Mechanism of cardiovascular disease benefit of glucagon like peptide-1 agonists

Short title: GLP-1 treatment for CV disease

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Abstract

Glucagon-like peptide 1 based therapies reduce hyperglycemia in type 2 diabetes. Diabetes cardiovascular co-morbidity remains prevalent though current treatments are effective at reducing hyperglycemia. Glucagon-like peptide 1 exerts specific actions on the cardiovascular system in both healthy individuals and patients with cardiovascular pathology, and glucagon-like peptide 1 therapies have improved the cardiovascular profile of diabetic patients. Glucagon-like peptide 1 exerts its action by binding to its receptor (glucagon-like peptide 1 receptor) at the cell surface. Mechanistically, it is not clear how GLP-1 therapies exert beneficial effects on the cardiovascular system. It is difficult to ascertain any conclusions on the ability of glucagon-like peptide 1 receptor agonism to reduce cardiovascular disease from animal/human studies due to varying experimental designs. This review highlights recent findings from long-term human glucagon-like peptide 1 therapy studies, and summarises postulated mechanisms as to how glucagon-like peptide 1 receptor agonism may alleviate cardiovascular disease.

Keywords: Type 2 diabetes (T2D), cardiovascular (CV) disease (CVD), CV system (CVS), glucagon-like peptide 1 (GLP-1), GLP-1 receptor (GLP-1R), cardiovascular outcome trials (CVOTs), major adverse cardiac event (MACE).

Type 2 diabetes (T2D) is a chronic complex multifactorial disease with an incompletely understood aetiology and pathogenesis [1,2]. The majority of T2D patients are overweight (60-90% in western countries) implying that diets involving excessive nutrient consumption provoke disease pathogenesis [3]. However, this does not explain how individuals with a body mass index (BMI) of ≤25 develop T2D, and the majority of overweight individuals remain disease free [2,4]. Interestingly, approximately 50% of T2D patients are not overweight in Japan[5]. It is also noteworthy that overweight patients have been reported to have a lower mortality rate due to cardiovascular (CV) disease (CVD) than normal-weight patients, termed 'the obesity paradox' [6]. The obesity paradox implies that the diabetic phenotype promotes CVD independent of patient BMI. Despite current treatments being effective at reducing hyperglycemia, diabetes CV co-morbidity remains prevalent, and therefore novel therapies are desirable: approximately 75% of diabetic patients die from CVD [7]. Evidence suggests that glucagon-like peptide 1 (GLP-1) exerts specific actions on the CV system (CVS) in both healthy individuals and patients with CV pathology, and GLP-1 therapies have improved the CV profile of diabetic patients [8,9].

The best characterised function of GLP-1 is its promotion of the incretin effect [9]. The incretin effect is reduced in T2D - incretin hormones account for <20% of the insulin release after glucose ingestion in T2D patients compared to 70% in non-diabetic individuals [10]. The current consensus is that GLP-1 levels

are normal in T2D but its action is reduced [11]. GLP-1 has a very short half-life (~1.5min) due to its rapid proteolytic degradation in plasma by dipeptidyl peptidase IV (DPP-IV) enzymes [11]. The DPP-IV resistant GLP-1 analogues are effective at reducing hyperglycemia in T2D patients, as they prolong the GLP-1 response due to their extended half-lives [8]. However, GLP-1 also has extrapancreatic functions (Fig. 1) [9]. Importantly, GLP-1 therapies induce weight loss, which is associated with reducing CVD in diabetic and non-diabetic subjects [8,9]. GLP-1 based therapies also appear to exert other specific actions in diabetes [9].

GLP-1 induces its effects by acting as an agonist to the GLP-1 receptor (GLP-1R). The effects induced by GLP-1 vary in different tissues as GLP-1R is coupled to a range of intracellular signalling pathways in different tissues, each of which promotes the desired physiological response elicited by receptor activation [12,13]. GLP-1 also indirectly effects organs through the insulin secretion it promotes - approximately 28% of the postprandial insulin released into circulation is due to the action of this hormone [14,15]. GLP-1R knock-out and knock-down studies in mice have demonstrated that the ability of GLP-1 to act as an incretin hormone is dependent on the presence of its receptor in islet beta-cells [16,17]. GLP-1R is a class B G-protein-coupled receptor (GPCR), consisting of a large hydrophilic N-terminal extracellular domain, seven hydrophobic transmembrane alpha-helices (TM1-7) joined by three hydrophilic extracellular loops (ECL1-3) and three intracellular loops (ICL1-3), and an intracellular C-terminal domain. The GLP-1R C-terminal domain interacts with heterotrimeric G-proteins that consist of alpha, beta and gamma subunits that activate down-stream signalling pathways upon agonist (GLP-1) binding (Fig. 2) [13,18-21].

