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STATE-OF-THE-ART REVIEW

# Glucagon-Like Peptide-1

## A Promising Agent for Cardioprotection During Myocardial Ischemia

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**SUMMARY**

Glucagon-like peptide-1-(7-36) amide (GLP-1) is a human incretin hormone responsible for the release of insulin in response to food. Pre-clinical and human physiological studies have demonstrated cardioprotection from ischemia-reperfusion injury. It can reduce infarct size, ischemic left ventricular dysfunction, and myocardial stunning. GLP-1 receptor agonists have also been shown to reduce infarct size in myocardial infarction. The mechanism through which this protection occurs is uncertain but may include hijacking the subcellular pathways of ischemic preconditioning, modulation of myocardial metabolism, and hemodynamic effects including peripheral, pulmonary, and coronary vasodilatation. This review will assess the evidence for each of these mechanisms in turn. Challenges remain in successfully translating cardioprotective interventions from bench-to-bedside. The window of cardioprotection is short and timing of cardioprotection in the appropriate clinical setting is critically important. We will emphasize the need for high-quality, well-designed research to evaluate GLP-1 as a cardioprotective agent for use in real-world practice. (J Am Coll Cardiol Basic Trans Science 2016;1:267–76) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Ischemic heart disease is the most important cause of morbidity and mortality in the developed world. Recent advances in revascularization of coronary arteries through percutaneous coronary intervention (PCI) and coronary artery bypass grafting have had a dramatic improvement in the fate of patients suffering with ischemic heart disease (1). Nonetheless, revascularization does not address damage from ischemia-reperfusion (IR) injury and indeed may even contribute to it. For example, up to fifty percent of the final infarct size of an acute myocardial infarction is attributable to IR injury (2). Additionally, IR injury is responsible for nonlethal effects, for example, myocardial stunning, arrhythmia and late remodeling. Therapies that reduce these detrimental effects of IR injury are desperately needed.

One promising target for cardioprotection is metabolic manipulation by optimizing use of myocardial glucose. The heart is an omnivore and can use a number of substrates for the generation of the adenosine triphosphate (ATP), required to power myocardial work. Glucose is the most efficient generator of ATP per unit of oxygen available (3). Therapies that increase glucose oxidation in preference to free fatty acids could reduce the impact of myocardial ischemia.

Glucagon-like peptide-1-(7-36) amide (GLP-1) is a human incretin hormone produced by the gut in response to food. It is primarily an insulinotropic hormone and has been extensively studied as a novel treatment for type 2 diabetes mellitus. It acts in a glucose-dependent manner, thus reducing the risk of hypoglycemia. However, in contrast to other oral

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**ABBREVIATIONS AND ACRONYMS**

**ATP** = adenosine triphosphate

**ANP** = atrial natriuretic peptide

**AMI** = acute myocardial infarction

**DPP** = dipeptidyl-peptidase

**GLP-1** = glucagon-like peptide 1-(7-36) amide

**GLP-1R** = GLP-1 receptor

**GLP-1RA** = GLP-1 receptor agonist

**IC** = ischemic conditioning

**IR** = ischemia reperfusion

**PCI** = percutaneous coronary intervention

**RISK** = reperfusion injury survival kinase

**SAFE** = survivor-activating factor enhancement

**STEMI** = ST-segment elevation myocardial infarction

hypoglycemic agents, GLP-1 has other potentially beneficial "off-target" cardiovascular properties including optimization of myocardial metabolism and possibly direct cardioprotection through binding to a cardiac receptor and signaling protection via subcellular ischemic conditioning pathways.

## GLP-1 STRUCTURE AND FUNCTION

GLP-1-(7-36) amide is a 30-amino acid cleavage product of pro-glucagon secreted by enteroendocrine L-cells in the gut (4). Oral ingestion of a meal is the primary physiological stimulus to GLP-1 secretion (5). GLP-1 is not secreted in response to an intravenous glucose infusion.

