

Perspective

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The effect of glucagon-like peptide-1 and glucose dependent insulintropic polypeptide receptor agonists on neurogenesis, differentiation, and plasticity (Neuro-GDP): potential mechanistically informed therapeutics in the treatment and prevention of mental disorders

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Abstract

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) receptor agonists (RAs) mimic naturally occurring GLP-1 and GIP and are highly effective anti-diabetic and anti-obesity agents. In addition to their robust acute and long-term effects on weight, metabolism, and blood pressure, these agents also reduce cardiovascular mortality as well as stroke risk and associated consequences. A replicated and convergent body of preclinical evidence also indicates that incretin receptor agonists activate molecular effectors critical to neuroplasticity, neuroprotection, and anti-apoptosis. Herein, we propose that GLP-1 RAs and GIP RAs are promising transdiagnostic mechanistically informed therapeutics in the treatment and prevention of multiple domains of psychopathology, including general cognitive, reward, and motivation systems and mental disorders. Major neurocognitive disorders (eg, Alzheimer's Disease, Parkinson's Disease), alcohol and substance use disorders, traumatic brain injury, and depressive disorders are near-term therapeutic targets. In addition, GLP-1 RAs and GIP RAs have robust effects on comorbidities that differentially affect persons with mental disorders (eg, cardiovascular, cerebrovascular, and metabolic disorders) and psychotropic drug-related weight gain.

Introduction

The mechanism of action of antidepressants is not fully ascertained. It is hypothesized that antidepressant agents alleviate symptoms in depressive disorders by triggering molecular cascades integral to neuroplasticity, neuroprotection, and anti-apoptosis (NNA).^{1,2} The aforementioned molecular and cellular effects collectively modulate synaptic connection and strength as well as resting-state functional connectivity (RSFC) in discrete neural circuits and networks subserving the phenomenology of depressive disorders (eg, default mode network).^{3–6}

Glucagon-like peptide-1 (GLP-1 RA) and glucose-dependent insulintropic polypeptide receptor agonists (GIP RA), herein referred to as incretin receptor agonists (IRAs), mimic naturally occurring GLP-1 and GIP and are highly effective antidiabetic and anti-obesity agents.⁷ In addition to their robust acute and long-term effects on weight, metabolism, and blood pressure, these agents also reduce cardiovascular mortality as well as stroke risk and associated consequences.^{7–9} During the past decade, a replicated and convergent body of preclinical evidence also indicates that IRAs activate molecular effectors critical to NNA.

Herein, we propose that IRAs are promising treatments for mental disorders that engage brain targets critical to NNA known to subserve transdiagnostic phenomenology, notably general cognitive, reward, and motivation systems. We succinctly synthesize extant evidence but do not intend a review of the topic as multiple comprehensive reviews have been previously published.^{10–19} Instead, we attempt to provide a mechanistic framework for considering IRAs as putative mechanistically informed therapeutics for disparate mental disorders. Articles selected for citation are articles that were determined by authors to be most impactful either as original research or as a synthesis of available research.

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GLP-1 and GIP physiology and pharmacology

Glucagon-like peptide-1 is the product of preproglucagon encoded in intestinal L-cells as well as in neurons of the nucleus tractus solitarius (NTS). GLP-1 receptors are G-protein-coupled receptors (GPCRs) and are expressed in many human tissues, including the central nervous system (CNS; eg, hippocampus, hypothalamus, and cortex).²⁰ GLP-1 receptors are expressed on endothelial cells, neurons, astrocytes, and microglia.^{21–23}

Neuronal projections from the NTS to the paraventricular nucleus (PVN) of the hypothalamus facilitate reductions in food intake and behavior.^{24,25} GLP-1-producing neurons in the NTS also project to mesolimbic nuclei [eg, ventral tegmental area (VTA) and nucleus accumbens (NAcc)] and cortical structures.²⁰ The aforementioned provides the basis for targeting these systems in the treatment and prevention of mental disorders.²⁶

GIP is secreted by enteroendocrine K-cells, whose cognate receptor is also a GPCR.^{27,28} Whether GIP is synthesized in the CNS remains uncertain. Mixed evidence suggests that mRNA for GIP may be detected in select brain regions (eg, hippocampus).²⁹ Notwithstanding, GIP receptors are expressed across disparate brain regions (eg, cortex, hippocampus, striatum).^{27,30} GIP receptor gene knockout results in reduced hippocampal NNA and impairs learning and memory in murine models.^{27,31}

GLP-1 and GIP effects on neuro-genesis, -differentiation, -plasticity (Neuro-GDP) (Figure 1)(Figure 2)

Glucagon-like peptide-1 receptor agonists activate multiple signal transduction pathways relevant to neuro-genesis, -differentiation, -plasticity (Neuro-GDP).³² For example, endogenous GLP-1, GIP, and GLP-1 RAs (eg, liraglutide) increase synthesis of cAMP response element-binding protein (CREB), brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), and nerve growth factor (NGF) via PI3K-Akt activation.^{33–35} Moreover, GLP-1 promotes neuronal progenitor cell differentiation and neurite outgrowth.^{36,37}

In rodent models and humans, GLP-1-mediated secretion of BDNF increases synaptic density in the hippocampus.^{38–41} It is

