Review

A mini review on glucagon-like peptide-1 receptor agonists and its role in blood pressure regulation

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A Mini Review on Glucagon-Like Peptide-1 Receptor Agonists and Its Role in Blood Pressure Regulation

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Abstract: Incretin effect helps in regulating glucose homeostasis and maintaining glycaemic control within the human body. This effect is achieved by the two naturally occurring incretin hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Such hormones released by specialized entero-endocrine cells of the gastrointestinal tract cause insulin augmentation after food consumption. However, incretin effects are impaired in type 2 diabetic, primarily attributed to the deterioration of GLP-1 function along with decreased GLP-1 receptor expression. Targeting this hormone has, therefore, become an important therapeutic approach to treat this diabetic condition. Native GLP-1's brief half-life and rapid proteolytic degradation have generated significant enthusiasm in uncovering the long-acting GLP-1 receptor (GLP-1R) agonists to manage type 2 diabetes. These synthetic peptides mimic the natural GLP-1 to activate GLP-1R and effectively exert various physiological benefits in terms of weight management, blood pressure, lipid profile, obesity and major adverse cardiovascular event. This review paper provides insights into the structure, function and expression of GLP-1 and its receptor. It also summarizes existing literature regarding different types of GLP-1 receptor agonists, their effects on blood pressure and how they exert their actions. While animal models have contributed significantly to this area of study, the scarcity of human studies is noted, indicating a need for more investigation in this domain. Expanding research in humans will help in comprehending the impact of GLP-1 receptor agonists on blood pressure regulation and their underlying mechanisms.

Keywords: Agonist; blood pressure; GLP-1; GLP-1 receptor; hypertension

1. Introduction

Plasma glucose serves as the primary metabolic fuel for the central nervous system (CNS) (McCrimmon, 2012). Brief episodes of hypoglycaemia can lead to significant CNS dysfunction while prolonged and severe hypoglycaemia may result in cellular damage or death. To prevent hypoglycaemia and to maintain proper functioning of various metabolic processes, the human body has therefore evolved a regulatory mechanism that tightly controls blood glucose levels. Because of this system, a healthy individual possesses a remarkable capacity to manage increasing glucose intake and maintain nearly unchanged postprandial (after meal) glucose excursions, regardless of the oral load of glucose consumed (Makroglou et al., 2006; Holst, 2019). The incretin effect is one such regulatory mechanism responsible for glucose homeostasis within the human body. Due to this effect, the blood sugar level is regulated by the augmentation of insulin secretion (by a factor of 2-3) from beta cells of pancreas after oral intake of glucose as opposed to intravenous infusion (Holst et al., 2021). This incretin effect is achieved by two types of incretin hormones released from specialized entero-endocrine cells, namely glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) (Drucker, 2006). Among these, GLP-1 receives much attention because it not only possesses glucose-lowering effects but also demonstrates its capability to delay gastric emptying process and suppress glucagon secretion (Donnelly, 2012). In addition, type 2 diabetic patients show reduced level of this incretin effect as a result of impaired insulin secretion, leading to hyperglycaemia. This deficit is attributed to the deterioration of GLP-1 function along with decreased GLP-1specific receptor expression (Nauck et al., 2011; Ten Kulve et al., 2016). Given its various physiological effects, GLP-1 emerges as an attractive candidate for therapeutic interventions for

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managing type 2 diabetes. Its multifunctional nature offers potential benefits for addressing various aspects of the condition other than its glycaemic control.

2. Glucagon-like peptide 1 (GLP-1)

2.1. Structure

Among GIP and GLP-1, GLP-1 holds great promise as an incretin hormone. This hormone exists in various forms like GLP-1 (1–37), GLP-1 (1-36amide), GLP-1 (7-36amide), GLP-1 (7-37) and their efficacy in boosting insulin secretion when glucose is present appears to vary among these forms (Müller et al., 2019). Of these forms, GLP-1 (7-36amide) and GLP-1 (7–37) are recognized as truncated versions of this hormone and are called amidated GLP-1 and glycine-extended GLP-1, respectively (Orskov et al., 1989). The distribution of various types of GLP-1 differs among different species (Kuhre et al., 2014). In humans, majority of the circulating GLP-1 are truncated ones, of which approximately 80% of them is GLP-1 (7-36amide) while only a few percentage (about 20%) corresponds to GLP-1 (7–37) as reflected from immunoreactivity data (Ørskov et al., 1994).