GLP-1 has receptor-dependent and -independent actions. It causes glucose-dependent insulin release through binding the GLP-1 receptor (GLP-1R) on pancreatic beta cells. GLP-1 does not cause hypoglycemia as its insulinotropic effect does not occur at a blood glucose concentrations <70 mg/dl (6). GLP-1 has a number of other physiological effects which serve to lower plasma glucose levels. These include stimulation of insulin gene transcription in the beta cell (7) and reduced gastric emptying (8). Enhancement of peripheral insulin sensitivity remain unproven with conflicting evidence (9).

The GLP-1R is a 463-amino acid, G protein-coupled receptor found on the cell surface membrane of numerous tissues throughout the body. Its presence within the myocardium has remained controversial. Both mouse and primate studies have suggested that GLP-1R remains confined to the atria and possibly just the sinoatrial node (10,11). The location of the receptor is important in elucidating the mechanism of GLP-1 cardioprotection. Evidence of receptor-independent effects suggest that there may be an alternative receptor or perhaps actions that do not require a receptor (12,13), discussed further below.

GLP-1 is cleaved by the enzyme dipeptidyl peptidase (DPP)-4 to GLP-1-(9-36) amide with a half-life of approximately 2 min (14). The biological role of this breakdown product is uncertain but it has reduced incretin activity. GLP-1 is further degraded by neutral endopeptidase to GLP-1 fragments whose biological activity is the subject of ongoing research.

A number of pharmaceutical products have been developed to use the incretin effect of GLP-1 while avoiding the difficulties associated with its rapid breakdown to an apparently inactive form. These drugs include DPP-4 inhibitors such as sitagliptin (Januvia, Merck, Kenilworth, New Jersey), saxagliptin (Onglyza, AstraZeneca, Macclesfield, United Kingdom), and vildagliptin (Galvus, Novartis, Basel, Switzerland), all of which increase levels of native GLP-1; and DPP-4-resistant GLP-1 receptor agonists (GLP-1RA) such as exenatide (Byetta, AstraZeneca, United Kingdom) and liraglutide (Victoza, Novo Nordisk, Bagsvaerd, Denmark).

## PRE-CLINICAL EVIDENCE OF GLP-1 CARDIOPROTECTION

GLP-1 protects cardiomyocytes from cell death. In vitro, GLP-1 has been shown to avert cell death in HL-1 murine adult cardiomyocytes treated with the pro-apoptotic agent staurosporine (15). Both wild-type and GLP-1R homozygous knockout mice experienced cardioprotection from GLP-1-(7-36) and -(9-36), suggesting the protective effect occurred independent of receptor binding (16). GLP-1 protection was similarly associated with reduced activation of pro-apoptotic molecules in rats, and occurred regardless of whether it was given prior to ischemia or in early reperfusion (17,18). In vivo, GLP-1 infusion given to dogs with pacing-induced cardiomyopathy improved left ventricular function with systemic changes such as reduced heart rate and blood pressure (19). Furthermore, GLP-1 infusion reduced infarct size after IR injury (20).

GLP-1 RAs have also been shown to protect against IR injury. Both albiglutide (Eperzan, GlaxoSmithKline, Stevenage Herts, United Kingdom) and lixisenatide (Lyxumia, Sanofi, Paris, France) reduced final infarct size in rat models (21,22), and pretreatment with liraglutide protects in mice (23). In a porcine model of IR injury, treatment with exenatide for 3 days reduced infarct size and improved left ventricular function (24). However, initiation of exenatide after onset of ischemia did not result in cardioprotection, suggesting that, at least for GLP-1RAs, there may be a time-dependent element to the cardioprotection (25).

## MECHANISM OF GLP-1-MEDIATED CARDIOPROTECTION

Many of the studies cited above have demonstrated aspects of cardioprotection that provide clues to how GLP-1 protects against IR injury. Several mechanisms have been proposed for GLP-1-mediated cardioprotection. A change in myocardial glucose utilization may result in increased metabolic efficiency and myocardial resistance to ischemia, thus limiting infarction. Vasodilation and reduction in systemic and/or pulmonary vascular resistance can also reduce