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Cardiovascular protective effects of GLP-1:

A focus on the MAPK signaling pathway

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Abstract

Cardiovascular and related metabolic diseases are significant global health challenges. Glucagon-like peptide 1 (GLP-1) is a brain-gut peptide secreted by ileal endocrine that is now an established drug target in type 2 diabetes (T2DM). GLP-1 targeting agents have been shown not only to treat T2DM, but also to exert cardiovascular protective effects through regulating multiple signaling pathways. The mitogen-activated protein kinase (MAPK) pathway, a common signal transduction pathway for transmitting extracellular signals to downstream effector molecules, is involved in regulating diverse cell physiological processes, including cell proliferation, differentiation, stress, inflammation, functional synchronization, transformation and apoptosis. The purpose of this review is to highlight the relationship between GLP-1 and cardiovascular disease (CVD), and discuss how GLP-1 exerts cardiovascular protective effects through MAPK signaling pathway. This review also discusses the future challenges in fully characterizing and evaluating the CVD protective effects of GLP-1 receptor agonists (GLP-1RA) at the cellular and molecular level. A better understanding of MAPK signaling pathway that are dysregulated in CVD may aid in the design and development of promising GLP-1RA.

Keywords

Glucagon-like peptide 1; type 2 diabetes; mitogen-activated protein kinase pathway; cardiovascular disease

1. Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality and is directly associated with atherosclerosis (AS). AS is characterized by the gradual development of chronic inflammation in vessel wall, which causes lipids to deposit and accumulate under the endothelial layer of large- and medium-sized arteries. Several risk factors have been associated with both chronic inflammation and disease development, including hypertension, hyperlipidemia, smoking, obesity, diabetes, and other genetic factors (Albany et al. 2019). In recent years, increasing evidence suggests a potential link between chronic low-grade inflammation in the heart and metabolic dysregulation (Palomer et al. 2013). Type 2 diabetes mellitus (T2DM) is a metabolic disorder that is one of the primary risk factors of developing CVD, affecting about 300 million people globally, a number that is expected to increase to 450 million by 2030 (Wild et al. 2004). It has been reported that hyperglycemic state in non-diabetic patients also affects the progression of cardiovascular disease (Bellis et al. 2021). High blood pressure and endothelial dysfunction are identified as CVD risk factors and also occur in 75% of T2DM patients (Jurado et al. 2009). T2DM and CVD share common risk factors and might be of mutual promotion. Remarkably, CVD is one of the common complications of T2DM and is the leading death cause in T2DM patients (Matheus et al. 2013).

Glucagon-like peptide 1 (GLP-1) is a peptide hormone secreted by intestinal L-cells. Previous studies showed effectiveness of GLP-1 receptor agonist (GLP-1RA) on lowering blood glucose levels through binding and activating the GLP-1 receptor (GLP-1R), thus they are widely used to treat T2DM (Campbell and Drucker 2013). With the deepening of research, it has been found that GLP-1RA not only has hypoglycemic effect, but also has protective effect on heart, kidney, liver and beneficial effect on

skeletal muscle and nervous system. It has also been found that GLP-1RA can effectively improve the skin lesions of psoriasis patients and the symptoms of ovarian syndrome(Dandona et al. 2018). But in general, GLP-1RA has the most prominent effect in terms of cardiovascular protection. Furthermore, it has been found that GLP-1RA can regulate insulin and glucagon secretion, improve β -cell function and maintain β -cell mass, reduce body weight, but also directly or indirectly exert cardiovascular protective effects (Ussher and Drucker 2012)(Ravassa et al. 2012). Recent work on the cardioprotective effects of GLP-1RA have demonstrated that anti-atherosclerotic and cardiovascular protective effects occur via improved endothelial cells (ECs) function, reduced vascular wall inflammatory cell adhesion and infiltration, inhibition of vascular intimal thickening, and indirect improvements in glucose and lipid metabolism (Song et al. 2015).

Cardiac physiology and pathology can be influenced by many intracellular signaling pathways, yet the mitogen activated protein kinase (MAPK) pathway has drawn significant attention because of its pleiotropic effects (Javadov et al. 2014). These effects occur when complex living organisms respond coordinately to different extracellular stimuli, and MAPK signals help cells regulate and control embryogenesis, proliferation, differentiation, gene expression, metabolism and cell survival (Chen et al. 2001)(Roux and Blenis 2004). Although the full molecular mechanisms by which GLP-1 functions in the cardiovascular system are still being elucidated, it has been observed recently that the MAPK signaling pathway is involved in regulating GLP-1-mediated cardiovascular protective effects.