2.2. Synthesis

GLP-1 is synthesized in the intestine from the proglucagon composed of 180-amino acids as a result of post-translational modifications (Müller et al., 2019). After its formation, prohormone convertase 1 (PC1) cleaves proglucagon to produce 37-amino acid immature GLP-1 along with GLP-2, glicentin, oxyntomodulin and intervening peptide-2. This immature GLP-1 is then rapidly modified into its active forms i.e., GLP-1(7-36) amide and glycine-extended GLP-1(7-37) as reported in rodents and humans (Poudyal, 2016).

2.3. Secretion

Enteroendocrine L-cells, that is present in ileum of distal part and colon, releases GPL-1 following the consumption of carbohydrate and non-carbohydrate foods (Cabou & Burcelin, 2011). Upon metabolism, glucose as well as fructose induce the secretion of GLP-1 by closing ATP-dependent K-channels. This closure induces membrane depolarization that releases voltage-dependent calcium channels (L-type) in the intestine (Poudyal, 2016). Opening of these channels results in Ca^{2+} influx inside enteroendocrine GLUTag cells and causes GLP-1 to secrete into the blood through vesicular exocytosis (Tolhurst et al., 2009). Stimulation of GLP-1 secretion is also caused by free fatty acids (FFAs) through various mechanisms. Both short and long-chain FFAs bind to their respective fatty acid receptors such as GPR43, GPR120 (Kaji et al., 2014) and causes calcium ions to enter through Ca^{2+} channels (most likely L-type) present on the cell surfaces (Sidhu et al., 2000). This influx subsequently increases the concentration of intracellular calcium ions, thereby inducing GLP-1 release. A receptor-independent mechanism regarding the secretion of GLP-1 is also evidenced as a result of uncoupling oxidative phosphorylation and glycolysis activation (Clara et al., 2016). Protein intake can also lead to the release of GLP-1 through the activation of Ca^{2+}/calmodulin-dependent kinase II (Kato et al., 2016) and transmission of signals to L-cells via peptide transporter 1 (PEPT1) and Ca^{2+} sensing receptor (CaSR) (Diakogiannaki et al., 2013).

2.4. Metabolism

The two active forms of GLP-1, namely, GLP-1(7-36) amide and the glycine-extended GLP-1(7-37) have a brief survival duration as they are converted into their inactive forms by a proteolytic enzyme at a faster rate (Eng et al., 2014). As soon as they are released from the L-cells of the intestine, around 33% of GLP-1(7-36) amides are truncated immediately at the site of secretion into the inactive form i.e. GLP-1(9-36) amide (Hansen et al., 1999) whereas the rest 43% molecules are degraded subsequently in the hepatocyte (Deacon et al., 1996). This rapid degradation leads to only 38% of GLP-1 to remain active. They are secreted from the intestine to enter the circulatory system where they are further subjected to proteolytic degradation. Consequently, only a few active molecules is

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destined to reach their targets (Deacon et al., 1996; Cabou & Burcelin, 2011) where they can bind with its receptor (GLP-1R) to induce its biological effects (Baggio & Drucker, 2007). The binding is followed by the recognition of the ligand mediated by the specific residues present in extracellular domain at the N-terminal region of GLP-1R interacting with the α-helical region of the ligand (Runge et al., 2008; Underwood et al., 2010). Following this, the N-terminal residues of ligand binds with the extracellular loops and transmembrane helices of the receptor to induce the activation of GLP-1R (Al-Sabah & Donnelly, 2003; De Maturana et al., 2003; Moon et al., 2012).

