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ABOUT COVER

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The primary aim of World Journal of Diabetes (WJD, World J Diabetes) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WID mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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MINIREVIEWS

AT1 receptor downregulation: A mechanism for improving glucose homeostasis

Diana L Lopez, Oscar E Casillas, Hiram J Jaramillo, Tatiana Romero-Garcia, J. Gustavo Vazquez-Jimenez

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Abstract

There is a pathophysiological correlation between arterial hypertension and diabetes mellitus, established since the pre-diabetic state in the entity known as insulin resistance. It is known that high concentrations of angiotensin-II enable chronic activation of the AT1 receptor, promoting sustained vasoconstriction and the consequent development of high blood pressure. Furthermore, the chronic activation of the AT1 receptor has been associated with the development of insulin resistance. From a molecular outlook, the AT1 receptor signaling pathway can activate the JNK kinase. Once activated, this kinase can block the insulin signaling pathway, favoring the resistance to this hormone. In accordance with the previously mentioned mechanisms, the negative regulation of the AT1 receptor could have beneficial effects in treating metabolic syndrome and type 2 diabetes mellitus. This review explains the clinical correlation of the metabolic response that diabetic patients present when receiving negatively regulatory drugs of the AT1 receptor.

Key Words: Type 2 diabetes mellitus; High blood pressure; Insulin receptor; Insulin signaling pathway; AT1 receptor; Angiotensin II signaling pathway

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Core Tip: Type 2 diabetes mellitus (T2DM) is one of the most prevalent diseases in the world, whose chronic lack of control is associated with the development of several manifestations that can incapacitate the patient. Recently, it has been described that the prescription of antihypertensive drugs in the presence of proteinuria in diabetic patients can prevent kidney failure, and notably, antihypertensive drugs can also be coadjuvant to improve glucose homeostasis. In this review, we disclose the pathophysiological mechanism in which hypertension is related to the development of insulin resistance, contrasting it with the results obtained during clinical practice, giving a new approach to the use of antihypertensive drugs that beyond avoiding kidney damage, are coadjuvant in the treatment of T2DM.

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INTRODUCTION

Diabetes is defined by The American Diabetes Association as a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing diabetes self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications[1]. In 2019, an estimated 442 million adults had been diagnosed with diabetes globally, and this number continues to rise at a rapid rate[2,3].

Notably, in patients with type 2 diabetes mellitus (T2DM), high blood pressure (HBP) prevalence is very high. It has been established that the association between these two diseases occurs from the prediabetic state known as metabolic syndrome, which is characterized by disturbances in lipid metabolism, insulin resistance, and HBP[4,5]. One of the mechanisms involved in the development of insulin resistance and hypertension is the chronic activation of the AT1 receptor (AT1R) by angiotensin-II (ANG-II). AT1R activation results in the c-Jun N-terminal kinase (JNK) activation enabling the insulin signaling pathway blocking[6], thus as a consequence of this mechanism, T2DM patients present higher blood pressure values[7] and in accordance, patients with HBP have carbohydrate metabolism disturbances[5].

This review aims to facilitate the reader's understanding of the mechanism of insulin resistance associated with BPH; therefore, we will describe the physiology of insulin and ANG-II signaling pathways before depicting the pathophysiology of these signaling pathways, emphasizing on the insulin resistance emergence *via* the chronic activation of the AT1R. Furthermore, we will delve into the clinical contrast between the treatment with hypoglycemic agents (metformin) in comparison to the treatment with hypoglycemic agents plus an AT1R downregulation drug.

INSULIN EFFECTS

Insulin is an anabolic hormone that regulates the metabolism of carbohydrates, lipids, and proteins. Apart from promoting glucose uptake, this protein monitors the levels of this monosaccharide and other carbohydrates as well as the levels of fatty acids, thus controlling the distribution, use, and storage of these through the activation of metabolic pathways such as glycogenesis, lipogenesis, and protein synthesis. In addition, insulin promotes cell division and growth[6,8,9].

INSULIN SIGNALING PATHWAY

Insulin exerts its effects by interacting with the insulin receptor (IR), which belongs to the tyrosine kinase receptor family constituted by two extracellular α -subunits and two intracellular β -subunits[10]. Insulin binding in at least one of the four IR insulin-binding sites produces a conformational change that leads to auto-phosphorylation of tyrosine residues inducing the recruitment of ISR-1 and ISR-2, which serve as adapters of the molecular complex[11,12].

