WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 8, 438-449. Review Article ISSN 2277– 7105

ROLE OF GLUCAGON LIKE PEPTIDE (GLP) AND THEIR RECEPTORS IN VARIOUS PATHOPHYSIOLOGICAL CONDITIONS

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Article Received on
28 Feb. 2018,

Revised on 21 March 2018,
Accepted on 11 April 2018,

DOI: 10.20959/wjpr20188-11929

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ABSTRACT

There are many cardiovascular molecules which act on specific class of receptors. Study of role some molecules and their receptor in the different disease condition is the scope of interest of this article. The main purpose is to do combined study the role of single family of molecule in diverse pathophysiological conditions. There are three major hormones, one is Glucagon, and other two are from glucagon like peptide family i.e. glucagon like peptide-1 and glucagon like Peptide-2 plays important role in many pathophysiological condition. This article provides the information about role of these hormones and their receptor in different pathophysiological conditions like diabetes, and many more.

KEYWORDS: Receptor, Glucagon, CAMP, Agonist.

INTRODUCTION

The three major hormones are-

1) Glucagon

2) Glucagon-like peptide-1 (glp-1) and

3) Glucagon-like peptide-2 (glp-2).

These three hormones plays an important role on different disease conditions.Preglucagon is the molecule which encodes this three hormones.Glp-1 is a major incretin hormone that potentiates insulin release by pancreatic islet beta cells in response to eating a meal.Glp-2 has

important roles in maintaining intestinal Function. Proglugacon derived peptides exert their physiological effects through binding to specific receptors. A cdna clone for a specific receptor for the glp-1 receptor (glp1r) was cloned in 1992 and found to encode a g-protein coupled receptor (gpcr). Receptors for the other two glucagon-like peptides encoded by gcg, glucagon (gcgr) and glp-2 (glp2r) are also g-protein coupled receptor.[1]

Highlights

- Glucagon and glucagon like peptides plays an important role in different pathophysiological condition by acting on the specific receptors.
- The GLP-1 receptor is a member of the class B/II family of seven transmembrane G protein-coupled receptors (GPCRs) that include receptors for peptide hormones such as secretin, GLP-1, glucose-dependent insulinotropic polypeptide (GIP), glucagon, vasoactive intestinal peptide (VIP), corticotropin-releasing factor (CRF), calcitonin, and parathyroid hormone.[1]
- GLP-1R receptors are distributed in many parts of cardiovascular system.

GLP-1R distribution in the cardiovascular system-

GLP-1R has been detected in cardiac and vascular tissues isolated from both human and animal models, in human coronary artery endothelial cells (HCAEC) and human umbilical vein endothelial cells (HUVEC), in coronary endothelial and smooth muscle cells of mouse.[2]

1. **Role of GLP in diabetes**-An increased in incretin hormone is the first aim. There are two types of incretin hormones.

1.1. Glucose-dependent insulinotropic polypeptide

The first incretin identified was glucose-dependent insulinotropic polypeptide (GIP). It is purified from porcine intestinal extracts GIP is a 42-aminoacid hormone synthesized in duodenal and Jejunal enteroendocrine K cells in the proximal small bowel. GIP had weak effects on gastric acid secretion but more potent insulinotropic actions in human beings. GIP receptor is predominantly expressed on islet β cells, and also in adipose tissue and in the central nervous system but to a lesser extent. GIP shows its shows insulinotropic action specifically in patients with type 2 diabetes.