3. Glucagon-like peptide 1 receptor (GLP-1R)

3.1. Structure

GLP-1 receptors (GLP-1R) belong to the class B type of G protein-coupled receptors (GPCRs) (Mayo et al., 2003). The GLP-1R protein of human comprises 463 amino acids (Müller et al., 2019). Immediately after its synthesis in the endoplasmic reticulum (ER), GLP-1R is translocated across the ER with the help of a signal peptide coded by its short leader sequence (Huang et al., 2010). Following translocation, this signal peptide is removed by a peptidase, giving rise to a complete structure of this protein. It has the α-helix at the N-terminal region of the extracellular domain and four β-strands arranged in two sheets antiparallelly. Three disulfide bonds connect these two sheets involving six cysteine (Cys) residues (Moon et al., 2012). The first disulfide bond between first and third Cys residues links the α-helix to the first β-sheet, whereas the second bond between second and fifth Cys residues connects two β-sheets. Lastly, the third one is formed between fourth and sixth residues which brings the central β-sheets in close proximity to the GLP-1R's C-terminal domain (Müller et al., 2019).

3.2. Expression

Attempts have been made to elucidate the expression pattern of this receptor across various species such as in rats, mice, monkey and human. Findings revealed the expression of GLP-1R in various regions including the lungs, gastrointestinal tract, pancreas, kidneys, and CNS in all these experimental models (Poudyal, 2016; Müller et al., 2019). However, the precise locations of this expression within these organs exhibited variations among the species. In the heart, its presence is reported in mice, monkeys and humans. Interestingly, GLP-1R does not express within the liver of rats, monkeys and humans. In mice, although GLP-1R expression is not present in hepatocytes, it is found in the portal vein walls situated close to the liver hilum (Richards et al., 2014).

3.3. Metabolism

GLP-1R can exist in both active and inactive forms which is determined by its interaction with the type of allosteric modulators. Binding of a negative allosteric modulator within the cleft formed by helices VI and VII of GLP-1R blocks the association of helix VI with the G protein, leading to the deactivation of the receptor (Song et al., 2017). Conversely, the positive allosteric modulator binds between helices V and VI and activates the receptor by facilitating the G-protein binding with the GLP-1 receptor. Once activated, the receptor triggers several signalling pathways including Gs signalling for cAMP formation, Gq/11 pathway for elevating intracellular Ca^{2+} concentration and ERK1/2 signalling for recruiting β-arrestin (Wheeler et al., 1993; Sonoda et al., 2008; Wootten et al., 2016). Although various GLP-1 forms can bind with the same receptor, each of them initiates signalling pathways different from the other and elicit diverse cellular responses (Wootten et al., 2013; Wootten et al., 2016). In pancreas, activated GLP-1 receptor stimulates the production of insulin through adenylyl cyclase pathway which is subsequently released into the bloodstream, aiding in regulating the plasma glucose level (Drucker et al., 1987).

4. Glucagon-like peptide 1 agonists (GLP-1RAs)

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Native GLP-1 acts as a multifaceted hormone that exhibit a plethora of physiological activities in the body (Müller et al., 2019). It primarily has the potential to reduce hypoglycaemia for which it has become an attractive candidate for pharmacists to manage patients having type 2 diabetes mellitus. Unfortunately, this hormone has a very short life-span (half-life of 1.5 mins) as it undergoes a rapid degradation by the dipeptidyl peptidase-4 (DPP-4) enzyme (Deacon, 2018). In order to achieve the therapeutic benefits of the native GLP-1, it is necessary to administer GLP-1 in patients continuously throughout the day (Larsen et al., 2001) which is impossible and therefore restricts its therapeutic use for type 2 diabetes. To overcome these issues, several drugs are being innovated and designed aiming to cure type 2 diabetes therapeutically. Among them, derivatives of native GLP-1 with an increased half-life, in contrast to natural GLP-1, are given much importance for their ability to produce prolonged therapeutic effects. GLP-1 receptor agonists (GLP-1RA) are a type of medication that that falls into this category. They are designed in such a way that they mimic the natural hormone but are not sensitive to enzymatic ubiquitination (Nauck et al., 2021). Hence, GLP-1RA has been considered as an important target in treating type 2 diabetes in recent years.

