Glucagon-Like Peptide 1: Possible Implications for Neuropsychiatry & Neurodegeneration

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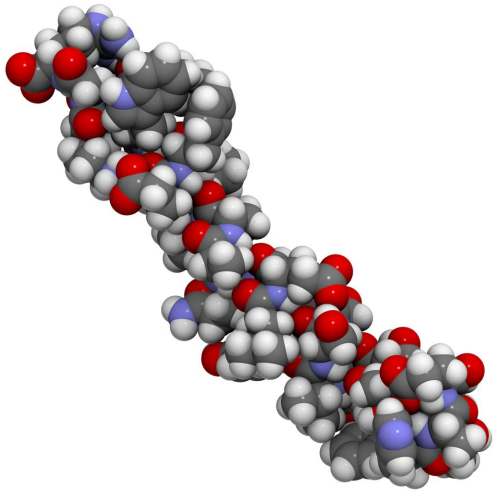
- Glucagon-like peptide 1 (GLP-1) is an incretin, a gut-derived hormone released from enteroendocrine L-cells (distributed along the entire gastrointestinal tract) after food intake, leading to the secretion of insulin from pancreatic beta cells in a nutrient-dependent manner.
- GLP-1 is also secreted from alpha cells in the pancreas and multiple regions in the central nervous system.
- There are two bioactive forms of this peptide hormone in the bloodstream:
    - **GLP-1-(7–36)-NH2**: the more abundant form (approximately 80%)
    - **GLP-1-(7–37)**: the less abundant form (approximately 20%)



- Both GLP-1-(7–36)-NH2 and GLP-1-(7–37) interact with a specific GLP-1 receptor, a class B G protein–coupled receptor.
- GLP-1 receptors are widely expressed throughout multiple human tissues (e.g., muscles, bones, and adipose) and organs (e.g., gastrointestinal tract, pancreas, kidneys, lungs, heart, blood vessels, and brain).
- GLP-1 receptors mediate the physiological actions of GLP-1, including:
    - Regulation of glucose homeostasis (decreasing glucose secretion)
    - Appetite control (i.e., cravings and satiety)
    - Body weight management
    - Metabolism
    - Glycogen synthesis in skeletal muscle and liver
    - Gastric peristalsis
    - Lipid metabolism and modulation of fat absorption
    - Cardiovascular function
    - **Neurologic function**

GLP-1 in the Brain

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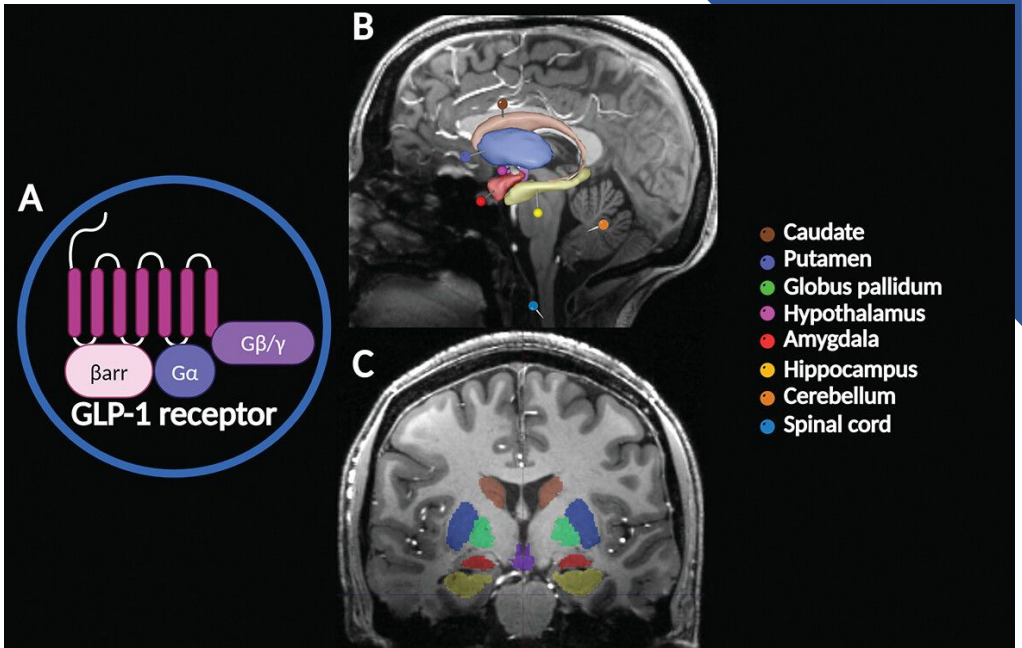
- GLP-1 and its analogs can readily cross the blood-brain barrier (BBB).
- GLP-1 is also synthesized in some brain regions, including hypothalamic nuclei, the nucleus tractus solitarius, and the caudal brainstem.
- GLP-1 receptors are expressed in the caudate, putamen, globus pallidum, hypothalamus, amygdala, hippocampus, cerebellum, and spinal cord.