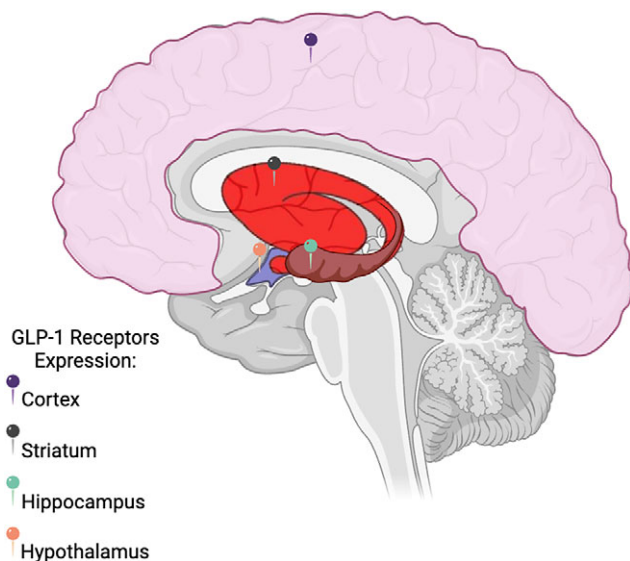


Figure 1. Distribution of GLP-1 receptors in the human central nervous system. Relevant structures that express GLP-1 receptors are highlighted.

hypothesized that trophic and plasticity effectors triggered by GLP-1 RAs mediate effects on cognition and/or motor function reported in Alzheimer's and Parkinson's Disease rodent models.^{42–48}

Preclinical evidence indicates that liraglutide prevents reductions in phosphorylation levels of mTORC1 and BDNF expression in rat hippocampal structures exposed to neurotoxic levels of dexamethasone.⁴⁹ The effect of liraglutide on BDNF expression and hippocampal dendrite length and spine density is blocked by rapamycin or the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor antagonist, 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide (NBQX).⁴⁹

Reduced long-term potentiation (LTP), increased long-term depression (LTD), and alterations in RSFC within and between brain circuits and networks are replicated findings in persons with depressive disorders.^{50–52} Glucagon-like peptide-1 receptor agonists rapidly increase excitatory postsynaptic currents and LTP.⁵³ Glutamatergic availability and function are integral to LTP and synaptic strength.⁵⁴

Glucagon-like peptide-1 receptor agonism modulates glutamatergic signaling by increasing AMPA trafficking, mTOR activation, and the transcription of synaptic proteins.^{55–57} In addition to the direct effects of GLP-1 RAs on molecular systems relevant to GDP, it is also observed that liraglutide increases intrinsic connectivity in bilateral hippocampal, medial-frontal, and lateral occipital regions, which inversely correlated with measures of insulin resistance in persons at genetic risk for Alzheimer's Disease.⁵⁸

Similar to the aforementioned effects of GLP-1 RAs on NNA, it is separately reported that GIP independently activates NNA systems. For example, GIP receptor knockout reduces neurogenesis and neurodifferentiation in the dentate gyrus of the hippocampus.⁵⁹ In addition, GIP increases hippocampal synaptic number and plasticity effects in murine models.^{60,61}

GLP-1 and GIP neuroprotective effects: anti-inflammatory and antioxidant

It is further reported that GLP-1 RAs exert neuroprotective effects via modulating immune-inflammatory processes and redox balance.^{43,62–66} Pro-inflammatory processes and redox imbalance are implicated in the pathogenesis and progression of depressive disorders.⁶⁷ Glucagon-like peptide-1 receptors are expressed on myeloid cells including monocytes, macrophages and glia (eg, microglia) where they modulate immune-inflammatory and redox balance systems.^{68,69} It is known that GLP-1 RAs decrease circulating C-reactive peptide (CRP), matrix metalloproteinase-9, monocyte chemoattractant protein-1, toll-like receptor 4 (TLR4), JNK-1 expression, nuclear factor-B as well as pro-inflammatory cytokines (eg, interleukin-6; IL-6) in human subjects.⁷⁰

Glucagon-like peptide-1 is also synthesized and released in response to exposure to lipopolysaccharide.⁷¹ Glucagon-like peptide-1 receptor agonists also affect glial homeostasis and reactivity insofar as they induce less transcription of pro-inflammatory markers.^{72,73} Finally, it has been observed that GLP-1 RAs decrease blood-brain barrier (BBB) permeability under toxic conditions.^{69,74,75}

The brain is especially susceptible to redox imbalance (ie, reactive oxygen species; ROS) due to its high oxygen utilization, lipid content, and relatively low endogenous antioxidant capacity.⁶⁷ Oxidative stress compromises neuronal and glial integrity, viability, and function and is hypothesized to be integral to the pathoetiology of depressive and other mental disorders.^{76,77}

