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Incretin-based therapies and renin-angiotensin system: looking for new therapeutic potentials in the diabetic milieu

Running Title: Incretin based therapies and renin-angiotensin system

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Running Title: Anti-diabetic mechanisms of imeglimin

Abstract

Incretin-based therapies include pharmacologic agents such as glucagon like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors which exert potent anti-hyperglycemic effects in the diabetic milieu. They are also shown to have extra-pancreatic effects. Renin-angiotensin system is part of the endocrine system which is widely distributed in the body and is closely involved in water and electrolyte homeostasis as well as renal and cardiovascular functions. Hence the renin-angiotensin system is the main target for treating patients with various renal and cardiovascular disorders. There is growing evidence that incretins have modulatory effects on renin-angiotensin system activity; thereby, can be promising therapeutic agents for the management of renal and cardiovascular disorders. But the exact molecular interactions between incretins and renin-angiotensin system are not clearly understood. In this current study, we have reviewed the possible molecular mechanisms by which incretins modulate renin-angiotensin system activity.

Keywords: incretin, glucagon like peptide-1 receptor agonists, dipeptidyl peptdase-4 inhibitors, renin-angiotensin system, Na + /H + exchanger isotope 3.

Introduction

Renin-angiotensin system (RAS) is a key player in salt and fluid homeostasis in the body and so is closely associated with renal and cardiovascular physiology (Schmieder et al. , 2007). RAS closely regulates hemodynamic states and promptly react to any changes in osmotic pressure and blood volume (Schmieder et al., 2007). RAS is a key component in regulating steady-state of hemodynamic status by modulating water and electrolyte balance (Schmieder et al., 2007). Any defect in RAS will lead to the development of cardiovascular and renal pathologies (Fyhrquist and Saijonmaa, 2008, Schmieder et al., 2007). Hence modulating the activity of RAS is the main target for normalizing renal and cardiovascular functions in various conditions including diabetes (Fyhrquist and Saijonmaa, 2008). Therefore, antidiabetic agents which can modulate RAS activity could provide further therapeutic effects more than reducing hyperglycemia (Kong et al. , 2014).

Incretin-based therapies are commonly used in patients with type 2 diabetes to lower blood and is developed based on the hypoglycemic effects of incretin hormones (Lovshin and Drucker, 2009). Incretins are a group of intestinal peptides which reduces postprandial glucose by several mechanisms (Koliaki and Doupis, 2011, Lovshin and Drucker, 2009). Two main class of antidiabetic drugs are available based on incretin physiology (Lovshin and Drucker, 2009). These agents have potent hypoglycemic effects (Lovshin and Drucker, 2009, Ussher and Drucker, 2014). However, there is growing evidence on the extrapancreatic effects of these drugs including renoprotective effects (Koliaki and Doupis, 2011, Lovshin and Zinman, 2014, Tonneijck et al. , 2014). This could potentially provide further beneficial effects, such as lowering blood pressure and improving renal function (Baretić et al. , 2018). In the current study, we reviewed the potential RAS modulatory effects of incretin-based medications with a focus on promising renoprotective potentials.

Incretin based therapies are used mainly in type 2 diabetes which is the most common type of diabetes and is associated with insulin resistance in the peripheral tissue (Association, 2014). The other main forms of diabetes are type 1 diabetes, gestational diabetes, maturity-onset diabetes of the young, latent autoimmune diabetes of the adults and secondary diabetes due to pancreatitis and medications such as steroids (Association, 2014, de Faria Maraschin, 2013, O'Neal et al. , 2016).

Renin-Angiotensin System; roles in renal disorders

Renin-angiotensin system (RAS) or renin–angiotensin–aldosterone system (RAAS) is a crucial hormonal system responsible for water and electrolytes homeostasis as well as systemic vascular resistance (Boulpaep et al. , 2009). This system is triggered by releasing the renin from the kidneys, mainly in response to hypovolemia or hyponatremia (Boulpaep et al., 2009). Renin is synthesized from its precursor prorenin and stored in the renal juxtaglomerular cells (Fountain and Lappin, 2019). Renin then cleaves angiotensinogen (produced by the liver) into angiotensin I (AngI), which is subsequently converted to angiotensin II (AngII) by the angiotensin-converting enzyme (ACE) predominantly on the surface of vascular endothelial cells of the lungs as well as proximal renal tubules (Fountain and Lappin, 2019). Ang II is a potent vasoconstrictive peptide that increases peripheral vascular resistance and blood pressure (Fountain and Lappin, 2019). This system is highly sensitive to any changes in plasma concentration, blood pressure and blood volume, and reacts to these changes promptly (Khanna et al. , 2017). Ang II primarily acts as a very strong vasoconstrictor (Khanna et al., 2017). This hormone acts by binding with type 1 (AT1) and type 2 (AT2) receptors (Okuyama et al. , 1999). Also, it stimulates the release of aldosterone

from the adrenal gland (zona glomerulosa) which regulates the homeostasis of mainly sodium and potassium in the body (McCormick and Bradshaw, 2006).

