

GLP-1 Receptor Activation and Cardioprotection: Mechanisms and Clinical Implications

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ABSTRACT

Glucagon-like peptide-1 receptor (GLP-1R) agonists have emerged as important agents with cardiovascular benefits beyond glycemic control. Increasing evidence demonstrates that GLP-1R activation exerts cardioprotective effects through a combination of direct myocardial signaling, vascular modulation, and systemic metabolic improvements. At the cellular level, GLP-1R activation enhances pro-survival pathways, reduces apoptosis, preserves mitochondrial function, and attenuates oxidative stress. Additionally, anti-inflammatory and anti-fibrotic effects contribute to improved cardiac remodeling. Vascular benefits include enhanced endothelial function, nitric oxide-mediated vasodilation, and improved microvascular perfusion. Systemically, GLP-1R agonists improve metabolic parameters such as glucose levels, body weight, and lipid profile, reducing cardiovascular burden. Emerging evidence also highlights GLP-1R-independent mechanisms mediated by peptide metabolites. Together, these mechanisms support the expanding role of GLP-1R agonists in cardiovascular protection, although further research is required to clarify their full therapeutic potential.

KEYWORDS: GLP-1 receptor; Cardioprotection; Myocardial ischemia; Endothelial function; Mitochondrial function; Oxidative stress; GLP-1 agonists.

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INTRODUCTION

Glucagon-like peptide-1 receptor (GLP-1R) agonists were initially developed for the treatment of type 2 diabetes mellitus due to their effects on insulin secretion and glycemic control. However, growing evidence has demonstrated that these agents exert significant cardiovascular benefits, including reductions in major adverse cardiovascular events and improved cardiac function (1,2).

These effects are mediated through a complex interplay of direct myocardial actions, vascular modulation, and systemic metabolic improvements. Understanding these mechanisms is essential for expanding the therapeutic role of GLP-1R agonists beyond diabetes management.

LITERATURE REVIEW

Cellular and Molecular Mechanisms in the Heart

GLP-1R activation promotes cardiomyocyte survival through multiple intracellular signaling pathways, including cAMP/PKA, Epac, PI3K/Akt, AMPK, ERK1/2, and mTOR (3–5). These pathways collectively reduce apoptosis by decreasing pro-apoptotic signaling (e.g., Bax, caspase-3) and enhancing anti-apoptotic mechanisms.

Mitochondrial protection is another key mechanism. GLP-1R stimulation reduces reactive oxygen species production, stabilizes mitochondrial membrane potential, and enhances mitochondrial dynamics and autophagy, thereby improving cellular resilience to ischemic injury (3,6).

Additionally, GLP-1R agonists exert anti-inflammatory and anti-fibrotic effects by suppressing NF- κ B signaling and reducing cytokine production, which contributes to improved cardiac remodeling and function (5,7).

Table 1. Major Cardioprotective Mechanisms of GLP-1R Activation

MECHANISM	EFFECT ON THE HEART
ANTI-APOPTOTIC SIGNALING	Reduced cardiomyocyte death, smaller infarct size
MITOCHONDRIAL PROTECTION	Improved energy metabolism, reduced oxidative stress
ANTI-INFLAMMATORY EFFECTS	Decreased cytokine-mediated damage
ANTI-FIBROTIC EFFECTS	Reduced cardiac remodeling and fibrosis
ENDOTHELIAL/MICROVASCULAR EFFECTS	Improved perfusion and vasodilation

Vascular and Endothelial Effects

GLP-1R activation improves endothelial function by increasing nitric oxide production via endothelial nitric oxide synthase activation and reducing oxidative stress (2,8). These effects enhance coronary microvascular function, increase myocardial perfusion, and improve vascular reactivity. Endothelial GLP-1R signaling, particularly in specialized vascular cell populations, plays a critical role in mediating these protective effects and contributes to improved outcomes in ischemic conditions (7,8).

Systemic Metabolic Contributions

Beyond direct cardiac effects, GLP-1R agonists reduce cardiovascular risk through systemic metabolic improvements. These include reductions in blood glucose, body weight, blood pressure, and lipid levels (1,9). Additionally, GLP-1R activation promotes a shift in myocardial substrate utilization toward more efficient glucose metabolism, which enhances cardiac performance under stress conditions such as ischemia (9).

GLP-1R–Independent Mechanisms

Emerging evidence suggests that GLP-1 metabolites, particularly GLP-1(9–36), exert cardioprotective effects independently of the classical receptor. These mechanisms involve nitric oxide and cyclic GMP pathways and contribute to improved coronary flow and reduced ischemic injury (10). This dual mechanism—both receptor-dependent and independent—adds complexity and therapeutic potential to GLP-1–based treatments.

