Potential of Glucagon like peptide-I in the therapy of obesity in association with metabolic syndrome

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ABSTRACT

Obesity and associated metabolic syndrome (type 2 diabetes mellitus and cardiovascular diseases) are one of the leading causes of death worldwide. Several drugs are currently approved and available in the market for obesity, type II diabetes mellitus and cardiovascular diseases. But, targeting a specific receptor which can potentially reduce obesity and associated metabolic syndrome will be helpful in future therapy. Current review mainly focuses on the possible mechanistic role of glucagon like peptide-1 (GLP-1), its agonists and glucagon like peptide-1 receptor (GLP1R) in the treatment of obesity and associated metabolic syndrome for future consideration.

Keywords: Glucagon like peptide-1(GLP-1), Glucagon like peptide 1 receptor (GLP1R), metabolic syndrome, obesity, Type II diabetes mellitus and cardiovascular diseases

I INTRODUCTION

Obesity and associated metabolic syndrome are at higher risk in the individuals nowadays [1]. Enteroendocrine L- cells produce gastrointestinal incretin hormones like Glucagon Like Peptide 1 (GLP-1) that increases the insulin secretion and decrease the pancreatic discharge of glucagon [2]. In addition, GLP-1 is expressed in the gut and the brainstem and it acts through the GLP-1 receptor (GLP1R) [3]. In addition, GLP-1 exerts its direct effects on the heart and blood vessels [4,5]. Based on these actions, GLP-1 and its active metabolites were thought to have a therapeutic role in obesity and associated metabolic disorders that includes type II diabetes and cardiovascular diseases.

II OBESITY AND ASSOCIATED METABOLIC SYNDROME- PREVALENCE

Now a days, obesity has increased prevalence and considered as a worldwide health concern. Worldwide, more than 39% of adults were overweight in 2016 [6]. By 2030, it is estimated that the prevalence of obesity and overweight are expected to reach a level of 89% in males and 85 % in females, respectively [7]. Obesity is also associated with metabolic disturbances such as insulin resistance and dyslipidemia leading to diabetes, hypertension and atherosclerotic disease, combinedly known as metabolic syndrome [8]. Metabolic syndrome ranges approximately from 20 to 25% in adults and 0 to 19.2% in children worldwide [9]. Metabolic syndrome prevalence is estimated to increase approximately by 53% by 2035[10].

III GLUCAGON-LIKE PEPTIDE-1 (GLP-1)

A Structure

GLP-1 is a gut derived peptide hormone made up of 30 amino acid long chain [11]. GLP-1 was synthesised and secreted in the form of two different biological active isoforms in the body concurrently. GLP-1(7-36) amide form is the amidated peptide form and GLP-1(7-37) is the glycine extended peptide form of GLP-1 [12]. However, GLP-1(7-36) amide form was observed mostly in human and rat intestines and acts as one of the most dominant isoforms in the brain [13]. The structure of the GLP-(7-36) amide form is shown in Figure 1.