ISR 1/2 serves as a scaffold for phosphatidylinositol-3 kinase (PI3K), allowing PI3K catalytic domains to be closer to the cell membrane, where it phosphorylates phosphatidylinositol 4-phosphate (PI4-P) and phosphatidylinositol 4,5-bisphosphate (PI4,5-P2) to transform them into phosphatidylinositol 3,4-bisphosphate (PIP2) and phosphatidylinositol 3,4,5-triphosphate (PIP3)[9,10].

PIP3 molecules serve as docking sites for kinases such as phosphoinositide-dependent protein kinase-1 (PDK1) and also for Akt[13], which can be activated via its phosphorylation by PDK1 and PDK2. In fact, it is through the activation of the Akt kinase that insulin exerts its effects, such as phosphorylation of downstream proteins involved in lipid synthesis, glycogenesis, and glycolysis, as well as being involved in apoptosis disruption and cell differentiation induction[14]. Hence, Akt has an essential effect on glucose uptake through the phosphorylation of AS160, allowing Rab GTPase to be activated, which increases the trafficking of glucose transporter 4 storage vesicles to the cell membrane and thus allows glucose uptake [15,16].

The mitogenic effects of insulin are carried out through the mitogen-activated kinase (MAPK)/Ras pathway, in which these two proteins are activated after insulin binds to the receptor. Then this phosphorylates the protein with the SH domain (Shc), promoting the interaction of protein 2 binding to growth factor receptor (Grb2) and the son of sevenless (SOS) complex with Shc[17]. Afterward, SOS can exchange guanine nucleotides converting guanosine diphosphate (GDP) into guanosine triphosphate (GTP), activating Ras proteins. Activated Ras (GTP-Ras) binds to Raf-1, which phosphorylates and recruits extracellular signal-regulated kinases (ERK) 1/2. Finally, activated ERK1 and ERK2 can translocate to the nucleus to promote the expression of genes involved in cell differentiation, growth, and proliferation [9,10,17]. IR and insulin receptor substrate (IRS) 1/2 proteins, due to their function as coupling proteins, play an essential role in insulin signaling cascade regulation[6].

INSULIN SIGNALING PATHWAY REGULATION

IR is upregulated by phosphorylation on tyrosine residues, so its dephosphorylation diminishes activation of the pathway[11]. In this respect, it has been proven that phosphotyrosine phosphatase 1B (PTP-1B) is the phosphatase with the highest activity, significantly downregulating the activation of the IR[17-19]. However, this is not the only mechanism for negative regulation of the insulin signaling pathway since the phosphorylation of IR and IRS 1/2 on serine and threonine residues has similar effects. This phosphorylation is mainly carried out by protein kinase C (PKC); however, other kinases can phosphorylate serine and threonine residues, such as protein kinase A, JNK, protein p38-kDa MAPK, and ERK1/2[10,12,20]. In addition, another form of negative regulation of this pathway is caused by an impairment in the interaction between IR and IRS 1/2, where the suppressor of cytokine signaling (SOCS) plays a vital role since it promotes IRS 1/2 degradation [17].

Moreover, downstream mechanisms can block the signaling pathway; for example, the phosphatase and tension homologue (PTEN) can dephosphorylate PI3K. Also, PTEN can modulate insulin signaling negatively by dephosphorylating IRS 1/2[17,20]. Another example is the SH-2 domain containing inositol 5-phosphatase-2 (SHIP-2) that dephosphorylates PIP3[21]. Specifically, these mechanisms interfere with properly activating the PI3K/Akt signaling pathway.

ANG-II EFFECTS

ANG-II is produced as a derivative of angiotensinogen, whose primary source is the liver, although angiotensinogen expression has also been reported in other tissues[22,23]. For angiotensinogen to transform into ANGII, a series of proteolytic events are necessary, with renin as the hormone initiating this process. First, renin converts angiotensinogen to ANG-I; subsequently, ANG-I is hydrolyzed by angiotensin-converting enzyme (ACE) to form ANG-II[23,24].

