ghrelin administration, insulin serum values were reduced; however, these physiological responses had no effect on alcohol craving. Those results were consistent with a previous study that found no relationship between the OCDS (total and sub score) and glucose level[33].

The investigation of the role of insulin in alcohol craving is, however, very active. A preclinical study using Drosophila found a potential link between the insulin/insulin receptor pathway and drinking behaviors[34]. A clinical trial was conducted to investigate this link and found that blood insulin levels and OCDS craving were strongly and positively correlated[35]. As a matter of fact, more recently, semaglutide, a drug used to treat patients

with type-2 diabetes and obesity, has shown promise in becoming a treatment option for patients with AUD. Semaglutide acts as a glucagon-like peptides (GLP-1) receptor agonist, hence increasing the secretion of insulin and reducing the production and secretion of glucagon[36]. Semaglutide has been shown to reduce both the intake of alcohol and relapse-like drinking behaviors in mice and rats[37,38]. In a broader scope of scientific literature, a growing body of preclinical literature suggests that semaglutide and other GLP-1 receptor agonists may be effective new drugs for AUD (for review, see: [39]), yet future RCTs are needed before drawing any conclusion[40]. Of note, the fact that it raises blood insulin levels while decreasing drinking, however, conflicts with the conclusions drawn from[35] and leads to speculate that glucagon could be a more useful hormonal biomarker for quantifying craving.

Currently, there are several RCTs that evaluate the effect of semaglutide on AUD and three of them that specifically test the effect of semaglutide with alcohol craving as an outcome. All three trials use a self-reported method of quantifying craving, but they do use different approaches and instruments. One study has the primary objective of determining if semaglutide reduces alcohol drinking compared to a placebo and will measure craving as a secondary outcome in real-time (no assessment specified) by interviewing their participants immediately after a cue-reactivity procedure in a bar-laboratory setting (NCT06015893). In the next study, reducing craving is the primary outcome, and it is measured in a longitudinal format using the VAS. The researchers do this in a cue-induced procedure, where they test craving levels in patients when presented with a cue both before and after six weeks of treatment. (NCT05892432). The last trial is recruiting individuals with AUD and comorbid obesity (NCT05895643). The primary outcome of this study is the reduction of the number of heavy drinking over 26 weeks. Alcohol craving is a secondary outcome measured by the PACS. This trial also includes other clinical biomarkers that may be used to evaluate craving response and utilizes fMRI to elucidate brain mechanisms. All of these studies consider craving to be a component of their primary or secondary objectives and, thus, could greatly benefit from utilizing a hormonal biomarker associated with the effect of semaglutide to quantify craving as additional exploratory aims.

CONCLUSIONS

Craving has become very important in studying and assessing AUD as it has now been included in the diagnostic criteria (e.g., DSM-5) for alcohol and substance use disorders. The lack of quantitative objective measures has presented challenges in researching it. Therefore, researchers are trying to develop novel methods that hold the promise of objectively and specifically quantifying craving in hormonal biomarkers, pending future studies that will need to expand and fortify this growing line of research. Due to the link between alcohol craving and other addiction-related behaviors and the neurological pathways within the gut-liver-brain axis, hormones involved in this cross-talk, such as ghrelin, insulin and GLP-1, may help shedding light on new methodologies to quantify and predict craving. This has been further displayed in research where the conditions of the gut-liver-brain axis have been affected, such as by introducing exogenous IV ghrelin or by being probed by a pharmacotherapy that boosts GLP-1 levels, have also shown changes in alcohol craving and drinking behaviors. This is important as craving is a criterion for diagnosing AUD and having the ability to objectively and effectively quantify craving could provide addiction clinicians with novel critical information regarding the severity of a patient's condition and, thus, be able to provide their patients with more personalized and effective treatments. It can also be used by researchers to analyze the efficacy of a treatment that is being tested in a clinical trial to help people with AUD.

Conflict of Interest

The author declares that they have no conflicts of interest.

Funding

LL is supported by the NIH Intramural Research Program (NIDA/NIAAA).

Author Contribution

MAK draft the manuscript and LL revised it critically. Both authors have given approval of the submitted and final versions.

References

1. American Psychiatric Association D, Association AP. Diagnostic and statistical manual of mental disorders: DSM-5. vol 5. American psychiatric association Washington, DC, 2013.
2. Swift RM. Medications and alcohol craving. Alcohol Res Health. 1999;23(3):207-213.
3. Kavanagh DJ, Statham DJ, Feeney GFX, Young RM, May J, Andrade J, Connor JP. Measurement of alcohol craving. Addict Behav. Feb 2013;38(2):1572-1584. Doi: 10.1016/j.addbeh.2012.08.004
4. Connor JP, Feeney GF, Young RM. A comparison of the Yale-Brown Obsessive Compulsive Scale for "heavy drinking" with a single item craving measure: construct validity and clinical utility. Subst Use Misuse. 2005;40(4):551-561. Doi: 10.1081/ja-200030723