There are currently five licenced GLP-1 based therapies, one of which has two modes of delivery (exenatide as twice daily Byetta or once weekly Bydureon) [22], and semaglutide is being considered by regulatory authorities [23]. These have differing levels of efficacy on glycaemic control and weight loss, perhaps due to differing GLP-1R activation of these drugs e.g. due to different penetration of the CNS [24]. Both animal and human studies generally suggest that GLP-1 therapies exert beneficial CV actions [9].

Chronic GLP-1R agonism in rodents was reported to reduce blood pressure (BP) and prevent hypertension [25-28]. However, acute GLP-1 infusion in rodents increases heart rate (HR) and BP [9,29]. Human short-term clinical trials have reported conflicting findings, as acute GLP-1 therapy has had no effect on BP and HR, or raised both [9]. GLP-1 analogue and DPP-IV inhibition based therapies reduced plasma lipid levels in healthy and diabetic rodents, and the same therapies also had similar effects on T2D patients [9,30,31]. However, one study found that exenatide treatment for 24 weeks had no effect on lipid profiles [32]. Rodent *in vitro* studies have reported vasorelaxant actions of GLP-1, and different studies postulated different mechanisms as to how this was achieved [9]. *In vivo* rodent studies have reported that GLP-1 induces vasodilation of certain blood vessels and promotes vasoconstriction of others, as well as improving endothelial function [9,33,34]. Similarly, improved blood flow and endothelial function has been reported in diabetic individuals in response to acute GLP-1 therapies [9,35,36]. Interestingly, exendin-4 treatment did not affect short-term triglyceride exposure induced endothelial dysfunction in rat femoral artery, which suggests that the reported *in vivo* beneficial actions of GLP-1 therapies on the endothelium likely occurs via extracardiovascular GLP-1 signalling [37]. Rodent and human studies have provided evidence that GLP-1 therapies have anti-atherosclerotic actions and angiogenic effects [9,38,39]. GLP-1 therapies have been reported to reduce levels of pro-inflammatory molecules (associated with atherosclerotic development) in patients [9], and one study reported that anti-inflammatory benefits persisted for 12 weeks in obese T2D patients after a single exenatide injection [40]. Finally, GLP-1 treatments during rodent and human *in vitro/in vivo* studies have been

reported to exert beneficial effects on the myocardium such as protection against diabetic cardiomyopathy [9].

Long-term human studies have demonstrated that chronic DPP-IV inhibition did not significantly confer any CV benefits [41,42]. In contrast, chronic GLP-1 based treatments demonstrated multiple CV benefits in diabetic subjects [9]. Four cardiovascular outcome trials (CVOTs) have been reported for GLP-1 analogues: ELIXA [43], LEADER [44], SUSTAIN 6 [23] and EXSCEL [45] trials have tested lixisenatide, liraglutide, semaglutide and exenatide, respectively. ELIXA showed no advantage over placebo in terms of influencing primary outcome of a 4-point major adverse cardiac event (MACE) which included CV mortality, non-fatal myocardial infarction, non-fatal stroke and hospital admission for unstable angina [43]. The other CVOTs all used a 3-point MACE primary end-point (excluding unstable angina); superiority was demonstrated for liraglutide and semaglutide (albeit not a pre-specified analysis for semaglutide) but not for exenatide. All-cause mortality benefit was shown for liraglutide and exenatide but not for semaglutide, although the latter agent was tested in a smaller study. The ELIXA population all had a CV event within 180 days of the study start, and it is reasonable to assume that the stability of their coronary lesions would have made any drug effect difficult to determine. Conversely, the EXSCEL study included 27% of subjects at much lower CV risk which may have resulted in the marginal lack of statistical superiority. Examination of components of the primary end-point showed heterogeneity between the two trials that reported reduced CVD with GLP-1 analogues, with the LEADER superiority being driven by a significant reduction in CV mortality whilst SUSTAIN 6 superiority was largely due to a reduction in non-fatal stroke. In both of these studies, the mechanisms by which these drugs reduced CV outcomes is elusive. A moderator analysis of the LEADER study suggests that the reductions in HbA1c, weight and systolic blood pressure were insufficient to account for all of the benefit. Recently, an analysis of severe hypoglycaemia has also been shown not to influence the outcome. The slow separation of the event curves in the Kaplan-Meier plots from both LEADER and SUSTAIN 6 suggest an impact on the atherosclerotic process, which is in contrast to that seen with the sodium-glucose cotransporter 2 (SGLT2) inhibitors [46].