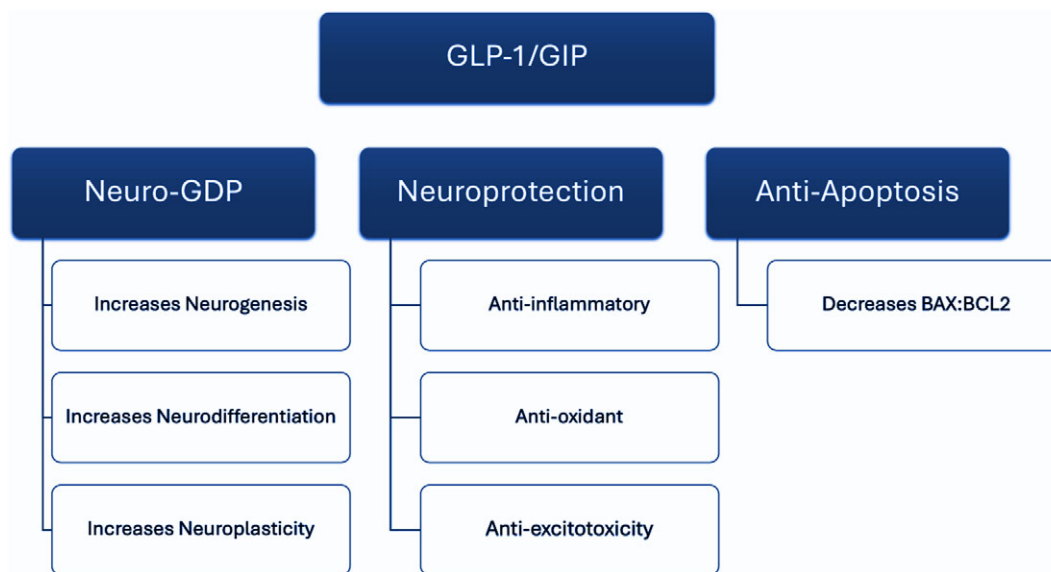


Figure 2. GLP-1 and GIP effects on neuro-genesis, -differentiation, - plasticity (GDP), neuroprotection and anti-apoptosis.

Glucagon-like peptide-1 receptor agonists exert direct and indirect regulatory effects on redox imbalance.⁷⁸ The antioxidant effects of GLP-1 RAs are observed whether oxidative stress is activated by glutamate or arachidonic acid.⁷⁸ A replicated finding is that the antioxidant effects of GLP-1 RAs are mediated via their effect on ERK5/CREB signaling.⁷⁸

Similar to GLP-1, disparate local and systemic anti-inflammatory effects are reported following GIP receptor activation. For example, GIP receptor activation results in decreased mRNA expression of macrophage chemoattractant protein 1 (MCP-1), vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule 1 (ICAM) as well as decreased circulating levels of interleukin IL-1 β and TNF α .⁷⁹ GIP knockout models report decrease in circulating monocytes and neutrophils, suggesting direct effects on hematopoietic lines.⁸⁰ Neuroprotective effects of GIP are hypothesized to be mediated via their anti-inflammatory effects.⁸¹ The effect of GIP on redox balance is also replicated with observations of increases in glutathione peroxidase (GPX) and superoxide dismutase (SOD1) levels as well as decreased reactive oxygen species and release of nitric oxide.⁸²

Beneficial effects of IRAs against post-stroke excitotoxicity as well as prevention involve many of the effectors previously covered.⁹ IRAs affect glutamatergic signaling via ionotropic receptor modulation. For example, it is separately reported that *N*-Methyl-D-Aspartate (NMDA) receptor antagonism increases GLP-1 synthesis and release improving glucose-insulin homeostasis in persons treated with NMDA antagonists (eg, dextromethorphan).^{83–85} Glucagon-like peptide-1 receptor agonists also modulate RSFC within and between circuits relevant to salience and cognitive control in persons with obesity and/or type 2 diabetes mellitus (T2DM).⁸⁶

Anti-apoptotic effects of GLP-1 and GIP

The pro-apoptotic BAX proteins are regulated by caspases and countered by the increased availability of SOD1, catalase (CAT), and GPX.⁸⁷ Indirectly, GLP-1 receptor agonism modulates redox imbalance by reducing advanced glycation endproducts (AGE), malondialdehyde (MDA), and thiobarbituric acid reactive substances

(TBARS).^{87,88} Glucagon-like peptide-1 receptor agonists, as well as dual GLP-1 agonists, reduce caspase-3 and BAX activity while simultaneously increasing Bcl-2 activity.^{31,89}

Clinical corollaries

Glucagon-like peptide-1 receptor agonists (eg, exenatide, liraglutide, semaglutide) and GLP-1/GIP co-agonists (eg, tirzepatide) are detectable in the brain and have differential CNS penetrance when using murine models.^{90,91} It remains uncertain the extent to which IRAs meaningfully penetrate (ie, target engagement) the BBB in human subjects and whether differential pharmacokinetics exist among the IRAs with respect to brain concentration.⁹² Preliminary evidence also suggests the benefit of IRAs in the treatment and/or prevention of alcohol-use, major neurocognitive (eg, Alzheimer's Disease), Parkinson's Disease, traumatic brain injury, and nicotine use.^{12,26,93–111} A critical issue bridging preclinical study results to critical translation is posology and route of administration. Doses implemented in many of the preclinical models approximate comparable human doses but are not identical. Moreover, the route of administration in animals is similar to (eg, parenteral) human administration of IRAs, although it is recognized that there is a growing interest in the oral administration of IRAs in humans. In addition, it is unknown whether the dosing of IRAs that are effective in the prevention and treatment of mental disorders is similar to anti-diabetic and anti-obesity dosing.

An emerging literature has also examined antidepressant efficacy associated with GLP-1 RAs. Chen et al.¹¹² identified 5 randomized controlled trials in diabetic and/or Parkinson's Disease patients ($n = 2071$) prescribed exenatide or liraglutide and reported a small but significant reduction in associated depressive symptoms in secondary analyses as compared to placebo or other antidiabetics such as insulin, sulfonylureas or pioglitazone. The presence of subthreshold depressive symptoms in the included samples may account for the small observed effect sizes (SMD = -0.12 , 95% CI = -0.21 to -0.03). A separate meta-analysis, focusing on GLP-1 RAs specifically to treat major depression (6 randomized trials, $n = 399$), reported a small effect size that just fell short of statistical significance (SMD = 0.25 , 95%

CI = -0.1 to 0.60).¹¹³ Exploratory subgroup analyses in the latter study suggested ethno-geographic variability as a moderator of GLP-1 RA antidepressant response.^{112,113}

