Anti-inflammatory potentials of incretin-based therapies used in the management of diabetes

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Abstract

GLP-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase 4 inhibitors (DPP-4i) are two classes of antidiabetic agents used in the management of diabetes based on incretin hormones. There is emerging evidence that they have anti-inflammatory effects. Since most long-term complications of diabetes have a background of chronic inflammation, these agents may be beneficial against diabetic complications not only due to their hypoglycemic potentials but also via their anti-inflammatory effects. However, the exact molecular mechanisms by which GLP-1RAs and DPP-4i exert their anti-inflammatory effects are not clearly understood. In this review, we discuss the potential molecular pathways by which these incretin-based therapies exert their anti-inflammatory effects.

Keywords: GLP-1 Receptor Agonist, DPP-4 Inhibitor, Diabetes Mellitus, Diabetic Complication, Inflammation.

Introduction

The global prevalence of diabetes mellitus (DM) is rising rapidly (1). DM is a chronic disorder that carries considerable morbidity and mortality (2, 3). Chronic hyperglycemia due to DM triggers a cascade of pathophysiologic pathways such as oxidative stress, inflammation, apoptosis, necrosis, fibrosis, polyol pathway and hexosamine pathways leading to various diabetic complications (2, 4). Many classes of anti-diabetic medications have been developed for normalizing glycemia and prevent various complications of DM (5-7). The exact pathophysiology behind developing diabetes complications is not fully elucidated yet (2, 8), however, the inflammatory response has a considerable role in this (9-11).

Glucagon-like peptide-1 (GLP-1) is a small peptide belonging to the family of incretin hormones predominantly secreted by the intestinal L-cells (as well as by neurons) which reduces blood glucose by stimulation of insulin release and inhibition of glucagon secretion (12). Based on the potent hypoglycemic effects of this peptide, two classes of antidiabetic medications have been developed. They are an agonist of GLP-1 receptors (GLP-1 receptor agonists) and inhibitors of enzyme metabolizing GLP-1 (as dipeptidyl peptidase-4 inhibitors or DPP-4i) (13-15). These antidiabetic medications have a lower risk of hypoglycemia and thereby, safely normalize the hyperglycemia to physiologic levels (16). Beyond their hypoglycemia effects, some evidence indicates that they have anti-inflammatory potentials and potentially have a protective effect against various diabetic complications by lowering the inflammatory response (17, 18). If so, they can be considered as therapeutic agents for the management of inflammation-dependent diabetic complications (18). In this study, we discuss the anti-inflammatory effects of GLP-1RA and DPP-4i which could potentially protect various tissues against diabetic complications.

GLP-1 RA and DPP-4i

GLP-1RA is a class of antidiabetic agents that are approved by the FDA for the management of patients with diabetes (19). These medications reduce blood glucose in patients with diabetes by mimicking the effect of incretin hormones. Incretin hormones belong to a family of metabolic peptides including GLP-1 and GIP (gastric inhibitory peptide), which reduces postprandial glycemia by inhibition of glucagon secretion and stimulation of insulin release in a blood glucose-dependent manner (20-23). They can have additional physiologic effects such as delaying the gastric emptying, decreasing nutrient absorption, appetite suppression, improvement of lipid metabolism, inhibition of pancreatic β-cell apoptosis and induction of beta-cell neogenesis (24, 25, 22). GLP-1 specific receptors are predominantly located in the pancreatic β-cells and are of G-protein coupled receptors that increase cAMP (cyclic adenosine monophosphate) production resulting in cellular events leading to insulin secretion from the pancreatic β-cells (21, 26). DPP-4i are a class of antidiabetic medications that produce their hypoglycemic effects through GLP-1 by increasing its active circulating levels by inhibiting DPP-4, which is an enzyme that inactivates GLP-1 (27, 28). Therefore, the DPP-4i have similar but less potent hypoglycemic effects compared to GLP-1RA, although they are differences in their effects on body weight and risk of some adverse effects (28).