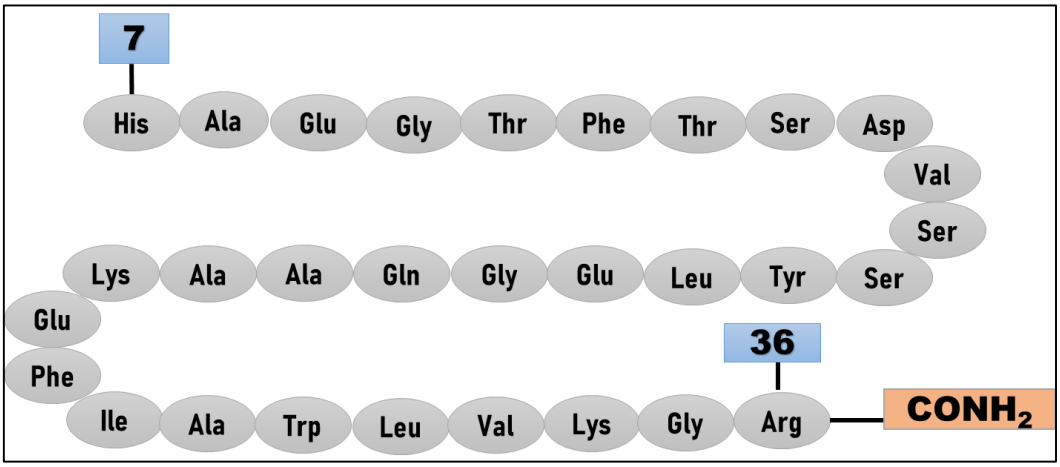

Figure 1- Glucagon like peptide-1 (7-36) amide form structure

B Synthesis, distribution and secretion

The gastrointestinal epithelium wall comprises numerous types of cells which includes enteroendocrine cells, one of the key components of the gut-brain-pancreas axis [14]. Glucagon-Like peptide-1 is synthesised from the small intestine and large intestine endocrine L- cells peripherally. Additionally, GLP-1 is also observed centrally to a lesser amount in the perikarya of neurons and also located within the solitary tract nucleus, the dorsal and ventral medulla, and the olfactory bulb [15,16].

GLP-1 is synthesised from proglucagon, a GLP-1 precursor molecule. Proglucagon is a peptide molecule made up of 160 amino acids and cleaved in between 78-107/8 amino acids by prohormone convertase 1/3 in intestinal L cells or the brain to produce Glucagon-like peptide-1 [17].

GLP-1 secretion is dependent upon meal intake [18]. GLP-1 excitation is regulated by the neural mechanism through Gastrin Releasing peptide (GRP) and Acetylcholine [19]. Upon ingestion, digestible carbohydrates were absorbed in the form of glucose, galactose and fructose which stimulates the secretion of GLP-1 via sodium-glucose cotransporter (SGLT-1) dependant slight inward current induction and through the glucose transporter-2 (GLUT 2) [20,21]. Whereas, ingestion of non-digestible carbohydrates undergoes fermentation that leads to the release of short-chain fatty acids and promotes the GLP-1 secretion via FFAR2 and FFAR3 receptors (Free fatty acid receptors 2 and 3), a G-Protein coupled receptors [22]. Ingestion of dietary lipids "majorly triglycerides" were absorbed in the form of glycerol and free fatty acids [23]. Long-chain unsaturated free fatty acids stimulate the GLP-1 secretion through interactions with free fatty acid receptors 1 and 4 (FFAR 1 and FFAR 4) [24]. Proteins/amino acid intake stimulates the secretion of GLP-1 via activation of calcium-calmodulin dependant kinase II [25].

C Glucagon-like Peptide -1 receptor (GLP1R)

GLP1R is one of the members of G- Protein-coupled receptor (GPCR) that is synthesized by the GLP1R gene present on chromosome 6 of humans [26]. GLP1R is composed of two domains, one extracellular domain and one transmembrane domain. Extracellular domain binds to the C- terminal helix of GLP-1 and the transmembrane domain binds to the N- terminal region of GLP-1 [27]. GLP1R is observed majorly in pancreatic beta cells and the brain; minorly in the stomach stretch-responsive vagal neurons and the intestine and also in cardiovascular systems [28,29]. Activation of pancreatic beta cells GLP1R causes insulin sensitivity and leads to synthesis and release of insulin and thereby reduces glucagon production [30]. Activation of GLP1R in the brain controls the appetite and improves memory and learning [31,32]. Changes in breathing and heart rate patterns were observed through the GLP1R activation located in the vagal neurons by communicating with other organs (Figure 2).

