Role of the ACE2/Ang-(1-7)/Mas axis in glucose metabolism

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The renin-angiotensin system (RAS) helps to regulate cardiovascular function, the maintenance of electrolyte and fluid balance, and blood pressure. The RAS contains two axes; the angiotensin-converting enzyme/angiotensin II/Ang II type 1 receptors (ACE/Ang II/AT$_1$) classic axis, which has a role in regulating blood pressure, vascular oxidative stress, coagulation, and cellular proliferation. The other is the angiotensin-converting enzyme 2/angiotensin-(1-7)/Mas receptors (ACE2/Ang-(1-7)/Mas) axis, which can inhibit the former axis, improve fat metabolism, reduce inflammation and oxidative stress, and enhance glucose tolerance and insulin sensitivity. The ACE2/Ang-(1-7)/Mas axis is found in blood vessels, kidneys, liver, pancreas and the brain. It can protect the body from abnormalities in glucose metabolism. The ACE2/Ang-(1-7)/Mas axis can enhance glucose tolerance and improve insulin sensitivity by protecting pancreatic β cells, increasing insulin secretion, improving glucose metabolism in adipose tissue, enhancing glucose uptake by skeletal muscle, and inhibiting hepatic gluconeogenesis. This article reviews the main characteristics and functions of the ACE2/Ang-(1-7)/Mas axis and its regulation of glucose metabolism in order to demonstrate its potential as a target for the treatment of metabolic diseases such as diabetes.

Keywords

ACE2/Ang-(1-7)/Mas axis; Glucose metabolism; Renin-angiotensin system; Pancreatic β cells; Insulin resistance; Diabetes

1. Introduction

The renin-angiotensin system (RAS) is involved in the regulation of fluids in the human body [1], and is found in the circulatory system, and local tissues in the form of autocrine and paracrine factors [2]. It helps to regulate the circulatory [3–5], renal [6, 7], and digestive systems [8, 9]. The RAS is composed of an enzyme cascade. Angiotensinogen is converted to angiotensin I (Ang I) under the action of renin, and then transformed into angiotensin II (Ang II) due to the effect of the angiotensin-converting enzyme (ACE). Ang II is an important active peptide in the RAS and is one of the most potent vasoconstrictors [10, 11]. It functions through Ang II type 1 receptors (AT$_1$) and Ang II type 2 receptors (AT$_2$) and plays an important role in the cardiovascular system, and in kidney, skeletal muscle, liver, and adipose tissues. Ang II promotes salt and water reabsorption [12], vasoconstriction, inflammation, sympathetic nerve activation, and oxidative

stress by activating AT$_1$ [13, 14]. New members of the RAS are constantly being discovered. Angiotensin-converting enzyme 2 (ACE2) was the first homologous gene cloned from human ACE in 2000 [15, 16]. ACE2 can catalyze the conversion of Ang II into angiotensin (1-7) [Ang-(1-7)], and Ang I into angiotensin (1-9) [Ang-(1-9)], which can be converted to Ang-(1-7) by ACE or neutral endopeptidase (NEP). Ang-(1-7) can also be directly produced by Ang I under the action of NEP, and then acts through Mas receptors (see Fig. 1). The ACE2/Ang-(1-7)/Mas axis can inhibit the effects of ACE/Ang II/AT$_1$ in the myocardium, blood vessesls, kidney, adipose tissue and other organs. Both the ACE/Ang II/AT$_1$ axis and the ACE2/Ang-(1-7)/Mas axis participate in the regulation of glucose metabolism. The ACE2/Ang-(1-7)/Mas axis has been shown to prevent the unfavorable metabolic effects of the ACE/Ang II/AT$_1$ axis [17, 18]. At present, the ACE2/Ang-(1-7)/Mas axis is being extensively studied in metabolic diseases such as diabetes [19, 20]. The ACE2/Ang-(1-7)/Mas axis may become a potential therapeutic target in the treatment of diabetes. Therefore, the role of the ACE2/Ang-(1-7)/Mas axis in glucose metabolism is the subject of this review.