While designing GLP-1RAs, it is desirable to minimize unnecessary alterations in amino acids in these analogues and maintain structural similarity between the analogues and native GLP-1 to avoid immunogenicity responses (Lau et al., 2015). Several GLP-1RAs are nowadays available in the market which are categorized into short- and long-acting groups (Uccellatore et al., 2015; Gentilella et al., 2019). Short-acting agents comprise of exenatide twice daily as well as lixisenatide while exenatide weekly once, albiglutide, liraglutide, semaglutide and dulaglutide belong to long-lasting groups.

Exenatide is a mimetic of exendin-4 that was originally derived from the saliva of *Heloderma suspectum*, also known as the Gila monster (Malhotra et al., 1992). This isolated peptide analogue shows more than 50% similarity with the sequence of native GLP-1 and possesses a half-life of around 2.4 hours (Garber, 2011). This compound was first approved in 2005 for its twice daily administration (Kolterman et al., 2005). Liraglutide closely resembles human GLP-1 which binds to the human-derived albumin with respect to and a spacer a fatty acid covalently linked with this peptide backbone (Agersø et al., 2002; Madsen et al., 2007). It has an increased half-life i.e., 8-10 hours after its administration intravenously and 13-15 hours after subcutaneous administration (Knudsen et al., 2000; Agersø et al., 2002; Elbrond et al., 2002). Hence, this analogue is approved in 2009 for its once-daily administration (Buse et al., 2009) whereas GLP-1RAs such as, dulaglutide, albiglutide, and semaglutide are aimed for once-weekly administration. Albiglutide comprises two Gly8 GLP-1 molecules fused with serum albumin of human in tandem order. This RA has a half-life of around 6-8 days and takes 2-4 days to reach the maximum plasma concentration (T_{max}) (Bush et al., 2009). Recently, dulaglutide was accepted as a second analogue for its once-weekly administration. Regarding semaglutide, substitutions are made at two amino acids in relation to human GLP-1 and is derivatized at lysine 26 (Lau et al., 2015). This analogue has approximately half-life of one week, allowing for its once-weekly subcutaneous administration. Apart from these, taspoglutide was also formulated as a long-acting GLP-1 RA but never reached commercialization due to challenges with its tolerability that significantly affected the cardiovascular outcome trial (CVOT) linked to its development (Müller et al., 2019). Efpeglenatide is another member of the long-acting group which contains an altered exendin linked to the human immunoglobulin 4 fragment using an advanced technology (Ha et al., 2016; Pratley et al., 2022). This conjugation increases the duration of efpeglenatide's action (Yoon et al., 2020) and the short flexible polyethylene glycol based linker helps to maintain its intrinsic activity. Currently, this RA is undergoing development with the aim to regulate glycaemia in patients suffering from type 2 diabetes through their sub-cutaneous administration once-weekly. Tirzepatide is another incretin mimetic which functions as a dual receptor agonist for both GIP and GLP-1 (Berndt et al., 2021). This synthetic peptide is composed of 39 amino acids and is formulated on the basis of the sequence of native GIP (Min & Bain, 2021). Both clinical and pre-clinical trials have demonstrated promising results regarding glucose reduction, weight management and effects on haemoglobin A1c (HbA1c) along with some adverse effects. Its

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impact on cardiovascular outcomes, long-term effectiveness and safety-profile have not been established and are currently under investigation.

Short-acting agonists for GLP-1R have a remarkable ability to lower glucose level following meal consumption (postprandial) and delay gastric emptying. In contrast, long-acting agents show glucose-lowering effects on not only postprandial glucose level but also on fasting glucose level. This regulation of glucose levels is achieved by stimulating (glucose-dependent) insulin secretion while inhibiting glucagon release (Gentilella et al., 2019). Moreover, these long-acting agonists cause smaller variations in fluctuations in drug concentrations of plasma and improve tolerability of gastrointestinal profiles. Due to their simplicity and convenience in terms of administration schedules, long-acting RAs increase treatment adherence and persistence patients, thereby improving their clinical outcomes.