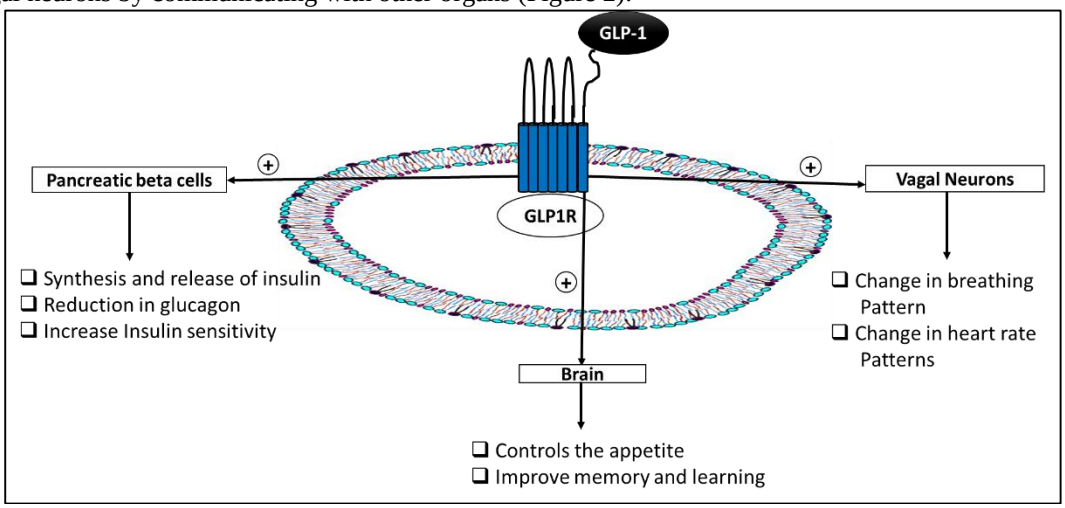

Figure 2- Various physiological functions of GLP1R upon activation by GLP-1

D Role of GLP-1 in type II diabetes mellitus

Diabetes mellitus occurs when there is a decrease in the GLP-1 release post oral intake of nutrients. Apart from this, decreased sensitivity to GLP1R in the beta cells of islets of Langerhans may also contribute to the occurrence of type II diabetes mellitus. Additionally, in the glomerular region endothelial cells, hyperactivity of dipeptidyl peptidase-4 (DPP-IV) contributes to an increased degradation of GLP-1 and also results in a low level of GLP-1 in the blood.

GLP-1 also promotes beta cell proliferation and apoptosis inhibition. In addition, GLP-1 enhances the differentiation of pancreatic epithelial cells into cells producing insulin. However, this regeneration is lost in subjects with type II diabetes mellitus and hence, contributes as a factor to its pathogenesis [33].

E Pharmacology of GLP-1 in control of Type II diabetes mellitus

GLP-1 lowers blood glucose by stimulating the production of insulin by enhancing the action of glucose [34]. GLP-1 released in the intestine enhances the insulin secretion through a vagal-vagal reflex which leads to islets beta cells cholinergic stimulation. Upon binding of GLP1 agonists to the GLP1R in the islets of Langerhans, adenylate cyclase signalling pathway was activated. Activation of this signalling pathway further stimulates the conversion of ATP to cAMP. This enhanced cAMP levels lead to phosphorylation of and Epac2 (cAMP-regulated guanine nucleotide exchange factor 2) and protein kinase A (PKA) [35]. Phosphorylated PKA inhibits the ATP-dependent potassium channel (K_{ATP}) that results in the prolongation of the action potential duration and further triggers the voltage dependant L-type calcium channel and causes the calcium (Ca^{2+}) influx and action potential generation [36]. PKA also stimulates the Ryanodine receptors (RyR) and activate IP3 mediated calcium release.

Phosphorylated Epac2 activates Rap 1 and phospholipase C (PLC) and then activates IP3 and DAG pathway that leads to the enhanced calcium induced calcium release (CICR) from Ryanodine receptors (RyR) and Inositol triphosphate (IP3) receptors respectively [37]. Cumulatively, phosphorylated activation of PKA and Epac2 pathways leads to increased cytoplasmic calcium levels and causes the mitochondrial synthesis of ATP and further causes exocytosis in the insulin granules of pancreatic beta cells of islets of Langerhans to produce insulin (Figure 3).