5. Drobes DJ, Thomas SE. Assessing craving for alcohol. Alcohol Res Health. 1999;23(3):179-186.
6. Li TK. Clinical perspectives for the study of craving and relapse in animal models. Addiction. Aug 2000;95 Suppl 2:S55-60. doi:10.1080/09652140050111645
7. Tabakoff B, Hoffman PL. Animal models in alcohol research. Alcohol Res Health. 2000;24(2):77-84.
8. Singleton E. Alcohol craving questionnaire, short-form (revised; ACQ-SF-R): background, scoring, and administration. Baltimore, MD, USA, 1995.
9. Singleton E, Tiffany S, Henningfield J. Development and validation of a new questionnaire to assess craving for alcohol: problems of drug dependence. 1994: Proceedings of the 56th Annual Meeting, The College on Problems of Drug Dependence, Inc. Volume II: Abstracts. NIDA Research Monograph 153. Rockville, Maryland: National Institute on Drug Abuse, 1995; p. 289.
10. Connolly KM, Coffey SF, Baschnagel JS, Drobes DJ, Saladin ME. Evaluation of the Alcohol Craving Questionnaire-Now factor structures: application of a cue reactivity paradigm. Drug Alcohol Depend. Jul 1 2009;103(1-2):84-91. Doi: 10.1016/j.drugalcdep.2009.03.019
11. Tiffany ST, Conklin CA. A cognitive processing model of alcohol craving and compulsive alcohol use. Addiction. Aug 2000;95(8 Suppl 2):145-153. Doi: 10.1080/09652140050111717.
12. Cacioppo JT, Martzke JS, Petty RE, Tassinary LG. Specific forms of facial EMG response index emotions during an interview: from Darwin to the continuous flow hypothesis affect-laden information processing. J Pers Soc Psychol. Apr 1988;54(4):592-604. Doi: 10.1037//0022-3514.54.4.592
13. Leshner AI. Addiction is a brain disease, and it matters. Science. Oct 3 1997;278(5335):45-47. Doi: 10.1126/science.278.5335.45
14. Heilig M, MacKillop J, Martinez D, Rehm J, Leggio L, Vanderschuren L. Addiction as a brain disease revised: why it still matters, and the need for consilience. Neuropsychopharmacology. Sep 2021;46(10):1715-1723. Doi:1 0.1038/s41386-020-00950-y
15. Everitt B. Craving cocaine cues: cognitive neuroscience meets drug addiction research. Trends Cogn Sci. Apr 1997;1(1):1-2. Doi: 10.1016/S1364-6613(97)01009-7
16. Kirsch M, Gruber I, Ruf M, Kiefer F, Kirsch P. Real-time functional magnetic resonance imaging neurofeedback can reduce striatal cue-reactivity to alcohol stimuli. Addict Biol. Jul 2016;21(4):982-992. Doi: 10.1111/adb.12278
17. Martz ME, Hart T, Heitzeg MM, Peltier SJ. Neuromodulation of brain activation associated with addiction: A review of real-time fMRI neurofeedback studies. Neuroimage Clin. 2020;27:102350. Doi: 10.1016/j.nicl.2020.102350
18. Stephens MA, Wand G. Stress and the HPA axis: role of glucocorticoids in alcohol dependence. Alcohol Res. 2012;34(4):468-483.
19. O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. Psychopharmacology (Berl). Feb 2002;160(1):19-29. Doi: 10.1007/s002130100919.
20. Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. Compr Physiol. Mar 15 2016;6(2):603-621. Doi: 10.1002/cphy.c150015.
21. Addolorato G, Leggio L, Hillemacher T, Kraus T, Jerlhag E, Bleich S. Hormones and drinking behaviour: new findings on ghrelin, insulin, leptin and volume-regulating hormones. An ESBRA Symposium report. Drug Alcohol Rev. Mar 2009;28(2):160-165. Doi: 10.1111/j.1465-3362.2008.00023.x.
22. Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philos Trans R Soc Lond B Biol Sci. Oct 12 2008;363(1507):3191-3200. Doi: 10.1098/rstb.2008.0107.
23. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. Dec 9 1999;402(6762):656-660. Doi: 10.1038/45230.
24. Jerlhag E, Egecioglu E, Dickson SL, Douhan A, Svensson L, Engel JA. Ghrelin administration into tegmental areas stimulates locomotor activity and increases extracellular concentration of dopamine in the nucleus accumbens. Addict Biol. Mar 2007;12(1):6-16. Doi: 10.1111/j.1369-1600.2006.00041.x.
25. Jerlhag E. Systemic administration of ghrelin induces conditioned place preference and stimulates accumbal dopamine. Addict Biol. Sep 2008;13(3-4):358-363. Doi: 10.1111/j.1369-1600.2008.00125.x.
26. Calissendorff J, Danielsson O, Brismar K, Rojdmark S. Inhibitory effect of alcohol on ghrelin secretion in normal man. Eur J Endocrinol. May 2005;152(5):743-747. Doi: 10.1530/eje.1.01905.
27. Addolorato G, Capristo E, Leggio L, Ferrulli A, Abenavoli L, Malandrino N, Farnetti S, Domenicali M, D'Angelo C, Vonghia L, Mirijello A, Cardone S, Gasbarrini G. Relationship between ghrelin levels, alcohol craving, and nutritional status in current alcoholic patients. Alcohol Clin Exp Res. Nov 2006;30(11):1933-1937. Doi: 10.1111/j.1530-0277.2006.00238.x.
28. Kraus T, Schanze A, Gröschl M, Bayerlein K, Hillemacher T, Reulbach U, Kornhuber J, Bleich S. Ghrelin

