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The Impact of GLP-1 Agonists on Depression Treatment: A Literature Review

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1.ABSTRACT

Introduction

Depression is increasingly recognized as a major global health issue, driven by neurobiological, genetic, and environmental factors. Despite extensive research, understanding depression remains challenging due to its complexity and the lack of biomarkers. Recent studies highlight a link between depression and metabolic disturbances, emphasizing the need for alternative therapeutic approaches.

Purpose

This review aims to explore the therapeutic potential of GLP-1 (glucagon-like peptide-1) in treating depression, focusing on its impact on neurogenesis, neuroinflammation, neurotransmitter imbalances, and synaptic dysfunction.

Materials and Methods

A systematic review was conducted by analyzing literature from databases such as PubMed and Google Scholar, covering studies from 2003 to 2024. The review focused on keywords related to GLP-1, depression, and diabetes.

Description of the State of Knowledge

This section discusses the neurobiological mechanisms of depression, including neuroinflammation, neurotransmitter imbalances, and impaired neurogenesis. It highlights the potential of GLP-1 agonists to address these issues and improve mood and cognitive function.

Conclusion

The review concludes that GLP-1 holds promise as a therapeutic target for depression. Beyond its metabolic roles, GLP-1 can influence brain regions involved in mood regulation, enhance neurogenesis, reduce neuroinflammation, and improve neurotransmitter balance. These effects suggest that GLP-1-based therapies could offer new treatment options for depression, potentially improving outcomes beyond traditional antidepressants.

2. KEYWORDS

GLP-1, depression, systematic review, diabetes

3.INTRODUCTION

Depression is increasingly recognized as a major cause of illness and death globally, with the number of individuals affected by the disorder continuing to grow [1]. Despite extensive research, depression remains poorly understood due to the lack of biomarkers and the diversity of triggering factors such as chronic stress. A recent study explored the link between depression and metabolism, revealing that metabolites, including advanced glycation end products, are altered in patients with depression compared to controls [23456].

Depression is a complex syndrome caused by a combination of neurobiological, genetic, and environmental factors. Changes in brain regions such as the prefrontal cortex, amygdala, and hippocampus play a role in its development. Despite extensive research, a full understanding of depression remains challenging. Recent studies have highlighted a link between depression and metabolism, suggesting that diabetes and obesity can increase the risk of neurophysiological conditions. Depression can lead to both physical and mental changes,

including sadness, feelings of emptiness, irritability, and loss of interest in activities. Without adequate treatment, these symptoms can worsen and lead to serious outcomes.[7]

Depression is prevalent in 25% of individuals with type 2 diabetes mellitus (T2DM). It not only elevates the likelihood of developing T2DM but also increases the risks of hyperglycemia, insulin resistance, and both micro- and macrovascular complications. Conversely, a diagnosis of T2DM heightens the risk of incident depression and can exacerbate its severity. This connection underscores a shared underlying cause characterized by complex bidirectional interactions among various factors, including autonomic and neurohormonal dysregulation, weight gain, inflammation, and structural changes in the hippocampus.[8]

The effectiveness of current antidepressant drugs, which primarily target the brain's monoaminergic systems by enhancing serotoninergic and noradrenergic neurotransmission, is often inadequate. Only about one-third of patients achieve complete relief from depressive symptoms after therapy. Therefore, alternative therapeutic strategies that differ from traditional antidepressants are being sought to enhance the effectiveness of depression treatment.[9]

Glucagon-like peptide-1 (GLP-1) is a hormone synthesized in the intestines and the brain that plays a crucial role in regulating glucose levels and maintaining energy balance. It exerts its effects by binding to its specific receptor (GLP-1R), which is present in various tissues throughout the body and in the central nervous system.[10] It enhances insulin secretion, supports the function and survival of pancreatic β-cells, and reduces glucagon release. This helps decrease glucose production, increase glycogen storage, and improve glucose uptake in muscles and fat cells. GLP-1 also suppresses appetite, slows down digestion, and reduces stomach acid secretion. It mildly increases sodium excretion in the kidneys and enhances heart function while protecting blood vessels. These actions make GLP-1 a key treatment for type 2 diabetes mellitus.[11]

GLP-1 can cross the blood-brain barrier, bind to GLP-1 receptors distributed in the hippocampus, improve learning and memory, and play a neuroprotective role. These actions have been associated with decreased depressive symptoms and improvements in quality of life.[12]

4.PURPOSE

This systematic review explores the therapeutic effects of GLP-1 on depression from various perspectives. We emphasize the promising benefits of GLP-1 in addressing issues such as impaired neurogenesis, neuroinflammation, neurotransmitter imbalance, and synaptic dysfunction in the depressive brain.