2. GLP-1

GLP-1 is a 30 amino acid long peptide hormone that is synthesized and secreted by enteroendocrine L-cells in response to nutrient ingestion (Campbell and Drucker 2013). Intestinal GLP-1 levels are highest postprandially and decrease when fasting. GLP-1 binding of its receptor (GLP-1R) on pancreatic β cells stimulates synthesis and release of insulin in a glucose-dependent manner. About 80% of the biological activity of GLP-1 comes from GLP-1 (7-36a) that has a short half-life (1-2 min) in vivo and will rapidly degrade to GLP-1 (9-36a) via the enzyme dipeptidyl peptidase-4 (DPP-4) (Ussher and Drucker 2014)(Avogaro et al. 2014)(Fig. 1). Neurons in the brain can also release GLP-1, which was shown to suppress food intake, however the interplay between the neuronal-released and gut-derived GLP-1 remains unclear (Holst 2007). GLP-1R is a member of the class B G protein-coupled receptor, which is mainly expressed in pancreatic β -cells, but also in endothelial cells, cardiomyocytes and vascular smooth muscle cells (VSMCs) (Campbell and Drucker 2013)(Kirkpatrick et al. 2012). Functional GLP-1R is expressed in the heart (Ban et al. 2008), thus cardiomyocytes signaling pathways can be directly activated by GLP-1RA (Vila Petroff et al. 2001). GLP-1R is also expressed in the endocrine pancreas. Hence, cardiac function may be indirectly regulated by GLP-1-mediated insulin secretion and metabolic control of glucose, glucagon and free fatty acids. Moreover, peripheral and central nervous system (CNS), especially CNS regions that control cardiovascular function, can be activated by GLP-1RA (Yamamoto et al. 2003)(Yamamoto et al. 2002). GLP-1RA has a very effective cardiovascular protective effect in non-diabetic patients with cardiovascular disease in hyperglycemic state (Caturano et al. 2021), while the beneficial effects of GLP-1 on cardiovascular health-related parameters (e.g., lipid metabolism, body weight and blood pressure) also appear to occur independently of glycemic control improvement (Bose et al. 2005)(Fig. 1).

Generally, the main approaches for GLP-1-related drugs discovery, whether is approved or is still in clinical trials, are developed aiming to avoid GLP-1 degradation by DPP-4 (Drucker 2006). Thus, GLP-1 preparations used in clinical practice are mainly divided into two categories: one is DPP-4 inhibitors, including sitagliptin, vildagliptin and salbutamol, which can raise endogenous GLP-1 levels to some extent. The other class is DPP-4-resistant GLP-1R agonists, including liraglutide and exenatide.

3. The role of MAPK signaling pathway in cardiovascular disease

3.1 MAPK signaling pathway

MAPKs are structurally and functionally conserved enzymes expressed in all eukaryotic cells, which transduce extracellular stimulatory signals into cells to regulate various cellular processes, such as innate cellular immunity, proliferation, differentiation, apoptosis, cell survival, and inflammation (Arthur and Ley 2013)(Peti and Page 2013)(Turjanski et al. 2007). The generic signaling pathway of MAPK is shared by four different cascades named based on their MAPK tier component: the extracellular signal-related kinases 1/2 (ERK1/2), Jun amino-terminal kinases 1/2/3 (JNK1/2/3), p38 mitogen-activated protein kinase (p38-MAPK) and extracellular signal-regulated kinase 5 (ERK5) (Chang and Karin 2001).

ERK signaling is the most important and classical signaling pathways in the MAPK pathway, which can be activated by receptor tyrosine kinases, G-protein-coupled receptors and some cytokine receptors. ERK1 and ERK2 are the prototypes of the eight isoforms of ERK and can be activated by MAPK/ERK kinase (MEK) 1 or 2 (Torii et al. 2006). Phosphorylated ERK1/2 translocates from the cytoplasm to the nucleus and is involved in diverse cellular physiological processes, including cell

proliferation, differentiation, morphology maintenance, cytoskeletal construction, apoptosis and cellular carcinogenesis.