Mechanistically, it is not clear how GLP-1 based therapies exert beneficial effects on the CVS, but studies have suggested several pathways (see Fig. 3). According to the postulated mechanisms, it appears that GLP-1 therapies mediate these effects directly and/or by promoting the incretin effect [2]. By promoting the incretin effect, GLP-1 based therapies alleviate the potential of the diabetic phenotype to promote CVD by reducing hyperglycemia and hyperlipidemia, as well as by improving blood flow systemically due to increasing vascular nitric oxide production [8,9]. These therapies also appear to promote the effects via direct mechanisms as well [9]. Additionally, studies have found that GLP-1 therapies improve angiogenesis, reduce atherosclerosis progression, increase cardiac function, and improve prognosis of cardiac ischemia via the incretin effect and extrapancreatic GLP-1R activity [8,9]. Chronic GLP-1 therapies have also been reported to prevent hypertension, and evidence suggests this was achieved via CV GLP-1R activity [9].

Currently, several studies are testing the chronic effects of other GLP-1 analogues [9]. It is difficult to ascertain any conclusions about conflicting findings on the ability of GLP-1 based therapies to reduce CVD from animal and human studies: animal species and trial design differed between animal studies, and trial design and cohorts varied between human studies. The notion that the 'inactive' forms of GLP-1 may have direct effects on the CVS warrants investigation [47]. The effect of allosteric GLP-1R agonists (discussed in [11]) on the CVS is another area of future research. Better understanding of T2D aetiology/pathogenesis and how the disease phenotype promotes CVD, as well as further elucidation of GLP-1 activity/targets could enable better insight into the therapeutic potential of GLP-1R agonism to reduce T2D associated CVD.

Figure Legends

Figure 1. Summary of the effects that GLP-1 has on various organs. *Organs highlighted green do not express GLP-1R but GLP-1 has mediated direct insulin-like effects during experimental settings. This figure is adapted from:* [8,12,14,48-50]

Figure 2. The canonical model of GLP-1R activation. *Upon GLP-1 binding, the Gα subunit is activated by exchanging GDP for GTP, and then the G-protein subunits dissociate. Both the active Gα and Gβγ subunits activate down-stream effectors to propagate GPCR signalling. The intrinsic GTPase activity converts the Gα subunit bound GTP to GDP, and the G-protein subunits then re-associate ready for arrival of a new agonist. Adapted from:* [11,13].

Figure 3. Reported benefits of GLP-1R agonism on CVD. *A summary of the reported benefits of GLP-1 based therapies on reducing CVD burden in patients and in experimental settings, and the postulated mechanisms as to how this was achieved. This figure is adapted from:* [9,11]

