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NEUROPROTECTIVE EFFECTS OF SEMAGLUTIDE: A COMPREHENSIVE REVIEW OF COGNITIVE FUNCTION AND NEUROINFLAMMATION

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Abstract: INTRODUCTION Semaglutide, a GLP-1 receptor agonist, has demonstrated significant potential in managing type 2 diabetes mellitus (T2DM) and offers promising neuroprotective benefits. Its structure allows it to mimic endogenous GLP-1, which plays a crucial role in modulating insulin secretion and glucose metabolism. Beyond metabolic regulation, semaglutide impacts the central nervous system (CNS), particularly in regions associated with cognition and neuroprotection. Evidence shows that GLP-1 receptor activation by semaglutide can enhance synaptic plasticity, reduce neuroinflammation, and promote neuronal survival, making it a potential therapeutic agent for cognitive decline and neurodegenerative diseases. **OBJETIVE** To analyze the neuroprotective effects of semaglutide, focusing on its impact on cognitive function and neuroinflammation in both preclinical and clinical settings. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Neuroprotection" AND "GLP-1 Receptor Agonists" AND Cognitive Function" OR "Neuroinflammation" OR "Diabetes and Brain Health" in the last years. **RESULTS AND DISCUSSION** Extensive preclinical studies have shown that semaglutide improves cognitive function and reduces neuroinflammation in rodent models of cognitive impairment. These effects are attributed to semaglutide's ability to enhance synaptic plasticity, promote neurogenesis, and modulate neuroinflammatory pathways. Clinical trials have further supported these findings, demonstrating significant improvements in cognitive performance among diabetic patients treated with semaglutide. The drug's capacity to cross the blood-brain barrier and exert direct CNS effects is critical for its neuroprotective benefits. Comparative studies indicate that semaglutide offers superior neuroprotection compared to other GLP-1 receptor agonists, due to its longer half-life and greater potency. Additionally, semaglutide has been shown to reduce biomarkers of neuroinflammation and oxidative stress, contributing to its overall efficacy in preserving cognitive function and potentially modifying the progression of neurodegenerative diseases. **CONCLUSION** Semaglutide represents a significant advancement in neuroprotection, providing therapeutic benefits that extend beyond glycemic control in diabetes. Its ability to modulate neuroinflammation, oxidative stress, synaptic plasticity, and neurogenesis underpins its potential to improve cognitive outcomes and protect against neurodegenerative diseases. Future research should focus on elucidating the molecular pathways influenced by semaglutide, optimizing its use in neurodegenerative conditions, and exploring its efficacy in non-diabetic populations at risk for cognitive decline. Semaglutide's diverse mechanisms of action and proven efficacy make it a valuable addition to treatments aimed at preserving brain health and enhancing the quality of life for patients with diabetes and beyond.

Keywords: Semaglutide; Neuroprotection; Cognitive Function; Neuroinflammation; GLP-1 Receptor Agonists.

INTRODUCTION

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has gained significant attention for its therapeutic potential beyond the management of type 2 diabetes mellitus (T2DM)[1]. Structurally, semaglutide is designed to mimic the actions of endogenous GLP-1, binding to GLP-1 receptors to stimulate insulin secretion, inhibit glucagon release, and slow gastric emptying[1]. These actions collectively contribute to its glucose-lowering effects, making it a critical component in diabetes management[1]. The pharmacokinetics of semaglutide are particularly advantageous, characterized by a long half-life that permits once-weekly dosing, thus enhancing patient adherence and compliance compared to daily therapies[2].

GLP-1 receptors are widely distributed in the central nervous system (CNS), including key regions involved in cognition and neuroprotection, such as the hippocampus and cortex[2]. The role of GLP-1 in neuroprotection is supported by evidence showing that GLP-1 receptor activation can enhance synaptic plasticity, reduce neuroinflammation, and promote neuronal survival[2]. Preclinical studies have demonstrated that GLP-1 receptor agonists, including semaglutide, exert protective effects against neurodegenerative processes by modulating pathways involved in oxidative stress and inflammation[3]. The pathophysiology of cognitive decline in diabetes is multifaceted, involving chronic hyperglycemia, insulin resistance, and vascular complications that collectively impair brain function[3]. These metabolic disturbances increase the risk of developing neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD)[3]. Chronic hyperglycemia and insulin resistance contribute to the formation of advanced glycation end products (AGEs) and oxidative stress, which exacerbate neuronal damage and cognitive deficits[4].

Semaglutide's potential CNS effects have been explored extensively in preclinical models, revealing promising results in improving cognitive function and reducing neuroinflammation[4]. These studies indicate that semaglutide can influence neurogenesis, synaptic plasticity, and the modulation of neuroinflammatory pathways[5]. Neuroinflammation, characterized by the activation of microglia and astrocytes, is a critical factor in the progression of neurodegenerative diseases[5]. The anti-inflammatory properties of semaglutide, mediated through the downregulation of pro-inflammatory cytokines and the inhibition of glial activation, suggest its potential as a neuroprotective agent[6].