Classes	Approved Forms	Mechanisms of Action	Ref.
GLP-1ra	Exenatide (Exendin-4), Liraglutide, Semaglutide, Dulaglutide, Lixisenatide, Albiglutide,	Mimic glucose-lowering effects of the incretin-based hormones via glucagon suppression, insulin release, appetite inhibition, and slowing the gastric emptying	(20, 23)
DPP-4i	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin	Increase the circulatory levels of active GLP-1	(27, 28)

Table 1; Two main classes of incretin-based diabetes medications

Inflammatory hypothesis for the development of diabetic complications

Various inflammatory pathways are activated in patients with diabetes (9, 29). There is growing evidence that there is activation of inflammatory pathways in the pathophysiology of various diabetes complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy and cardiovascular disease (9, 29, 30, 10). In addition, higher levels of inflammatory cytokines are typically found in the plasma of patients with diabetic complications (29, 31).

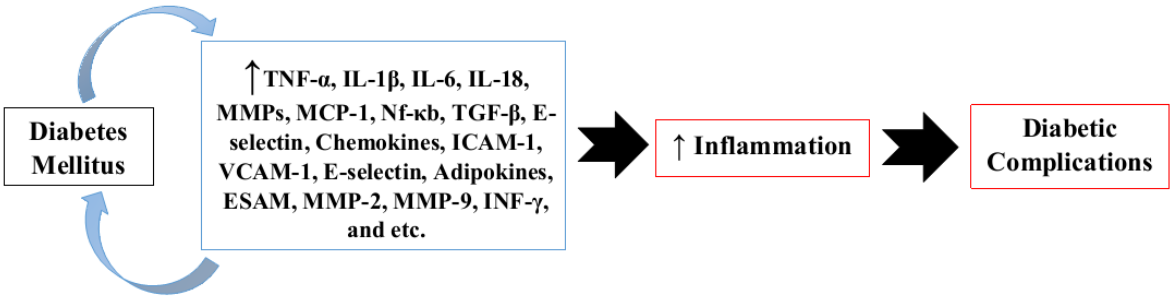

Figure 1; diabetes mellitus has bi-directional interaction with inflammatory mediators both of which intensify each other. This leads to inflammatory responses contributing to a higher risk for diabetic complications (TNF-α =tumor necrosis factor-alpha, IL=interleukin, MMPs=matrix metalloproteinase, MCP-1=monocyte chemoattractant protein-1, nf-κb=nuclear factor kappa b, TGF-β=transforming growth factor-beta, ICAM-1=intercellular adhesion molecule 1, VCAM-1=vascular cell adhesion protein-1, ESAM=endothelial cell-selective adhesion molecule, MMP-2=matrix metalloproteinase-2, INF-γ=interferon gamma)

Various inflammatory mediators such as TNF-α (tumor necrosis factor-alpha), IL (interleukin)-1β, IL-6, IL-18, MMPs (matrix metalloproteinase), MCP-1 (monocyte chemoattractant protein-1), nf-κb (nuclear factor kappa b), TGF-β (transforming growth factor-beta), E-selectin, chemokines, different adhesion molecules as ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion protein-1), TLRs (toll-like receptors), E-selectin, different adiponectin, endothelial cell-selective adhesion molecule (ESAM), MMP-2 (matrix metalloproteinase-2), MMP-9, and INF-γ (interferon-gamma) are involved in various forms of diabetic complications (figure 1) (32-34). These mediators are highly expressed and secreted in diabetic milieu resulting in the development of, an "inflammation hypothesis" which emphasizes the crucial role of inflammatory responses in the pathophysiology of diabetic complications (29, 35).

Anti-inflammatory effects of GLP-1RA and DPP-4i

These agents can exert anti-inflammatory effects via several molecular mechanisms and signaling pathways (36, 37). In the following paragraphs, we review the potential mechanisms by which GLP-1RA and DPP-4i exert these anti-inflammatory effects (table 2).

1. Glucotoxicity

GLP-1RA and DPP-4i are commonly used in the management of type 2 diabetes and have potent hypoglycemic effects and thereby attenuate glucotoxicity which is typically observed in a diabetic milieu (38, 39). GLP-1 has multiple physiologic effects that enable it to optimize glucose metabolism and reverse glucotoxicity (40-42). Glucotoxicity is associated with a higher incidence of inflammatory responses (43). Glucose-induced inflammation is well recognized in the hyperglycemic milieu and is reported in several studies (44-46). Therefore, one can speculate that by lowering the glucotoxicity via improvement of glucose homeostasis can be potentially translated into lower inflammatory responses (47).