Concluding remarks

We propose that IRAs, via their effect on, NNA hold tremendous promise as therapeutics across multiple mental disorders. In addition, extant evidence provides a rationale for potential preventative effects, especially as it relates to cognitive dysfunction and possibly depressive symptoms with these agents. There is a need for target engagement studies in human clinical populations with these agents to better characterize the NNA effects on circuit and network connectivity. There is also the need for large, adequate, well-controlled phase II and phase III studies with these agents in the disorders that are lead candidates (eg, Parkinson's Disease, major neurocognitive, alcohol use, and depressive disorders). In addition, preliminary evidence suggests allelic variants for gene barriers so the GLP-1 receptor gene may be associated with risk for select mental disorders (eg, alcohol use disorders, Alzheimer's Disease).^{114,115}

Both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued public statements that no causal evidence exists linking IRAs to suicidality.^{116–120} Moreover, replicated results from cohort observational studies also suggest that GLP-1RAs are associated with no increase in suicidality and in some reports a decrease reporting in suicidality and/or conditions associated with suicide (eg, depressive disorders).^{110,121–128} In addition, there is a need for adequate well-controlled studies targeting psychotropic drug-related weight gain (PDWG) and metabolically associated comorbidity (eg, cardiovascular disease, metabolic dysfunction associated with steatotic liver disease; MASLD).^{129,130} The greater effect size of GLP-1/GIP co-agonists when compared to GLP-1 RAs on body weight reduction and associated metabolic morbidity, along with the direct NNA effects documented with GIP, introduce the rationale that incretin co-agonists may have additional but different mechanistic effects on systems subserving psychopathological domains.¹³¹

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References

1. Rădulescu I, Drăgoi AM, Trifu SC, Cristea MB. Neuroplasticity and depression: rewiring the brain's networks through pharmacological therapy (Review). *Exp Ther Med*. 2021;**22**:1131.
2. Hunsberger J, Austin DR, Henter ID, Chen G. The neurotrophic and neuroprotective effects of psychotropic agents. *Dialogues Clin Neurosci*. 2009;**11**:333–348.
3. McIntyre RS, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. 2021;**178**: 383–399.
4. Wong S, et al. A comparison between psilocybin and esketamine in treatment-resistant depression using number needed to treat (NNT): a systematic review. *J Affect Disord*. 2024;**350**:698–705.
5. Cooper T, Seigler MD, Stahl S. Rapid onset brain plasticity at novel pharmacologic targets hypothetically drives innovations for rapid onset antidepressant actions. *J Psychopharmacol*. 2023;**37**:242–247.
6. Wang L, et al. The effects of antidepressant treatment on resting-state functional brain networks in patients with major depressive disorder. *Hum Brain Mapp*. 2015;**36**:768–778.
7. Drucker DJ. The GLP-1 journey: from discovery science to therapeutic impact. *J Clin Invest*. 2024;**134**.
8. Drucker DJ. Prevention of cardiorenal complications in people with type 2 diabetes and obesity. *Cell Metab*. 2024;**36**:338–353.
9. Vergès B, et al. Protection against stroke with glucagon-like peptide-1 receptor agonists: a comprehensive review of potential mechanisms. *Cardiovasc Diabetol*. 2022;**21**:242.
10. Hölscher C. The role of GLP-1 in neuronal activity and neurodegeneration. *Vitam Horm*. 2010;**84**:331–354.
11. Grieco M, et al. Glucagon-like peptide-1: a focus on neurodegenerative diseases. *Front Neurosci*. 2019;**13**:1112.
12. McIntyre RS, et al. The neuroprotective effects of GLP-1: possible treatments for cognitive deficits in individuals with mood disorders. *Behav Brain Res*. 2013;**237**:164–171.
13. Labandeira CM, et al. Diabetes, insulin and new therapeutic strategies for Parkinson's disease: focus on glucagon-like peptide-1 receptor agonists. *Front Neuroendocrinol*. 2021;**62**:100914.
14. Bae CS, Song J. The role of glucagon-like peptide 1 (GLP1) in type 3 diabetes: GLP-1 controls insulin resistance, neuroinflammation and neurogenesis in the brain. *Int J Mol Sci*. 2017;**18**.
15. Kopp KO, Glotfelty EJ, Li Y, Greig NH. Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: implications for neurodegenerative disease treatment. *Pharmacol Res*. 2022;**186**:106550.
16. Hölscher C. Glucagon-like peptide-1 class drugs show clear protective effects in Parkinson's and Alzheimer's disease clinical trials: a revolution in the making? *Neuropharmacology*. 2024;**253**:109952.
17. Liu W, et al. Liraglutide reduces alcohol consumption, anxiety, memory impairment, and synapse loss in alcohol dependent mice. *Neurochem Res*. 2024;**49**:1061–1075.
18. Rădulescu S, et al. Glucagon-like peptide 1 agonist and effects on reward behaviour: a systematic review. *Physiol Behav*. 2024;**283**:114622.
19. Drucker DJ. The benefits of GLP-1 drugs beyond obesity. *Science*. 2024;**385**:258–260.
20. Muscogiuri G, DeFronzo RA, Gastaldelli A, Holst JJ. Glucagon-like peptide-1 and the central/peripheral nervous system: crosstalk in diabetes. *Trends Endocrinol Metab*. 2017;**28**:88–103.
21. Fukuda S, et al. Glucagon-like peptide-1 strengthens the barrier integrity in primary cultures of rat brain endothelial cells under basal and hyperglycemia conditions. *J Mol Neurosci*. 2016;**59**:211–219.

