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Review Article

Mitochondrial remodeling as a effector of glp-1 therapy in obesity and diabetes: review

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have rapidly evolved from glucose-lowering agents into pleiotropic cardiometabolic therapeutics with established benefits in obesity, type 2 diabetes, cardiovascular disease, and chronic kidney disease. Although their classical actions are well defined, emerging evidence suggests that mitochondrial remodeling may represent a central mechanistic layer through which GLP-1RAs exert tissue-protective effects. Across pancreatic beta cells, myocardium, liver, adipose tissue, skeletal muscle, kidney, vasculature, and neural tissues, GLP-1 signaling is repeatedly associated with improved mitochondrial quality control, lower oxidative stress, improved respiratory efficiency, and reduced apoptosis. However, the literature is mechanistically heterogeneous. Some mitochondrial effects appear to be direct and receptor-mediated, whereas others are likely secondary to weight loss, reduced glucotoxicity, improved insulin sensitivity, or lower inflammatory burden. This review argues that mitochondria are not merely downstream beneficiaries of improved metabolism during GLP-1 therapy. Rather, mitochondrial rescue likely represents a recurrent intracellular effector system through which GLP-1RAs translate receptor activation into durable organ protection. Framing GLP-1 pharmacology through a mitochondrial lens helps unify otherwise disparate observations across metabolic tissues and provides a clinically meaningful framework for future translational research.

Keywords: GLP-1 receptor agonists, Mitochondria, Obesity, Type 2 diabetes, Insulin resistance, Metabolic disease

Introduction

GLP-1 receptor agonists (GLP-1RAs) have emerged as central agents in the management of obesity and type 2 diabetes, with benefits extending beyond glycemic control to cardiovascular, renal, and metabolic outcomes [1-7]. While classical incretin-mediated mechanisms are well established, they do not fully account for the breadth of tissue-level effects observed in clinical and experimental settings [1-4, 8, 9].

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Increasing attention has therefore been directed toward intracellular mechanisms that may integrate these diverse effects. Among these, mitochondrial remodeling has been proposed as a unifying framework. However, whether mitochondrial changes represent a primary pharmacologic effect or a downstream consequence of systemic metabolic improvement remains incompletely resolved [8-15].

Given that mitochondrial dysfunction is a shared feature across insulin resistance, β-cell failure, steatotic liver disease, and cardiometabolic disorders, this framework is biologically plausible [16-20]. Nevertheless, interpretation requires caution, as improvements in mitochondrial function may arise from both direct receptor-mediated signaling and indirect effects such as weight loss, reduced glucotoxicity, and improved inflammatory profiles [21-27].

The central aspect of this review is that mitochondria are not merely passive downstream beneficiaries of improved

metabolism during GLP-1 therapy; rather, they likely represent a recurrent intracellular effector system through which GLP-1RAs translate receptor activation into durable organ protection [10-15].

GLP-1 signaling and why mitochondria matter

GLP-1 receptor activation classically increases intracellular cAMP, activates protein kinase A and Epac2, augments glucose-dependent insulin secretion, and modulates ion-channel and vesicular pathways [1-4, 9, 28-31]. However, downstream signaling extends into AMPK, PI3K-Akt, CREB, SIRT1, and autophagy-related pathways that interpatch directly with mitochondrial homeostasis [2, 3, 10-15, 28-33].

This is particularly relevant because mitochondria sit at the center of fuel sensing and stress adaptation. In beta cells, mitochondrial ATP production drives insulin secretion. In heart and skeletal muscle, mitochondrial function determines energetic supply. In liver and adipose tissue, mitochondria regulate substrate processing, lipid oxidation, and inflammatory pathways [16-18, 34-49]. Thus, mitochondrial biology provides a vital framework for understanding how a receptor known for endocrine effects can generate cross-organ metabolic protection.

Core mitochondrial mechanisms influenced by GLP-1 medications

From the literature mitochondrial themes across the GLP-1 are: (i) improved mitochondrial biogenesis, (ii) enhanced oxidative phosphorylation and ATP generation, (iii) reduced mitochondrial reactive oxygen species, (iv) healthier fission-fusion balance, (v) improved mitophagy and lysosomal quality control, and (vi) suppression of mitochondria-linked apoptosis [10-15, 19, 20, 28-32, 34-38, 43-49, 50-60].