JNK and p38 signaling pathways can be activated in response to cellular stresses including genotoxic, osmotic, hypoxic or oxidative stress. Proinflammatory cytokines including tumor necrosis factor (TNF)- α and interleukin (IL)-1 β can also activate JNK and p38 signaling pathways (Kim and Choi 2010). Apoptosis signal-regulating kinase 1 (ASK1), a MAP3K in both the JNK and p38 signaling pathways, is activated in response to various stressors such as endoplasmic reticulum (ER) stress, lipopolysaccharide (LPS) and reactive oxygen species (ROS) (Nagai et al. 2007).

ERK5, also named big mitogen-activated protein kinase 1 (BMK1), is the latest identified MAPK family member. It consists of an amino-terminal kinase domain with a relatively big carboxy-terminal of unique structure and function, differentiating it from other MAPK members (Nithianandarajah-Jones et al. 2012)(Rovida et al. 2015). ERK5 is expressed in many tissue types, including the heart, kidneys, lungs, skeletal muscle, and placenta (Nithianandarajah-Jones et al. 2012), specifically activated by a different upstream kinase MEK5, which induces an open conformation of ERK5 and translocation into the nucleus (Gomez et al. 2016).

3.2 MAPK signaling pathway in cardiovascular disease

Though the cardiac physiological and pathological microenvironment can be manipulated by multiple intracellular signaling pathways, the MAPK family has drawn notable attention for its vast implications in signaling and crosstalk with other signaling networks. The key components of the MAPKs signaling cascade, including ERK1/2, p38, JNK and ERK5, have unique intracellular signaling mechanisms, and have been extensively studied in their response to a myriad of mitogens and stressors for their

influence on heart metabolism, development, performance and pathogenesis (Javadov et al. 2014).

Atherosclerosis-related inflammatory pathways that result in cytokine production are mediated by the MAPKs. Losmapimod, a p38 MAPK inhibitor, has potentially beneficial effects on vascular function. It was demonstrated that the protective effects of Losmapimod in the vascular wall were mediated by attenuated inflammatory response, plaque stabilization, and reduced levels of C-reactive protein. Inhibition of the MAPK signaling pathway can also reduce LPS-induced inflammatory response in ECs (Li et al. 2021). Recently, the inhibition of p38 MAPK in cardiomyocytes has been found to ameliorate autophagy (Hou et al. 2021)(Fig. 2).

Oxidative stress, disruption of endothelial integrity and platelet activation are involved in the progression of chronic inflammatory diseases like atherosclerosis. Antiplatelet drugs are often recommended to treat CVD (Davi 2007)(Spadaccio et al. 2020). The rate of cardiovascular events (e.g., stroke, myocardial infarction, and cardiovascular death) can also be reduced by some drugs (i.e. statins) whose effects are likely to be mediated by inhibiting the MAPK signaling pathway (Gallone et al. 2018)(Nenna et al. 2021). Generally, the extensive crosstalk of four different MAPK cascades, including ERK1/2, JNK, p38-MAPK and ERK5, provide a complex interplay of processes in pathogenesis of CVD (Reustle and Torzewski 2018).

4. GLP-1 exerts cardiovascular protective effects through modulating MAPK signaling pathway

4.1 GLP-1 and the classical MAPK pathway

As described above, ERK signaling can regulate cell proliferation, differentiation and many other biological responses. There is a clear correlation between abnormal

ERK pathway activation and disease progression. The molecular mechanism of beneficial GLP-1 effects on the cardiovascular system is unknown, yet preliminary evidence suggests it is tied to the GLP-R. Liraglutide, a GLP-1RA, shows ability to protect cardiomyocytes from high glucose-induced apoptosis. GLP-1 exerts its anti-apoptotic activity on cardiomyocytes through activating PI3K/Akt and ERK1/2 signaling pathway. Other studies have shown that GLP-1 (9-36a) and the GLP-1RA Exendin-4 both reduce infarct size and protect cardiomyocytes from ischemia and oxidative stress through increasing ERK1/2 phosphorylation (Noyan-Ashraf et al. 2009)(Ban et al. 2010)(Ravassa et al. 2011)(Fig. 2). In addition, GLP-1 and GLP-1RA are able to reduce ER stress and inflammation in pancreatic β -cells and improve patient survival, and can thus be used for treating patients with T2DM (Tsunekawa et al. 2007). Insulin resistance and β -cell dysfunction are associated with a variety of cardiometabolic diseases. Exendin-4 significantly induces ERK phosphorylation in pancreatic cells of BTC6 mice, and had a protective effect against oxidative stress through regulating ERK1/2 activity (Madhu et al. 2020). These observations suggest that ERK1/2 activation may be a driver of beneficial GLP-1 and GLP-1-based drug effects in myocardial protection occurring in diabetic and non-diabetic states.