The literature was searched extensively through the PubMed database with the combinations of the key words: ACE2/Ang-(1-7)/Mas axis, angiotensin-converting enzyme 2, angiotensin-(1-7), Mas receptors, glucose metabolism, diabetes (see Fig. 2). The included literatures were published from 1996 to 2021. In order to prevent omissions, relevant articles in the reference list of the primary literatures were included. Inclusion criteria were: (1) diabetes-related animal models or patients; (2) experimental studies related to the ACE2/Ang-(1-7)/Mas axis; (3) researchs related to the glucose metabolism of the RAS. Exclusion criteria were: (1) non-English language; (2) repeated reports; (3) animal models or research unrelated to glucose metabolism in ACE2/Ang-(1-7)/Mas axis study.

2. Composition of ACE2/Ang-(1-7)/Mas axis

2.1 ACE2

ACE2 is the first homologous gene of human ACE, which was cloned from complementary DNA of human lymphoma
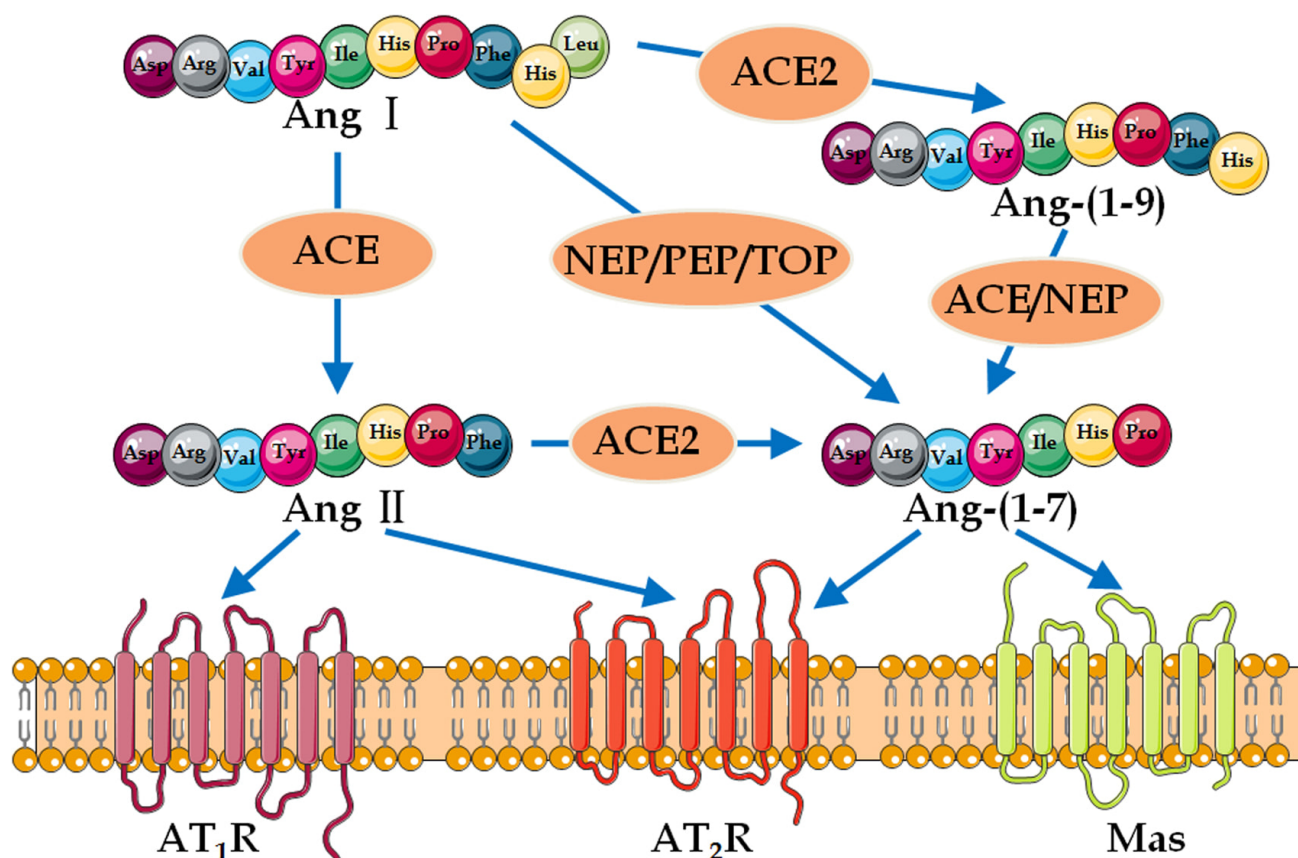
Fig. 1. Simplified view of ACE/Ang II/AT$_1$ axis and ACE2/Ang-(1-7)/Mas axis. Ang I, angiotensin I; Ang II, angiotensin II; Ang-(1-7), angiotensin-(1-7); Ang-(1-9), angiotensin-(1-9); Mas, Mas receptor; AT$_1$R, Ang II type 1 receptor; AT$_2$R, Ang II type 2 receptor; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; NEP, neutral endopeptidase; PEP, prolyl endopeptidase; TOP, thimet oligopeptidase.