RAAS has an important role in renal function by regulating fluid and electrolyte homeostasis (Fountain and Lappin, 2019). Since the kidney has all elements involved in the RAS (or RAAS), it has its specific system known as "intrarenal RAS" (Siragy and Carey, 2010). Intrarenal RAAS not only regulates glomerular hemodynamics and tubular sodium transport but also activates a number of inflammatory, oxidative and fibrotic processes involved in the development of diabetic and non-diabetic nephropathies (Siragy and Carey, 2010). It has been well confirmed that abnormal RAS activity is involved in the development of various renal disorders (Balamuthusamy et al. , 2008, Molitch et al. , 2015, Nangaku and Fujita, 2008). Both Ang II and aldosterone can initiate and worsen various pathophysiologic pathways such as inflammation, oxidative stress, apoptosis and fibrosis (Siragy and Carey, 2010, Urushihara and Kagami, 2017). It has been demonstrated that RAAS inhibitors can reduce albuminuria and improve renal efficiency (Parving et al. , 2012). Activation of intrarenal RAAS is the main feature of diabetic kidney diseases (Thomas, 2017). Also, patients with diabetic renal failure usually have higher activities of mineralocorticoid receptors that are probably driven by increased levels of circulating aldosterone due to higher RAAS activity (Messaoudi et al. , 2012). Therefore, many pharmacological agents targeting this system were developed for improving renal function through modulating RAAS activities (Fountain and Lappin, 2019). Inhibitors of ACE, agents blocking Ang II receptors and direct renin inhibitors are three known classes of medications targeting RAS activities that are widely used in patients with renal and cardiovascular diseases (Fountain and Lappin, 2019).

Incretin-based antidiabetic medications

Incretins are a group of intestinal metabolic hormones such as glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), which decline postprandial glycaemia through

several metabolic pathways such as inhibition of glucagon release, stimulation of insulin secretion, delaying gastric emptying, suppression of appetite, diminishing intestinal absorption of nutrients, improving lipid metabolism and promoting functions of pancreatic β-cells (Baggio and Drucker, 2007, Ding et al. , 2006, Drucker and Nauck, 2006, Meier, 2012, Scott and Moran, 2007). The two main classes of antidiabetic agents developed based on incretin physiology are GLP-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 inhibitors (DPP-4i) (Table 1) (Drucker and Nauck, 2006, Islam, 2016).

GLP-1RA is a group of medications used in the management of type 2 diabetes that provide glucose-lowering effects by stimulation of GLP-1 receptors and thereby mimicking the hypoglycemic effects of incretin hormones (Drucker and Nauck, 2006, Islam, 2016). These medications bind to GLP-1 receptors on the surface of pancreatic β-cells. This GLP-1 receptor is a member of G-protein coupled receptors and its activation followed by generation of cyclic adenosine monophosphate (cAMP) and cellular depolarization leads to insulin secretion (Baggio and Drucker, 2007, Wootten et al. , 2011). GLP-1 is naturally metabolized by a protease known as dipeptidyl peptidase-4 (DPP-4) (Association, 2018). This enzyme is primarily a serine exopeptidase peptide cleaving X-proline or X-alanine dipeptides from the N-terminus of targeted polypeptides including GLP-1 thereby deactivating them (Baetta and Corsini, 2011). Inhibition of DPP-4 activity results in more physiologic effects of its substrates including GLP-1 (Baetta and Corsini, 2011). Therefore, DPP-4 inhibitors (DPP4-i) can reduce blood glucose by increasing the active circulatory levels of GLP-1 (Ahren, 2007, Association, 2018). GLP-1RA and DPP-4i have some differences such as the effect on body weight, degree of improvement in glycemic control and their adverse effect profile (Association, 2018).