ANG-II effects are mediated by AT1R and depend on the target organ[22,23]. For instance, in blood vessels, ANG-II produces vasoconstriction and increases blood pressure; in the heart enhances contractility; in the kidney promotes sodium reabsorption and inhibits renin production; and in the adrenal cortex stimulates aldosterone production; while at the cellular level, ANG-II has effects on growth, proliferation, and inflammatory responses[24-27].

ANG-II SIGNALING PATHWAY

AT1R is activated by ANG-II and is responsible for translating the effects of this hormone, producing most of the physiological and pathophysiological outcomes. The activation of AT1R allows the transduction of the G protein ($G\alpha q$) signaling pathway^[28]; specifically, the interaction of ANG-II with ATR1 produces a conformational change in Gαq which induces the exchange of a GDP for a GTP, thereby Gaq-GDP can interact with phospholipase C (PLC) to activate it[29].

PLC can cleave PIP2 to form inositol triphosphate (IP3) and diacylglycerol (DAG). Regarding IP3, the interaction with its receptor (IP3 receptor; IP3R) in the sarcoplasmic reticulum induces the release of calcium, promoting muscle contraction (also the contraction of blood vessels), while released calcium and DAG can activate PKC. Although PKC promotes aldosterone production (in the adrenal gland), it



can also function as a regulator of other signaling pathways [30,31]. As well as the activation of AT1R is associated with the activation of proinflammatory responses, this receptor can also trigger the activation of the MAPK pathway and the activation of JNK, whose chronic activation contributes to the development of insulin resistance^[23,32-34].

MOLECULAR MECHANISMS OF INSULIN RESISTANCE

From the clinical outlook, insulin resistance is defined as the decreased ability of tissues to take up glucose as a consequence of reduced insulin sensitivity, while from a molecular perspective, insulin resistance is due to the reduced activation of the PI3K pathway by insulin[35]. Also, another mechanism involved is the sustained activation of phosphatases that negatively regulate the PI3K pathway, such as PTP-1B[36,37].

One of the most studied mechanisms associated with the downregulation of the PI3K signaling pathway is the phosphorylation of RI and IRS 1/2 in serine residues by kinases like PKC, JNK, and MAPK[34,38]. Interestingly, the activation of these kinases is mediated by several physiological processes, with obesity being a pathophysiological entity associated with all of them. Obesity is a state of chronic inflammation where the growth of adipose tissue leads to the release of adipokines (leptin and adiponectin) and proinflammatory cytokines (tumor necrosis factor α and interleukins 6, 8, and 18) and free fatty acids (FFA)[39]. Adipokines and cytokines activate the Toll-like receptors (TLR), particularly TLR2 and TLR4 variants. When TLR4 is activated, an increase in the expression of JNK and MAPK is induced, which can block the insulin signaling pathway. Furthermore, FFA promotes mitochondrial dysfunction through disturbances on β -oxidation, then mitochondrial dysfunction produces reactive oxygen species (ROS), which can also activate kinases such as JNK and PKC[34,40,41].

As shown in Figure 1, there is evidence that chronically elevated ANG-II levels may promote the development of insulin resistance. Indeed, many molecular mechanisms that generate insulin resistance conjugate high concentrations of FFA and elevated levels of ANG-II. For instance, insulin resistance as a consequence of high concentrations of ANG-II develops through the activation of proinflammatory effects, such as increasing ROS production as a result of the activation of NADPH oxidase; thereby, the increase in ROS production triggers JNK activation. On the other hand, activation of AT1R induces the activation of PKC and MAPK[32,42], which means that the chronic activation of AT1R is not only associated with vasoconstriction and increased blood pressure but also with the development of insulin resistance. Therefore, decreasing AT1R activity could be associated with better management of blood glucose levels in T2DM patients.