and heart failure tissue by Donoghue et al and Tipnis et al in 2000 [15, 16]. Its relative molecular weight is 120 kD, and it is located at the Xp22 site of the X chromosome. ACE2, as a dedicated mono-carboxypeptidase, can only hydrolyze one amino acid residue. ACE2 is expressed on the cell surface, mainly in vascular endothelial cells, and the expression of vascular smooth muscle cells is low. It is expressed to varying degrees in the hypothalamus, heart (endothelial cells of the coronary artery), kidney (epithelial cells of renal vessels and renal tubules), liver, spleen, and gastrointestinal tract [15]. The main biological effect of ACE2 is the degradation of Ang II to produce Ang-(1-7), and it acts on Ang I to generate Ang-(1-9), which is further transformed into Ang-(1-7). The hydrolytic activity of ACE2 on Ang II is 400 times higher than that of Ang I. It plays an important role in myocardial protection [21, 22], fibrinolytic resistance [23] and as an anti-atherosclerosis agent [24, 25]. Overexpression of ACE2 can inhibit oxidative stress, inflammation and monocyte adhesion caused by Ang II [26]. Studies have found that ACE2 overexpression can restore the functional damage of pancreatic β cells mediated by Ang II and improve glucose tolerance [27]. ACE2 deficiency can reduce the number of pancreatic β cells and slow the proliferation of β cells in obese C57BL/6 mice [28]. Following ACE2 gene therapy in diabetic db/db

mice, the function of pancreatic β cells was significantly improved and insulin secretion was increased [29].