	Approved Forms	Mechanisms of Action	Ref.
GLP-1RA	Exenatide (Exendin-4), Albiglutide, Liraglutide, Lixisenatide, Semaglutide, Dulaglutide	Potentiate glucose-lowering effects of incretins	(Drucker and Nauck, 2006, Islam, 2016)
DPP-4i	Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin	Increase the active circulatory levels of incretins	(Ahren, 2007, Association, 2018)

Table 1: incretin-based antidiabetic drugs

Incretin-based therapies and Renin-Angiotensin System

Incretin-based therapies are effective in improving glycemia in patients with type 2 diabetes (Drucker and Nauck, 2006, Islam, 2016). However, they also have some extrapancreatic effects such as RAAS modulation and renoprotective effects (Muskiet et al. , 2014, Pyke et al. , 2014). There is growing evidence that GLP-1 interacts with RAAS activities, decline Na reabsorption in the proximal tubule and can modulate renal hemodynamics (Skov et al. , 2013). These observations suggest that incretins-based therapies and RAS blockades have synergistic effects in combination and so, not recommended to use together (Molitch et al., 2015). In the following sections, we discuss the possible interactions between incretin-based therapies and RAAS, which may provide promising renoprotective effects, especially in the diabetic milieu.

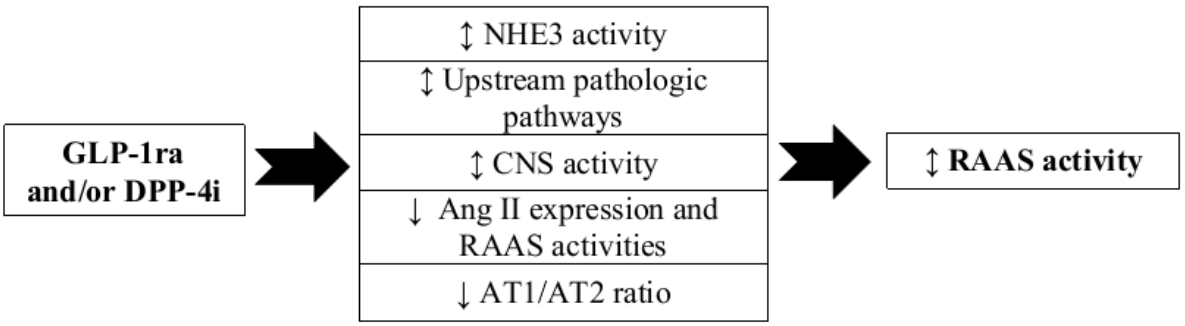

Fig 1; Molecular mechanisms by which incretins modulate RAAS activity (RAAS= renin–angiotensin–aldosterone system, CNS=central nervous system, AT=angiotensin receptor)

1. Direct Ang II inhibition

GLP based therapies can attenuate RAAS activity by decreasing Ang II expression and activity (Baretić et al., 2018, Beraldo et al. , 2019, Kawase et al. , 2016). Beraldo et al. in 2019 found that 8 week treatment with sitagliptin down-regulated Ang II while increased Ang 1-7 in cardiac tissues of nephrectomized rats (Beraldo et al., 2019). Koibuchi et al. in 2014 found that linagliptin (DPP-4i) down-regulated Ang II in cardiac tissues (Koibuchi et al. , 2014). Also, Mima et al. in 2012 provided evidence showing that GLP-1 receptor signaling attenuated Ang II signaling by a PKC dependent mechanism in glomerular endothelial cells of diabetic mice overexpressing PKC (Mima et al. , 2012). Moreover, Baretic et al. in 2018 conducted a clinical study demonstrating GLP-1 infusion suppressed Ang II circulating level in healthy participants (Baretić et al., 2018). The key finding of these studies was that GLP-1 interfere with Ang II secretion. But the exact molecular interactions are not fully understood. Current knowledge suggests that GLP-1 can inhibit Ang II actions via PKA[1] dependent phosphorylation, direct effects of GLP-1 on renal juxtaglomerular cells, damping the tubuloglomerular feedback by inhibition of proximal sodium transport and direct Ang II down-regulation (Baretić et al., 2018, Koibuchi et al., 2014, Mima et al., 2012, Sedman et al. , 2017). However, more studies are still required to confirm these effects.

2. Modulation of Na + /H + exchanger isotope 3 Activity

Na + /H + exchanger isotope 3 (NHE3) is a protein located in the brush border and apical membrane of intestinal cells as well as proximal renal tubules (Tamura et al. , 2018, Yip and Tse, 2014). This protein is mainly responsible for sodium and water balance and acid-base

[1] Protein kinase A

homeostasis via exchanging sodium with hydrogen ions and regulating the osmotic pressure and diuresis (Tamura et al., 2018, Yip and Tse, 2014). Experimental evidence demonstrates that NHE3 activity is involved in the effects of Ang II via AT1 receptor activation (Du Cheyron et al. , 2003, Riquier-Brison et al. , 2010, Tamura et al., 2018). It has been shown that Ang II induces NHE3 activity via promoting its localization on the cellular membrane (Du Cheyron et al., 2003).