22. Chen F, et al. The glucagon-like peptide-1 receptor agonist exendin-4 ameliorates warfarin-associated hemorrhagic transformation after cerebral ischemia. *J Neuroinflammation*. 2016;**13**:204.
23. Wang M-D, et al. Exendin-4 improved rat cortical neuron survival under oxygen/glucose deprivation through PKA pathway. *Neuroscience*. 2012;**226**:388–396.
24. López-Ferreras L, et al. Lateral hypothalamic GLP-1 receptors are critical for the control of food reinforcement, ingestive behavior and body weight. *Mol Psychiatry*. 2018;**23**:1157–1168.
25. Liu J, et al. Enhanced AMPA receptor trafficking mediates the anorexiogenic effect of endogenous glucagon-like peptide-1 in the paraventricular hypothalamus. *Neuron*. 2017;**96**:897–909.e5.
26. Cooper DH, et al. Glucagon-like peptide 1 (GLP-1) receptor agonists as a protective factor for incident depression in patients with diabetes mellitus: a systematic review. *J Psychiatr Res*. 2023;**164**:80–89.
27. Lennox R, et al. Effects of glucose-dependent insulinotropic polypeptide receptor knockout and a high-fat diet on cognitive function and hippocampal gene expression in mice. *Mol Med Rep*. 2015;**12**:1544–1548.
28. Campbell JE. Targeting the GIPR for obesity: to agonize or antagonize? Potential mechanisms. *Mol Metab*. 2021;**46**:101139.
29. Adriaenssens AE, Gribble FM, Reimann F. The glucose-dependent insulinotropic polypeptide signaling axis in the central nervous system. *Pepptides*. 2020;**125**:170194.
30. Nyberg J, Jacobsson C, Anderson MF, Eriksson PS. Immunohistochemical distribution of glucose-dependent insulinotropic polypeptide in the adult rat brain. *J Neurosci Res*. 2007;**85**:2099–2119.
31. Fontanella RA, et al. Tirzepatide prevents neurodegeneration through multiple molecular pathways. *J Transl Med*. 2024;**22**:114.
32. Li M, Li S, Li Y. Liraglutide promotes cortical neurite outgrowth via the MEK–ERK pathway. *Cell Mol Neurobiol*. 2015;**35**:987–993.
33. Cheng L, et al. Liraglutide attenuates palmitate-induced apoptosis via PKA/ β -catenin/Bcl-2/Bax pathway in MC3T3-E1 cells. *Naunyn-Schmiedeberg Arch Pharmacol*. 2024;**397**:329–341.
34. Hölscher C. Glucagon-like peptide 1 and glucose-dependent insulinotropic peptide hormones and novel receptor agonists protect synapses in Alzheimer's and Parkinson's diseases. *Front Synaptic Neurosci*. 2022;**14**:955258.
35. Yang J-L, et al. The neurotrophic function of glucagon-like peptide-1 promotes human neuroblastoma differentiation via the PI3K–AKT axis. *Biology*. 2020;**9**.
36. Perry T, Haughey NJ, Mattson MP, Egan JM, Greig NH. Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. *J Pharmacol Exp Ther*. 2002;**302**:881–888.
37. Cui QN, Stein LM, Fortin SM, Hayes MR. The role of glia in the physiology and pharmacology of glucagon-like peptide-1: implications for obesity, diabetes, neurodegeneration and glaucoma. *Br J Pharmacol*. 2022;**179**:715–726.
38. Belsham DD, et al. Ciliary neurotrophic factor recruitment of glucagon-like peptide-1 mediates neurogenesis, allowing immortalization of adult murine hypothalamic neurons. *FASEB J*. 2009;**23**:4256–4265.
39. Harkavyi A, Whitton PS. Glucagon-like peptide 1 receptor stimulation as a means of neuroprotection. *Br J Pharmacol*. 2010;**159**:495–501.
40. Salcedo I, Tweedie D, Li Y, Greig NH. Neuroprotective and neurotrophic actions of glucagon-like peptide-1: an emerging opportunity to treat neurodegenerative and cerebrovascular disorders. *Br J Pharmacol*. 2012;**166**:1586–1599.
41. Diz-Chaves Y, Herrera-Pérez S, González-Matías LC, Mallo F. Effects of glucagon-like peptide 1 (GLP-1) analogs in the hippocampus. 2022; *Vitam Horm*:**118**, 457–478.
42. Sharma HS, Sharma A. *Progress in Nanomedicine in Neurologic Diseases*. Springer Nature; 2023.
43. Athauda D, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;**390**:1664–1675.
44. McGarry A, et al. Safety, tolerability, and efficacy of NLY01 in early untreated Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2024;**23**:37–45.