1.2. Glucagon-like peptide 1 *(GLP-1)*

A second incretin hormone, glucagon-like peptide-1 (GLP-1) was identified after the cloning of the cDNAs and genes encoding Proglucagon.[2] GLP-1 is a hormone derived from the preproglucagon molecule and is secreted by intestinal L cells.[3] Glucagon-like peptide 1 (GLP-1) is a gut-derived incretin hormone that stimulates insulin and suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake. Adverse event associated with GLP-1 receptor agonists is mild nausea, which lessens over time.[2] The expression of the PC2 enzyme predominates in pancreatic cells, which cleaves proglucagon to glucagon and other products, including the major proglucagon fragment. Proglucagon cleavage is catalyzed by the PC1/3 enzyme in intestine and brain, leading to the formation of glucagon-like peptide-1 (GLP-1), glucagon like peptide-2 (GLP-2), glicentin and oxintomodulin.[4]

Glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP) are called glucoincretin because this both are responsible to potentiate the effect of glucose on insulin secretion. Glucoincretin will show stimulatory effect only when the presence of glucose at or above the normal physiological concentration of about 5mM. Due to this activation of adenylate cyclase and ultimately rise in the intracellular concentration of cyclic amp.[3] This cyclic adenosine monophosphate (cAMP) is the primary effector of GLP-1 Receptor induced glucose-dependent secretion of insulin or GCGR induced glycogenosis and gluconeogenesis.[5] Furthermore,GLP-1 exists in two circulating equipotent molecular forms,

I) GLP-1(7-37) and

II) GLP-1(7-36) amide-is more abundant.[2]

GLP-1R is G protein-coupled receptor (GPCR) .They composed of two domains e the N-terminal extracellular domain (NTD) comprising the first ~115 residues, and the transmembrane domain (TMD) comprising the remaining 7 transmembrane helices and connecting regions. GLP-1 interacts with GLP-1R through a two-domain mechanism in which the C-terminal half of the a-helical ligand binds to the NTD, while the N-terminal half binds to the TMD.[8]

The GLP-1 receptor expressed in pancreatic islets alpha and beta cells and in peripheral tissue including, the lungs, the brain, the heart, the kidney, and the gastrointestinal tract.[4] GLP-1R remained associated with Gαs. Internalization of the receptor results into sustained cyclic AMP generation upon GLP-1R activation. Paradoxically, betaarrestin which is known to

desensitize the receptor, establish stable interaction with many class B GPCRS. When a beta arrestion and GLP-1R are associated and ablation of beta arrestin expression ultimately reduction in GLP-1R mediated cyclic AMP generation and glucose stimulated insulin secretion in pancreatic beta cells.[6] GLP-1 is essential for control of fasting glycaemia, since acute antagonism or genetic disruption of GLP-1 action leads to increased levels of fasting glucose in rodents GLP-1 is essential for glucose control in human beings: studies with the antagonist exendin (9-39) show defective glucose-stimulated insulin secretion, reduced glucose clearance, increased levels of glucagon, and quicker gastric emptying after disruption of GLP-1 action.[2]

Circulating GLP-1 is inactivated by the proteolytic enzyme dipeptidyl peptidase-4 (DPP-4), which is an exopeptidase that cleaves dipeptides.DDP4 inhibition induces an increase in GLP-1 levels and therefore prolongs the half-life of insulin's action.DPP4 can be inhibited by a class of drugs named gliptins.[4]

2. Role of GLP in Antidiabetic action by inhibiting inflammatory response-

GLP-1, its analogues or drugs that inhibit GLP-1 metabolism may have a doubly beneficial effect in diabetic patients by inhibiting the inflammatory response and reducing glycaemia.The activation of GLP-1R inhibits LPS-induced inflammation both in vivo and in vitro. GLP-1 analogues decrease LPS-induced microvascular permeability and the expression of adhesion molecules, including VCAM-1, ICAM-1 and E-selectin, by the HUVEC cell line in vitro.The activation of GLP-1R by GLP-1 or exogenous agonists, including exendin-4 andliraglutide, decreases the inflammatory response in several modelcombined use of a MAP3 kinase tumor progression locus 2 (Tpl2) inhibitor and the GLP-1R agonists produces

powerful anti-apoptotic and anti-inflammatory effects on INS-1E β-cells and mouse and human islets.