12-month neurological and psychiatric outcomes of semaglutide use for type 2 diabetes: a propensity-score matched cohort study

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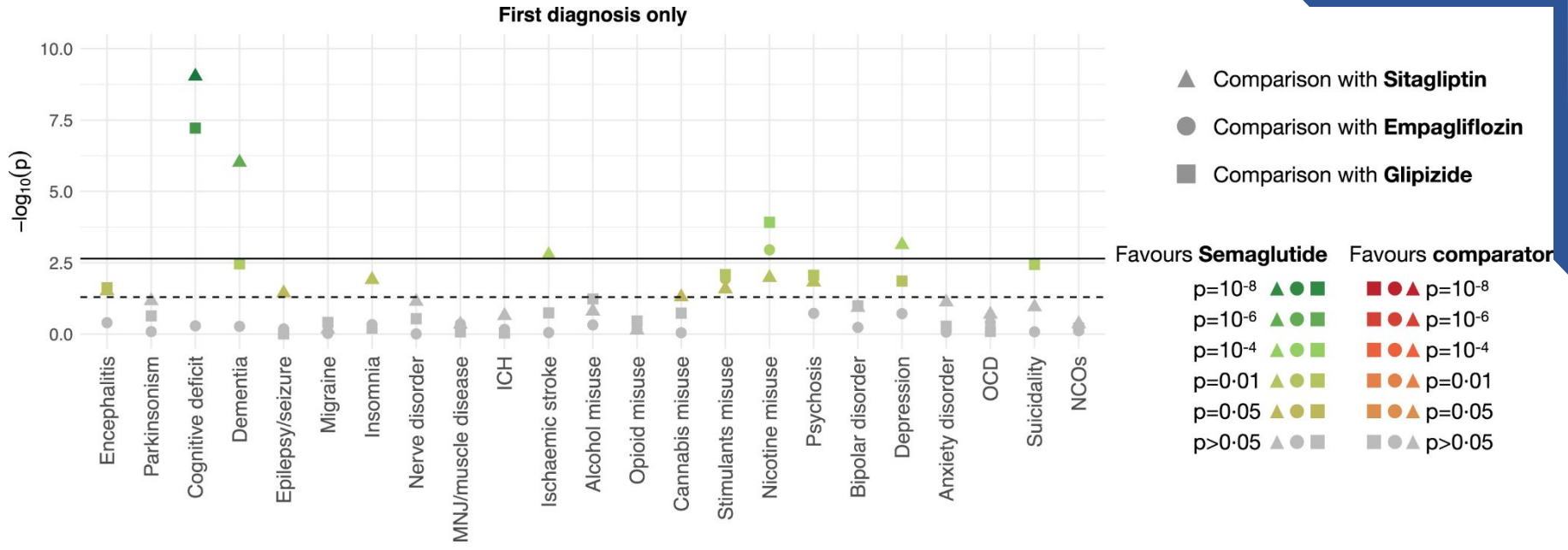
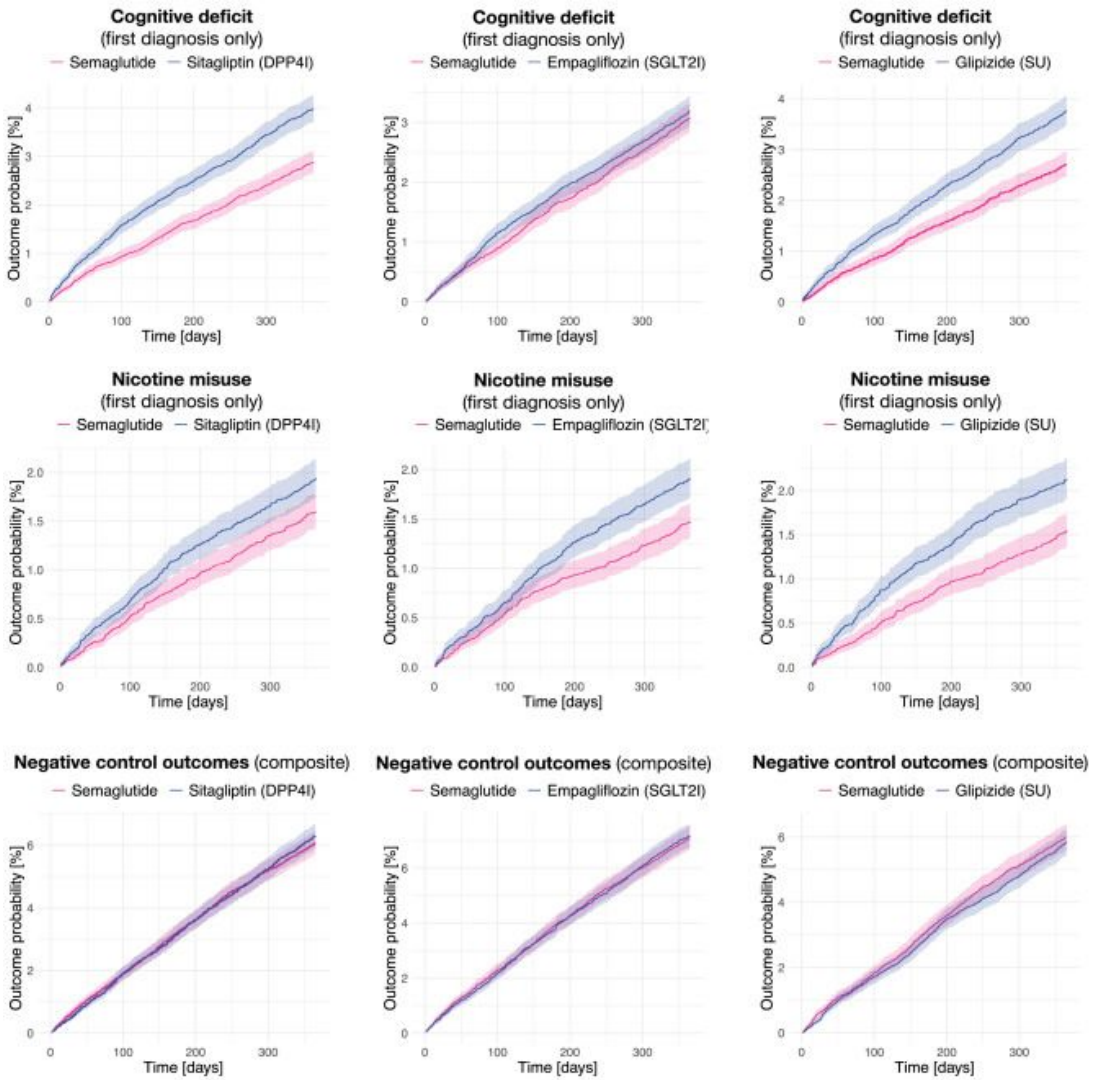
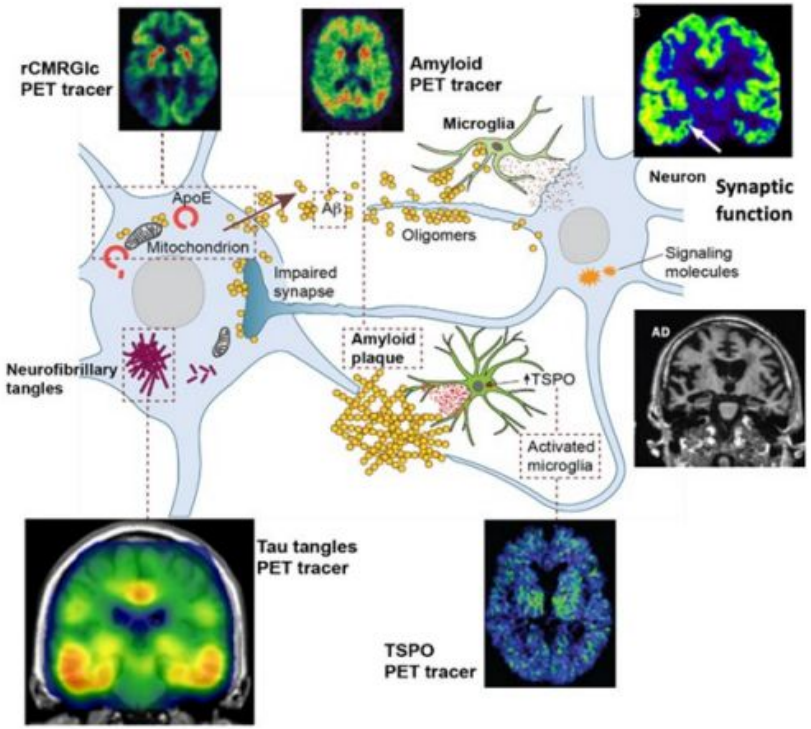