45. Leon N, LaCoursiere R, Yarosh D, Patel RS. Lixisenatide (Adlyxin): a once-daily incretin mimetic injection for type-2 diabetes. *P T*. 2017;**42**:676–711.
46. Cai H-Y, et al. Lixisenatide rescues spatial memory and synaptic plasticity from amyloid β protein-induced impairments in rats. *Neuroscience*. 2014;**277**:6–13.
47. McClean PL, Hölscher C. Lixisenatide, a drug developed to treat type 2 diabetes, shows neuroprotective effects in a mouse model of Alzheimer's disease. *Neuropharmacology*. 2014;**86**:241–258.
48. Liu W, et al. Neuroprotective effects of lixisenatide and liraglutide in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. *Neuroscience*. 2015;**303**:42–50.
49. Park SW, et al. Liraglutide activates mTORC1 signaling and AMPA receptors in rat hippocampal neurons under toxic conditions. *Front Neurosci*. 2018;**12**:756.
50. Reyes-Lizaola S, Luna-Zarate U, Tendilla-Beltrán H, Morales-Medina JC, Flores G. Structural and biochemical alterations in dendritic spines as key mechanisms for severe mental illnesses. *Prog Neuropsychopharmacol Biol Psychiatry*. 2024;**129**:110876.
51. Zhou Z, et al. Distinctive intrinsic functional connectivity alterations of anterior cingulate cortex subdivisions in major depressive disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2024;**159**:105583.
52. Coveleskie K, et al. The effect of the GLP-1 analogue Exenatide on functional connectivity within an NTS-based network in women with and without obesity. *Obes Sci Pract*. 2017;**3**:434–445.
53. McClean PL, Gault VA, Harriott P & Hölscher C. Glucagon-like peptide-1 analogues enhance synaptic plasticity in the brain: a link between diabetes and Alzheimer's disease. *Eur J Pharmacol*. 2010;**630**:158–162.
54. Lüscher C, Malenka RC. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harb Perspect Biol*. 2012;**4**.
55. Hölscher C. Glucagon-like peptide 1 and glucose-dependent insulinotropic peptide hormones and novel receptor agonists protect synapses in Alzheimer's and Parkinson's diseases. *Front Synaptic Neurosci*. 2022;**14**:955258.
56. Gould TD, Zanos P, Zarate CA, Jr. Ketamine mechanism of action: separating the wheat from the chaff. *Neuropsychopharmacology*. 2017;**42**:368–369.
57. Zanos P, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature*. 2016;**533**:481–486.
58. Watson KT, et al. Neural correlates of liraglutide effects in persons at risk for Alzheimer's disease. *Behav Brain Res*. 2019;**356**:271–278.
59. Nyberg J, et al. Glucose-dependent insulinotropic polypeptide is expressed in adult hippocampus and induces progenitor cell proliferation. *J Neurosci*. 2005;**25**:1816–1825.
60. Faivre E, Hölscher C. D-Ala2GIP facilitated synaptic plasticity and reduces plaque load in aged wild type mice and in an Alzheimer's disease mouse model. *J Alzheimers Dis*. 2013;**35**:267–283.
61. Faivre E, Hamilton A, Hölscher C. Effects of acute and chronic administration of GIP analogues on cognition, synaptic plasticity and neurogenesis in mice. *Eur J Pharmacol*. 2012;**674**:294–306.
62. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;**132**:2131–2157.
63. Xiong H, et al. The neuroprotection of liraglutide on Alzheimer-like learning and memory impairment by modulating the hyperphosphorylation of tau and neurofilament proteins and insulin signaling pathways in mice. *J Alzheimers Dis*. 2013;**37**:623–635.
64. Shi L, Zhang Z, Li L, Hölscher C. A novel dual GLP-1/GIP receptor agonist alleviates cognitive decline by re-sensitizing insulin signaling in the Alzheimer icv. STZ rat model. *Behav Brain Res*. 2017;**327**:65–74.
65. Zhu H, et al. The neuroprotection of liraglutide against ischaemia-induced apoptosis through the activation of the PI3K/AKT and MAPK pathways. *Sci Rep*. 2016;**6**:26859.
66. Diz-Chaves Y, Mastoor Z, Spuch C, González-Matías LC, Mallo F. Anti-inflammatory effects of GLP-1 receptor activation in the brain in neurodegenerative diseases. *Int J Mol Sci*. 2022;**23**.