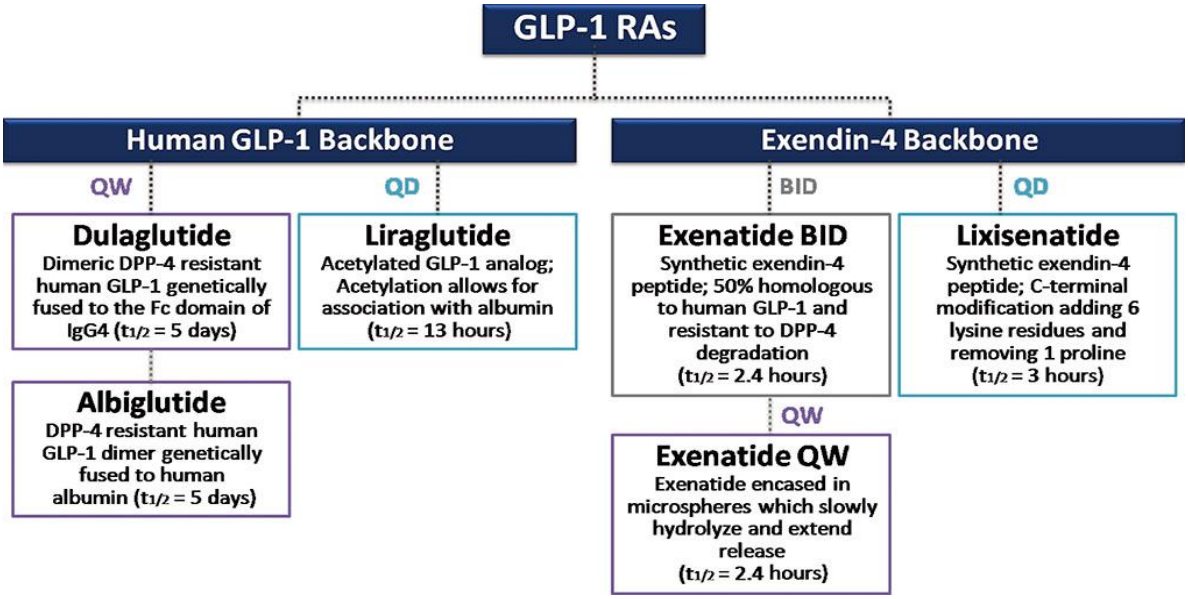
GLP-1 analogue inhibits LPS-induced macrophage infiltration and secretion of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, which is associated with impairment of insulin-stimulated glucose uptake.[4] Therapeutic approaches for enhancing incretin action include degradation-resistant GLP-1 receptor agonists (incretinmimetics), and inhibitors of dipeptidyl peptidase-4 (DPP-4) activity incretin enhancers.[2]

2.1. GLP-1R agonists

2.1.1. Exenatide-GLP-1 analogue, exendin-4, also protected cardiac remodelling and diastolic dysfunction in an experimental diabetes model, associated with a reduction in macrophage infiltration, expression of IL-1β and IL-6 and an increase in IL-10 in the heart.Secretin-like sequences have been identified in some vertebrate species including the exendins, which were first identified in the reptile Gila monster and relatives (Heloderma suspectum and Heloderma horridum). Exendin-1 and -2, from the Gila monster, are most similar to GLP-1, while-3 and -4 are very divergent and more similar to othersecretin-like hormones.

In addition, the GLP-1 receptor agonist exenatide inhibited the levels of TNF-α and MCP-1 and the expression of F4/80 in the testes of mice. Application of Exendin-9 (Exn9), a specificGLP-1R antagonist, blocked GCG neuronalactivation-induced c-Fos expression in the PVN, suggesting an involvement of GLP-1R signaling inNTS-to-PVN neural pathways.[13]

2.1.2. Liraglutide- In the brain, liraglutide reduced IL-6, IL1β, IL-12 and NO levels in a model of a chronic inflammation response induced by irradiation. Liraglutide in an ovalbumin-induced chronic asthma model inhibits inflammatory cell infiltration and decreases the expression of E-selectin, TNF-α, IL-4, IL5 and IL-13 in the lung tissue and bronchoalveolar lavage fluid (BAL), which is associated with the reduction of NF-κB activation.[4]