5.MATERIALS AND METHODS

The review was based on the analysis of materials collected from databases such as PubMed, Google Scholar, and other scientific sources. It focused on articles published between 2003 and 2024, using keywords like "GLP-1," "Depression," "Systematic review," and "Diabetes."

6.DESCRIPTION OF THE STATE OF KNOWLEDGE

Depression is closely associated with various neurological issues, including neuroinflammation, neurotransmitter imbalances, increased permeability of the blood-brain barrier, deficits in neurogenesis, and synaptic dysfunction [13] [14]. Research indicates that individuals suffering from depression frequently exhibit impaired neurogenesis, slowed neuronal growth, and reduced synaptic adaptability [15].

Key brain regions responsible for regulating emotions, stress responses, and motivation, such as the prefrontal cortex (PFC), amygdala, and hippocampus, often display altered functionality in people with depression [16]. Specifically, the PFC and hippocampus typically exhibit decreased activity, while the amygdala tends to be overactive in this population [17].

GLP-1 agonists, in particular, show promise as treatments for depression, as they can improve mood and cognitive functions through their effects on neurotransmitter release, neurogenesis, and synaptic plasticity [18]. By focusing on the gut-brain connection, researchers aim to develop more effective treatments for mental health and neurological conditions.

6.1. Neuroinflammation in Depression and How it Relates to GLP-1.

Neuroinflammation plays a pivotal role in the pathophysiology of depression by triggering the activation of microglia and astrocytes, which release pro-inflammatory cytokines in response to various stressors, including chronic psychological stress [19]. These cytokines, such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), are crucial components of the inflammatory cascade within the brain and are closely linked to the development and progression of depressive symptoms [20]. Consistently elevated levels of these cytokines have been observed in the cerebrospinal fluid and brain tissues of individuals with depression, underscoring their role in neuroinflammatory processes [21]. In addition to cytokine dysregulation, oxidative stress (OS) represents another hallmark of neuroinflammation in depression. The brain's high metabolic activity,

coupled with its abundance of polyunsaturated fatty acids and relatively low antioxidant defenses, renders it particularly vulnerable to oxidative damage caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS) [22]. This oxidative damage can exacerbate neuroinflammation, leading to neuronal dysfunction and apoptosis, which are characteristic features of depressive disorders [23]. Glucagon-like peptide-1 (GLP-1) and its analogs have emerged as promising therapeutic agents for depression due to their diverse effects on neuroinflammation and oxidative stress [24]. GLP-1 receptors are widely distributed throughout the brain, including regions involved in mood regulation and cognitive function [25]. Activation of these receptors by GLP-1 or its analogs has been shown to modulate microglial activation and reduce the production of pro-inflammatory cytokines such as TNF-α and IL-6, thereby exerting potent anti-inflammatory effects [26]. Furthermore, GLP-1 analogs like exendin-4 have demonstrated the ability to bolster antioxidant defenses and mitigate oxidative stress in experimental models, highlighting their potential for neuroprotection [27]. Recent research has also implicated neuroinflammation and oxidative stress in the dysregulation of neurotransmitter systems implicated in depression, such as the serotonin, dopamine, and noradrenaline pathways [28]. These pathways are critical for mood regulation and cognitive function, and their dysfunction is closely associated with depressive symptoms.

Moreover, the gut-brain axis has garnered attention as a potential mediator of neuroinflammation in depression. Gut microbiota dysbiosis can lead to increased intestinal permeability, allowing bacterial products to enter systemic circulation and trigger immune responses in the brain, contributing to neuroinflammation and depressive symptoms [29].

GLP-1 analogs may also influence gut microbiota composition and function, potentially mitigating neuroinflammation via modulation of the gut-brain axis [30]. Understanding the precise mechanisms through which GLP-1 and its analogs influence neuroinflammation, oxidative stress, and the gut-brain axis is crucial for developing targeted therapeutic strategies for depression. Future research should focus on elucidating these mechanisms further and exploring the clinical potential of GLP-1-based therapies to enhance outcomes for individuals with depressive disorders.