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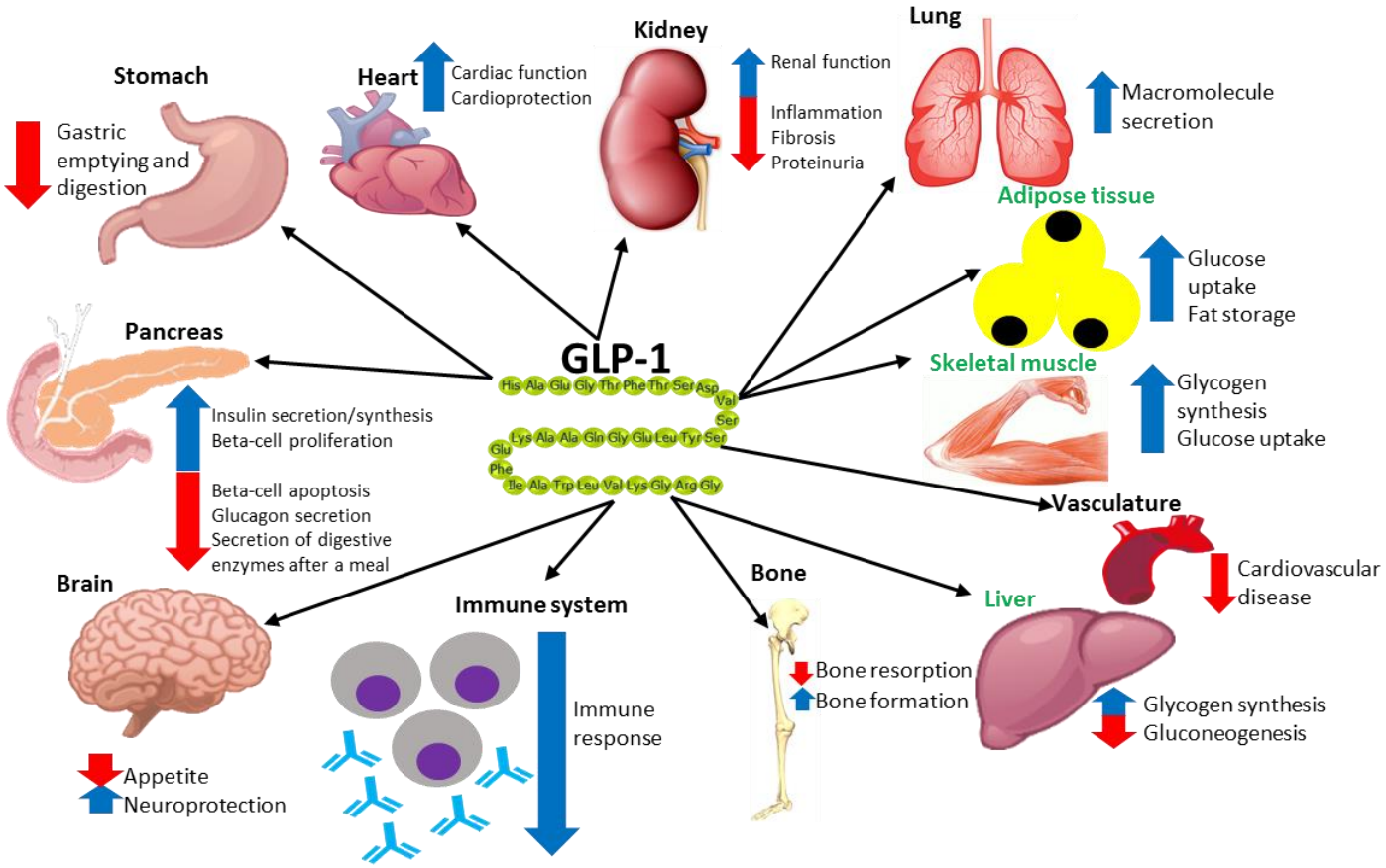
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Glucose uptake
Fat storage
Skeletal muscle
Glycogen synthesis
Glucose uptake
Pancreas
Insulin secretion/synthesis
Beta-cell proliferation
Beta-cell apoptosis
Glucagon secretion
Secretion of digestive enzymes after a meal
GLP-1
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Lys Ala Ala Gln Gly Glu Leu Tyr Ser Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
Vasculature
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Neuroprotection