5. Effects of GLP-1RAs on blood pressure

Among all known GLP-1R agonists, utilization of albiglutide, dulaglutide, semaglutide and liraglutide as a new treatment option for diabetic patients in pharmaceutical industries gain more popularity. They are safe in effectively controlling blood glucose level without causing hypoglycaemia upon administration. Additionally, these RAs are reported to lower occurrences of major adverse cardiovascular event (MACE) associated with diabetes such as stroke, acute coronary syndrome, myocardial infarction, heart failure and cardiovascular death substantially (Berndt et al., 2021; Helmstädter et al., 2022). Evidences from cardiovascular outcome trials have shown that GLP-1RAs play crucial roles in modifying several risk factors of cardiovascular diseases including blood pressure, obesity, lipid profile and body weight that contribute significantly in the observed cardioprotective effects among diabetic population. The present review focuses only on impacts of GLP-1RAs specifically on the blood pressure along with their mechanisms behind these beneficial effects in both diabetic as well as non-diabetic subjects.

5.1. Clinical outcomes of different GLP-1RAs on blood pressure

Hypertension is found to be one critical risk factor that causes cardiovascular diseases. Because diabetes mellitus (DM) coexist with arterial hypertension at a higher rate, effectively managing blood pressure becomes crucial in handling patients suffering from DM to prevent their health complications or mortality (Colosia et al., 2013; Cosentino et al., 2020). The clinical trials on experimental models of hypertension demonstrated that GLP-1 RAs can potentially lower the blood pressure (Laugero et al., 2009; Hirata et al., 2009), particularly systolic blood pressure (SBP) with 2-3 mm Hg of average reduction (Robinson et al., 2013; Sun et al., 2015). However, diastolic blood pressure (DBP) either remains unchanged (Marso et al., 2016) or shows no significant impact (Husain et al., 2019) upon administering agonists for GLP-1 receptors.

Administration of exenatide at 10 μg twice daily appeared to ameliorate SBP (least squares mean difference was 2.8 mm Hg) in comparison to insulin or placebo, as derived from a pooled analysis encompassing data involving 2171 subjects from six trials (Okerson et al., 2010). The reduction of SBP was most significant between exenatide and placebo (difference of 8.2 mm Hg) among subjects whose baseline SBP was ≥ 150 mm Hg. However, those people having normal BP level at the baseline showed no between-group differences in the alteration of SBP or DBP between the two groups (exenatide and placebo) (Okerson et al., 2010). Upon administering a subcutaneous injection of 2 mg exenatide once-weekly to 14752 patients having T2DM, the least squares mean for SBP values were reduced (1.6 mm Hg) at six months when compared with patients injected with the placebo (Holman et al., 2017). Another randomized comparator-controlled trial involving 1379 individuals demonstrated notable reductions in SBP and DBP by 2.8- and 0.8-mm Hg respectively in patients after treated with exenatide once-weekly for 24-30 weeks (Grimm et al., 2013).

On the other hand, dulaglutide at 1.5 mg resulted in the reduction of SBP (2-3 mm Hg) than the placebo which was evidenced by four weeks and remained consistent throughout 26 weeks

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(Ferdinand et al., 2014). Along with this, dulaglutide was able to reduce the mean 24-hour pulse pressure in these patients.

The effect of lixisenatide on the reduction of BP was also evaluated in a randomized placebo-controlled (ELIXA) trial. This trial randomly assigned 6068 patients diagnosed with T2DM and had recently encountered an acute coronary syndrome to receive either lixisenatide or placebo. Throughout the 40-month follow-up period, a slight decrease in SBP of 0.8 mm Hg was observed and sustained within the lixisenatide group unlike in the placebo group (Pfeffer et al., 2015).