2.2 Ang-(1-7)

Ang-(1-7) is an endogenous heptapeptide. The amino acid sequence is NH_2-^{1}Asp-^{2}Arg-^{3}Val-^{4}Tyr-^{5}Ile-^{6}His-^{7}Pro. Ang-(1-7) is predominately obtained by the hydrolysis of Ang II by ACE2 [30]. It can also be obtained from the hydrolysis of Ang I by NEP, prolyl carboxypeptidase, and oligopeptidase. The hydrolysis by ACE2 is the main reaction for the production of Ang-(1-7). Ang-(1-7) activates the prostaglandin-bradykinin-nitric oxide (NO) system through the Ang-(1-7)/Mas pathway, thereby inhibiting Ang II and negatively regulating the RAS. Ang-(1-7) not only results in vasodilation, but also has anti-inflammatory, anti-proliferation, and anti-fibrosis properties which contribute to ventricular remodeling, and improve endothelial function [18, 31]. It also has anti-arrhythmic effects, and inhibits tumor proliferation, improves glucose and lipid metabolism, improves vascular cognitive impairment and inflammation-related memory dysfunction [32–34]. Studies have shown that the ACE2/Ang-(1-7)/Mas axis plays an important role in maintaining normal glucose metabolism [35, 36].
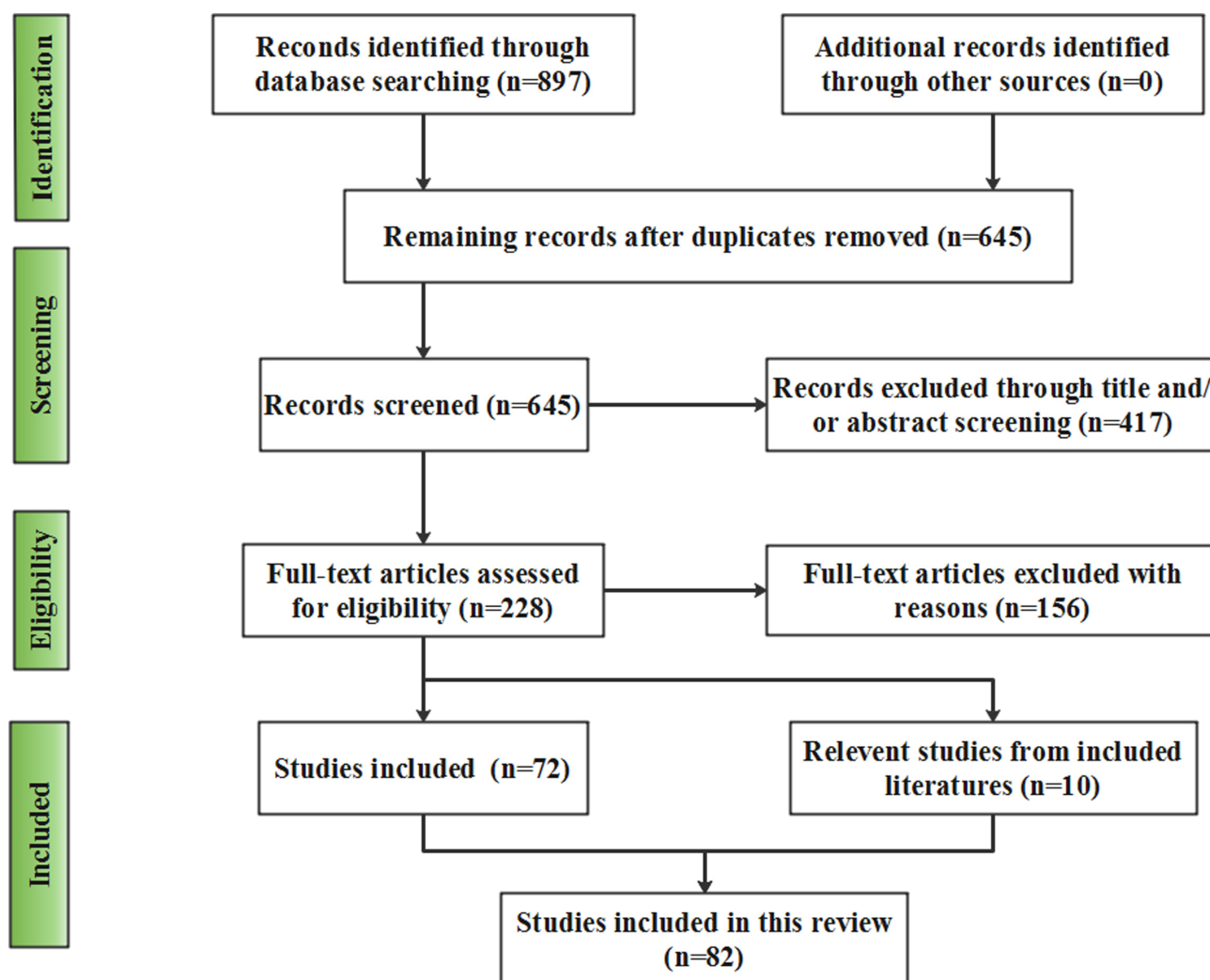
Fig. 2. Flowchart of study selection.

2.3 Mas receptor

The Mas receptor, a G protein-coupled receptor, contains 325 amino acid residues, and its endogenous binding substance is Ang-(1-7) [37, 38]. Ang-(1-7) can inhibit cellular dysfunction by promoting cell proliferation and reduce cell apoptosis by binding to the Mas receptor [39, 40]. Proliferation of NIT-1 cells were significantly increased after pretreatment with Ang-(1-7) in a model of hyperglycemia by inhibiting NIT-1 cells' proliferation, which was reversed after the addition of the Mas receptor specific antagonist A-779. It has been shown that Ang-(1-7) can promote cell proliferation by binding to the Mas receptor [41]. After knocking out the Mas gene, FVB/N mice showed abnormal glucose tolerance [42]. Mas deficiency can lead to increased plasma glucagon levels and affect glucose homeostasis [43]. The Mas receptor itself is not an Ang II receptor, but it can form a constitutive hetero-oligomeric complex with the AT_1 receptor, which interferes with the functional activity of AT_1 and further inhibits the effect of Ang II [44].