Importantly, these effects are not equally established in all tissues. In beta cells and cardiometabolic models, mitochondrial rescue appears strongly integrated into therapeutic action [28-31, 34-38]. In liver, kidney, and skeletal muscle, mitochondrial advantages are likely real but are more difficult to separate from secondary improvements in glycemia, adiposity, and systemic inflammation [40-49]. This distinction is crucial for deep mechanistic interpretation.

Figure 1 demonstrates a proposed conceptual framework showing how GLP-1 medications may influence mitochondrial biology through both direct intracellular signaling and indirect systemic remodeling, ultimately converging on organ-protective outcomes.

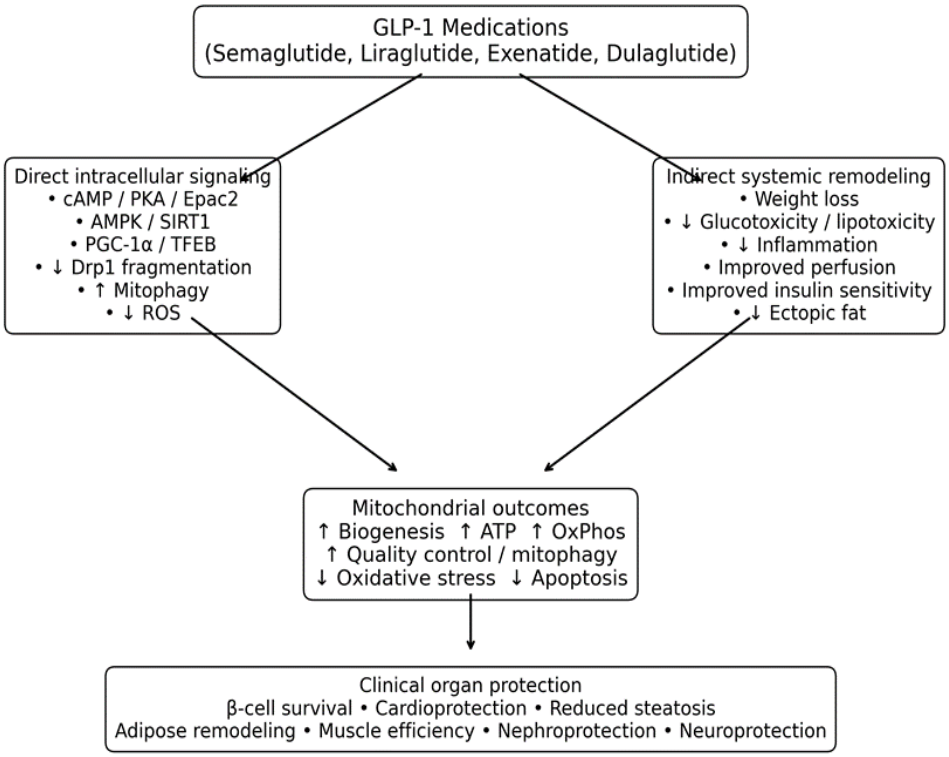

Figure 1. Direct and indirect mitochondrial mechanisms of GLP-1 medications

Figure 1 proposed conceptual framework showing how GLP-1 medications may influence mitochondrial biology through both direct intracellular signaling and indirect systemic remodeling, ultimately converging on organ-protective outcomes.

Tissue-specific mitochondrial effects

Pancreatic beta cells provide the clearest example in which mitochondrial rescue is integral rather than incidental to GLP-1

pharmacology. Exendin-4 and related agonists improve autophagic flux, reduce oxidative injury, preserve ATP-generating function, and attenuate apoptosis under glucotoxic and lipotoxic stress [28-33].

In the heart, GLP-1RAs have been linked to improved mitochondrial membrane potential, reduced fragmentation, less ROS generation, and preservation of bioenergetic function [34-39]. These findings are mechanistically attractive because cardiovascular outcome benefits are now well established clinically [61-67].