AT1R INHIBITION IMPROVES GLUCOSE HOMEOSTASIS IN PATIENTS WITH T2DM

There is substantial evidence of the role of ANG-II on insulin resistance emergence^[43,44]; accordingly, inhibiting the activation of the AT1R could improve the efficiency of the T2DM treatment. That premise could be supported by Dominguez et al[45], who reported that patients with T2DM who took ACE inhibitors (drugs that decrease ANG-II levels) had enhanced IR activation compared to those who took a placebo. Furthermore, the DREAM trial investigators carried out a clinical trial including 5269 patients with impaired glucose tolerance; in this double-blind protocol, one treatment group received ACE inhibitors, and the other group received a placebo. After three years of follow-up, T2DM incidence was lower in patients who took ACE inhibitors[46]. Likewise, the NAVIGATOR study group also conducted a randomized clinical trial including 9306 patients with impaired glucose tolerance. In this study, one group of patients received AT1R antagonists (drugs that bind to AT1R acting as antagonists, thus blocking the action of ANG-II), and the other group received a placebo; after an average follow-up of 5 years, it was demonstrated that patients who received AT1R antagonists had a lower risk of developing T2DM[47].

In accordance with these reports, our results in clinical practice are represented in Figures 2 and 3, which show two groups of patients who attended the internal medicine department for consultation to manage their condition: On the one hand patients who only suffer from T2DM and on the other hand patients with HBP and T2DM. As shown in Figure 2, glycemic control in patients with HBP and T2DM is easier than those with just T2DM, as the hemoglobin A1c (HbA1c) levels are close to therapeutic goals [48-51]. This response could be due to the fact that the second group of patients, apart from treatment for T2DM (metformin), received AT1R antagonists (losartan or telmisartan) or ACE inhibitors (captopril or enalapril) as hypertension treatment as either of these drugs decreases the activation of the AT1R[52, 53]. The ability of the AT1R to activate the JNK kinase is evident[31], and as previously mentioned, JNK inhibits the insulin signaling pathway. In fact, it has been shown in a human umbilical cord endothelial cell model that inhibiting JNK activation prevents the state of resistance to insulin[54]. Therefore, prevention of AT1R activation could prevent the blockade of the insulin signaling pathway, so this mechanism could be considered to improve the efficiency of T2DM treatment. Although renal insufficiency was not diagnosed among these patients, previous data, such as that of Brenner et al[55], proved



Lopez DL et al. Chronic AT1 receptor activation induces insulin resistance



Figure 1 Mechanism of insulin resistance induced by chronic activation of the AT1 receptor. The binding of insulin to its receptor induces phosphorylation in tyrosine residues of the receptor; from there insulin can exert its function through two signaling pathways. In the first pathway, tyrosine phosphorylation allows the coupling of the IRS1/2, which serves as a scaffold protein for phosphatidylinositol-3 kinase (PI3K). In this way, PI3K has access to plasmatic membrane lipids and phosphorylates phosphatidylinositol 3,4-bisphosphate (PIP2) and converts them into phosphatidylinositol 3,4,5-triphosphate (PIP3). This serves as a storage site for phosphoinositide-dependent protein kinase 1 (PDK1), which together with PDK2 causes the activation of Akt. When Akt is active, it inhibits AS160, allowing GLUT 4 to be released to the cell membrane. The second pathway is the mitogen-activated kinase (MAPK) kinase. This signaling pathway starts with Shc coupling, which serves as a scaffold protein for Grb and son of sevenless (SOS). Activation of SOS can transform guanosine diphosphate or guanosine triphosphate in small G proteins, inducing the MAPK pathway which results in cellular growth and proliferation. Conversely, insulin signaling is negatively regulated by various proteins phosphatases like PTB1B that acts by inhibiting the receptor, phosphatase and tension homologue and suppressor of cytokine signaling (SOCS), which inhibit IRS 1/2 or SH-2 domain containing inositol 5-phosphatase-2 that dephosphorylates PIP3. Chronic activation of the AT1 receptor by angiotensin Il induces activation of phospholipase C transforming PIP2 into IP3 and diacylglycerol (DAG). IP3 heads to the reticulum and releases calcium, so by itself it is involved in contraction. Together with DAG, IP3 can activate protein kinase C (PKC), which phosphorylates extracellular signal-regulated kinases and activates it; once activated it can phosphorylate c-Jun N-terminal kinase (JNK). When JNK is activated, it can phosphorylate the insulin receptor and IRS on serine residues, reducing IR and IRS function and resulting in insulin resistance development. Indeed, AT1R can induce NADPH oxidase activation, which produces reactive oxygen species that can activate JNK in a PKC-independent pathway. Another mechanism to activate JNK is through free fatty acid (FFA), these lipids can be sensed by TLR 2/4, and the activation of TLR promotes the enhancement of PTB1 and SOCS as well as the production of reactive oxygen species by the inflammatory response, ultimately activating JNK. Also, an increase in FFA in the mitochondria promotes excessive β-oxidation and induces mitochondrial dysfunction, resulting in oxidative stress and JNK activation. FFA: Free fatty acid; ISR 1/2: Insulin receptor substrate; ANG-II: Angiotensin II; GDP: Guanin diphosphate; GTP: Guanin triphosphate; PLC: Phospholipase C; PIP2: Phosphatidylinositol biphosphate; DAG: Diacylglycerol; IP3: Inositol-3-phosphate; PKC: Protein kinase C; ROS: Reactive oxygen species; PI3K: Phosphatidylinositol-3-kinase; PIP3: Phosphatidylinositol triphosphate; PDK1/2: Phosphoinositide-dependent protein kinase-1/2; AS160: Akt substrate of 160b; ERK: Extracellular regulated kinase; Shc: Src homology and collagen; SOCS: Suppressor of cytokine signaling; SOS: Sons of sevenless complex; Grb: Growth factor receptor binding protein; PTP-1B: Phosphotyrosine phosphatase 1-B; JNK: c-Jun amino-terminal kinase; PTEN: Phosphatase and tensin homolog; SHIP-2: The SH-2 domain containing inositol 5-phosphatase-2; MAPK: Mitogen-activated protein kinase. Created with BioRender.com.