DISCUSSION

The cardioprotective effects of GLP-1 receptor (GLP-1R) activation represent a paradigm shift in the management of cardiometabolic disease, extending far beyond glycemic control. Unlike traditional therapies that target isolated pathways, GLP-1R agonists exert multilevel and pleiotropic effects involving direct myocardial signaling, vascular modulation, and systemic metabolic improvements (1,2). This integrative mechanism likely explains the consistent cardiovascular benefits observed across preclinical and clinical studies.

At the myocardial level, one of the most robust and reproducible findings is the activation of pro-survival intracellular signaling pathways, including PI3K/Akt, AMPK, and ERK1/2 (3–5). These pathways converge on the inhibition of apoptosis, reduction of oxidative stress, and preservation of cardiomyocyte integrity during ischemic and

metabolic injury. Importantly, this anti-apoptotic effect translates into reduced infarct size and improved ventricular function, suggesting a clinically meaningful impact in ischemia-reperfusion scenarios (3,4).

Mitochondrial preservation emerges as another cornerstone of GLP-1–mediated cardioprotection. The ability of GLP-1R activation to stabilize mitochondrial membrane potential, reduce reactive oxygen species, and enhance mitophagy provides a critical survival advantage to cardiomyocytes under stress conditions (3,6). This mechanism is particularly relevant in diabetic cardiomyopathy, where mitochondrial dysfunction plays a central role in disease progression (5,6). Beyond direct myocardial effects, the role of GLP-1R signaling in the vascular endothelium and microcirculation is increasingly recognized. Enhanced nitric oxide bioavailability, reduced endothelial oxidative stress, and improved microvascular perfusion contribute to better oxygen delivery and myocardial efficiency (2,8). These vascular effects may be especially relevant in conditions such as coronary microvascular dysfunction and heart failure with preserved ejection fraction (7,8).

Another critical dimension is the systemic metabolic unloading of the heart. GLP-1R agonists improve glycemic control, reduce body weight, lower blood pressure, and improve lipid profiles, thereby decreasing myocardial workload and oxygen demand (1,9). Additionally, the shift toward glucose utilization enhances energetic efficiency, particularly under ischemic conditions (9).

A particularly intriguing concept is the existence of GLP-1R–independent cardioprotective mechanisms, mediated by peptide metabolites such as GLP-1(9–36). These metabolites exert vasodilatory and cytoprotective effects through nitric oxide and cyclic GMP pathways, even in the absence of classical receptor activation (10). This dual mechanism expands the understanding of GLP-1–based therapies beyond receptor-dependent pathways.

Despite these promising mechanisms, several limitations remain. First, a substantial portion of the mechanistic evidence derives from preclinical and experimental models, which may not fully capture the complexity of human cardiovascular disease (3,5). Therefore, translating these findings into clinical benefit requires careful interpretation. Second, the relative contribution of direct versus indirect effects remains unclear. While metabolic improvements are undoubtedly significant, the extent to which direct myocardial and vascular actions independently drive cardiovascular outcomes is still under investigation (1,2).

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Third, patient heterogeneity likely influences therapeutic response. Factors such as baseline cardiovascular risk, presence of diabetes, and degree of inflammation may determine the magnitude of benefit from GLP-1R agonists (2,9).

Additionally, although GLP-1R agonists have demonstrated reductions in major adverse cardiovascular events, their role in specific clinical settings such as heart failure and acute ischemic injury is still evolving (2,8). Early data suggest benefits in endothelial function and perfusion, but further targeted studies are required.

From a therapeutic perspective, the expanding role of GLP-1R agonists raises interest in combination strategies with other cardioprotective agents. Their complementary mechanisms may offer synergistic benefits, although this hypothesis requires further clinical validation (1,2).

Finally, GLP-1-mediated cardioprotection reflects a broader shift toward integrated cardiometabolic therapy, where treatments target shared pathophysiological pathways rather than isolated disease processes. This approach may ultimately lead to more effective and comprehensive cardiovascular risk reduction.

CONCLUSION

GLP-1R activation provides significant cardioprotective effects through a combination of cellular, vascular, and systemic mechanisms. These include reduced apoptosis, improved mitochondrial function, enhanced endothelial performance, and favorable metabolic changes.

The growing body of evidence supports the expanding role of GLP-1R agonists in cardiovascular disease management.

Future research should focus on refining therapeutic indications and clarifying underlying mechanisms to maximize clinical benefit.

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