Yet, not all ERK activation events may be beneficial for CVD (Gallo et al. 2019). Ventricular remodeling, a primary manifestation of cardiovascular disease, shows the typical morphologic features of collagen deposition, interstitial fibrosis and excessive proliferation of myocardial fibroblasts. In the diabetic environment, glucose is a critical stimulus for the formation of collagen in heart. It has been demonstrated in vitro that ERK1/2 pathway activation following hyperglycemia promotes collagen synthesis (Tang et al. 2007). Additionally, ERK1/2-NF- κ B pathway activation helps with the organization of cytoskeleton in multiple types of cells, as well as the formation of

collagen in fibroblasts (Choi and Helfman 2014)(Fig. 2). Both Liraglutide and Linagliptin (the DPP-4 inhibitor) significantly decrease ERK1/2 and NF- κ B activation (Wang et al. 2016). Targeting components of these intracellular signals and ameliorating their toxic effects may be the mechanism by which Liraglutide and Linagliptin modulate pathogenic cardiac fibroblast biology in vivo.

Atherosclerotic plaques formation in vessels is accelerated by the enhanced proliferation and/or the reduced apoptosis of VSMCs, leading to intimal thickening and vascular remodeling (Doran et al. 2008). Liraglutide can decrease ERK1/2 phosphorylation via GLP-1R. Activation of the ERK1/2 pathway may be a crucial event mediating increased proliferation and migration as well as decreased apoptosis of VSMCs, but Liraglutide shows significant inhibition against these effects through decreasing ERK1/2 phosphorylation (Shi et al. 2015)(Koga et al. 2019)(Fig. 3).

Platelets are not only involved in the process of stopping coagulation and maintaining the integrity of vascular endothelium, but also play a key role in sustaining inflammation and AS progression (Jurk and Kehrel 2010). Previous studies have shown that the treatments of platelet with GLP-1 influence platelet function by decreasing oxidative stress, reducing the activation of PI3K and MAPK pathways through mechanisms independent of GLP-1 binding to GLP-1R, in spite of that GLP-1R is normally expressed on the platelet membrane. Nitric oxide (NO) is involved in antiplatelet aggregation by promoting the synthesis of cyclic guanosine monophosphate (cGMP) and subsequent activation of cGMP-dependent protein kinase (PKG). GLP-1 exerts a platelet inhibitory effect by increasing the activation of NO/cGMP/PKG/VASP pathway and reducing the activation of MAPK/ERK-2 pathway (Barale et al. 2017). GLP-1 (7–36), the degradation product of GLP-1 (9–36), and Liraglutide all inhibit

platelet activation under specific conditions, which may have protective effects on the cardiovascular system.

Overall, these data indicate that the divergent roles of ERK cascade, especially in cell proliferation, apoptosis, antiplatelet aggregation and vascular remodeling, necessitate a conditional cell specific approach considering the promising therapies targeting GLP-1 for CVD.

4.2 GLP-1 and JNK/P38 MAPK pathway

It is well appreciated that ECs apoptosis signals are triggered by the JNK1/2 and p38 MAPK signaling pathways (Ye et al. 2015)(Veluthakal et al. 2015). Some studies suggested that the p38-MAPK pathway was closely related to GLP-1-induced inhibition of apoptosis in human umbilical vein endothelial cells (HUVECs). Metabolic diseases, such as T2DM, are associated with a high glucose and high lipid (HG/HL) state that can impair cellular function through triggering mitochondrial dysfunction and oxidative/nitrative stress (Haidara et al. 2006). GLP-1 has been shown to inhibit HG/HL-induced endothelial apoptosis through inhibition of the p38-MAPK and JNK1/2 signaling pathways (Liao et al. 2017). Meanwhile, as the precursors of vascular ECs, endothelial progenitor cells (EPCs) involved in the repair of injured blood vessels under the stimulation of pathological factors and play a key role in cardiovascular and cerebrovascular diseases and vascular regeneration. Exendin-4, a GLP-1RA, ameliorates HG-induced EPCs dysfunction through regulating the SDF-1 β /CXCR7/AMPK/p38-MAPK signaling pathway (Yang et al. 2020), thereby exerting protective effects on the heart(Fig. 3). Liraglutide, another GLP-1RA, has also been shown to protect diabetic myocardium by decreasing hyperglycemia-induced expression of p38-MAPK and JNK (Dong et al. 2020).