Oxidative stress, another pivotal factor in cognitive decline, particularly in diabetes, results from the overproduction of reactive oxygen species (ROS) that damage cellular components, leading to neuronal dysfunction and death[6]. GLP-1 receptor agonists, including semaglutide, have been shown to attenuate oxidative stress by enhancing the activity of antioxidant enzymes and reducing ROS production[7]. This neuroprotective effect is further supported by studies demonstrating improvements in mitochondrial function, which is essential for maintaining cellular energy balance and reducing oxidative damage[7].

Clinical trials focusing on the cognitive outcomes of semaglutide treatment have provided encouraging results[8]. Patients treated with semaglutide exhibit better cognitive performance compared to those receiving placebo, with significant improvements in executive function, memory, and attention[8]. These benefits are believed to be mediated through several mechanisms, including the reduction of chronic hyperglycemia, improvement of insulin sensitivity, and direct neuroprotective effects[9]. The ability of semaglutide to cross the blood-brain barrier

and interact with GLP-1 receptors in the CNS enhances its potential to modulate cognitive processes directly[9].

The comparative efficacy of semaglutide with other GLP-1 receptor agonists has highlighted its superior neuroprotective effects, attributed to its unique pharmacokinetic profile and potency[10]. Clinical trial data support these findings, demonstrating significant improvements in cognitive outcomes in patients with T2DM treated with semaglutide[10]. Furthermore, semaglutide has shown promise in reducing biomarkers of neuroinflammation, such as TNF-α, IL-6, and IL-1β, which are associated with cognitive impairment and neurodegeneration[11]. The future research directions for semaglutide in neuroprotection are promising, with ongoing studies aiming to elucidate the mechanisms underlying its CNS effects and optimize its therapeutic use in neurodegenerative diseases[11]. Understanding the molecular pathways influenced by semaglutide will be crucial in developing targeted interventions for cognitive decline and neuroinflammation, potentially expanding its use beyond diabetes management to include neuroprotective applications in a broader range of neurological disorders[12].

OBJETIVES

To analyze the neuroprotective effects of semaglutide, focusing on its impact on cognitive function and neuroinflammation in both preclinical and clinical settings.

SECUNDARY OBJETIVES

1. To evaluate the effects of semaglutide on synaptic plasticity and neurogenesis.
2. To assess the impact of semaglutide on oxidative stress and mitochondrial function in the brain.
3. To investigate the comparative efficacy of semaglutide with other GLP-1 receptor agonists.
4. To discuss the potential of semaglutide in preventing neurodegenerative diseases such as Alzheimer's and Parkinson's.
5. To explore the future research directions and clinical implications of semaglutide in neuroprotection.

METHODS

This is a narrative review, in which the main aspects of the neuroprotective effects of semaglutide, focusing on its impact on cognitive function and neuroinflammation in both preclinical and clinical settings in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Neuroprotection" AND "GLP-1 Receptor Agonists" AND Cognitive Function" OR "Neuroinflammation" OR "Diabetes and Brain Health" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

The neuroprotective effects of semaglutide have been rigorously evaluated in preclinical models, where it has consistently demonstrated the ability to enhance neuronal survival and function[12]. In rodent models of cognitive impairment, semaglutide treatment has been associated with significant improvements

in learning and memory, suggesting a direct benefit on cognitive function[13]. These improvements are likely due to semaglutide's influence on synaptic plasticity and neurogenesis, as evidenced by increased expression of synaptic proteins and the promotion of dendritic spine growth[13]. Clinical trials have reinforced these findings, showing that semaglutide can significantly improve cognitive performance in diabetic patients[14]. The mechanisms underlying these cognitive benefits include the reduction of chronic hyperglycemia, improvement of insulin sensitivity, and direct neuroprotective effects of GLP-1 receptor activation in the CNS[14]. The ability of semaglutide to cross the blood-brain barrier is crucial for its direct effects on brain function, allowing it to modulate neuroinflammatory and oxidative stress pathways that are implicated in cognitive decline[15].

Semaglutide's impact on neuroinflammation has been extensively studied, with results showing a reduction in pro-inflammatory cytokines and inhibition of microglial activation[15]. These anti-inflammatory effects help to create a neuroprotective environment that mitigates neuronal damage and promotes cognitive health[16]. In addition to reducing neuroinflammation, semaglutide has been shown to enhance mitochondrial function and reduce oxidative stress, further protecting neurons from damage[16]. Comparative studies have demonstrated that semaglutide may offer superior neuroprotective effects compared to other GLP-1 receptor agonists[17]. This is attributed to its longer half-life and greater potency, which allow for sustained activation of GLP-1 receptors and prolonged therapeutic effects[17]. These advantages make semaglutide a particularly promising candidate for the treatment of cognitive impairment in diabetes and other neurodegenerative conditions[18].