6.2.The role of neurogenesis in depression and its relationship with GLP-1.

Neurogenesis, the process of generating new neurons in the brain, is increasingly recognized as pivotal in depression, particularly within the hippocampus—a region crucial for memory, emotion regulation, and stress response [3117]. Evidence suggests that depressed individuals often exhibit decreased neurogenesis, which correlates with hippocampal atrophy and impaired cognitive function [3117].

In addition to the disturbed neuroimmune and neuroendocrine crosstalk, disruptions in brain metabolism and mitochondrial functions have emerged as significant factors in depression pathogenesis [3233]. Alterations in mitochondrial functions such as oxidative phosphorylation (OXPHOS) and membrane polarity, which enhance oxidative stress and apoptosis, may precede the development of depressive symptoms [3233]. Dysfunction of the GLP-1 pathway, known for its role in regulating glucose homeostasis, has also been implicated in depression, contributing to mitochondrial dysfunction and metabolic disturbances[3425]. Glucose, as the primary metabolic substrate in the brain, plays a critical role in maintaining neuronal function under normal conditions [3536].

Chronic stress, a hallmark of depression, can suppress neurogenesis by elevating glucocorticoid levels, thereby impeding the proliferation and differentiation of neural stem cells in the hippocampus [3117]. Conversely, antidepressant treatments have been shown to enhance neurogenesis, suggesting that stimulating neuronal growth in the hippocampus may underlie their therapeutic effects [3117].

A promising area of investigation centers on glucagon-like peptide-1 (GLP-1) and its receptors in the brain [3425]. GLP-1 not only exerts neuroprotective and neurotrophic effects but also promotes neurogenesis in animal models [3425]. For instance, GLP-1 receptor agonists such as exendin-4 and liraglutide have demonstrated the ability to enhance proliferation of neural progenitor cells and stimulate neuronal differentiation in the hippocampus, which could potentially counteract neurogenic deficits seen in depression [3425].

Clinical studies investigating GLP-1 receptor agonists in depression have yielded promising results, showing improvements in cognitive function and mood symptoms among patients with mood disorders [3425]. These findings highlight the potential of targeting neurogenesis via the GLP-1 pathway as a novel therapeutic approach for treating depression [3425].

6.3. Dysregulation of Neurotransmitters in Depression and Their Connection to GLP-1.

Neurotransmitters play a pivotal role in transmitting signals in the brain, influencing behavior and emotional states [37]. In the context of depression, dysregulation of neurotransmitters, especially serotonin (5-HT), norepinephrine (NE), and dopamine (DA), is central to its pathophysiology [3839]. Deficiencies in these monoaminergic neurotransmitters not only exacerbate depressive symptoms but also serve as significant diagnostic markers for the disorder.

Serotonin is crucial for mood regulation and emotional processing within brain regions such as the amygdala and hippocampus [4041]. Dysfunctions in serotonin pathways are strongly linked to the onset and severity of depressive symptoms. Furthermore, disturbances in other neurotransmitter systems are evident in depression. For example, disruptions in glutamatergic signaling, heightened acetylcholine activity, and decreased gamma-aminobutyric acid (GABA) transmission are observed [4243]. These changes significantly contribute to the neurochemical basis of depressive symptoms, which can be observed through advanced brain imaging techniques like magnetic resonance spectroscopy [44]. Chronic stress, a significant trigger for depression, exacerbates these neurotransmitter dysregulations by disrupting glutamate transmission in key brain areas such as the prefrontal cortex (PFC), leading to impaired cognitive functions and worsening depressive symptoms [45]. Additionally, chronic stress

induces structural changes in the brain, including atrophy of the PFC and hippocampus due to glucocorticoid disturbances [4647].

Brain-derived neurotrophic factor (BDNF) plays a critical role in depression, essential for neurogenesis, synaptic plasticity, and neuronal survival, all of which are disrupted in depressive states [48]. Consistent reductions in BDNF levels are found in key brain regions such as the hippocampus and PFC in individuals with depression [4950]. Antidepressant therapies that enhance BDNF signaling show efficacy in alleviating depressive symptoms by promoting neuronal plasticity and reducing neuronal apoptosis [5152]. Conversely, chronic stress diminishes BDNF-TrkB signaling pathways, contributing to synaptic dysfunction and neuronal damage in depression [5354].