In another randomization trial (SUSTAIN-6), nearly 3297 patients diagnosed with T2DM were administered with semaglutide once-weekly at two different (0.5 and 1.0 mg) doses (Marso et al., 2016a). Compared to the placebo, semaglutide at 1.0 mg only was able to significantly lower the average SBP by 2.6 mmHg while no significant reduction was observed with semaglutide 0.5 mg. When semaglutide was taken orally once daily at a dosage of 14 mg, patients having type 2 diabetes and prone to cardiovascular issues had lower SBP by 2.6 mmHg at week 83 (Husain et al., 2019). Similar such lowering effect of liraglutide on SBP were noticed in patients with similar characteristics conducted in the double-blind (LEADER) trial by Marso et al. (2016b). In this case, SBP was decreased by 1.2 mmHg from baseline to 36 months.

The collected evidences from clinical trials and meta-analyses indicate that various types of GLP-1 RAs can notably decrease the blood pressure in diabetic patients with or without cardiovascular risks but at different levels. However, these RAs do not demonstrate such lowering effect in normotensive subjects or individuals showing normal blood pressure (del Olmo-Garcia & Merino-Torres, 2018).

5.2. Mode of action

According to Ferdinand et al., (2014), patients who were treated with dulaglutide and showed reduction in SBP did not exhibit significant alterations in plasma renin activity, serum aldosterone, plasma meta-nephrines, normetanephrines and N-terminal pro-brain natriuretic peptides. As a result, the authors proposed that dulaglutide probably lowers blood pressure in these patients through some mechanisms that are not related to neurohormonal and renin–angiotensin–aldosterone systems. On the contrary, Le et al., (2016) established that exendin-4 significantly reduced levels of angiotensin (Ang) II within the kidney of mice. It also inhibited the signalling pathway involving Ang II that mediates transforming growth factor (β1) and Smad3. These data showed that exendin-4 has the ability to modulate the renin-angiotensin system in mice. These discrepancies in experimental findings have resulted in an inconclusive reports of the impact of GLP-1 RAS on the renin–angiotensin system which prompts the need of further investigation to elucidate the relationship between the two.

It is reported that GLP-1 RAs can induce natriuresis among healthy, obese and T2DM individuals, potentially contributing to the reduction of blood pressure (Lovshin et al., 2015). According to Kim et al., (2013), liraglutide stimulates its receptor to secrete atrial natriuretic peptide (ANP) from atrial cardiomyocytes in male mice treated with Ang II which triggers various effects including vasodilation mediated by cyclic guanosine monophosphate (cGMP), improved permeability of endothelium and excretion of sodium from the renal system (Kim et al., 2013). Although antihypertensive effects of GLP-1 RAs against hypertension through ANP release were found in animals, such mechanism has not been fully elucidated in humans (Li et al., 2014; Lovshin et al., 2015).

Existing research has indicated that GLP-1 RAs reduces SBP by their ability to induce vasodilation within the arterial vasculature and decrease vascular contraction (Liu et al., 2015; Zelniker et al., 2019). The function of the endothelium is also enhanced which can also aid in normalizing blood pressure (Basu et al., 2007). Murine models subjected to liraglutide treatment improved endothelial functions (Gaspari et al., 2011). GLP-1 analogues inhibit inflammation and oxidative stress, particularly in individuals diagnosed with diabetes mellitus (Type 1), thereby mitigating the impairment of endothelial functions (Ceriello et al., 2013). Additionally, Liu et al., (2015b) showed that endothelial cell functions is improved by triggering nitric oxide (NO) release

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and reducing oxidative stress, thereby regulating vascular contractions. Helmstädter et al. (2020) observed that liraglutide could downregulate the NF-κB signalling pathway and effectively suppress the inflammatory cascade induced by angiotensin II in vascular walls. Consequently, several adhesion molecules such as ICAM-1, P-selectin, VCAM-1 could not express on the surface of endothelial cells which diminishes vascular oxidative stress and restores NO level. Because NO has a pivotal role in preserving vascular homeostasis (Costa et al., 2021), mice treated with liraglutide therefore had a lower risk of endothelial dysfunction induced by hypertension and angiotensin II (Helmstädter et al., 2020).