The potential of semaglutide to prevent neurodegenerative diseases such as Alzheimer's and Parkinson's has been a focus of recent research[18]. Preclinical studies have shown that semaglutide can reduce the accumulation of amyloid-beta plaques and tau tangles, which are characteristic of Alzheimer's disease[19]. These findings suggest that semaglutide may have a role in modifying disease progression, rather than merely providing symptomatic relief[19]. In clinical settings, semaglutide has shown promise in improving cognitive outcomes and reducing neuroinflammatory markers in patients with T2DM[20]. These benefits are likely mediated through its multifaceted effects on glucose metabolism, insulin sensitivity, neuroinflammation, and oxidative stress[20]. Long-term studies are needed to further elucidate the potential of semaglutide to provide lasting cognitive benefits and to determine its efficacy in non-diabetic populations at risk for cognitive decline[21].

The impact of semaglutide on biomarkers of neuroinflammation has been well documented, with significant reductions observed in markers such as TNF-α, IL-6, and IL-1β[21]. These reductions are associated with improvements in cognitive function, suggesting a direct link between the anti-inflammatory effects of semaglutide and its cognitive benefits[22]. Additionally, semaglutide has been shown to modulate glial cell function, reducing the activation of microglia and astrocytes, which play key roles in neuroinflammation[22]. Oxidative stress is another critical factor in the pathogenesis of cognitive decline, particularly in diabetes[23]. Semaglutide's antioxidant effects, mediated through the enhancement of antioxidant enzyme activity and reduction of ROS production, help to protect neurons from oxidative damage[23]. Improved mitochondrial function further supports neuronal health by maintaining cellular energy balance and reducing oxidative stress[24].

The potential of semaglutide to enhance synaptic plasticity and promote neurogenesis has been supported by both preclinical and clinical studies[24]. Increased expression of synaptic proteins and growth of dendritic spines are indicative of enhanced synaptic connectivity and plasticity, which are essential for cognitive function[25]. In the hippocampus, a critical region for memory and learning, semaglutide promotes the proliferation and differentiation of neural progenitor cells, contributing to neurogenesis and cognitive resilience[25]. Semaglutide's ability to cross the blood-brain barrier and exert direct CNS effects is a key factor in its neuroprotective potential[26]. Advanced imaging techniques have confirmed that semaglutide can penetrate the CNS and interact with GLP-1 receptors in brain regions involved in cognition[26]. This ability to access the brain allows semaglutide to modulate neuroinflammatory and oxidative stress pathways directly, providing comprehensive neuroprotection[27].

The neuroprotective effects of semaglutide are multifaceted, involving mechanisms that reduce neuroinflammation, oxidative stress, and neuronal damage, while enhancing synaptic plasticity and neurogenesis[27]. These effects translate into significant cognitive benefits in both preclinical models and clinical settings, particularly in patients with T2DM[28]. Comparative studies highlight the superior efficacy of semaglutide over other GLP-1 receptor agonists, making it a promising candidate for the treatment of cognitive impairment and neurodegenerative diseases[28]. The multifaceted mechanisms of semaglutide, including its anti-inflammatory, antioxidant, and synaptic-enhancing properties, contribute to its efficacy in preserving cognitive function and potentially modifying the progression of neurodegenerative diseases[29].

CONCLUSION

Semaglutide, a GLP-1 receptor agonist, offers promising neuroprotective benefits that extend beyond its established role in managing T2DM. The pharmacokinetics and pharmacodynamics of semaglutide support its potent activation of GLP-1 receptors, which are distributed throughout the CNS. These receptors play crucial roles in modulating neuroinflammation, oxidative stress, synaptic plasticity, and neurogenesis, all of which are essential for maintaining cognitive function and protecting against neurodegenerative processes.Clinical and preclinical studies consistently demonstrate that semaglutide can improve cognitive performance, reduce neuroinflammatory markers, and protect neurons from oxidative damage. Its ability to cross the blood-brain barrier and directly interact with GLP-1 receptors in the brain further enhances its potential to provide comprehensive neuroprotection. The multifaceted mechanisms of semaglutide, including its anti-inflammatory, antioxidant, and synaptic-enhancing properties, contribute to its efficacy in preserving cognitive function and potentially modifying the progression of neurodegenerative diseases.

Future research should focus on further elucidating the molecular pathways influenced by semaglutide and optimizing its therapeutic use in neurodegenerative conditions. Long-term studies are needed to confirm the lasting cognitive benefits of semaglutide and to explore its efficacy in non-diabetic populations at risk for cognitive decline. Additionally, comparative studies with other GLP-1 receptor agonists will help to establish semaglutide's position as a leading neuroprotective agent. In summary, semaglutide represents a significant advancement in the field of neuroprotection, offering potential therapeutic benefits for cognitive impairment and neurodegenerative diseases. Its diverse mechanisms of action

and proven efficacy in improving cognitive outcomes make it a valuable addition to the arsenal of treatments aimed at preserving brain health and enhancing quality of life for patients with diabetes and beyond.

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