Glucagon-like peptide-1 receptors (GLP-1Rs) are widely distributed in brain regions involved in mood regulation and energy balance, including the amygdala, hippocampus, and dorsal raphe nucleus [55]. Activation of GLP-1Rs modulates neurotransmitter systems implicated in depression, such as serotonin and dopamine [5657]. GLP-1 agonists like exendin-4 and liraglutide influence dopamine turnover in the amygdala, associated with improvements in reward-related behaviors observed in animal models of depression and addiction [5658].

6.4. Disturbances in Brain Connections and Cognitive Decline in Depression: The Role of GLP-1.

In patients suffering from depression, neuronal circuit dysfunctions arise from impaired communication between neurons, affecting various brain regions such as the prefrontal cortex (PFC) and hippocampus [59]. Advanced brain imaging studies consistently report reduced synaptic connectivity and neuronal circuitry in these areas in depressed individuals [1617]. Moreover, postmortem examinations of brains from depressed patients reveal significant structural changes, including reduced brain volume, loss of specific pyramidal neurons and GABAergic interneurons, and decreased density of glial cells in the PFC [6061]. Detailed electron microscopy studies also indicate fewer synaptic connections and alterations in synaptic proteins in the PFC of individuals with depression [62]. Additionally, abnormalities in glutamate receptors and synaptic proteins in both the PFC and hippocampus underscore the extensive synaptic pathology in depression [4263]. Chronic unpredictable stress, a commonly used depression model, exacerbates neuronal damage in brain regions such as the PFC and hippocampus. This stress model is associated with reduced dendritic complexity, loss of functional synaptic spines, and altered synaptic transmission patterns [6465]. It also affects emotion processing areas like the amygdala and nucleus accumbens, disrupting motivation and reward systems [66]. Chronic stress further impairs glutamate signaling and synaptic transmission, contributing to observed cognitive deficits in depression [67]. Decreased levels of synaptic density proteins and alterations in ERK signaling, critical for synaptic plasticity and neuronal function, are also noted in depressed individuals [686970]. Glycogen synthase kinase 3 (GSK3) is implicated in reducing synaptic spines in depression, influencing synaptic plasticity and transmission [7172]. Studies indicate that synaptic plasticity, transmission, and long-term potentiation (LTP) are significantly attenuated in depression [7374]. Activation of the mammalian target of rapamycin (mTOR) signaling pathway, crucial for synaptogenesis and BDNF release, is diminished in depression, further compromising synaptic function [7576]. Patients with depression often experience mood disturbances, cognitive impairments, and an increased risk of dementia development [77787980]. Neuroimaging studies highlight structural changes in depressed patients' brains, such as atrophy and

abnormal alterations in the frontal cortex, thalamus, and hippocampus, correlating with cognitive decline [81]. Synaptic dysfunction, altered transmission, and decreased synaptic density proteins are common features in the depressed brain, significantly contributing to memory deficits. Thus, improving synaptic function is a crucial therapeutic goal in managing depressive neuropathology. Recent studies suggest that glucagon-like peptide 1 (GLP-1) may play a therapeutic role in alleviating these effects. GLP-1 is associated with lower body mass index (BMI) and has been shown to increase neurogenesis in the dentate gyrus [34]. Research on liraglutide demonstrates its ability to promote cortical neurite outgrowth under severe oxidative stress conditions via Wnt signaling and enhance hippocampal synaptic plasticity, potentially alleviating depressive symptoms [8283]. In animal models, the DPP inhibitor sitagliptin has been shown to improve cognitive function and protect neurons under oxidative stress , while exendin-4 promotes neurite growth and neuronal survival in vitro [8485]. Activation of GLP-1 receptors enhances GABAergic signaling and synaptic plasticity in the hippocampus , improves learning and memory in high-fat diet models, and modulates LTP in neurodegenerative disease models [86278788]. Mice lacking GLP-1 receptors show impaired LTP, highlighting the role of GLP-1 in synaptic function, hile overexpression of GLP-1 receptors in mice improves learning and memory performance [2589]. Importantly, GLP-1 and exendin-4 reduce depression-like behaviors in animal models by modulating serotonin signaling in the amygdala [90].