2.2. Long-acting GLP-1R agonists

For development of long-acting GLP-1R agonists include the use of chemical linkers to form covalent bonds between GLP-1 (CJC-1131) or exendin-4 (CJC-1134).87 Similarly, recombinant albuminGLP-1 proteins have been developed that mimic the full range of GLP-1 actions in preclinical studies.[2]

2.2.1. Oxyntomodulin (OXM) - a 37-amino acid hormones containing the entire 29-amino acid sequence of glucagon followed by other eight amino acid carboxy-terminal extension has been known as a GLP-1R/ GCGR dual agonist that reduces the body weight, lowers the lipid and so on.[5]

3. Role of GLP-2 in directed differenciation from Osteosarcoma

GLP2 inhibits the expression and activity of NFκB, triggering the decrease of C-Myc, PKM2, and CyclinD1 in osteosarcoma cells.

The overexpression of GLP2 significantly increased the expression of osteogenesis-associated genes (e.g. Ocn and PICP) dependent on C-Fos-BMP signaling which promotes directed-differentiation from osteosarcoma cells to osteoblast with higher alkaline phosphatase activity.

GLP2 inhibits the expression and activity of inflammation related gene NFκB in osteosarcoma cells.NFκB fully abrogates the function of cancerous suppression of GLP2 in osteosarcoma cells

According to experiments

(1) GLP2 increased the activity of BALP, PICP In osteoblast dependent on C-FOS, as GLP-2 increases the activity of BALP, PICP increases.

(2) The depletion of C-FOS abrogated the GLP2 action in osteoblast. It suggests that GLP2 may inhibit osteosarcoma progression by triggering differentiation of osteosarcoma.

The final step of glycolysis is carried out by PKM2 which is key tumor metabolism. Pyruvate kinase M2 (PKM2) dephosphorylation by Cdc25A promotes the Warburg effect and tumorigenesis.GLP2 inhibited the expression of C-mycCyclinD1pyruvate kinase M2 (PKM2) dependent on NF-κB β-catenin plays an important role in the WNT signaling pathway. In osteosarcomaGLP2 decreased the interaction between β-catenin and NFκB.[9]

4. Role of GLP in Parkinson's disorder-

GLP-1 analogs can cross the blood–brain barrier and stimulate the GLP-1 receptor in the brain.Stimulation of the GLP-1 receptor has shown effects on mitochondrial function, protein aggregation, neuroinflammation, synaptic plasticity, learning and memory in multiple experimental models of PD and AD.A process analogous to peripheral insulin resistance may initiate/exacerbate neurodegeneration in PD.Restoration of brain insulin sensitivity is one possible explanation for the neuroprotective effects seen in models of Parkinson's disease PD and Alzheimer's disease.[10]