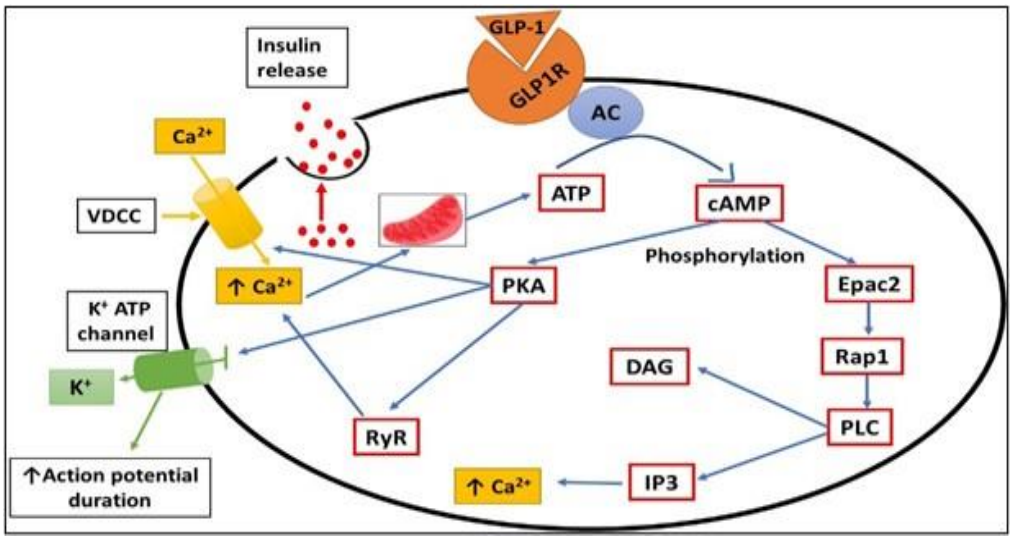

Figure 3- Mechanism of GLP-1 in insulin release for control of TDM

F GLP1R agonists as a target for type II diabetes therapy

To date, several GLP1R agonists are approved therapeutically as second line therapy for the treatment of type 2 diabetes. These include liraglutide, exenatide, dulaglutide, lixisenatide, albiglutide, semaglutide and some other drugs [38].

G GLP-1 pharmacology in control of obesity

Pharmacological actions of GLP1R agonists were produced by the activation of brown adipose tissue which is thought to be mediated by the central nervous system adrenergic and AMP-activated protein kinase (AMPK) pathways activation [39]. Preclinical studies has revealed that GLP1R agonists result in an increased energy expenditure that contributes to weight loss [40]. In addition, inhibition of food intake is one of the major approaches to the control of obesity. Post peripheral administration of GLP1R agonists, vagal afferent neurons and other brain regions contributes to the food intake suppression [41]. Some studies provide evidence that central nervous system GLP-1 signalling is essential to mediate the therapeutic effect on energy metabolism [42].

In CNS, the brain stem plays a key role in communication of peripheral satiety signals to higher brain centres [43]. Activation of GLP1R by GLP-1 agonists in the lateral parabrachial nucleus inhibits the feed intake mechanism [44]. Additionally, the hypothalamus acts as an important centre for mediating the therapeutic effects of GLP1R agonists on energy metabolism. In specific, the arcuate nucleus (ARC) located in the hypothalamus acts as one of the main sites of action for GLP1R agonists [45]. The specific neuronal populations that mediate the anorectic action of GLP1R signalling in ARC are being investigated currently. Most of the reported studies suggest that activation of anorexigenic pro-opiomelanocortin (POMC) neurons and simultaneous inhibition of orexigenic neuropeptide Y/Agouti-related peptide (NPY/AgRP) neurons in the ARC leads to food intake inhibition which is one of the critical mechanisms for pharmacological action of GLP1R agonists [46]. GLP1R is also expressed in other hypothalamic nuclei such as the dorsomedial nucleus of the hypothalamus (DMH) and the medial preoptic area (MPOA) where its function is closely related to thermogenesis control [47]. GLP-1 slows gastric emptying thereby reducing the feed intake capacity [48].