- Semaglutide was not associated with an increased risk for any psychiatric outcomes
- Semaglutide use was associated with lower risks of cognitive deficits
- Semaglutide with lower risks of nicotine use disorder



- Due to the clear neuroprotective effects of liraglutide in preclinical trials (McClean et al., 2011), a placebo-controlled double-blind phase II clinical trial (ELAD) testing liraglutide in 204 patients with mild AD was conducted.
- Liraglutide or placebo was given daily for 12 months. Cognition and memory (the ADASexec test battery) and neuroimaging markers were measured.
- The study's primary endpoint was change in the cerebral glucose metabolic rate in the cortical regions of the brain (hippocampus, medial temporal lobe and posterior cingulate), which was not met.
- However, the secondary endpoint of change in scores for clinical and cognitive measures and the exploratory endpoint of brain volume showed statistically significant benefit.
- Researchers found that, compared to placebo, liraglutide:
    - **Significantly slowed down the deterioration in cognitive impairments (~18% slower)**
    - **Temporal lobe and parietal lobe revealed less volume loss (~50%)**
    - **Total grey matter cortical volumes showed less reduction (~50%)**
- This suggests that neuronal loss in the brain has been reduced by liraglutide (Edison et al., 2022, 2023). The effects of Liraglutide were relatively modest but offered a proof of concept that GLP-1 receptor agonists can slow AD progression in a meaningful and significant way.



Edison AAIC 2024

Ongoing Research

- The EVOKE/ EVOKE+ trials are randomized, double-blind, placebo-controlled clinical trials investigating the efficacy and safety of oral semaglutide in subjects with early Alzheimer's disease.
- The primary objective of the EVOKE trial is to confirm the superiority of oral semaglutide compared to placebo in the change in cognition and function in subjects with mild cognitive impairment (MCI) or mild dementia of the Alzheimer's type. The trial will also assess the safety and tolerability of oral semaglutide in this patient population.
- Secondary objectives of the trial include evaluating the effect of oral semaglutide on cerebral glucose metabolism, markers of inflammation, and cardiovascular outcomes. The trial will enroll approximately subjects across multiple sites globally and follow them for up to three years.
- EVOKE and EVOKE+ are almost identical in design but considered different studies due to the latter allowing for cerebral vascular changes as part of the inclusion criteria.