The treatments of cancer with the most commonly used chemotherapies and targeted agents not only exert anti-tumor effects but also damage the heart of cancer patients and in some cases lead to death (Lenneman and Sawyer 2016). Receptor tyrosine kinases (RTK) are major extracellular signal transducers, and overexpression or mutation of RTKs has been related to the progression of various cancer (Chen et al. n.d.)(Hervent and Keulenaer 2012). Gemfibrozil (GEF) is an RTK inhibitor (RTKI) that inhibits cancer cell growth, proliferation and differentiation, yet also has cardiotoxic side effects (Hervent and Keulenaer 2012)(Lynch et al. 2011). GEF-mediated cardiotoxicity occurs by increasing the oxidative stress gene NF- κ B, activating phosphorylation of JNK and p38-MAPK, and reducing antioxidant protein (SOD) and pro-survival kinases (p-ERK1/2 and p-Akt). Liraglutide can attenuate these effects however, by reducing phosphorylation of JNK and P38, activating pro-survival kinases, and inducing antioxidant enzymes(AlAsmari et al. 2020).

All these detailed studies revealed that GLP-1 and GLP-1 based drugs can inhibit the p38-MAPK/JNK pathway, while there has shown the cardioprotective effects of p38-MAPK inhibitors, which may be beneficial in some contexts (Papaconstantinou 2019).

4.3 GLP-1 and ERK5 pathway

Cardiovascular benefits of the ERK5 signaling pathway are thought to occur through a protective effect on ECs, and studies have shown that the MEKK3/MEK5/ERK5 signaling cascade is necessary for cardiovascular development *in vivo*. The activated ERK5 translocates to the plasma membrane and regulates the tight junction formation and reduces the permeability in cardiac microvascular ECs (Wilkinson et al. 2018). ERK5 activation also has a preventive effect on endothelial

inflammation and dysfunction (Le et al. 2014). Krueppel-like factor 2(KLF2), highly expressed in ECs, has been identified as a critical modulator for improving endothelial function. Other work has shown that the GLP-1RA Liraglutide could recover oxidized low-density lipoprotein (ox-LDL)-induced endothelial inflammation and dysfunction deactivation through rescuing ERK5-dependent KLF2 expression (Yue et al. 2019)(Fig. 3). The ox-LDL-induced endothelial dysfunction is related to a variety of cardiovascular disorders including atherosclerosis. Therefore, a Liraglutide-mediated activation of ERK5-KLF2 axis may be beneficial in scenarios requiring ECs-based vascular repair and regeneration during dyslipoproteinemia, such as atherosclerosis and diabetes-related vascular disease.

5. Conclusion and Perspectives

DPP-4 protein is a serine protease, which is expressed in endothelial cells, T lymphocytes, liver, kidney, lung and intestine, so its inhibitors can make different effects through different tissues of action(Chen et al. 2015). Within these tissues, DPP-4 acts on a variety of substrates, while the two most important substrates are GLP-1 and glucose-dependent insulintropic polypeptide (GIP). Incretins lower blood glucose levels via GLP-1 and GIP, which are secreted from the endocrine cells of the intestinal mucosa in response to food intake (Nauck et al. 1986). However, mounting evidence suggests that the insulintropic effects of GLP-1 are more effective than GIP, leading to a significant focus on pharmaceutical development of GLP-1-based treatments. GLP-1 has several effects on the cardiovascular system. Native GLP-1 (7-36a) promotes glucose uptake through GLP-1R-dependent pathways in cardiomyocytes, while its metabolite GLP-1 (9-36a) exerts cardiovascular effects through GLP-1R-independent pathways, including vasodilation, protecting cardiomyocytes from ischemia-