3. ACE2/Ang-(1-7)/Mas axis and glucose metabolism

Insulin resistance and defects in pancreatic β-cell function are involved in the pathogenesis of type 2 diabetes. Insulin resistance is characterized by the reduction of glucose uptake by muscle and adipose tissues. The RAS is closely related to the function of pancreatic β cells. Ang II inhibits insulin synthesis and secretion by affecting the insulin signaling pathway. Ang-(1-7) acts through Mas receptors, and inhibits the physiological effects of Ang II on multiple organ systems [45, 46]. The ACE2/Ang-(1-7)/Mas axis also plays a protective role in diabetic nephropathy [47–50]. Studies have shown that nuclear factor erythroid 2-related factor 2 (Nrf2) mediates the expression of RAS gene in the kidney, interferes with the transcription of ACE2 and Mas [51], and induces hypertension and kidney damage in diabetic patients. Ang-(1-7) can counteract the pro-inflammatory effect of Ang II and protect kidney function [52]. Through the Mas/PI3K/Akt signaling pathway, it can also enhance the protection of vascular endothelium of diabetic patients [53].

3.1 ACE2/Ang-(1-7)/Mas axis and pancreatic β cells

The ACE2/Ang-(1-7)/Mas axis can affect the structure and function of adult pancreatic islets, promote the proliferation and differentiation of pancreatic islet stem cells, and the regeneration of β cells [54]. The ACE2/Ang-(1-7)/Mas axis can regulate the production of pancreatic cells during mouse embryonic development. In the mouse model, the endogenous expression levels of Ang-(1-7) and Mas receptors were up-regulated at the late stage of mouse embryonic pancreatic development. In a vitro culture model, Ang-(1-7) treatment increased the ratio of β cells and α cells and the secretion of insulin. It has been shown that the axis can stimulate the development of embryonic pancreatic cells [55]. Increased glucose levels can induce activation of the ACE2/Ang-(1-7)/Mas axis and stimulate pancreatic β cells to produce insulin [56]. Ang-(1-7) regulates insulin secretion *in vivo and in vitro* by increasing intracellular cyclic adenosine monophosphate [57]. The ACE2/Ang-(1-7)/Mas axis can improve islet cell microcirculation and inhibit the production of islet cell nitric oxide synthase (NOS), thereby improving the dedifferentiation of β cells and exerting a protective effect [58, 59]. Xiuping *et al.* [58] found that the ACE2/Ang-(1-7)/Mas axis may be one of the paracrine mechanisms of communication between pancreatic α cells and β cells. Ang-(1-7) resists oxidative damage and protects pancreatic β cells [60]. The ACE2/Ang-(1-7)/Mas axis also has a protective effect on injured pancreatic cells and reduces the production of inflammatory factors by activating the endothelial NOS and NO signaling pathways [61]. The lack of ACE2 can reduce the number and proliferation of pancreatic β cells in obese c57bl16 mice [28].

3.2 ACE2/Ang-(1-7)/Mas axis and skeletal muscle

Skeletal muscle is the main site of insulin resistance in patients with type 2 DM. It processes more than 70% of glucose in the body. Studies have shown that after the addition of Ang II, glucose uptake by skeletal muscle cells was significantly reduced both *in vivo and in vitro*, and the phosphorylation levels of protein kinase B (AKt) and glycogen synthase kinase3β (GSK-3β) were significantly down-regulated. It is hypothesized that Ang II activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, increases reactive oxygen species (ROS) levels and oxidative stress, inhibits the insulin signal transduction pathway and glucose transporter-4 (GLUT4) activity [62]. Ang-(1-7) activates the PI3K/AKt pathway of skeletal muscle endothelial cells, increases insulin-induced glucose uptake, and improves insulin resistance through its anti-oxidative stress effect [63]. The expression of GLUT4 and myocyte enhancer factor (MEF) 2A was significantly reduced in skeletal muscle tissue of ACE2 knockout mice receiving a regular diet. After Ang-(1-7) intervention, the expression of GLUT4 and MEF 2A increased. The expression of GLUT4 and MEF 2A was significantly decreased in wild-type mice treated with the Mas antagonist A779. The mouse C2C12 skeletal muscle cell line was used as a model of muscle cell differentiation *in vitro*. The expression of GLUT4 and MEF 2A was significantly up-regulated

at 6 h after Ang-(1-7) intervention during the process of myoblast differentiation, and insulin-induced glucose supplementation was increased at 24 h [64]. Mujalin Prasannarong *et al.* [65] found that Ang-(1-7) could improve the inhibition of insulin signal transduction and glucose transport activity caused by Ang II through the dependence of the Mas receptor, and improve insulin resistance caused by RAS overactivity by enhancing the phosphorylation of AKt.