Retnakaran and coworkers in 2014 reported that liraglutide (GLP-1RA) preserves beta-cell function by eliminating the glucotoxicity in patients with early T2DM (48). Also, Kong et al in 2014 reported that GLP-1 attenuated glucotoxicity by a mechanism dependent on RhoA-ROCK (Rho-associated kinase) signaling pathway in beta cells (40). Moreover, Tremblay et al in 2014 provided direct evidence in a clinical study demonstrating that sitagliptin markedly decreases inflammatory markers such as CRP (C-reactive protein), IL-6, IL-18 and E-selecting in plasma of patients with T2DM (47). They demonstrated that the anti-inflammatory potential of sitagliptin is related to the improvement in glucose homeostasis (47). Although there is not enough direct evidence, intuitively, it is intuitive that eliminating the glucotoxicity via improvement in glucose homeostasis is one of the potential molecular mechanisms by which GLP-1RA and DPP-4i exert their anti-inflammatory effects.

2. Recruitment of immune cells

Recruitment of different types of immune cells such as T lymphocytes, NK (natural killer) cells, B-lymphocytes, leucocytes and dendritic cells into the inflamed tissues is a well-known event during inflammatory responses (49-51). Therefore, suppressing these phenomena and lowering the infiltration by immune cells is one of the main mechanisms for attenuating the inflammatory responses in various tissues (50, 52). There is some evidence implying that GLP-1RA and DPP-4i can suppress or reduce the recruitment of immune cells (36, 37). Kodera and coworkers in 2011 found that exendin-4 ameliorates the inflammatory responses by preventing macrophage infiltration into the inflamed kidneys in diabetic rats (36). Also, Lee and colleagues in 2012 reported that GLP-1 reduced macrophage infiltration in adipocytes of obese mice (53). Moreover, Higashijima et al in 2015 demonstrated that DPP-4i (alogliptin) prevents the infiltration of CD68-macrophages into the kidneys in a non-diabetic milieu via GLP-1 specific signaling pathways (37). Wang et al in 2014 provided further evidence implying that exendin-4 reduced inflammatory responses by suppressing macrophage infiltration in inflamed liver tissues (54). It has suggested that GLP-1 exerts these anti-inflammatory effects via reducing the chemoattractant factors such as IFN-γ-induced STAT1 (signal transducer and activator of transcription-1) which is essential for T-cell recruitment (55, 18). Therefore, suppressing the leukocyte infiltration towards the inflamed tissue is another possible pathway by which GLP-1RA and DPP-4i inhibit inflammatory responses.

3. Nf-κb signaling pathway and cytokines' expression

Nf-κb is a nuclear factor that is primarily recognized as a regulator of DNA expression but also plays essential roles in other cellular processes such as cell survival, response to external stimuli, synaptic plasticity and memory (56). It is a complex protein that regulates the transcription of various genes as well as inflammatory mediators and thereby, is responsible for immune responses and cytokine production in almost all types of human cells (57). Modulation of the nf-κb signaling pathway has been tried in different studies (58, 57).

Emerging data demonstrate that GLP-1 can modulate nf-κb activities (36, 59-62). GLP-1RA and DPP-4i can potentially reduce the nf-κb activity in inflamed tissues that in turn down-regulates the expression of pro-cytokines (59-62).

Lee and coworkers in 2012 found that GLP-1 reduced the nf-κb activation leading to lower cytokine production in the adipocytes of obese mice (53). Also, Kaidashev et al recently provided clinical evidence demonstrating that six weeks of liraglutide (GLP-1RA) therapy had an anti-inflammatory effect and reduced the expression of TNF-α, IkB, TLR2, and TLR4 via nf-κb inhibition in patients with T2DM (62). Furthermore, Nader and coworkers in 2018 revealed that sitagliptin markedly reduces the nf-κb function in non-diabetic mice (61). El-Sahar and coworkers in 2015 have shown that sitagliptin exerts its anti-inflammatory effects at least partly via nf-κb inhibition (60). This evidence strongly suggest that inhibition of nf-κb signaling pathways is another potential mechanism by which GLP-1 and DPP-4i provide anti-inflammatory potentials in both diabetic and non-diabetic milieu.