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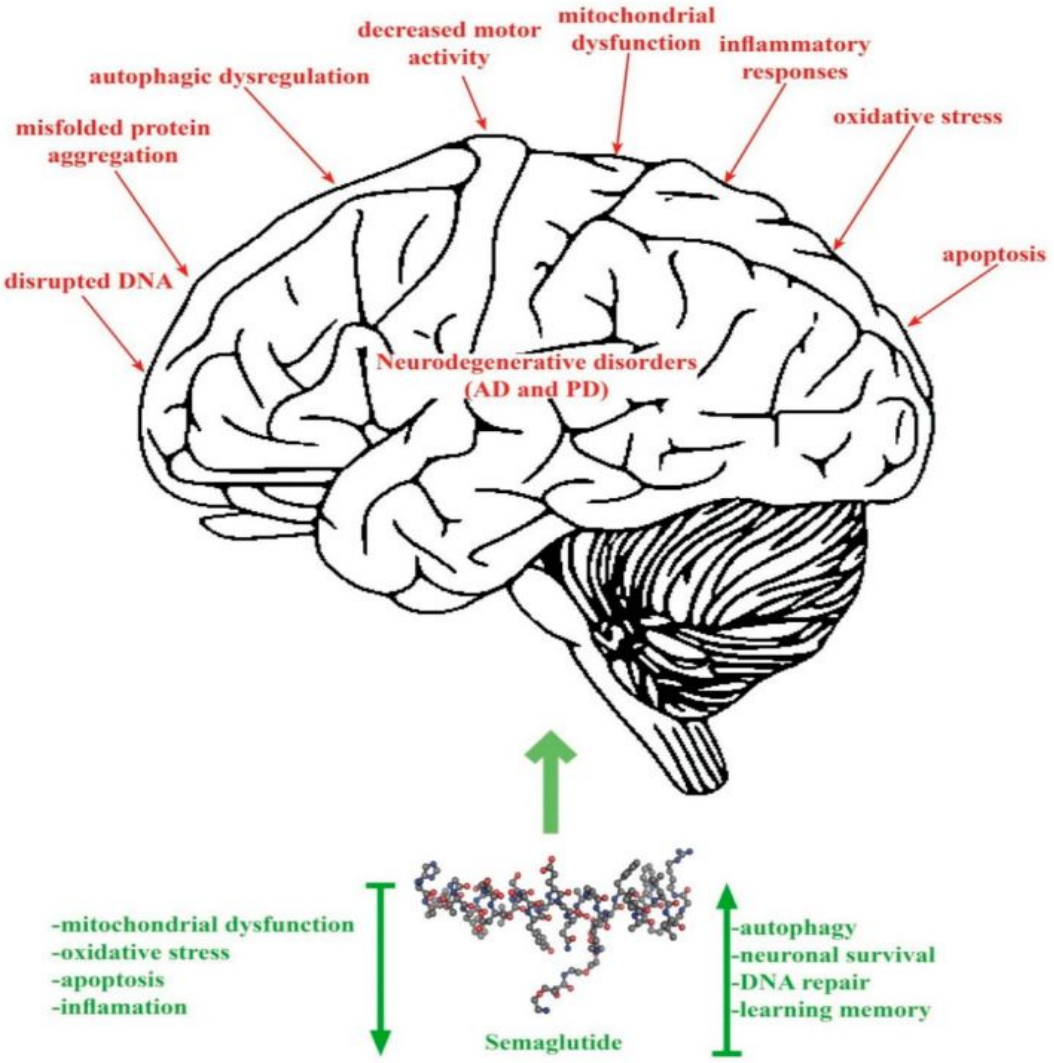
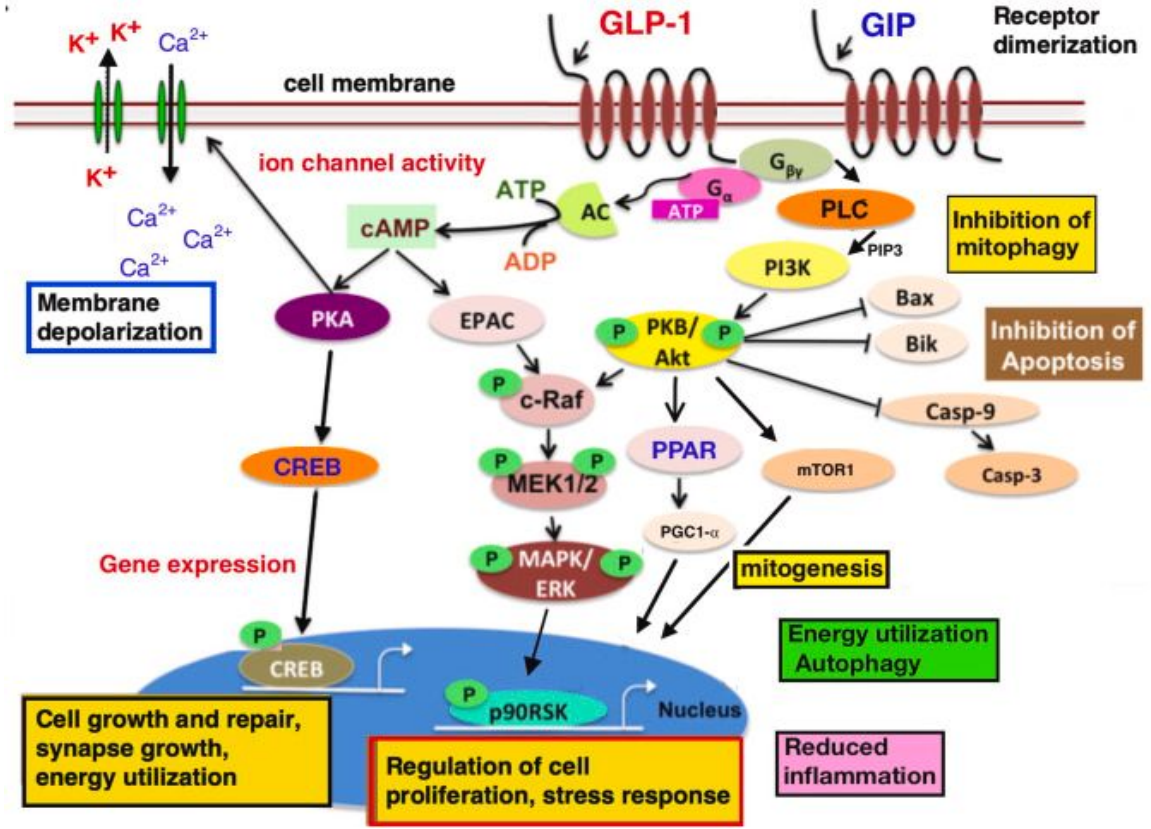
What is the underlying mechanism of GLP-1 drug action?