3.3 ACE2/Ang-(1-7)/Mas axis and adipose tissue

Adipose tissue participates in glucolipid metabolism by secreting a series of adipocytokines. Adiponectin (APN) produced by white adipose tissue is considered to be a key regulator of insulin sensitivity and tissue inflammation, and its expression is negatively correlated with body fat content [66, 67]. The fat content was decreased, and APN levels were increased in TGR(A1-7)3292 rats, whose level of Ang-(1-7) increased approximately 2-fold compared with control rats. The increase in total AKt and phosphorylated AKt in adipose tissue suggests that the PI3K/AKt pathway can be activated by chronically high levels of Ang-(1-7). *In vitro* experiments showed that APN levels were up-regulated, and the insulin-induced glucose uptake increased 2-fold after adipocytes were pretreated with Ang-(1-7), which was blocked by A779 [36]. In rats given fructose, after continuous infusion of Ang-(1-7), the phosphorylation of AKt and GSK-3β in the liver, skeletal muscle and adipose tissue was increased, and the insulin resistance in the rats was significantly improved. This effect was blocked by A-779, which confirmed that Ang-(1-7) could increase the activity of the PI3K/AKt signal transduction pathway related to insulin metabolism in adipose tissue [68]. The adipose tissue of obese Zucker rats showed increased expression and release of angiotensinogen (AGT) [69], which is considered to be an important feature of preadipocyte differentiation [70]. The expression of AGT was significantly increased in adipose tissue of Mas knock-out rats, suggesting that the ACE2/Ang-(1-7)/Mas axis inhibited the expression of AGT in adipose tissue [71]. Studies showed that Mas-deficient mice had decreased insulin sensitivity, impaired glucose tolerance (increased fasting blood glucose), and increased insulin resistance. In adipose tissue, the expression of fat content was increased, APN and GLUT4 was significantly down-regulated, and glucose uptake in adipose tissue was decreased, which suggested that the ACE2/Ang-(1-7)/Mas pathway plays an important role in insulin sensitivity [72]. Liu *et al.* [45] reported that Ang-(1-7) can inhibit the expression of NAPDH oxidase mRNA in adipose tissue, reduce the production of ROS, and increase insulin-stimulated glucose uptake, thereby improving glucose metabolism. Ang-(1-7) may also decrease obesity by stimulating brown adipose tissue [73].