Upon administration, liraglutide was reported to diminish vascular inflammation and curb neointimal hyperplasia in another study, which is achieved through the enhancement of nitric oxide bioavailability (Kushima et al., 2017). Development of atherosclerosis within vascular walls has a notable influence on blood pressure regulation (Berndt et al., 2021). This process encompasses the interaction between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which significantly influences the development of atherosclerosis (Amin et al., 2016). The expression of these two proteins in both endothelial cells and smooth muscle cells within the coronary artery in humans were found to be modulated by exenatide of by inhibiting NF-kB and Akt signalling pathways (Garczorz et al., 2017; Gallego-Colon et al., 2018), thereby indirectly regulating blood pressure. In addition, it was observed that GLP-1 RAs have been able to diminish the precursor for atherosclerotic disease i.e. vascular adhesion molecules in vitro (Gaspari 2011). Researches have shown that liraglutide has the ability to decrease the elevation of vascular adhesion molecules, specifically vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin in endothelial cells after treatment, potentially by activating signalling pathways involving AMP-activated protein kinase (AMPK) and calcium/calmodulin-dependent protein kinase I. Moreover, this GLP-1RA exhibits the capacity to reduce Endothelin-1 (ET-1)'s activity which tends to get upregulated in the endothelium during atherosclerosis and constricts the blood vessels (Dai et al., 2013). This effect might in turn lower the activity of NF-kB. On the other hand, the phenotypic change of macrophages from M1 to M2 induced by exenatide not only reduces adverse alterations in the vascular wall but also stabilizes atherosclerotic lesions (Shiraishi et al., 2012). These actions collectively indicate the potential of GLP-1RAs in mitigating factors involved in vascular inflammation and vasoconstriction to manage atherosclerosis-related changes. The administration of semaglutide or liraglutide to mice reduced the development of plaques during atherosclerosis (Gaspari et al., 2013), possibly due to the increase in the levels of AMPK intracellularly (Sudo et al., 2017) and decrease in proinflammatory cytokines, including NF-κB, tumour necrosis factor or TNF-α and monocyte chemoattractant protein-1 in cells treated with GLP-1RAs (Arakawa et al., 2010). These alterations in cellular responses provide insights into the probable mechanisms through which GLP-1RAs could mitigate atherosclerosis development.

6. Conclusion

In recent years, numerous GLP-1 analogues were designed and made available in the market that can mimic the natural hormone but are resistant to proteolytic degradation. These novel drugs are not only helpful in effectively controlling blood glucose level with a low risk of hypoglycaemia upon administration but also have shown to modify several risk factors of cardiovascular diseases including lipid profile, blood pressure, obesity and weight gain. Clinical trials and meta-analyses suggest that GLP-1 RAs show promise in regulating blood pressure, especially in diabetes mellitus (DM) patients at cardiovascular risk. Exenatide, dulaglutide, lixisenatide, semaglutide and liraglutide have the potential to lower systolic blood pressure (SBP) among DM patients, though effects varied between agents and dosages. Impact on diastolic blood pressure (DBP) was less consistent. Reductions in SBP were more notable in those with elevated baseline SBP, indicating potential benefits for higher-risk patients. However, normotensive subjects did not exhibit blood pressure-lowering effects. These findings highlight GLP-1 RAs as an effective strategy to treat hypertensive subjects with diabetes and cardiovascular risks. They also emphasize the need of further studies to investigate sustained effects and safety profiles across diverse populations.

GLP-1 receptor agonists exhibit a complex influence on blood pressure regulation, involving vasodilation, improved endothelial function, and reduced inflammation. Despite conflicting findings on their impact on the renin–angiotensin system, these agonists show potential in inducing natriuresis and modulating endothelial function, possibly explaining observed reductions in systolic blood pressure. Additionally, they hold promise in mitigating atherosclerosis-related changes by affecting adhesion molecules, vasoconstrictors, and inflammatory markers. Nevertheless, additional research on this topic will help in better understanding the precise mechanisms as well as their application in human cardiovascular treatment.

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