In adipose tissue and skeletal muscle, GLP-1 therapies appear to improve mitochondrial respiration, browning-related signatures, oxidative metabolism, and metabolic flexibility [43-49]. However, these tissues also exemplify the interpretive challenge of separating direct intracellular signaling from secondary effects of weight loss and nutrient unloading [13, 47-49].

In liver, kidney, and neural tissues, the literature consistently points toward lower oxidative stress, improved mitochondrial quality control, and reduced apoptosis during GLP-1 therapy [40-42, 50-60, 68, 69]. Yet the degree to which these are direct receptor-mediated events remains incompletely resolved. **Table 1**. Demonstrates the Mitochondrial effects of GLP-1 receptor agonists across tissues.

Table 1. Mitochondrial effects of GLP-1 receptor agonists across tissues

Tissue	Main mitochondrial abnormality	Reported GLP-1RA effect	Key pathways	Evidence level
Pancreatic β-cells	ROS, ATP failure, defective autophagy	↑ ATP, ↑ autophagy, ↓ apoptosis	Epac2, TFEB, cAMP	Strong
Heart	Fragmentation, ROS, energetic failure	↓ fission, ↑ respiration, ↓ apoptosis	AMPK, SIRT1, Parkin	Moderate-strong
Liver	Mitochondrial overload, oxidative stress	↓ ROS, ↑ oxidation, improved lipid handling	AMPK, PGC-1α	Moderate
Adipose tissue	Low mitochondrial density, inflammation	↑ browning, ↑ respiration, ↓ inflammation	PGC-1α, UCP1	Moderate
Skeletal muscle	Low oxidative efficiency	↑ mitochondrial efficiency, ↑ oxidative metabolism	SIRT1, AMPK	Moderate
Kidney	Oxidative stress, tubular injury	↓ ROS, ↑ quality control	AMPK, antioxidant signaling	Emerging
Brain/retina	Mitophagy failure, oxidative injury	↑ membrane potential, ↓ apoptosis	TFEB, antioxidant signaling	Emerging

Core mitochondrial mechanisms influenced by GLP-1 medications

Several preclinical studies indicate that GLP-1RAs increase expression of PGC-1alpha and associated biogenic programs involving NRF1, TFAM, and oxidative phosphorylation genes [11-15, 43-47]. This has been described in adipocytes, osteoblasts, myocardium, and some muscle models [34-38, 43-47]. Increased mitochondrial content is often accompanied by improved respiration [10-15].

GLP-1 therapies have been associated with improved mitochondrial membrane potential, greater ATP generation, and more efficient oxidative phosphorylation [11-15, 34-38, 44, 47]. In human and animal studies of obesity and diabetes, semaglutide and liraglutide have been linked to improved skeletal-muscle or adipocyte mitochondrial respiration, although not all studies distinguish direct effects from those mediated by weight loss [1, 44, 47-49].

One of the most reproducible mitochondrial signatures of GLP-1RAs is lower oxidative stress [10-12, 70, 71]. Reduced mitochondrial ROS production, enhanced antioxidant enzyme activity, improved Nrf2 signaling, and suppression of oxidative damage markers have been reported in heart, liver, retina, endothelium, kidney, and brain models [34-38, 40-42, 50, 51, 54, 60]. Pathologic mitochondrial fragmentation driven by Drp1 activation is increasingly recognized in metabolic disease [19, 20, 72-77]. GLP-1 agonists have been shown in several cardiac and adipose models to reduce fragmentation, restore tubular mitochondrial morphology, and favor a healthier balance between fission and fusion through effects on Drp1, Opa1, Mfn1, and Mfn2 [34, 36, 38, 43].

Damaged mitochondria are cleared by mitophagy, a process crucial for beta-cell and neuronal integrity [19, 20, 78-82]. Exendin-4 and liraglutide have been linked to improved autophagic flux, TFEB activation, lysosomal function, and restoration of mitochondrial quality-control programs under glucotoxic, lipotoxic, tacrolimus, and inflammatory stress conditions [28-31, 83].

Mitochondria-linked apoptosis via reduced cytochrome-c release, lower caspase activation, preservation of membrane potential, and modulation of Bcl-2 family proteins, GLP-1 medications often appear to shift cells away from mitochondrial apoptosis [28-31, 34-38, 50, 51, 84-92].