3.4 ACE2/Ang-(1-7)/Mas axis and hepatic gluconeogenesis

There are few reports on the role of ACE2/Ang-(1-7)/Mas axis in liver glucose metabolism. Bilman *et al.* [74] used SD rats and TGR(A1-7)3292 rat models to observe
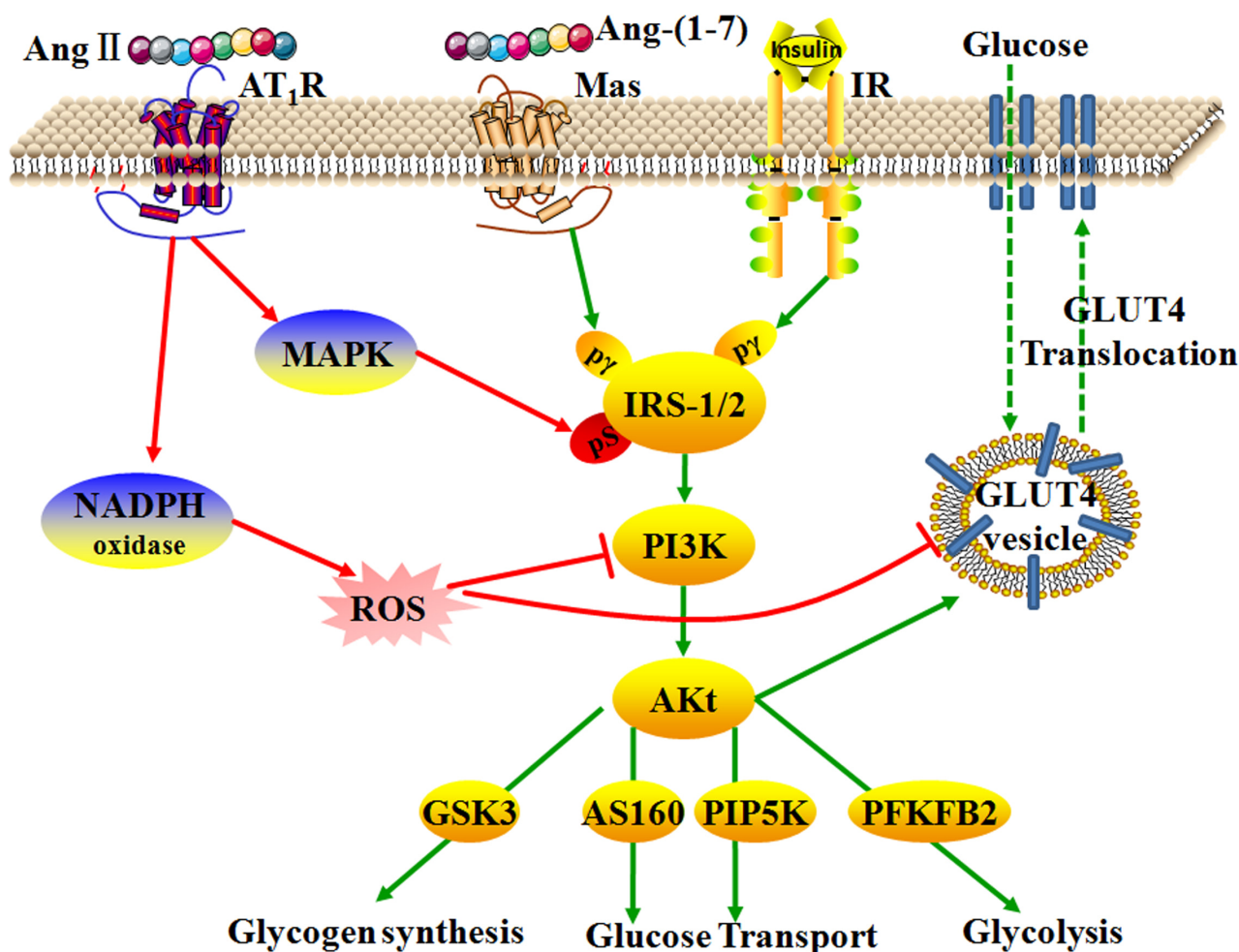
Fig. 3. Potential mechanisms of Ang II and Ang-(1-7) in regulating glucose metabolism. Ang II, angiotensin II; Ang-(1-7), angiotensin-(1-7); AT_1R, Ang II type 1 receptor; Mas, Mas receptor; IR, insulin receptor; NADPH, nicotinamide adenine dinucleotide phosphate; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species; PI3K, phosphatidylinositol 3-kinase; AKt, protein kinase B; GLUT4, glucose transporter-4; GSK3, glycogen synthase kinase-3; AS160, AKt substrate of 160 kDa; PIP5K, phosphatidylinositol 4-phosphate 5-kinase; PFKFB2, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2.

changes in hepatic gluconeogenesis and glycogen synthesis. After fasting overnight, the two groups of rats were treated with pyruvate. Compared with SD rats, TGR (A1-7) 3292 rats had decreased gluconeogenesis and glycogen synthesis. The main underlying mechanism may be as follows: high concentrations of Ang-(1-7) down-regulate the transcription of hepatocyte nuclear factor 4α, which down-regulates the expression of phosphoenolpyruvate carboxykinase, which is the main rate-limiting enzyme of gluconeogenesis [74]. Recent studies have shown that Mas-deficient mice can lead to dysfunction of hepatocyte mitochondria, increase fatty liver degeneration and gluconeogenesis, and ultimately lead to apoptosis. The Ang-(1-7)/Mas axis can improve liver mitochondrial energy utilization and glucolipid metabolism through the IRS-1/Akt/AMPK pathway [75]. In addition, studies have found that the ACE2/Ang-(1-7)/Mas axis is involved in inhibiting the glucose transport mediated by sodium-dependent glucose transporter 1 in the jejunal enterocytes of type 1 diabetic rats, suggesting that the ACE2/Ang-(1-7)/Mas axis may take part in the regulation of postprandial blood sugar [76]. These observations need to be confirmed by further research.

4. The relationship between ACE2/Ang-(1-7)/Mas axis and ACE/Ang II/AT_1 axis

The ACE2/Ang-(1-7)/Mas and ACE/Ang II/AT_1 axes can both act to regulate glucose metabolism, and contribute to the development of the metabolic syndrome and obesity [77, 78]. In the pancreas, Ang II causes islet β cell dysfunction, ACE2/Ang-(1-7) reduces the dedifferentiation of islet β cells in high-fat diet rats [58], and ACE2 promotes the secretion of insulin from islet cells. In the liver, exercise helps the ACE2/Ang-(1-7)/Mas axis to inhibit the effects of the ACE/Ang II/AT_1 axis, reduce metabolic disorders and decrease the incidence of nonalcoholic fatty liver disease [79].