67. Bhatt S, Nagappa AN, Patil CR. Role of oxidative stress in depression. *Drug Discov Today*. 2020;**25**:1270–1276.
68. Timper K, et al. GLP-1 receptor signaling in astrocytes regulates fatty acid oxidation, mitochondrial integrity, and function. *Cell Metab*. 2020;**31**:1189–1205.e13.
69. Diz-Chaves Y, Mastoor Z, Spuch C, González-Matías LC, Mallo F. Anti-inflammatory effects of GLP-1 receptor activation in the brain in neurodegenerative diseases. *Int J Mol Sci*. 2022;**23**.
70. Chaudhuri A, et al. Exenatide exerts a potent antiinflammatory effect. *J Clin Endocrinol Metab*. 2012;**97**:198–207.
71. Wong CK, et al. Central glucagon-like peptide 1 receptor activation inhibits Toll-like receptor agonist-induced inflammation. *Cell Metab*. 2024;**36**:130–143.e5.
72. Paolicelli RC, et al. Microglia states and nomenclature: a field at its crossroads. *Neuron*. 2022;**110**:3458–3483.
73. Qian Z, et al. Activation of glucagon-like peptide-1 receptor in microglia attenuates neuroinflammation-induced glial scarring via rescuing Arf and Rho GAP adapter protein 3 expressions after nerve injury. *Int J Biol Sci*. 2022;**18**:1328–1346.
74. Shan Y, et al. The glucagon-like peptide-1 receptor agonist reduces inflammation and blood-brain barrier breakdown in an astrocyte-dependent manner in experimental stroke. *J Neuroinflammation*. 2019;**16**:242.
75. Gault VA, Hölscher C. GLP-1 receptor agonists show neuroprotective effects in animal models of diabetes. *Peptides*. 2018;**100**:101–107.
76. Liu T, et al. A meta-analysis of oxidative stress markers in depression. *PLoS One*. 2015;**10**:e0138904.
77. Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BWJH. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology*. 2015;**51**:164–175.
78. Wang S, Liu A, Xu C, Hou J, Hong J. GLP-1(7-36) protected against oxidative damage and neuronal apoptosis in the hippocampal CA region after traumatic brain injury by regulating ERK5/CREB. *Mol Biol Rep*. 2024;**51**:313.
79. He X. Glucose-dependent insulinotropic polypeptide and tissue inflammation: implications for atherogenic cardiovascular disease. *Eur J Inflam*. 2022;**20**:20587392211070402.
80. Morrow NM, Morissette A, Mulvihill EE. Immunomodulation and inflammation: role of GLP-1R and GIPR expressing cells within the gut. *Peptides*. 2024;**176**:171200.
81. Ji C, Xue G-F, Li G, Li D, Hölscher C. Neuroprotective effects of glucose-dependent insulinotropic polypeptide in Alzheimer's disease. *Rev Neurosci*. 2016;**27**:61–70.
82. Spielman LJ, Gibson DL, Klegeris A. Incretin hormones regulate microglia oxidative stress, survival and expression of trophic factors. *Eur J Cell Biol*. 2017;**96**:240–253.
83. Liu J, et al. Enhanced AMPA receptor trafficking mediates the anorexigenic effect of endogenous glucagon-like peptide-1 in the paraventricular hypothalamus. *Neuron*. 2017;**96**:897–909.e5.
84. Scholz O, et al. Protection of pancreatic islets from oxidative cell death by a peripherally-active morphinan with increased drug safety. *Mol Metab*. 2023;**75**:101775.
85. Cyranka M, et al. NMDA receptor antagonists increase the release of GLP-1 from gut endocrine cells. *Front. Pharmacol.*. 2022;**13**:861311.
86. Farr OM, et al. GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled trial. *Diabetologia*. 2016;**59**:954–965.
87. Yarbeygi H, Maleki M, Sathyapalan T, Jamialahmadi T, Sahebkar A. Antioxidative potentials of incretin-based medications: a review of molecular mechanisms. *Oxid Med Cell Longev*. 2021;**2021**:9959320.
88. Lambadiari V, et al. Effects of a 12-month treatment with glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, and their combination on oxidant and antioxidant biomarkers in patients with type 2 diabetes. *Antioxidants (Basel)*. 2021;**10**.
89. Chen J, et al. Glucagon-like peptide-1 receptor regulates endoplasmic reticulum stress-induced apoptosis and the associated inflammatory response in chondrocytes and the progression of osteoarthritis in rat. *Cell Death Dis*. 2018;**9**:212.
90. Salameh TS, Rhea EM, Talbot K, Banks WA. Brain uptake pharmacokinetics of incretin receptor agonists showing promise as Alzheimer's and Parkinson's disease therapeutics. *Biochem Pharmacol*. 2020;**180**:114187.
91. Rhea EM, et al. Brain uptake pharmacokinetics of albiglutide, dulaglutide, tirzepatide, and DA5-CH in the search for new treatments of Alzheimer's and Parkinson's diseases. *Tissue Barriers*. 2023;**22**:292461.
92. Christensen M, et al. Transfer of liraglutide from blood to cerebrospinal fluid is minimal in patients with type 2 diabetes. *Int J Obes*. 2015;**39**:1651–1654.
93. Svenningsson P, et al. Reduced incidence of Parkinson's disease after dipeptidyl peptidase-4 inhibitors—a nationwide case-control study. *Mov Disord*. 2016;**31**, 1422–1423.
94. Hunter K, Hölscher C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. *BMC Neurosci*. 2012;**13**:33.
95. Mansur RB, et al. The effect of body mass index on glucagon-like peptide receptor gene expression in the post mortem brain from individuals with mood and psychotic disorders. *Eur Neuropsychopharmacol*. 2019;**29**:137–146.
96. Mansur RB, Lee Y, Subramaniapillai M, Brietzke E, McIntyre RS. Cognitive dysfunction and metabolic comorbidities in mood disorders: a repurposing opportunity for glucagon-like peptide 1 receptor agonists? *Neuropharmacology*. 2018;**136**:335–342.
97. Barkas F, Elisaf M, Milionis H. Protection against stroke with glucagon-like peptide 1 receptor agonists: a systematic review and meta-analysis. *Eur J Neurol*. 2019;**26**:559–565.
98. Brauer R, et al. Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes. *Brain*. 2020;**143**:3067–3076.
99. Malhotra K, et al. GLP-1 receptor agonists in diabetes for stroke prevention: a systematic review and meta-analysis. *J Neurol*. 2020;**267**:2117–2122.
100. Yammine L, et al. Exenatide adjunct to nicotine patch facilitates smoking cessation and may reduce post-cessation weight gain: a pilot randomized controlled trial. *Nicotine Tob Res*. 2021;**23**:1682–1690.
101. De Giorgi R, et al. 12-month neurological and psychiatric outcomes of semaglutide use for type 2 diabetes: a propensity-score matched cohort study. *eClinicalMedicine*. 2024. doi: 10.1016/j.eclim.2024.102726.
102. Vaccari C, Grotto D, Pereira T da V, de Camargo JLV, Lopes, LC. GLP-1 and GIP receptor agonists in the treatment of Parkinson's disease: translational systematic review and meta-analysis protocol of clinical and preclinical studies. *PLoS One*. 2021;**16**:e0255726.
103. Liu C, et al. Discovery of a novel GLP-1/GIP dual receptor agonist CY-5 as long-acting hypoglycemic, anti-obesity agent. *Bioorg Chem*. 2021;**106**:104492.
104. Klausen MK, et al. Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. *JCI Insight*. 2022;**7**.
105. Chuong V, et al. The glucagon-like peptide-1 (GLP-1) analogue semaglutide reduces alcohol drinking and modulates central GABA neurotransmission. *JCI Insight*. 2023;**8**.
106. Meissner WG, et al. Trial of lixisenatide in early Parkinson's disease. *N Engl J Med*. 2024;**390**:1176–1185.
107. Quddos F, et al. Semaglutide and Tirzepatide reduce alcohol consumption in individuals with obesity. *Sci Rep*. 2023;**13**:20998.
108. Tang H, et al. Newer glucose-lowering drugs and risk of dementia: a systematic review and meta-analysis of observational studies. *J Am Geriatr Soc*. 2023;**71**:2096–2106.
109. Xie Y, et al. Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of major adverse cardiovascular events: emulation of a randomised target trial using electronic health records. *Lancet Diabetes Endocrinol*. 2023;**11**:644–656.
110. Wang W, et al. Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nat Med*. 2024;**30**:168–176.
111. Tang H, et al. Glucagon-like peptide-1 receptor agonists and risk of Parkinson's disease in patients with type 2 diabetes: a population-based cohort study. *Mov Disord*. 2024;**39**:1960–1970.