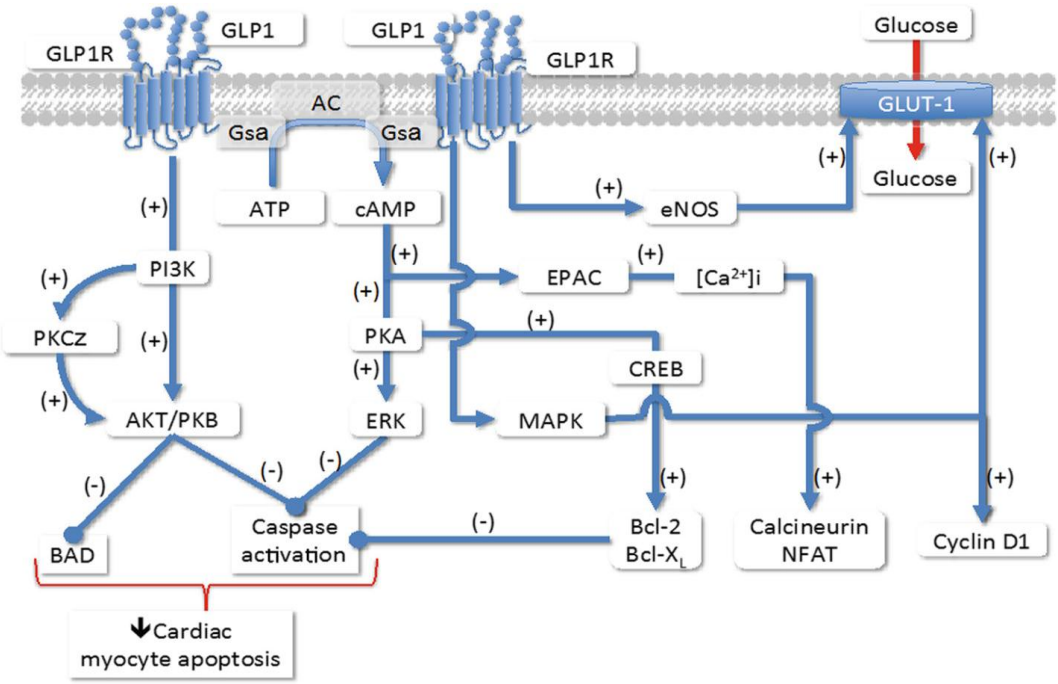
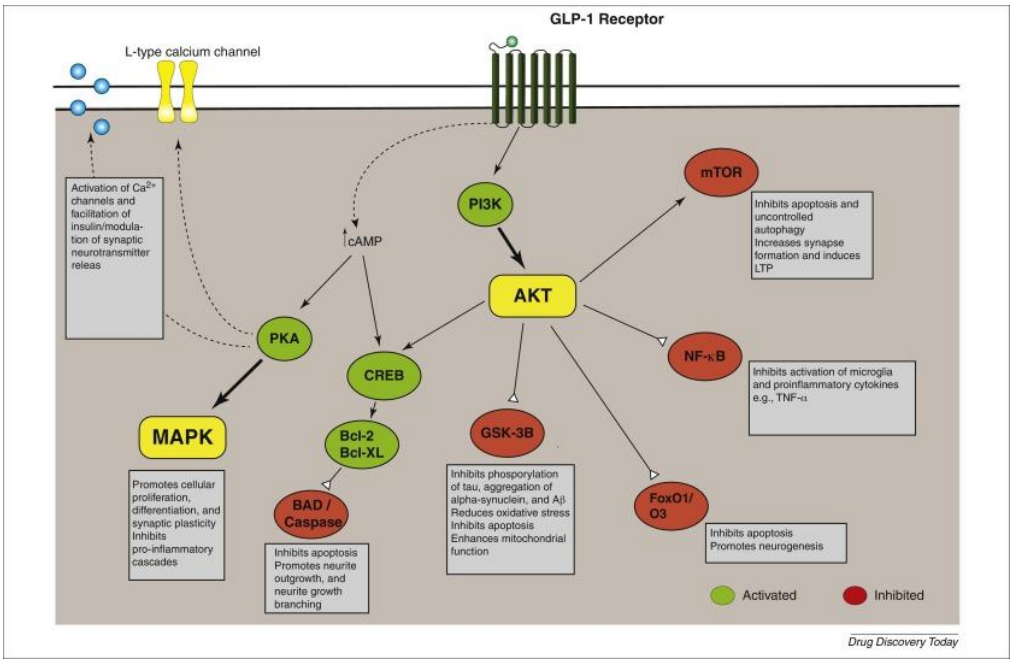


Fig. 1: Intracellular signaling pathways of GLP-1R in the cardiomyocytes.[2]