Pancreatic beta cells: mitochondria at the center of incretin action

Among all tissues, beta cells provide the strongest biologic rationale for a mitochondria-centered interpretation of GLP-1 action [28-33]. Beta-cell insulin secretion is tightly coupled to mitochondrial ATP generation, and beta-cell failure in type 2 diabetes is strongly linked to glucolipotoxicity stress, mitochondrial ROS, altered mitochondrial morphology, and defective autophagy [16-18, 28-33, 70-73, 93-97].

Exendin-4 and related GLP-1 agonists have repeatedly protected beta cells from apoptosis and improved insulin secretory capacity under glucotoxic and lipotoxic conditions [28-31]. Mechanistic studies have shown improved autophagic flux, enhanced lysosomal function, and activation of a RAPGEF4/Epac2-calcium-calcineurin-TFEB axis that supports organelle quality control [29-31]. In autophagy-deficient beta cells, exendin-4 improves glucose tolerance and cell survival even when the primary autophagy defect is not fully corrected, suggesting that mitochondria-protective signaling may operate alongside broader stress-relief effects [28, 31-33].

The mitochondrial interpretation is compelling because GLP-1 signaling in beta cells simultaneously improves fuel-stimulated ATP production, limits ROS accumulation, and reduces ER-stress-linked mitochondrial injury [28-33]. This makes beta cells the clearest example in which mitochondrial rescue is not peripheral but integral to therapeutic action [28-31, 95].

Heart and vasculature: mitochondrial rescue as a cardioprotective pathway

Cardiovascular outcome trials established that several GLP-1RAs reduce major adverse cardiovascular events [64-67, 92], but the cell biology behind these benefits remains incompletely resolved [12, 34-39]. In cardiac tissue, mitochondrial dysfunction contributes to diabetic cardiomyopathy, ischemia-reperfusion injury, endothelial impairment, and right-ventricular failure [16, 34-39, 70-73, 97]. Studies of liraglutide, semaglutide, exendin-4, and other GLP-1 agonists repeatedly show improved mitochondrial membrane potential, ATP preservation, less fragmentation, reduced ROS, and attenuation of inflammatory and apoptotic signaling [34-39].

Particularly notable are studies in diabetic and inflammatory cardiomyocyte models in which liraglutide preserved mitochondrial function through SIRT1, AMPK, Parkin-mediated mitophagy, and suppression of Drp1-dependent fission [34, 36, 37]. Experimental work also suggests that GLP-1 agonism can normalize metabolic inflexibility and excessive fatty-acid oxidation in the diabetic heart, thereby improving mitochondrial efficiency [35-38]. These changes provide a plausible mechanistic bridge between cell-level protection and observed cardiovascular benefits in clinical trials [12, 34-39, 64-67].

In the vasculature, GLP-1RAs appear to reduce leukocyte-endothelial interaction, oxidative stress, and endothelial dysfunction, again with mitochondria as a recurring downstream node [12, 39]. However, translational caution is warranted: cardiovascular outcome benefits in humans likely reflect combined mitochondrial, hemodynamic, anti-inflammatory, weight-loss, renal, and atherosclerotic effects rather than a purely mitochondrial mechanism [12, 64-68].

Liver: steatotic liver disease, mitochondrial overload, and GLP-1 therapy

Steatotic liver disease is characterized by mitochondrial overload, incomplete fatty-acid oxidation, oxidative injury, inflammation, and impaired mitophagy [17, 18, 40-42]. GLP-1RAs reduce liver fat and improve biochemical and histologic markers of liver disease in many preclinical and clinical settings [40-42, 69]. Although hepatocyte GLP-1 receptor expression remains debated, mitochondrial improvement is a recurring phenotype during GLP-1 therapy [40-42, 69].

Proposed mechanisms include reduced hepatic lipid influx secondary to weight loss, improved adipose tissue buffering, enhanced insulin sensitivity, suppression of inflammatory signaling, and activation of AMPK-SIRT1-PGC-1alpha programs [10-15, 40-42, 69]. Whether these are direct hepatocyte actions or mostly systemic effects is still unresolved [40-42]. For a mechanistic review, this uncertainty is important: liver mitochondrial benefits may be substantial, yet they may not always represent primary receptor-mediated intracellular pharmacology [6, 7, 10-15, 69].