There is growing evidence that GLP-1 inhibits NHE3 protein and its activities (Crajoinas et al. , 2016, Du Cheyron et al., 2003, Skov, 2014). They found that GLP-1 receptor induction via either GLP-1RA and DPP-4i inhibits NHE3 trafficking and reduce its downstream effects (Crajoinas et al., 2016, Girardi et al. , 2008). There is also some evidence that GLP-1 could directly downregulate NHE3 protein (Crajoinas et al. , 2011). This suggests the GLP-1 has a role in hypertensive disorders and sodium retention (Crajoinas et al., 2011). While the effects of Ang II is dependent on NHE3 activity, these inhibitory effects of GLP-1 on NHE3 may be the other possible link by which GLP-1 modulates Ang II activities (Carraro-Lacroix et al. , 2009, Crajoinas et al., 2016, Kim et al. , 2013, Skov, 2014, Skov et al., 2013). Therefore, the natriuretic effects of Ang II is under the influence of GLP-1, which can modulate NHE3 activity (Carraro-Lacroix et al., 2009, Girardi et al. , 2004, Kim et al., 2013). However, the exact mechanism by which GLP-1 modulate NHE3 activities is not well understood.

3. Modulation of upstream RAAS-induced pathophysiology

RAAS activity is under the influence of various pathophysiologic pathways such as oxidative stress and inflammation (Husain et al. , 2015, Touyz, 2004, Virdis et al. , 2011). It has been shown that oxidative stress and inflammation promote RAAS activation in several ways and thereby induce its downstream effects (Husain et al., 2015, VAZIRI, 2008). Therefore, one can hypothesize that modulation of these deleterious pathways could modulate RAAS activation indirectly. There is evidence implying that GLP-1 exerts antioxidant and

anti-inflammatory effects (Alam et al. , 2015, Li et al. , 2016, Yaribeygi et al. , 2020). These effects of GLP-1 based therapies could be another link between these agents and RAAS activation (Skov, 2014) which needs further evaluation.

4. Modulation of CNS-Induced RAAS Activation

The central nervous system (CNS) has a regulatory role in RAAS activity (Choi et al. , 2011, Tsuda, 2012, Von Bohlen und Halbach and Albrecht, 2006). It has been well confirmed that the CNS has its own RAS with all its related components and receptors such as AT1 and AT2 (Choi et al., 2011). This system is expressed in most area of CNS and produce bioactive compounds such as Ang 1–7, Ang II, Ang IV and Ang 1-8 (Nakagawa et al. , 2020). CNS dependent RAAS is involved not only in the hemodynamic processes and regulation of BP, but also in many biological and neurobiological activities as processing sensory information, learning, memory, and emotional responses (Nakagawa et al., 2020).

There is some evidence suggesting that incretins have modulatory effects of CNS-dependent RAAS activities, although this complex relationship has not fully understood yet (Zhang et al. , 2019). Beside GLP-1, DPP-4i cleaves several biologic peptides such as substance P, which are released from the ends of primary afferent sensory nerve fibers producing vasodilatory and sympathomimetic effects (Tonneijck et al., 2014, Wilson et al. , 2019). It is also responsible for cleaving neuropeptide Y (NPY) which is a metabolic neurotransmitter in the sympathetic nervous system (Tonneijck et al., 2014). Both of these two peptides (substance P and NPY) have modulatory effects on RAAS activity and when incretins-based therapies are combined with ACE inhibitors, these effects will be exaggerated (Devin et al. , 2014, Molitch et al., 2015, Tonneijck et al., 2014). Therefore, DPP-4i has been suggested as having antihypertensive potential by negatively modulating the RAAS activities (Zhang et al., 2019). Stromal-cell-derived factor-1 (SDF-1) and natriuretic peptide B (BNP) are other main substrates of DPP-4i which have modulatory effects of CNS as well as RAAS (Zhang et

al., 2019). However, some studies revealed that high doses of ACE inhibitors in combination with DPP-4i increases BP (Jackson et al. , 2015, Marney et al. , 2010). Hence, more studies are required to confirm these effects.