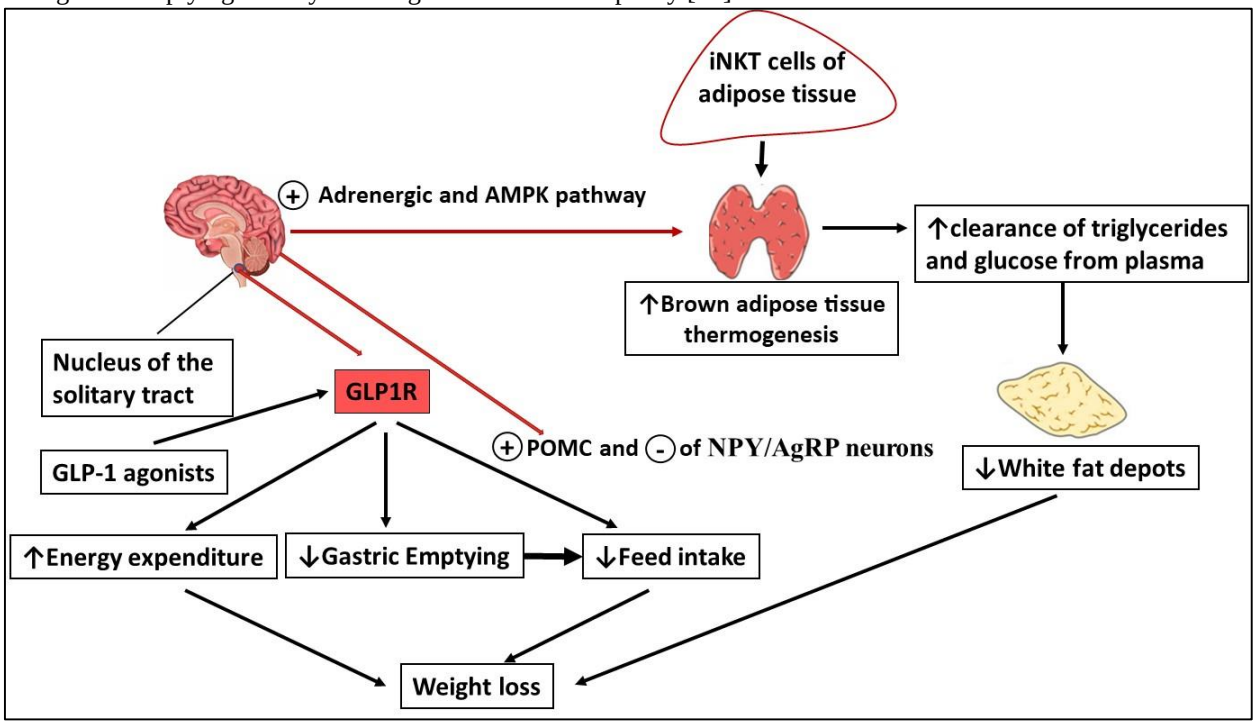

Figure 4- Possible mechanism of GLP-1 in control of obesity; iNKT- invariant natural killer T cells; POMC-proopiomelanocortin; NPY/AgRP- Neuropeptide Y/Agouti-related peptide

In addition to the occurrence of feed intake changes, body weight change is also regulated by the activation of central GLP1R and further causes enhanced brown adipose tissue (BAT) thermogenesis [49]. In one study it is reported that the GLP1R located in the ventromedial nucleus of the hypothalamus (VMH) is activated by the GLP-1 analogue and triggers the AMP-activated protein kinase (AMPK) inhibition that promotes BAT thermogenesis mediated by the sympathetic system and further leads to the browning of white adipose tissue (WAT) and reduction in the feed intake [50]. The AMPK-VMH-SNS-BAT/WAT hypothalamic pathway which is activated by several peripheral signals is a well reported pathway [51]. Some preclinical studies in mice reported that the central infusion of GLP1R agonists increases the sympathetic tone of the fibres innervating the thermogenesis of brown adipose tissue. This high brown fat activity promotes triglycerides and glucose clearance from the plasma and reduces white fat depots that lead to body weight loss [52]. Other preclinical studies suggest that GLP1R centrally mediates the metabolism of adipocytes and further inhibition of white fat depots triglyceride storage. This further signifies that GLP1R centrally elevates a catabolic state in adipose tissue by activation of the sympathetic system [53]. Some studies suggest that the immune system also plays a key role in energy homeostasis mediated by GLP1R. Among these, adipocyte resident invariant natural killer T (iNKT) cells are located in higher amounts in the adipose tissue and play a key role in weight loss [54]. Recent data reported that iNKT cells favour BAT thermogenesis and further causes GLP-1 receptor associated weight loss effects [55]. The possible mechanism is clearly represented in figure 4.