levels are increased in alcoholism. Alcohol Clin Exp Res. Dec 2005;29(12):2154-2157. Doi: 10.1097/01.alc.0000191753.82554.7e.
29. Leggio L, Zywiak WH, Fricchione SR, Edwards SM, de la Monte SM, Swift RM, Kenna GA. Intravenous ghrelin administration increases alcohol craving in alcohol-dependent heavy drinkers: a preliminary investigation. Biol Psychiatry. Nov 1 2014;76(9):734-741. Doi: 10.1016/j.biopsych.2014.03.019.
30. Haass-Koffler CL, Aoun EG, Swift RM, de la Monte SM, Kenna GA, Leggio L. Leptin levels are reduced by intravenous ghrelin administration and correlated with cue-induced alcohol craving. Transl Psychiatry. Sep 29 2015;5(9):e646. Doi: 10.1038/tp.2015.140.
31. Haass-Koffler CL, Giovenco DE, Lee MR, Zywiak WH, de la Monte SM, Kenna GA, Swift RM, Leggio L. Serum Insulin Levels Are Reduced by Intravenous Ghrelin Administration but Do Not Correlate with Alcohol Craving in Alcohol-Dependent Individuals. Int J Neuropsychopharmacol. 2016 May 10;19(10):pyw048. Doi: 10.1093/ijnp/pyw048.
32. Steiner JL, Crowell KT, Lang CH. Impact of Alcohol on Glycemic Control and Insulin Action. Biomolecules. Sep 29 2015;5(4):2223-2246. Doi: 10.3390/biom5042223.
33. Leggio L, Ray LA, Kenna GA, Swift RM. Blood glucose level, alcohol heavy drinking, and alcohol craving during treatment for alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) Study. Alcohol Clin Exp Res. Sep 2009;33(9):1539-1544. Doi: 10.1111/j.1530-0277.2009.00982.x.
34. Corl AB, Rodan AR, Heberlein U. Insulin signaling in the nervous system regulates ethanol intoxication in Drosophila melanogaster. Nat Neurosci. Jan 2005;8(1):18-19. Doi: 10.1038/nn1363.
35. Leggio L, Ferrulli A, Malandrino N, Miceli A, Capristo E, Gasbarrini G, Addolorato G. Insulin but not insulin growth factor-1 correlates with craving in currently drinking alcohol-dependent patients. Alcohol Clin Exp Res. 2008 Mar;32(3):450-458. Doi: 10.1111/j.1530-0277.2007.00589.x.
36. Mahapatra MK, Karuppasamy M, Sahoo BM. Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. Rev Endocr Metab Disord. Jun 2022;23(3):521-539. Doi: 10.1007/s11154-021-09699-1.
37. Aranäs C, Edvardsson CE, Shevchouk OT, Zhang Q, Witley S, Blid Sköldheden S, Zentveld L, Vallöf D, Tufvesson-Alm M, Jerlhag E. Semaglutide reduces alcohol intake and relapse-like drinking in male and female rats. EBioMedicine. Jul 2023;93:104642. Doi: 10.1016/j.ebiom.2023.104642.
38. Chuong V, Farokhnia M, Khom S, Pince CL, Elvig SK, Vlkolinsky R, Marchette RC, Koob GF, Roberto M, Vendruscolo LF, Leggio L. The glucagon-like peptide-1 (GLP-1) analogue semaglutide reduces alcohol drinking and modulates central GABA neurotransmission. JCI Insight. 2023 Jun 22;8(12):e170671. Doi: 10.1172/jci.insight.170671.
39. Klausen MK, Thomsen M, Wortwein G, Fink-Jensen A. The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. Br J Pharmacol. Feb 2022;179(4):625-641. Doi: 10.1111/bph.15677.
40. Leggio L, Hendershot CS, Farokhnia M, Fink-Jensen A, Klausen MK, Schacht JP, Simmons WK. GLP-1 receptor agonists are promising but unproven treatments for alcohol and substance use disorders. Nat Med. 2023 Dec;29(12):2993-2995. Doi: 10.1038/s41591-023-02634-8.