- No single mechanism of action that underlies the improvements observed in the brain.



- Cell culture and animal studies demonstrate that when activating the GLP-1 or GIP receptors in the brain, energy utilization in neurons is normalized, **cell repair** and **gene expression** returns to normal, synaptic activity is normalized, and the **chronic inflammation** response in the brain is reduced.
- This is due to the loss of growth factor signaling, in particular insulin. Insulin is an important growth factor in the brain, and previous studies have shown that **insulin signaling** is impaired in the brains of AD patients.
- GLP-1 is a growth factor as well and can compensate for the loss of insulin signaling, and **can re-sensitize insulin signaling in the brain** In diabetes patients, GLP-1 agonists can improve insulin sensitization and in patients with AD or PD, they can, too .

- There are several other mechanisms, such as the **reduction of the chronic inflammation** response found in the brains of PD patients. GLP-1 agonists such as exendin-4, liraglutide and lixisenatide have shown good effects in reducing the inflammation response.
- Other mechanisms of action include:
    - **improvement of mitochondrial activity**
    - **synaptic activity**
    - **normalization of autophagy to remove misfolded proteins**
    - **reduction of oxidative stress**.



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Reducing Aβ Aggregation/Deposition and Tau Protein Hyperphosphorylation

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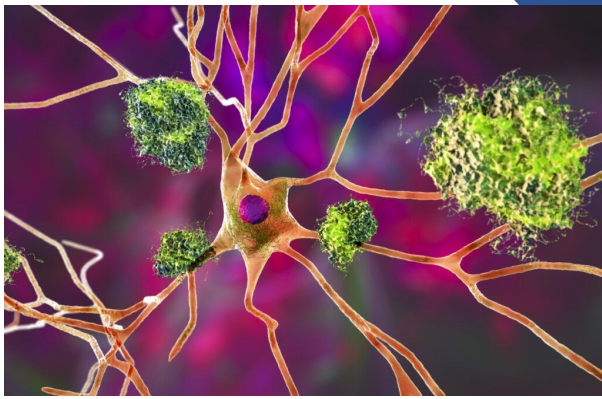
- Some studies have reported that GLP-1 can also affect the pathological process of **Aβ deposition and tau hyperphosphorylation**.
- Perry et al. found that GLP-1 can reduce the levels of endogenous Aβ in the brain and reduce the levels of APP in cultured neuronal cells.
- Exendin-4 (an endogenous insulin releasing incretin, GLP-1) reduces Aβ accumulation and tau hyperphosphorylation in cellular and animal models of AD.
- Total brain APP and Aβ oligomer levels are reduced in Liraglutide-treated AD mice and intervention with liraglutide can prevent tau hyperphosphorylation.
- In another study, (Val8)GLP-1 might prevent age-related neurodegenerative changes (such as AD) by preventing decline of learning and memory formation, reduction of tau hyperphosphorylation and protection of subcellular structures and morphology of neurons.