112. Chen X, Zhao P, Wang W, Guo L, Pan Q. The antidepressant effects of GLP-1 receptor agonists: a systematic review and meta-analysis. *Am J Geriatr Psychiatry*. 2024;**32**:117–127.
113. Zhang J, et al. Efficacy and safety of antidiabetic agents for major depressive disorder and bipolar depression: a meta-analysis of randomized, double-blind, placebo-controlled trials. *J Clin Med Res*. 2024;**13**.
114. Farokhnia M, et al. Differential association between the GLP1R gene variants and brain functional connectivity according to the severity of alcohol use. *Sci Rep*. 2022;**12**:13027.
115. Tang B, et al. Genetic variation in targets of antidiabetic drugs and Alzheimer disease risk: a Mendelian randomization study. *Neurology*. 2022;**99**:e650–e659.
116. McIntyre RS. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: what do we know and future vistas. *Expert Opin Drug Saf*. 2024;1–4.
117. McIntyre RS, Mansur RB, Rosenblat JD, Kwan ATH.. The association between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: reports to the Food and Drug Administration Adverse Event Reporting System (FAERS). *Expert Opin Drug Saf*. 2023;1–9.
118. Center for Drug Evaluation & Research. *Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking a certain type of medicines approved for type 2 diabetes and obesity*. U.S. Food and Drug Administration; 2024. <https://www.fda.gov/drugs/drug-safety-and-availability/update-fdas-ongoing-evaluation-reports-suicidal-thoughts-or-actions-patients-taking-certain-type>.
119. Meeting highlights from the pharmacovigilance risk assessment committee (PRAC) 8-11 April 2024. <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-8-11-april-2024>.
120. Wang W, et al. Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nat Med*. 2024;**30**:168–176.
121. Wadden TA, et al. Psychiatric safety of semaglutide for weight management in people without known major psychopathology: post hoc analysis of the STEP 1, 2, 3, and 5 trials. *JAMA Intern Med*. 2024;**184**:1290–1300.
122. Kornelius E, Huang J-Y, Lo S-C, Huang C-N, Yang Y-S. The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon like peptide-1 receptor agonist therapy. *Sci Rep*. 2024;**14**:24433.
123. Ueda P, et al. GLP-1 receptor agonist use and risk of suicide death. *JAMA Intern Med*. 2024;**184**:1301–1312.
124. Tang H, et al. Glucagon-like peptide-1 receptor agonists and risk for suicidal ideation and behaviors in U.S. older adults with type 2 diabetes : a target trial emulation study. *Ann Intern Med*. 2024;**177**:1004–1015.
125. Nassar M, Misra A, Bloomgarden Z. Impact of treatment with GLP-1RAs on suicide attempts in adults persons with type 2 diabetes: a retrospective comparative effectiveness study based on a global TriNetX health research database. *J Diabetes*. 2024;**16**:e13547.
126. Gamble J-M, Chibrikov E, Midodzi WK, Twells LK, Majumdar SR. Examining the risk of depression or self-harm associated with incretin-based therapies used to manage hyperglycaemia in patients with type 2 diabetes: a cohort study using the UK Clinical Practice Research Data-link. *BMJ Open*. 2018;**8**:e023830.
127. Hurtado I, Robles C, Peiró S, García-Sempere A, Sanfeliix-Gimeno G. Association of glucagon-like peptide-1 receptor agonists with suicidal ideation and self-injury in individuals with diabetes and obesity: a propensity-weighted, population-based cohort study. *Diabetologia*. 2024;**67**:2471–2480.
128. Kerem L, Stokar J. Risk of suicidal ideation or attempts in adolescents with obesity treated with GLP1 receptor agonists. *JAMA Pediatr*. 2024;**178**:1307–1315.
129. McIntyre RS, Kwan ATH, Rosenblat JD, Teopiz KM, Mansur RB. Psychotropic drug-related weight gain and its treatment. *AJP*. 2024;**181**:26–38.
130. Jawad MY, et al. The bidirectional association of nonalcoholic fatty liver disease with depression, bipolar disorder, and schizophrenia. *CNS Spectr*. 2023;**28**:541–560.
131. Frías JP, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;**385**:503–515.