that these antihypertensive drugs help improve function and prevent kidney damage, being well tolerated by patients with T2DM.

Furthermore, our data demonstrated that patients with lower HbA1c also presented a higher body mass index (BMI) (Figure 2); this fact was correlated with an upward trend in the serum levels of total cholesterol (Figure 3B), triglycerides (Figure 3C), and HDL cholesterol (Figure 3D). The preceding could be linked to the fact that in a condition with better glucose homeostasis, the activation of the pathways that promote gluconeogenesis decreases, preventing the muscle and adipose tissue lysis, and enabling the patient to gain weight[38]. Taken together, these data allow us to conclude that the decrease in AT1R activation could be an adjuvant for T2DM treatment.



number 0985/2017). *P < 0.05. AHTD: Antihypertensive drugs; BMI: Body mass index; HbA1c: Hemoglobin A1c.





Figure 3 AT1 receptor antagonists promote gluconeogenesis decrease in type 2 diabetes mellitus patients. A-D: Comparison between type 2 diabetes mellitus patients and patients diagnosed with type 2 diabetes mellitus and high blood pressure, whose treatment consisted of metformin or metformin + antihypertensive drugs (AHTD), respectively. The age of the patients was reported (A), and the levels of total cholesterol (B), triglycerides (C), and HDL cholesterol (D) in the blood were determined. Data are expressed as the mean \pm SE using GraphPad 7.0 for Windows. *n* = 18 patients for the metformin group (white bars) and 43 patients for AHTD + metformin group (black bars). Data was collected from the database of patients who came to the internal medicine clinic at Mexicali General Hospital. The protocols carried out in the present study were previously approved by the Hospital General 5 de Diciembre of ISSSTE Mexicali, Mexico, ethics committee (Circular Letter number 0985/2017). AHTD: Antihypertensive drugs.

CONCLUSION

In conclusion, this is a new prospect for the use of antihypertensive drugs in patients with T2DM. The ADA (American Diabetes Association) guideline on the treatment of diabetes mellitus mentions the use of ACE inhibitors or AT1R antagonists in patients with proteinuria and hypertension to reduce the albuminuria progression; still in no-hypertensive patients the evidence is low. However, the Kidney Disease Improving Global Outcomes recommend the administration of these drugs in patients with albuminuria[56-58]. It is important to mention that the use of antihypertensive medications in diabetic patients should not be provided just as a protector of renal function but also as an improver of glucose homeostasis.

FOOTNOTES

Author contributions: Vazquez-Jimenez JG designed the research study; Lopez DL and Jaramillo HJ performed the research; Casillas OE, Romero-Garcia T, and Vazquez-Jimenez JG analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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