Adipose tissue: browning, mitochondrial density, and metabolic flexibility

Adipose tissue has emerged as one of the most interesting sites of mitochondrial remodeling during GLP-1 therapy [10-15, 43-45]. Liraglutide and semaglutide have been associated with adipocyte browning signatures, improved mitochondrial biogenesis, enhanced respiration, and remodeling toward a less inflammatory phenotype [43-45]. Human adipocyte work suggests liraglutide can stimulate mitochondrial respiration and biogenesis and partially rescue TNF-induced metabolic defects [44].

These findings support the idea that GLP-1 medications do more than reduce calorie intake; they may also improve adipose tissue quality [10, 11, 43, 44]. Increased UCP1 expression, healthier mitochondrial morphology, lower inflammatory cytokine output, and better lipid-handling capacity could contribute to systemic insulin sensitization [43-45]. Nevertheless, it remains difficult to disentangle direct adipocyte signaling from secondary adaptations to negative energy balance and reduced adiposity [10-150, 43-45].

Skeletal muscle: from insulin sensitivity to mitochondrial efficiency

Skeletal muscle is a major determinant of whole-body insulin sensitivity and physical function [17, 18, 46-49]. Mitochondrial dysfunction in muscle contributes to lipid accumulation, impaired substrate switching, reduced exercise tolerance, and

sarcopenic obesity [17, 18, 46-49]. Clinical and preclinical evidence increasingly suggests that GLP-1 therapies improve aspects of muscle mitochondrial function, especially in obesity and type 2 diabetes [13, 46-49].

Recent human studies indicate that semaglutide-associated weight loss can improve skeletal-muscle mitochondrial efficiency [13, 47-49]. Preclinical work has also linked liraglutide and semaglutide to SIRT1-dependent protection against obesity-induced muscle atrophy and to broader improvements in oxidative metabolism [46-49]. Still, the interpretive challenge is substantial: in muscle, some mitochondrial improvements may be downstream of fat loss, lower ectopic lipid burden, and greater insulin sensitivity rather than direct myocellular GLP-1 receptor activation [13, 46-49].

Kidney: mitochondrial stress, inflammation, and nephroprotection

Kidney disease in diabetes involves mitochondrial oxidative stress, inflammation, defective fatty-acid oxidation, and tubular injury [17, 18, 68, 70, 71]. Experimental studies suggest GLP-1RAs can attenuate mitochondrial dysfunction in renal tissue by reducing ROS, improving antioxidant defenses, preserving membrane potential, and modulating autophagy or mitophagy pathways [10, 11, 68]. These effects align with the broader renoprotective profile emerging for the class [69].

As in liver and muscle, however, mechanistic interpretation should remain cautious [6, 7, 10-15]. Improved glycemia, blood pressure, weight, and systemic inflammation all indirectly benefit renal mitochondria [64-68]. The kidney, therefore, illustrates an important principle for this review: mitochondrial rescue may be a common final pathway of benefit even when it is not the first pharmacologic event after receptor binding [11-15, 68].

Brain and neuroprotection: mitochondrial implications beyond metabolism

GLP-1 medications are increasingly studied in neurodegenerative and neuroinflammatory disorders [50-60]. In models of Alzheimer's disease, Parkinson's disease, retinal injury, and stress-related neural damage, GLP-1 agonists frequently reduce oxidative injury, improve mitochondrial membrane potential, dampen apoptosis, and promote mitophagy or lysosomal quality control [50-60].

These observations are biologically credible because neurons are highly energy dependent and vulnerable to mitochondrial injury [16, 19, 20, 50-60, 70-73]. The neuroprotective literature also strengthens the argument that GLP-1 pharmacology extends beyond classical peripheral endocrine actions [51-57]. Yet this area remains preclinical-heavy, and the extent to which mitochondrial benefits translate into meaningful neurologic outcomes in humans remains an open question [51-57].