Some of the GLP1R agonists such as liraglutide and more recently semaglutide are considered as the most efficient weight loss drugs in clinical trials [56,57].

H Pharmacological actions of GLP-1 in the cardiovascular system

GLP1R is also located in the cardiovascular system and has been observed primarily on cardiomyocytes and endothelial cells. GLP1R has also been located on the autonomic nervous system peripherally that promotes direct and indirect effects on the heart and vessels [58]. The mechanistic approach regarding cardiovascular effects of GLP1R focuses mainly on heart rate, microvascular function, blood pressure, lipids, and inflammation which are discussed briefly below.

Some studies reported that GLP1R agonists increases the heart rate slightly to a certain extent which is thought to be weakened immediately by not changing the normal heart rate [59]. Till now, a conclusive mechanism behind the increase in heart rate remains unclear. However, a recent study in mice reported that stimulation of the arterial GLP1R induces a chronotropic effect produced by the sinoatrial node [60]. Although this animal data may provide clarity on the mechanism, confirmation in human studies is needed. GLP1R agonists decrease blood pressure in subjects suffering with type II diabetes and obesity. Clear mechanisms are yet to be resolved, but some of the clinical studies demonstrated the blood pressure lowering effect may be due to GLP1R agonist induced weight loss [61]; involvement of the sympathetic nervous system as it influences both cardiac output and vascular resistance. Pre-clinical studies suggested that activation of GLP1R via serum atrial natriuretic peptide (ANP) reduces blood pressure [62]. The clinical mechanism is yet to be understood.

One of the clinical studies reported that GLP1R agonist exenatide reduces dyslipidemia by reducing the increased apo C-III, triglycerides, apoB-48 production, remnant lipoprotein cholesterol and triglycerides in type II diabetic and obese patients [63]. Further contributes to atherosclerosis and cardiovascular disease reduction [64]. Clear mechanisms are yet to be investigated. Some of the clinical studies reported that GLP1R agonists such as liraglutide and exenatide reduce some of the systemic inflammatory cytokines like tumour necrosis factor- α (TNF-α), interleukins (IL) 1β and IL-6, c-reactive protein (CRP) and also leucocyte adhesion molecules like vascular cell adhesion molecule-1 (V-CAM-1) and intercellular adhesion molecule-1 (ICAM-1) thereby reduces inflammation for prevention of the atherosclerosis formation and cardiovascular risk [65,66,67].