Fig. 1

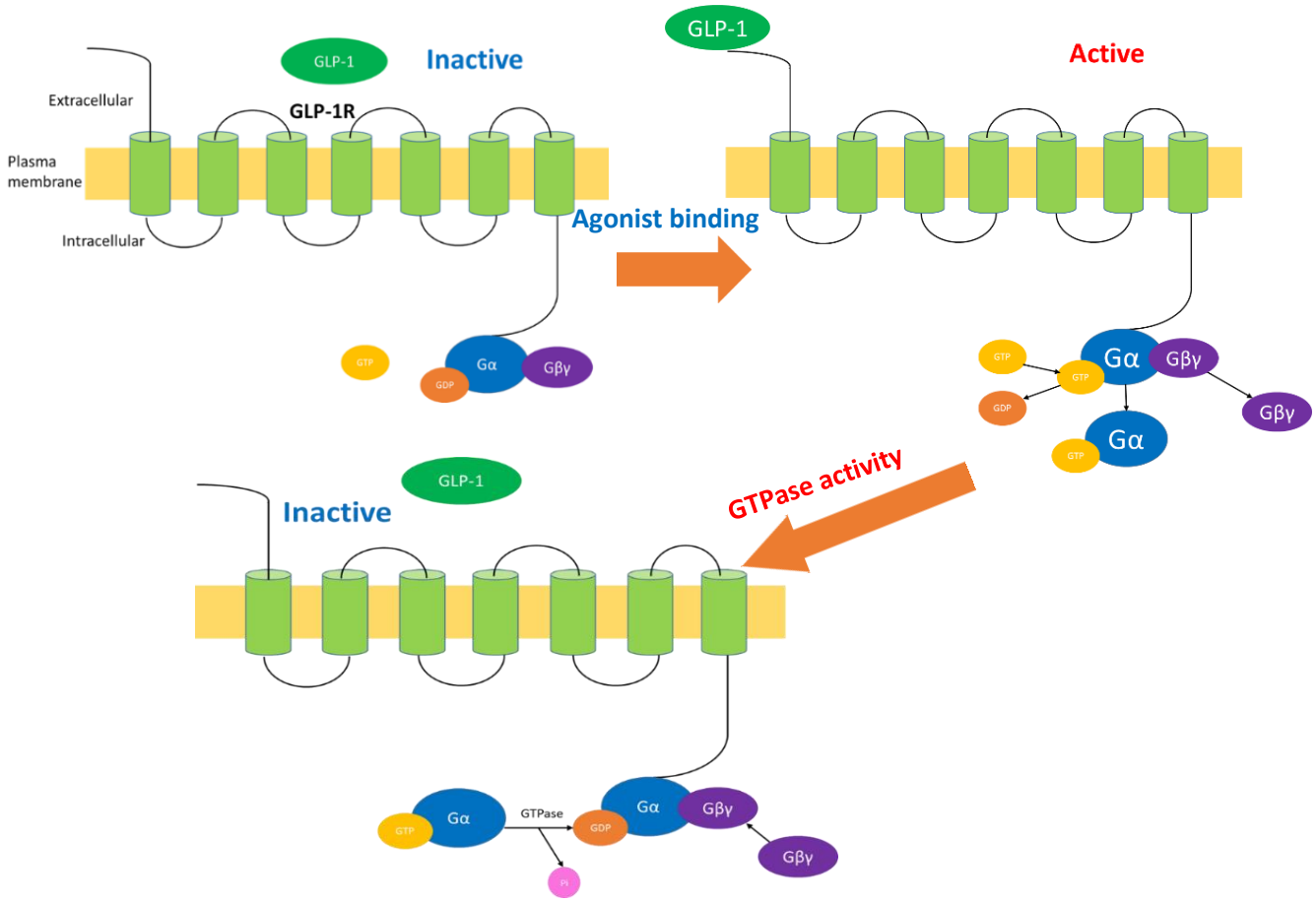
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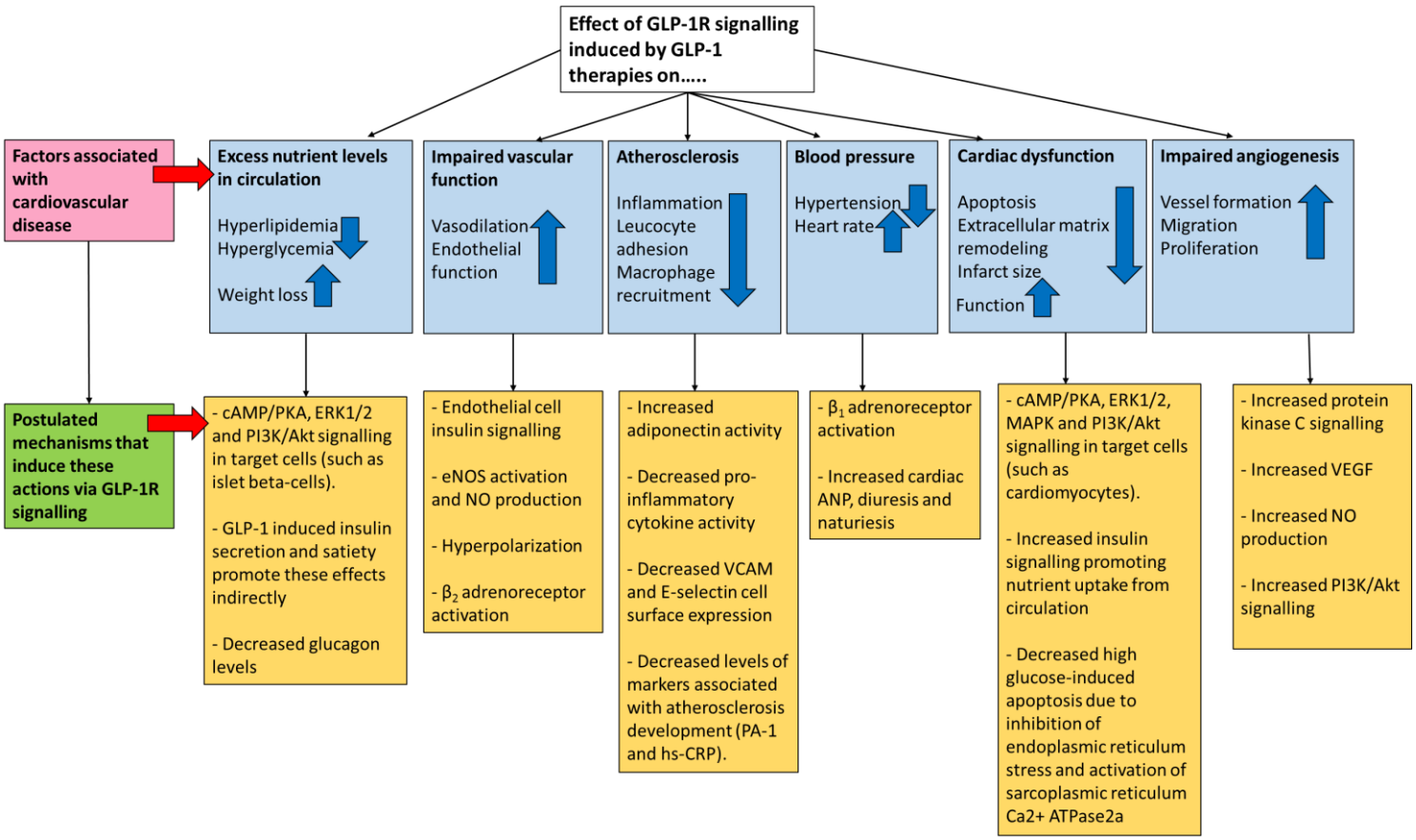
Fig. 2