Direct versus indirect mitochondrial effects: a critical distinction

A critical distinction in interpreting the literature is whether mitochondrial effects of GLP-1RAs are direct or secondary. Demonstrating direct effects requires clear evidence of receptor expression in the relevant cell type, appropriate pharmacologic or genetic modulation, and mitochondrial outcomes that persist independently of systemic changes [2-5, 6, 7, 10-15, 98-100].

In contrast, indirect mechanisms are likely substantial and should not be undervalued. Weight loss, improved glycemic control, reduced lipotoxicity, and attenuation of systemic inflammation are all well-established effects of GLP-1 therapy that can secondarily improve mitochondrial function across multiple tissues [13, 42, 47-49, 61-69].

Notably, some of the most robust human data, particularly with semaglutide, may reflect integrated physiological improvement rather than isolated cell-autonomous mitochondrial signaling. This distinction is essential to avoid over-attribution of causality [101, 102].

Are mitochondrial effects class-wide or molecule-specific?

The available literature suggests substantial overlap across liraglutide, semaglutide, exenatide/exendin-4, and some experimental GLP-1 analogues, especially regarding redox improvement, anti-apoptotic signaling, and quality-control pathways [10-15, 28-31, 34-38, 43-49, 50-60]. However, differences in half-life, tissue exposure, receptor engagement patterns, and weight-loss potency may create molecule-specific mitochondrial signatures [2-7, 61-69].

Semaglutide-associated data in obesity and muscle increasingly emphasize systemic metabolic unloading and mitochondrial efficiency [13, 47-49, 63, 103-106]. Exendin-4 literature is especially rich in beta-cell autophagy and neuronal cryoprotection [28-31, 50, 58]. Liraglutide has a broad preclinical portfolio covering heart, adipose tissue, retina, osteoblasts, and inflammatory injury [34, 43-46, 50, 107]. Whether these differences reflect true pharmacologic diversity or simply unequal research intensity remains unresolved [10-15, 108, 109].

Clinical relevance and translational importance

Mitochondrial framing matters clinically because it helps unify otherwise disparate therapeutic effects of GLP-1RAs. Improved beta-cell durability, cardio protection, lower liver fat, adipose remodeling, skeletal-muscle efficiency, nephroprotection, and neuroprotection all become easier to interpret if GLP-1 therapies repeatedly restore mitochondrial quality control under nutrient and inflammatory stress [28-31, 34-49, 50-60, 68-73].

This perspective also raises an important translational possibility: mitochondrial phenotypes may help explain heterogeneity of response. Patients with different burdens of oxidative stress, mitochondrial dysfunction, sarcopenic obesity, steatosis, or inflammatory injury may derive different organ-specific benefits from the same drug [13, 47-49, 56, 57]. However, human data are still limited in this era.

Future directions

Several questions remain unresolved and should define the next phase of research. First, which mitochondrial effects are truly cell-autonomous and receptor-mediated in hepatocytes, adipocytes, myocytes, and renal cells? Second, which mitochondrial signatures are most predictive of clinically meaningful response? Third, are mitochondrial effects class-wide or molecule-specific? Fourth, do dual and triple incretin agonists amplify mitochondrial remodeling beyond GLP-1 monotherapy? Finally, can mitochondrial biomarkers be used to stratify patients most likely to derive organ-specific benefit [56, 57, 61, 62]?

Methodologically, the field now needs more human biopsy-based work, better receptor-validation studies, more standardized mitochondrial endpoints, and more careful control for confounders such as weight loss and glycemic improvement [13, 47-49, 56].

Conclusion

In summary, mitochondria represent a consistent downstream convergence point in the biological effects of GLP-1 receptor agonists across multiple tissues. While substantial evidence supports improvements in mitochondrial biogenesis, function, and quality control, these changes likely arise through a combination of direct and indirect mechanisms.

Importantly, mitochondrial remodeling should not be interpreted as a singular or universal primary mechanism of action. Rather, it appears to function as an integrative effector layer through which metabolic and organ-protective benefits are expressed.

Future work should focus on clarifying tissue-specific receptor-mediated effects, standardizing mitochondrial endpoints, and expanding human translational studies to better define the clinical relevance of these observations.

Statements

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