However, these anti-diabetic medications can also suppress the expression of cytokines via nf-κb independent pathways (63). Velmurugan and coworkers in 2012 reported that exendin-4 prevent cytokines' expression by a CREB (cAMP response element-binding protein) dependent mechanism in the pancreatic islets (63). Also, He et al in 2013 found that exendin-4 ameliorated the expression of inflammatory mediators by p38 MAPK (phospho-mitogen activated protein kinase) pathways in CD4+ T cells (64). Moreover, Que and coworkers suggested that liraglutide (GLP-1RA) down-regulated the cytokines through the PKA/CREB pathway in rats (65). This evidence strongly suggests that GLP-1 can prevent the expression of cytokines not only via nf-κb modulation but also through other molecular mechanisms such as CREB and p38 MAPK pathways (63-65).

4. Oxidative stress

Oxidative stress is a common event in the diabetic milieu (66). This deleterious state induces other pathophysiologic pathways such as apoptosis, fibrosis, autophagy and inflammation (67). It has well confirmed that oxidative stress has dual interaction with inflammatory responses which both intensify others (67, 68). Thus, improvement in redox state translated to a lower incidence of inflammation (69, 68). GLP-1RA and DPP-4i can improve oxidative stress via several pathways such as nuclear factor erythroid 2-related factor 2 (nrf2) pathway, potentiation of antioxidant defense system, down-regulation of pro-oxidant enzymes such as NAD(P)H oxidase thereby lowering the free radical generation and improvement in glucose metabolism leading to lesser amount of toxic by-products such as AGEs (advanced glycation end-products) (70-72).

There is strong evidence indicating that GLP-1RA and DPP-4i inhibit inflammatory responses through the re-adjustment of the redox state (73, 64, 60, 70, 74-76, 61). He et al in 2013 found that exendin-4 ameliorates the inflammatory processes by lowering the oxidative stress in patients with diabetes (64). Also, Chen and coworkers in 2017 demonstrated that exendin-4 can reduce inflammation via its antioxidative potentials in diabetic rats (74). Moreover, Chang and colleagues in 2017 reported that exendin-4 attenuates AGEs-induced inflammatory responses by its antioxidative effects in the mesangial cells of diabetic rats (70). Moustafa et al in 2018 provided further evidence indicating that anti-inflammatory potentials of liraglutide are at least partially related to its antioxidative effects (76). This evidence strongly suggests that GLP-1RA and DPP-4i can attenuate the inflammatory events via normalizing the redox state and thereby reducing oxidative stress-induced inflammation (73, 60, 75, 61).

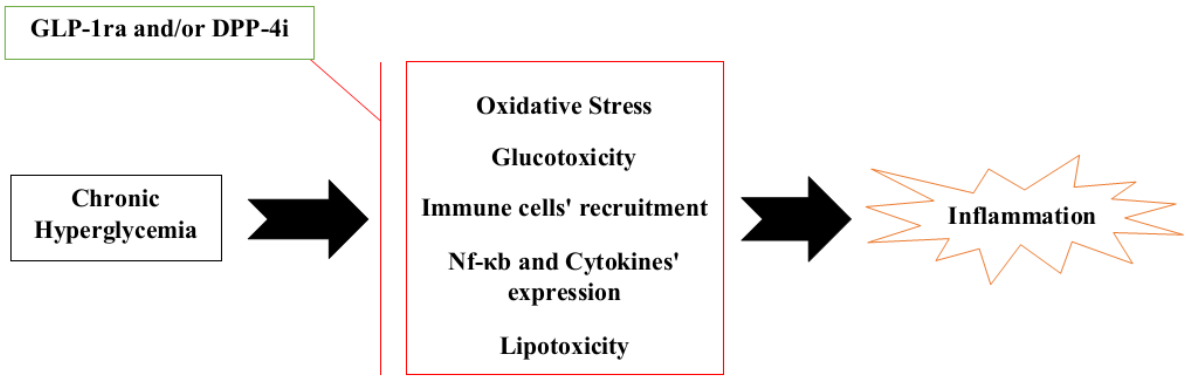

Figure 2; GLP-1RA and DPP-4i suppress molecular pathways involved in diabetes-induced inflammatory responses