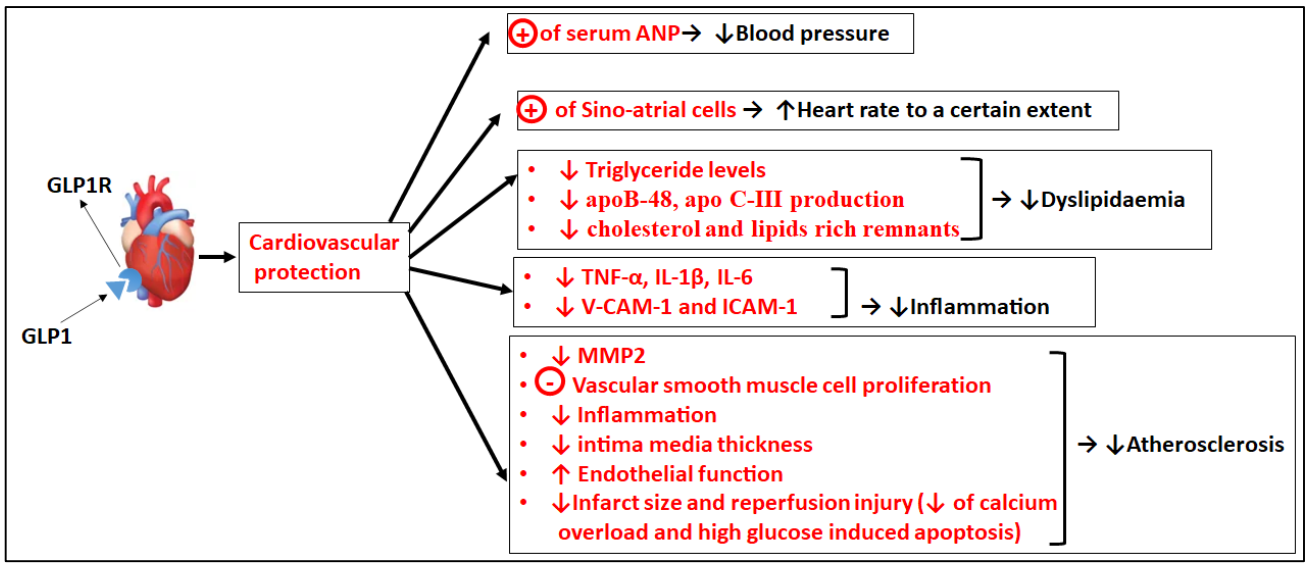

Figure 5- Possible mechanism of GLP-1 in control of cardiovascular diseases; ANP: atrial natriuretic peptide; MMP2: Matrix Metallo proteinase-2; TNF-α: Tumour necrosis factor-α; IL-1β: Interleukin-1β; IL-6: Interleukin-6; V-CAM-1: Vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1

Some of the preclinical and clinical studies reported that GLP1R agonists inhibit the development of atherosclerosis by reducing matrix metalloproteinase-2 (MMP-2) levels [68], inhibiting vascular smooth muscle cell proliferation [69], regulating the inflammation [70], reducing intima-media thickening [71] and increase endothelial function via nitric oxide mediated vasodilation and decreased oxidative stress [72]; however, the specific mechanisms in clinical studies are yet to be observed. Some studies reported that GLP1R agonists prevent atherosclerotic effects by blocking the p53protein inhibition on kruppel-like factor 2 (KLF2) located on human aortic endothelial cells [73,74]. Some of the pre-clinical and clinical studies reported that, GLP1R agonists prevents atherosclerosis via infarct size reduction and reperfusion injury mediated by intracellular calcium overload reduction and high glucose induced apoptosis [75,76]. In another study, it is reported that liraglutide can also initiates vascular smooth muscle cell cycle arrest via the AMPK pathway thereby

delaying formation of atherosclerosis [77]. To date, as there are no GLP1R agonists approved for the treatment of atherosclerosis and cardiovascular diseases, these preclinical and clinical findings can provide novel approaches for the pharmacological therapy of cardiovascular diseases associated with obesity and type II diabetes mellitus. The possible mechanism is clearly represented in figure 5.

IV CONCLUSIONAND FUTURE PERSPECTIVES

Currently, GLP1R agonists have been considered as novel antidiabetic drugs that are used in type II diabetes mellitus treatment as a second line of therapy [78]. In addition to this, GLP-1 agonists have advantages in obesity by body weight reduction, brown fat thermogenesis and elevated energy expenditure. In the United States, currently, one FDA-approved drug of GLP-1 agonist- liraglutide (saxenda) is used for the treatment of obesity. Some of the clinical data support the roles of central GLP1R and peripheral GLP1R agonistic actions in feed intake and weight reduction. Hence, it became an important target for the pharmacological therapy of obesity and overweight.

Some of the clinical trials conducted with GLP1R agonists and cardiovascular outcome trials suggested that liraglutide and semaglutide displayed beneficial effects on cardiovascular benefits in the presence of both placebo and standard treatment. Although the mechanisms through which GLP1R agonists (liraglutide and semaglutide) produce cardiovascular protection is still clearly unknown, they may be used in routine clinical practice. Still, more clinical studies should be performed to observe clear mechanisms through which GLPIR agonists act as cardioprotective agents. Since cardiovascular diseases and type II diabetes mellitus is the major cause of death in obese and overweight people, choosing GLP1R agonists as a therapeutic drug might be the best option for control of obesity and associated metabolic syndrome (Type 2 diabetes mellitus and cardiovascular diseases) in the future.

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