Additional Neuropsychiatry Targets

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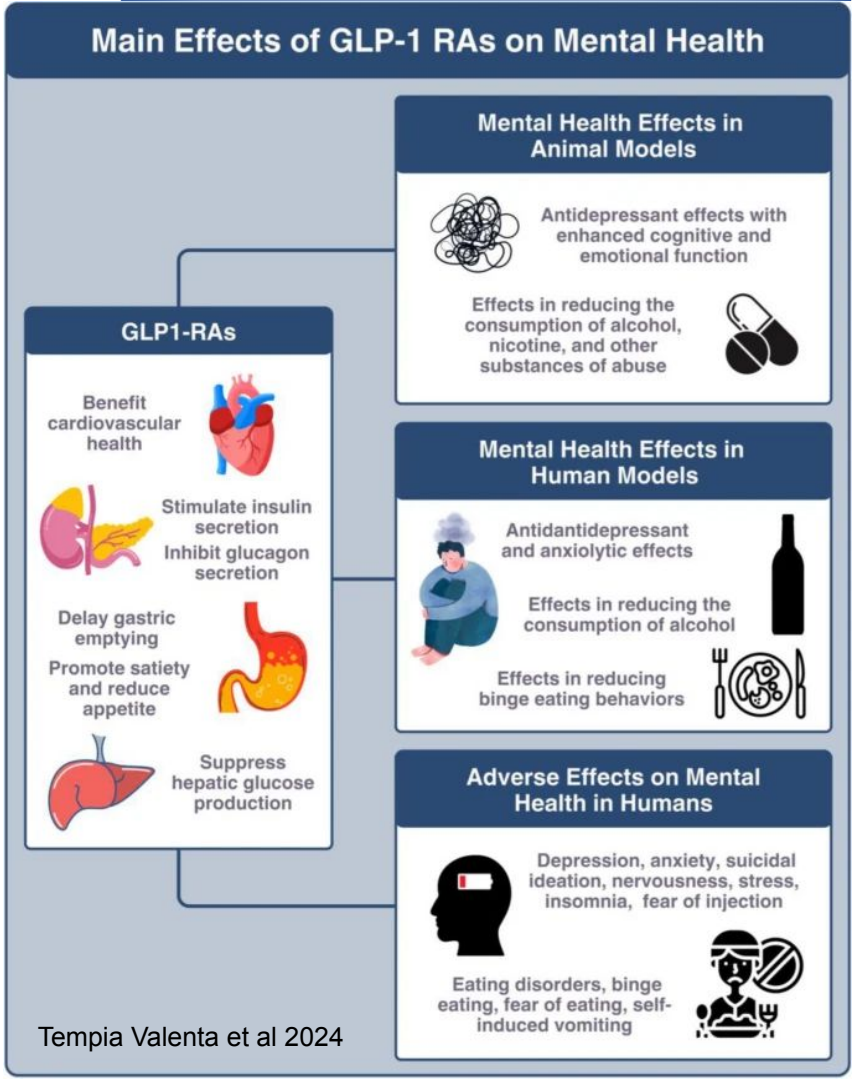
- GLP-1 receptors are expressed in brain regions that regulate mood and emotion, including the prefrontal cortex, amygdala, and hypothalamus.
- Activation of these receptors modulates the release of neurotransmitters such as serotonin, dopamine, and glutamate, which play critical roles in mood regulation and stress response.
- Chronic inflammation and oxidative stress have been implicated in the pathophysiology of psychiatric disorders.
- Since GLP-1 agonists possess anti-inflammatory and antioxidant properties, attenuating neuroinflammatory processes and oxidative damage, potentially mitigating neurodegenerative changes associated with psychiatric illness.

- A 2024 meta-analysis by Chen et al. comprising 2,071 participants included 5 randomized controlled trials and 1 prospective cohort study.
- The meta-analysis indicated that the change from baseline in depression rating scale scores decreased significantly when patients received treatment with GLP-1 agonists compared to control treatments.
- The subgroup analysis showed that the effects of GLP-1 agonists on depressive symptoms were consistent in patients with Type 2 diabetes mellitus
- Potential Neuropsychiatric Targets:
    - **Depression (Vascular depression)**
    - **Bipolar Disorder**
    - **Schizophrenia**
    - **Anxiety**



Summary

- GLP-1 class drugs that are on the market to treat diabetes showed clear neuroprotective effects in first clinical trials in AD and PD patients.
- Further clinical trials of GLP-1 receptor agonists in AD and PD patients are currently underway, a phase III clinical trial testing.
- GLP-1 agonists also hold promise for addressing psychiatric conditions such as depression, anxiety, alcohol and substance use disorders