6.5. GLP-1 receptor (GLP-1R) plays a role in enhancing communication between the gut and brain.

Recent studies have increasingly underscored the critical role of the gut-brain axis and the stability of gut microbiota in the development and progression of mood disorders such as depression [91929394]. The gut-brain axis is a sophisticated bidirectional communication network between the gastrointestinal tract and the brain, involving neurotransmitters, cytokines, and peptide hormones that regulate mood and emotional states [9596]. Individuals suffering from depression often exhibit a significant reduction in both the number and diversity of microorganisms within their gastrointestinal tract [97]. This dysbiosis, or imbalance in the microbial community, can adversely affect the central nervous system, potentially triggering or exacerbating depressive symptoms [2998]. Conversely, the presence of depression can further destabilize the gut microbiome, creating a vicious cycle of mutual reinforcement between gut health and mental health [99100]. This bidirectional influence has been supported by numerous human and animal studiem [101102]. For instance, fecal microbiota transplants from depressed patients into antibiotic-treated rats led to the development of depressive-like behaviors in the Animals [103]. These behaviors included reduced sucrose consumption, increased immobility in the forced swim test, and altered responses in other behavioral assays. Such findings underscore the potential causative role of gut microbiota in depression [104]. Furthermore, chronic stress has been shown to disrupt microbial diversity in the gut, highlighting the intricate link between stress, gut dysbiosis, and depression [105]. Antidepressant medications, due to their antimicrobial properties, can also inadvertently alter gut microbiota, further complicating the relationship between gut health and mental health [106]. The gut microbiota influences the host organism by modulating both innate and adaptive immune responses [107]. It also plays a crucial role in metabolizing indigestible carbohydrates into short-chain fatty acids (SCFAs), which activate specific G protein-coupled receptors [108]. This activation promotes the secretion of peptide hormones from enteroendocrine cells, thereby influencing various physiological processes, including mood regulation [109]. Emerging research suggests that probiotics and prebiotics can positively impact gut microbiota and subsequently influence GLP-1 (glucagon-like peptide-1) signaling [110111].

GLP-1 is a peptide hormone involved in enhancing communication between the gut and brain, regulating mood and stress responses. For example, administration of probiotic strains in mice has been shown to elevate plasma levels of GLP-1, and similar effects have been observed in human studies[112]. Daily intake of certain Lactobacillus strains has led to increased GLP-1 secretion, associated with improved mood and metabolic health [101].

Moreover, GLP-1 receptor (GLP-1R) agonists, such as liraglutide, have demonstrated protective effects on the gastrointestinal tract by modulating the diversity of gut microbiota [113]. In patients with type 2 diabetes, liraglutide treatment increased the relative abundance of beneficial bacteria like Akkermansia, associated with improved gut barrier function and potentially better mood regulation [114]. These findings suggest that enhancing gut microbiota diversity could be a promising strategy for treating mood disorders [91].

The interplay between gut microbiota and mental health has led to the burgeoning field of psychobiotics, which involves the use of probiotics and prebiotics to positively influence the gut-brain axis [92]. This approach holds potential for developing new treatments for depression and other mood disorders, offering a novel avenue for therapeutic intervention [9394].

7.CONCLUSION

The article explores the therapeutic potential of glucagon-like peptide-1 (GLP-1) in addressing depression through multiple biological pathways. Depression is increasingly recognized as a significant global health issue, with complex neurobiological, genetic, and environmental factors contributing to its onset and progression. Current treatments, primarily targeting monoaminergic systems, often fall short in providing complete relief from depressive symptoms.

GLP-1, a hormone involved in glucose regulation and energy balance, exerts its effects through binding to GLP-1 receptors (GLP-1R) in various tissues, including the brain. Beyond its metabolic functions, GLP-1 crosses the blood-brain barrier and influences brain regions crucial for mood regulation, such as the hippocampus and amygdala. Studies highlight GLP-1's role in enhancing neurogenesis, reducing neuroinflammation, restoring neurotransmitter balance, and promoting synaptic plasticity—all mechanisms implicated in depression.

The review synthesizes evidence from studies investigating GLP-1 and its analogs (like exendin-4 and liraglutide) in animal models and clinical trials. GLP-1R agonists demonstrate potential in alleviating depressive symptoms by modulating inflammatory responses, oxidative stress, and gut microbiota composition. These effects suggest GLP-1-based therapies could offer novel avenues for treating depression, potentially enhancing treatment outcomes beyond conventional antidepressants.

Overall, the article underscores the multifaceted role of GLP-1 in addressing the complex pathophysiology of depression, highlighting its promise as a therapeutic target to improve mental health outcomes globally.

8. DISCLOSURES

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