reperfusion damage and improving cardiac function and may therefore be used as an ideal drug for the treatment of insulin resistance-related CVD (Fig. 1). Both GLP-1 and its primary metabolite have other indirect cardiovascular effects, by acting on glucose and lipid metabolism, body weight, and insulin resistance, all of which can improve the prognosis of patients with CVD. As one of GLP-1-based drugs, DPP-4 inhibitors have shown some cardioprotective effects in most basic medical research. Studies have shown that DPP-4 inhibitors can improve cardiac function by increasing endogenous DPP-4 substrates(Zaruba et al. 2009), the use of which in ApoE^{-/-} mice can also increase plaque stability(Vittone et al. 2012). However, it was also found that myocardial fibrosis and cardiac dysfunction occurred after treatment of diabetic mice with DPP-4 inhibitors(Mulvihill et al. 2016). What's more, in addition to basic research, clinical trials have shown that GLP-1RA can reduce cardiovascular events in patients with T2DM(Marso et al. 2016b)(Marso et al. 2016a). However, DPP-4 inhibitors have not found corresponding cardiovascular protective effect in clinical trials, and even showed data of increased risk of heart failure in clinical trials(Scirica et al. 2013). Thus, GLP-1RA showed stronger antihyperglycemic efficacy as well as more cardiovascular benefits than DPP-4 inhibitors. The effectiveness GLP-1 and GLP-1RA used in the treatment of T2DM has been identified by clinical studies (Sivertsen et al. 2012), which clear GLP-1-based therapy benefits on cardiovascular risk and diabetes phenotype. GLP-1RA stimulates insulin secretion is glucose dependent which are effective in controlling blood glucose with low risk of hypoglycemia in patients with T2DM. In addition, GLP-1RA has a broader application prospect due to its advantages of reducing body weight and cardiovascular protective effects.

Atherosclerosis is a complex pathological process related to various inflammatory reactions (Ross 1999), and is closely related to the development of CVD.

Cardiovascular cell growth, differentiation, proliferation and apoptosis are important cytological factors in CVD development. The MAPK signaling pathway is a key transmitter of signals from the cell surface to the nucleus that can regulate many of these pathways. Thus, we set out to explore how GLP-1 exerts cardiovascular protective effects by regulating the MAPK signaling pathway.

ERK is a classical target of MAPK signaling pathway and has effects on cell proliferation, migration and apoptosis. Importantly, the treatment of GLP-1 induced changes in ERK pathway resulted in cardiovascular protective effects through inhibition of cell migration and fibrosis. ERK5 acts quite differently than ERK and plays important roles in many ECs functions, yet studies have also shown that GLP-1 exerts cardiovascular benefits via ERK5 activation. The JNK/p38-MAPK pathway is closely related to inflammation and oxidative stress. GLP-1 reduces apoptosis and oxidative stress by inhibiting the JNK/p38-MAPK pathway, thereby improving ECs and cardiomyocytes function. It will be crucial for future studies to investigate the crosstalk between the ERK1/2, p38-MAPK pathway and other signaling pathways to help identify therapeutic targets for the treatment of CVD, T2DM and other diseases involving these pathways. Although detailed molecular explanations for beneficial GLP-1 effects in cardiovascular disease remain unknown, understanding the MAPK signaling pathway provides a critical first step in developing novel GLP-1 receptor agonists or other agents to better treat CVD.

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Conflict of interest

All authors declare that no conflict of interest exists.

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Figure 1

Figure 1. GLP-1 and its related drugs act directly or indirectly to exert cardiovascular protective effects.

Native GLP-1 (7-36) levels are highest after food intake but are readily broken down to GLP-1 by DPP-4 (9-36). GLP-1 related drugs aim to avoid GLP-1 degradation by DPP-4 so that it can stimulate the synthesis and release of insulin. It has been shown that GLP-1 (7 – 36) directly affects cardiac function not only by controlling insulin levels but also by mediating other factors. In addition, its metabolite GLP-1 (9 – 36) also exerts cardiovascular protective effects.

Figure 2

Figure 2. GLP-1 and its related drugs act in the myocardium through the MAPK pathway.

GLP-1 and its related drugs bind to GLP-1 receptor and inhibit myocardial apoptosis and oxidative stress by inhibiting p38 and JNK expression and promoting the expression of ERK1/2; they also inhibit the formation and accumulation of collagen in cardiac fibroblasts by decreasing the expression of ERK1/2 induced by high glucose, thus exerting a cardiovascular protective effect. In addition, the metabolite GLP-1 (9 – 36) also exerted cardiomyocyte protection by promoting the expression of ERK1/2.

Figure 3

Figure 3. GLP-1 and its related drugs act in the cardiac vessels through the MAPK pathway.

GLP-1 and its related drugs bind to GLP-1 receptor and inhibit the apoptosis of endothelial cells by inhibiting the expression of p38 and JNK induced by high glucose and promoting the expression of ERK5; they also inhibit the proliferation and migration of vascular smooth muscle cells by decreasing the expression of ERK1/2, thus exerting a protective effect on cardiac vessels.