5. Modulating the expression of AT1/AT2 receptors

AT1 causes contraction of the smooth muscle resulting in sodium and water retention leading to increased systemic vascular resistance and an increase in blood pressure. However, AT2 stimulation has opposite effects and can act as an antagonist to AT1 (Kawase et al., 2016). Hence the balance of AT1/AT2 expression determines the RAAS activity (Kaschina and Unger, 2003, Kawase et al., 2016). Some recent evidence suggests that incretins alter this relation toward more AT2 expression (Kawase et al., 2016). For example, Zhang et al. in 2015 demonstrated that liraglutide improved cardiac remodeling via altering AT1/AT2 level in cardiomyocytes of hypertensive rats (Zhang et al. , 2015). Also, Bai and colleagues in 2020 demonstrated that liraglutide and linagliptin reduced AT1/AT2 ratio in the glomerular capillaries and proximal tubules of the renal cortex of rats (Bai et al. , 2020). They suggested that incretins prevented the renal fibrosis via lowering the RAAS activity by altering AT1/AT2 ratio (Bai et al., 2020). This suggests that altering the AT1/AT2 ratio could be one of the pathways by which incretins affects the activity of RAAS.

Molecular Pathways	Effects	Ref.
Direct RAAS Inhibition	Directly inhibit RAAS activity via several ways	(Baretić et al., 2018, Beraldo et al., 2019, Mima et al., 2012, Sedman et al., 2017)
Modulation of NHE3 Activity	Inhibits NHE3 activity and thereby reverses RAAS action	(Carraro-La croix et al., 2009, Crajoinas et

		al., 2016, Du Cheyron et al., 2003, Kim et al., 2013, Skov, 2014, Skov et al., 2013)
Modulation of Inflammation & Oxidative stress	Indirectly reduces RAAS activity via damping upstream events as oxidative stress and inflammation	No direct evidence
Modulation of CNS related RAAS activity	Decline RAAS activity via modulating upstream pathways located in CNS such as sympathetic system and NPY	(Tonneijck et al., 2014, Wilson et al., 2019, Zhang et al., 2019)
Modulating AT1/AT2 Level	Reduce AT1/AT2 ratio leading to lower Ang II effects	(Bai et al., 2020, Zhang et al., 2015)

Table 2; Possible molecular mechanisms by which GLP-1RA and/or DPP-4i modulate RAAS activity

Clinical Evidence

Some clinical studies have confirmed the RAAS-modulatory effects of incretins in human (Baretić et al., 2018, Gutzwiller et al. , 2004, Skov et al., 2013). For instance, Baretic et al. in 2018 found that GLP-1 infusion significantly altered RAAS activity and reduced aldosterone release in healthy subjects (Baretić et al., 2018). Also, Skove and coworkers in 2013 conducted a clinical study demonstrating GLP-1 infusion reduced Ang II secretion and related activities in healthy participants (Skov et al., 2013). Other main related clinical studies are presented in table 3.

Trial Number	**Population of the study**	**Drug/dose/duration**	**Effects**	**Ref.**

NCT02130778	14 healthy participants	GLP-1 infusion/1.5 pmol/kg/min/dissolved in 0.9% saline/3h	Decreased aldosterone release	(Baretić et al., 2018)
NCT01333163	12 healthy young men	GLP-1 infusion/1.25 pmol/kg/min/dissolved in 0.9% saline/2h	Declined tubular sodium reabsorption and Ang II secretion	(Skov et al., 2013)
-	15 healthy subjects and 16 obese men	GLP-1 infusion/1.5 pmol/kg/min/dissolved in 0.9% saline/3h	Increased urinary sodium excretion	(Gutzwiller et al., 2004)
-	11 males with T2DM	Liraglutide/1.2 mg/a single dose	Decreased Ang II level	(Skov et al. , 2016)
-	61 patients with T2DM	Sitagliptin/50mg/day/24 weeks	Potentiated BP lowering effects of ACE inhibitors	(Fukui et al. , 2015)
-	34 patients with metabolic syndrome	Sitagliptin/100 mg/day for 5 days	Reversed maximal ACE inhibition-induced hypotension	(Marney et al., 2010)

Table 3; Clinical studies on the RAS modulatory effects of GLP-1RA and DPP-4i

Conclusion

Renin-angiotensin system dysfunction is involved in the pathophysiology of various cardiovascular and renal disorders and thereby, RAS modulatory pharmacologic agents are commonly used to manage patients with these disorders. Incretins based pharmacological agents including GLP-1 receptor agonists and DPP-4 inhibitors, are commonly used in patients with type 2 diabetes but has shown to have some extra-pancreatic effects. In the current study, we conclude that incretins can potentially modulate RAS activity via at least five molecular pathways. This suggests that incretins-based medications are promising agents for managing patients with cardiovascular and renal disorders which need to be confirmed in clinical studies.

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Conflict of Interests

The authors declare that they do not have any conflict of interest in this study.

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