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Abstract

Semaglutide: A Potential Therapeutic for Mitochondria-Associated Disorders

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Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, was initially approved for improving glycemic control in patients diagnosed with type 2 diabetes and later for cardiovascular indications (Astrup & Finer, 2000; Goldenberg & Steen, 2019; Mahapatra et al., 2022a, 2022b). Interestingly, the mechanisms associated with glucagon- and insulin-like chemical messengers are present and functionally similar in both insects and mammals (Bednářová et al., 2013; Tager et al., 1976). This apparent evolutionary conservation underscores the significance of this pathway in metabolism and mitochondria-associated processes.

Individuals diagnosed with autoimmune and neurodegenerative diseases often experience chronic inflammation and elevated levels of inflammatory cytokines; this can lead to systemic complications, including insulin resistance (Esch & Stefano, 2002) that may be mitigated by anti-inflammatory agents. One such agent is semaglutide, a GLP-1 analog that reduces serum glucose levels and also exhibits anti-inflammatory activity (Zhang et al., 2019). For example, both semaglutide and the GLP-1 receptor agonist liraglutide reverse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonian-type motor impairment (Zhang et al., 2019). These drugs also restore tyrosine hydroxylase levels, reduce α-synuclein accumulation, alleviate chronic brain inflammation, decrease lipid peroxidation, inhibit mitochondrial mitophagy signaling, and increase the expression of the growth factor, glial-cell-line-derived neurotrophic factor, which protects dopaminergic neurons in the substantia nigra and striatum (Zhang et al., 2019). Recent evidence suggests that mitochondria may be a critical semaglutide target, a finding that may substantiate recent hypotheses that link energy metabolism with the impact of stress on inflammation and obesity (Büttiker et al., 2023; Esch & Stefano, 2002; Esch et al., 2002; Esch et al., 2020; Luna-Marco et al., 2023; Tamayo-Trujillo et al., 2024).

In addition to its potential impact on Parkinsonian symptoms, semaglutide also enhances nerve cell function, reduces inflammation, and improves vascular health, all of which have the potential to slow the progression of Alzheimer's disease. Semaglutide has a positive impact on brain health, has been associated with a lower risk of cognitive issues, and reduces nicotine dependence (De Giorgi, 2024). Importantly, results from a recent study published by Ma and colleagues (Ma et al., 2024) revealed that semaglutide can also support and preserve mitochondrial structure and function under conditions of chronic stress. GLP-1 receptor agonists may also be effective at reducing neurological complications, cognitive impairment, and peripheral neuropathy (García-Casares et al., 2023). Results from metabolomic analyses reveal that semaglutide reduces mitochondrial damage, lipid accumulation, and ATP deficiency by promoting the entry of

pyruvate into the tricarboxylic acid cycle and thus increasing the rate of fatty acid oxidation. Transcriptional analysis shows that semaglutide regulates myocardial energy metabolism via the Creb5/NR4a1 axis of the PI3K/AKT pathway, reducing NR4a1 expression and its translocation to mitochondria. Of note, Ma and colleagues (Ma et al., 2024) also reported that NR4a1 knockdown can reverse mitochondrial dysfunction as well as abnormal glucose and lipid metabolism in the heart.

Collectively, current and emerging research findings suggest that semaglutide's impact on several seemingly unrelated disorders is based on a shared underlying mechanism. Semaglutide's capacity to reduce inflammation may lead to targeted protective outcomes, including cognitive improvement. We hypothesize that this commonality may be represented by semaglutide's positive influence on mitochondrial function, specifically its impact on energy metabolism (Li et al., 2024). Mitochondrial abnormalities have already been linked to a diverse cohort of physiological disorders. The impact of semaglutide on mitochondrial function underscores its critical importance to future medical and biological research and provides important insights into the development of novel targeted pharmaceuticals. We speculate this includes disorders associated with obesity, which also may be associated with attention deficit hyperactivity disorder. In this regard, the role of mitochondria in both normal and abnormal processes suggests an even more provocative role for these organelles within a eukaryotic organism than is currently understood. Functionally intact mitochondria have also been found in the extracellular environment where they may have a role in sensory function and exhibit characteristics of independent cells (Stefano et al., 2023). Taken together, semaglutide-mediated mitochondrial targeting reveals a critical role for these "organelles" in food consumption, overall well-being, and healthy longevity (Stefano & Kream, 2017).

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