5. Role of GLP in Neuroinflamation-

Prevention of initiation of the apoptotic intrinsic pathway is the main aim in neuroinflamation.GLP-1 have beneficial effects for mitochondrial functions by means of different molecular mechanisms, including the stabilisation of the outer membrane through activation of the PI3K/AKT pathway, and ultimately preventing the initiation of the apoptotic intrinsic pathway.GLP-1 receptors are capable of stimulating neurite outgrowth, promoting adult neurogenesis with cell proliferation and survival, interrupting proapoptotic processes, and reducing neuroinflammation**.** Mitochondriadysfunctions represent a common feature of different neurodegenerative disorders it is also worth noting that GLP-1 and GLP-1R have important effects also on learning and memory formation both under physiological and pathological conditions. AKT has the ability to phosphorylate over 50 substrate proteins, such as glycogen synthase kinase 3 beta (GSK-3B), Forkhead box protein O1 (FOXO1), and mammalian target of rapamycin (mTOR), and can modulate several cellular processes found to be disrupted in PD, such as protein synthesis, apoptosis, inflammation, mitochondrial biogenesis, and autophagy. GLP-1 act on AKT.Broadly speaking, activation of these pathways promotes cellular survival, while inhibiting proapoptotic pathways.[11]



6. Role of GLP-1 in Type 3 Diabetes-

Diabetes-induced dementia has been called “type 3 diabetes”.GLP-1 could attenuate the inflammatory responses in brain caused by amyloid beta (Aβ)-induced oxidative stress.

GLP-1 can regulate the activation of microglia and protect neurons against oxidative stress.GLP-1 can also promote neurogenesis in AD brain.

GLP-1 could stimulate the generation of new neurons to replace damaged neurons in the AD brain. Finally, GLP-1 can alleviate insulin resistance in the AD brain, suggesting that impaired glucose metabolism and insulin resistance leads to severe memory dysfunction.[12]

7. Role of GLP in Anorexia-

Glucagon-like peptide 1 (GLP-1) in a subpopulation of hindbrain nucleus tractus solitaries (NTS) neurons. The NTS GLP-1-producing GCG neurons send robust projectionsto many forebrain regions, including the paraventricular nucleusof the hypothalamus (PVN). The PVN is one of several brain centres implicated in food intake behaviour.

Moreover, PVN neurons express GLP-1R and infusionof GLP-1 into the PVN suppresses food intake and GLP-1 antagonists increase food intake.

PVN neuronal activity is modulated by the activity of NTS GLP-1 producing GCG neurons.

CRH neuronal activity can be driven by activation of NTS GCG neurons. The application of Exendin-9 (Exn9), a specific GLP-1R antagonist, blocked GCG neuronal activation-induced c-Fos expression in the PVN suggesting an involvement of GLP-1R signaling in NTS-to-PVN neural pathways.

GCG (i.e., GLP-1) fibers were located in close proximity to the CRH neurons in the PVN.CRH neuronal activation in the PVN by GLP-1 contributes to suppression of food intake. NTS GCG-to-PVN projection is sufficient to suppress food intake and this effect is likely independent of local glutamate release. The long-term depletion of GLP-1R signaling within the PVN caused a 30% increase in body weight over a 6-week period, with mice developing elevated fasted glucose levels and impaired insulin sensitivity.[13]

8. Role of GLP in Diabetes retinopathy-

GLP-1R existed in both mRNA and protein levels of GLP-1R in the retina of SD rats. The existence of GLP-1R in human retina and the expression was higher than that in the liver and intestine, but no difference in diabetic and non-diabetic subjects. Contrastly, GLP-1 levels

were down regulated in patients with DR. It is speculated that GLP-1 may be involved in the development of DR