Ang-(1-7) inhibits liver fat synthesis [80], and ACE2/Ang-(1-7)/Mas axis reduces hepatic steatosis [81]. In skeletal muscle, normal doses of Ang II results in skeletal muscle insulin resistance, but high doses of Ang II decreases insulin resistance, which may be related to the increased expression of ACE2 and Mas protein expression [82]. In addition, the ACE2/Ang-(1-7)/Mas axis can reverse the adverse effects of the ACE/Ang II/AT_1 axis on bone metabolism, thereby improving bone metabolism [83]. The ACE/Ang II/AT_1 axis is associated with glucose metabolic disorders in adipose tissue, while the ACE2/Ang-(1-7)/Mas axis can improve glucose metabolism [84].

The activity of ACE2 plays an important role in the balance of the two axes, not only because it increases the level of Ang-(1-7), but more importantly, it reduces the concentration of Ang II. Ang II is an active peptide in RAS, and is one of the most potent vasoconstrictors [85]. Ang II acts through AT_1 and AT_2 receptors [86], and phosphorylates the serine/threonine insulin receptor substrate-1 (IRS-1)/insulin receptor substrate-2 (IRS-2) in the insulin signaling pathway, which affects normal tyrosine phosphorylation. This negatively regulates the signal transduction downstream of IRS-1/IRS-2 and alters glucose metabolism [82, 87]. Ang II can also directly inhibit the phosphorylation of AKt and prevent the transfer of the GLUT4 to the muscle cell membrane, leading to insulin resistance [88, 89]. It also inhibits ligandin between IRS-1 and phosphatidylinositol 3-kinase (PI3K), which reduces the cellular activity of PI3K and affects the activity of Akt [90, 91]. The activity of phosphofructokinase-2 and glycogen synthase kinase is reduced, which ultimately decreases glycolysis and glycogen synthesis, and reduces the use of glucose by peripheral tissues [92, 93]. In addition, Ang II also inhibits the activation of Ras protein, weakens the insulin-mediated Ras/mitogen-activated protein kinase (MAPK) signal pathway, reduces the production of GLUT4 through gene regulation, and reduces the uptake of glucose in peripheral tissues, which increases insulin resistance (see Fig. 3) [94–96]. ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) can also be used to treat diabetes. Studies have shown that the mechanism of ACEi and ARBs involved in regulating glucose metabolism is not only related to its reduction of Ang II levels and inhibition of AT_1R activation, but also the increase of ACE2 expression and Ang-(1-7) levels [97–99].

5. Conclusions

The ACE2/Ang-(1-7)/Mas pathway is involved in promoting the proliferation of pancreatic β-cells and increasing insulin secretion and increases the sensitivity of skeletal muscle and adipose tissue to insulin and reduces liver gluconeogenesis, in order to improve insulin resistance. Further investigations of the effects of Ang-(1-7) on the function of pancreatic islet cells and related mechanisms will provide new therapeutic targets for protecting the function of pancreatic β cells.

Abbreviations

ACE, angiotensin-converting enzyme; ACEi, ACE inhibitors; AGT, angiotensinogen; Ang, angiotensin; AKt, protein kinase B; APN, adiponectin; ARBs, angiotensin receptor blockers; AS160, AKt substrate of 160 kDa; AT_1, Ang II type 1 receptors; AT_2, Ang II type 2 receptors; GLUT4, glucose transporter-4; GSK-3β, glycogen synthase kinase3β; IR, insulin receptor; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; MEF, myocyte enhancer factor; NADPH, nicotinamide adenine dinucleotide phosphate; NEP, neutral endopeptidase; NO, nitric oxide; NOS, nitric oxide synthase; Nrf2, nuclear factor erythroid 2-related factor 2; PFKFB2, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2; PI3K, phosphatidylinositol 3-kinase; PIP5K, phosphatidylinositol 4-phosphate 5-kinase; RAS, rennin-angiotensin system; ROS, reactive oxygen species.

Author contributions

SZ designed the study and wrote the manuscript draft; WS and PJ supervised the project and generated the final version of the paper.

Ethics approval and consent to participate

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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