Effect of GLP-1R signalling induced by GLP-1 therapies on.....
Factors associated with cardiovascular disease
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Hyperglycemia
Weight loss
Impaired vascular function
Vasodilation
Endothelial function
Atherosclerosis
Inflammation
Leucocyte adhesion
Macrophage recruitment
Blood pressure
Hypertension
Heart rate
Cardiac dysfunction
Apoptosis
Extracellular matrix remodeling
Infarct size
Function
Impaired angiogenesis
Vessel formation
Migration
Proliferation
Postulated mechanisms that induce these actions via GLP-1R signalling
- cAMP/PKA, ERK1/2 and PI3K/Akt signalling in target cells (such as islet beta-cells).
- GLP-1 induced insulin secretion and satiety promote these effects indirectly
- Decreased glucagon levels
- Endothelial cell insulin signalling
- eNOS activation and NO production
- Hyperpolarization
- β2 adrenoreceptor activation
- Increased adiponectin activity
- Decreased pro-inflammatory cytokine activity
- Decreased VCAM and E-selectin cell surface expression
- Decreased levels of markers associated with atherosclerosis development (PA-1 and hs-CRP).
- β1 adrenoreceptor activation
- Increased cardiac ANP, diuresis and naturiesis
- cAMP/PKA, ERK1/2, MAPK and PI3K/Akt signalling in target cells (such as cardiomyocytes).
- Increased insulin signalling promoting nutrient uptake from circulation
- Decreased high glucose-induced apoptosis due to inhibition of endoplasmic reticulum stress and activation of sarcoplasmic reticulum Ca2+ ATPase2a
- Increased protein kinase C signalling
- Increased VEGF
- Increased NO production
- Increased PI3K/Akt signalling

Fig. 3