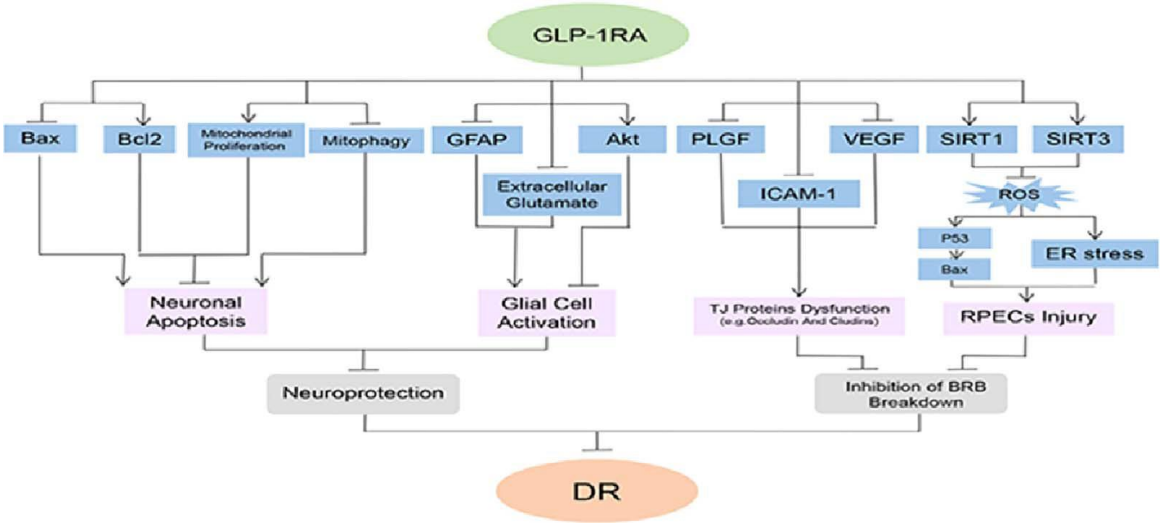


Fig. 1: A mechanism of beneficial effects of Glucagon-like peptide-1.

Receptor agonists (GLP-1RA) for DR. GLP-1RA inhibits neuronal apoptosis by regulating bax/bcl2 pathway. By promoting mitochondrial proliferation and reducingmitophagy, GLP-1RA exerts beneficial effects on neurocytes. Reduction of extracellular glutamate, activation of Akt pathway and down regulation of glial fibrillary acidic protein (GFAP) expression may prevent glial activation. The above effects play a neuroprotective role in DR. In addtion, GLP-1RA inhibits the production of cytokines such as PlGF, VEGF and ICAM-1, which could protect the tight junction proteins like occludin and claudins in patients with DR. GLP-1RA increases SIRT1 and SIRT3 production, and decreases ROS induced p53 expression and ER stress, further inhibiting the Bax pathway. It plays a protective role for cells of outer blood retinal barrier (oBRB) like RPECs. GLP-1RA also protects retina from BRB damage. The protective effect ofGLP-1RA on nerve and blood retinal barrier (BRB) may prevent the development of DR.[14]

9. Effects of GLP-1R activation in the heart-

GLP-1 decreases contractility in primary culture of adult rat cardiomyocytes, despite increasing cAMP levels, has also been reported in isolated rat hearts. Studies in dogs demonstrated an increased myocardial glucose uptake during a hyperinsulinemic-euglycemic clamp.Moreover, cardiometabolic effects of GLP-1 are attenuated in obesity and T2D, via mechanisms that may involve impaired p38-MAPK signaling. Using a swine experimental model, where GLP-1 significantly increased myocardial glucose uptake under basal

conditions in lean humans, but this effect was impaired in T2D. GLP-1 did not increase myocardial oxygen consumption or blood flow in humans or in swine, increasing p38-MAPK activity in lean, but not obese cardiac tissue.

Incretin may preserve cardiomyocyte viability, increase metabolic efficiency, inhibit the structural and functional remodeling after MI.GLP-1-mediated control of heart rate (HR) and blood pressure (BP) is complex and species specific.Intravenous infusion of GLP-1 for 48 h in healthy human subjects increased muscle sympathetic nerve activity but had no effect on BP, norepinephrine plasma concentration, or the sympathetic/parasympathetic balance as estimated by the HR variability, suggesting that the increase in sympathetic drive is at least partially compensated by an increase in the parasympathetic activity . In the cardiovascular system, incretins have been recently associated to the increase of endogenous antioxidant defenses, inhibition of cardiomyocyte apoptosis, attenuation of endothelial inflammation and dysfunction.[2]

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