5. Lipotoxicity

Lipotoxicity occurs when the excess byproducts of lipid metabolism accumulate in non-adipose tissues which in turn, trigger a cascade of deleterious pathways such as apoptosis and inflammation (77). Some studies emphasized the role of lipotoxicity as a missing link between diabetes and various inflammatory disorders (77, 78). They suggested that lipotoxicity is the main cause of inflammatory processes in a diabetic milieu (79, 78). Thus, improving the lipid metabolism and correcting the plasma lipid profile can prevent or suppress inflammatory responses (80, 79, 81). There is some evidence confirming that GLP-1RA and DPP-4i have this effect (73, 82-84).

Huang et al in 2015 found that intra-islet GLP-1 secretion is a potent intrinsic defense against lipotoxicity (82). They also reported that liraglutide can prevent lipotoxicity and in turn, inhibits the inflammatory response (82). Pastel and coworkers in 2016 illustrated that exendin-4 ameliorates the inflammatory processes via improvement in lipid metabolism in cultured human adipocytes (83). Similarly, Ferreira and coworkers in 2010 found that can reduce inflammatory events through correcting the lipid metabolism in diabetic animals (73). Yin et al in 2016 demonstrated that exendin-4 attenuates lipotoxicity by correcting cholesterol homeostasis in the glomerular cells of diabetic mice (84). They also found that this effect was

accompanied by lowering the inflammatory responses in this tissue (84). More studies have reported the same results implying that GLP-1RA and DPP-4i prevent lipotoxicity in various tissues (85, 86). This evidence suggests that these classes of compounds can suppress inflammatory events through ameliorating lipotoxicity.

Molecular Mechanisms	**Effects of GLP-1ra and/or DPP-4i**	**Ref.**
Glucotoxicity	Eliminate glucotoxicity leading to a lower rate of glucose-induced inflammation	(40, 41, 48, 47, 42-46)
Immune cells' recruitment	Reduce leukocyte immigration toward the inflamed tissue	(36, 37)
Nf-κb and Cytokines' expression	Directly down-regulate different inflammatory cytokines in several ways such as nf-κb inhibition	(59-62) (55, 63, 64, 83, 70, 74, 76, 87-89, 62, 65)
Lipotoxicity	Correct lipid homeostasis leading to a lower rate of lipotoxicity-induced inflammation	(73, 82, 83)
Oxidative stress	Improve redox state toward physiologic state leading to lower oxidative stress-induced inflammation	(73, 64, 60, 70, 74-76, 61)

Table 2; Possible molecular mechanisms by which GLP-1RA and DPP-4i exert their anti-inflammatory effects

Treatment	Population of study	Mechanism of reducing inflammation	Ref.
Exendin-4	Patients with T2DM	Normalize redox state	(64)
Liraglutide	Patients with T2DM	Reduce the glucotoxicity	(48)
Liraglutide	Patients with T2DM	Decline nf-κb dependent cytokines' expression	(62)
Sitagliptin	Patients with T2DM	Reduce the glucotoxicity	(47)
Sitagliptin	Patients with T2DM	Reduce the glucotoxicity, down-regulate inflammatory mediators	(90)
Sitagliptin	Patients with T2DM	Improve glucose homeostasis and thereby reduce glucotoxicity	(47)
Sitagliptin	Patients with T2DM and cardiovascular diseases	Normalize glucose homeostasis and reduce inflammatory cytokines	(91)

Table 3; Clinical studies on anti-inflammatory potentials of GLP-1RA and DPP-4i

Conclusion

GLP-1RA and DPP-4i are novel classes of anti-diabetic medications, in addition to their hypoglycemic effects can provide anti-inflammatory effects on various tissues. They can potentially prevent inflammatory events via at least five molecular mechanisms such as improvement in glucose homeostasis and lowering the glucotoxicity, normalizing the redox state and reducing the oxidative stress-induced inflammation, suppressing the leukocyte recruitment towards the inflamed tissue, reducing the lipotoxicity and down-regulation of various inflammatory mediators. These agents may be considered as potential therapeutic agents against various inflammatory disorders as well as diabetic complications.

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Conflict of Interests

The authors declare that have no conflict of interest in this study.

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