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AT1 receptor downregulation: A mechanism for improving glucose homeostasis

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

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Abstract

There is a pathophysiological correlation between arterial hypertension and diabetes mellitus, which is 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 this kinase is activated, it can block the insulin signaling pathway, favoring the resistance to this hormone. In accordance to the previously mentioned mechanisms, the negative regulation of the AT1 receptor could have beneficial effects in the treatment of metabolic syndrome and type 2 diabetes mellitus. This review explains the clinical correlation of the metabolic response that diabetic patients present when receiving negative 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.

INTRODUCTION

Diabetes is defined by The American Diabetes Association's 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 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].

The aim of this review is to facilitate the readers understanding of the mechanism of insulin resistance associated with BPH; therefore, we will describe the physiology of insulin and ANG-II signaling pathways, before depict 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 amid the treatment with hypoglycemic agents (metformin) in comparison the treatment with hypoglycemic agents plus a AT1R downregulator drug.

INSULIN EFFECTS

Insulin is an anabolic hormone that regulates the metabolism of carbohydrates, lipids, and proteins. This protein, apart from promoting glucose uptake, 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 important effect on glucose uptake by means of the phosphorylation of AS160 allowing Rab GTPase to be activated, which increases the trafficking of GLUT 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 and 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]. Afterwards, SOS can exchange guanine nucleotides converting guanosine diphosphate (GDP) in 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]. Both IR and IRS 1/2 protein, due to their function as couplings proteins, bear an important role in the insulin signaling cascade regulation[6].

INSULIN SIGNALING PATHWAY REGULATION

IR is upregulated by phosphorylation on tyrosine residues, so its dephosphorylation diminish 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 on the interaction between IR and IRS 1/2, where the suppressor of cytokine signaling (SOCS) plays an important role, since it promotes IRS 1/2 degradation[17].

Moreover, there are downstream mechanisms that 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-phosphatese-2 (SHIP-2) that dephosphorylate PIP3[21]. Specifically, these mechanisms interfere with the proper activation of the PI3K/Akt signaling pathway.

ANG-II EFFECTS

ANG-II is produced as a derivative of angiotensinogen whose main 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. 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 increases 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 (Gαq) 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 Gαq-GDP can interact with phospholipase C (PLC) to activate it[29].

PIP2 to inositol triphosphate (IP3) and diacylglycerol (DAG). Regarding IP3, the interaction with its receptor (the IP3 receptor; IP3R) in the sarcoplasmic reticulum induces the release of calcium, promoting muscle contraction (also 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 contribute 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, whilst from a molecular outlook, insulin resistance is due to decreased 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 are 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, 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, interleukins 6, 8, and 18) and free

fatty acids (FFA)[39]. Adipokines and cytokines stimulate the activation of the toll-like receptor (TLR), in particular 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 promote mitochondrial dysfunction through disturbances on b-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 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 a better management of blood glucose levels in T2DM patients.

AT1R INHIBITION IMPROVES GLUCOSE HOMEOSTASIS IN PATIENTS WITH T2DM

There is substantial evidence on 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 other group received placebo. After

three years of follow-up, T2DM incidence was lower in the group of 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 shows two groups of patients who attended to 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 decrease the activation of the AT1R[52,53]. The ability of the AT1R to activate the JNK kinase is clear[54], 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[55]. 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*[56] proved 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 (Figures 3B), triglycerides (Figures 3C), and HDL

cholesterol (Figures 3D). The foregoing could be linked to the fact that in a condition with a better glucose homeostasis, the activation of the pathways that promote gluconeogenesis decrease, preventing the muscle and adipose tissues lysis, enabling the patient to gain weight[57]. Taken together, these data allow us to conclude that the decrease on AT1R activation could be an adjuvant for T2DM treatment.

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, but in no-hypertensive patients the evidence is low. However, the Kidney Disease Improving Global Outcomes recommend the administration of this drugs in patients with albuminuria[58-60]. It is important to mention that the use of antihypertensive drugs in diabetic patients should not be provided just as a protector of renal function, but also as an improver of glucose homeostasis.

Figure 1 Mechanism of insulin resistance induced by chronic activation of 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 phosphorylations allow 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 cause 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 guanin diphosphate or guanin triphosphate in small G proteins inducing the MAPK pathway which results in celullar 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-phosphatese-2 that desphophorylates PIP3. Chronic activation of the AT1 receptor by angiotensin II 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 serin residues which reduces IR and IRS function resulting in insulin resistance development. Indeed, AT1R by itself can induce the activation of NADPH oxidase, which produce 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 enhancing of PTB1 and SOCS as well as the production of reactive oxigen species by inflamatory response ultimately activating JNK. Also, in the mitochondria, an increase in FFA promotes excessive b-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-phosphatese-2; MAPK: Mitogen activated protein kinase. Created with BioRender.com.

Figure 2 AT1 receptor antagonists boost glucose homeostasis and body mass index increase in type 2 diabetes mellitus patients. A and B: 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. Glycated hemoglobin A1c was determined for these two groups (A), as well as body mass index (B). Data are expressed as mean ± SE using GraphPad 7.0 for Windows. n = 18 patients for Metformin group (white bars) and 43 patients for AHTD + Metformin group (black bars). Data was collected from the database made up of patients who came to the internal medicine clinic; 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). $^{a}P <$ 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. 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 mean ± SE using GraphPad 7.0 for Windows. n = 18 patients for Metformin group (white bars) and 43 patients for AHTD + Metformin group (black bars). Data was collected from the database made up of patients who came to the internal medicine clinic; Mexicali General Hospital. The protocols carried out in the

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