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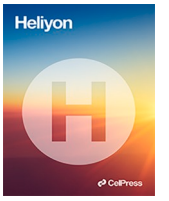

Review article

ACE inhibitors and their interaction with systems and molecules involved in metabolism

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ABSTRACT

The main function of the renin-angiotensin-aldosterone system (RAAS) is the regulation of blood pressure; therefore, researchers have focused on its study to treat cardiovascular and renal diseases. One of the most widely used treatments derived from the study of RAAS, is the use of angiotensin-converting enzyme inhibitors (ACEi). Since it was discovered, the main target of ACEi has been the cardiovascular and renal systems. However, being the RAAS expressed locally in several specialized tissues and cells such as pneumocytes, hepatocytes, spleenocytes, enterocytes, adipocytes, and neurons the effect of inhibitors has expanded, because it is expected that RAAS has a role in the specific function of those cells. Many chronic degenerative diseases compromise the correct function of those organs, and in most of them, the RAAS is overactivated. Therefore, the use of ACEi must exert a benefit on an impaired system. Accordingly, the objective of this review is to present a brief overview of the cardiovascular and renal actions of ACEi and its effects in organs that are not the classic targets of ACEi that carry on glucose and lipid metabolism.

1. Introduction

The renin-angiotensin-aldosterone system (RAAS) is one of the systems involved in the regulation of multiple cellular processes. The wide variety of peptides conforming this system includes molecules exerting vascular, cellular growth, electrolyte and water balance, inflammatory processes as well as signaling activation at different organs at physiological and pathological conditions [1].

The effects of RAAS overactivation can be controlled using angiotensin receptor antagonists (ARA) or angiotensin converting enzyme inhibitors (ACEi). In this work, we will focus on ACEi. They are used to treat diseases such as arterial hypertension, congestive heart failure, left ventricular dysfunction, and myocardial infarction, as well as renal diseases [2]. Interestingly, it has been described that ACEi enhance glucose uptake and can reduce total cholesterol, LDL, and triglyceride levels [3].

This review presents a brief overview of the cardiovascular and renal actions of ACEi and its effects in organs that are not the classic targets of ACEi that carry on glucose and lipid metabolism. Finally, we will discuss studies that have been used to discover new molecules involved in ACE inhibition and that could help in future studies.

2. The renin-angiotensin-aldosterone system (RAAS)

The RAAS begins with the hepatic release of angiotensinogen and the renal enzyme renin, which produces the decapeptide AngI;

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this can then be metabolized by the ACE into AngII, one of the most active vasoconstrictor metabolites known. AngI can also be metabolized by ACE type 2 (ACE2) producing Ang-(1–9). In addition, neprilysin and neutral endopeptidase (NEP) can both act on AngII favoring the formation of the heptapeptide: Ang-(1–7). Furthermore, ACE2 converts AngII to Ang-(1–7), to which a variety of physiological actions opposite to those produced by AngII have been attributed. AngII is also a substrate for other enzymes, such as glutamyl aminopeptidase (aminopeptidase A or APA) and dipeptidyl peptidase 3 (DPP3), which produce AngIII and AngIV, respectively. AngI can also be modified by carboxypeptidase A3 (CPA3) and cathepsin A (CTSA) yielding Ang-(1–9), or by enzymes such as prolyl endopeptidase (PREP), thimet oligopeptidase 1 (THOP1), membrane metallo-endopeptidase (MME), neurolysin (NLN), and prolyl carboxypeptidase (PrCP), producing Ang-(1–7). In turn, the action of mononuclear leukocyte-derived aspartate decarboxylase (MLDAD) on AngI yields angiotensin A (AngA), which, through the action of ACE2, produces alamandine (Fig. 1) [4,5].

All these peptides exert their effects by binding to receptors. AngII binds mainly to AngII type 1 (AT_1) receptors, and this will allow acting on different systems promoting vasoconstriction (Fig. 2). AngII and AngIII can interact with both, AT_1-and AngII type 2 (AT_2)-receptors to promote various cellular responses. On the other hand, the peptide Ang-(1–7) produces its effects upon binding to the Mas receptor (Mas) [4]. New participants in this cascade were described recently, such as alatensins, which are characterized by showing an alanine instead of aspartic acid as the amino-terminal amino acid. The resulting peptide: Ala1-AngII has been reported to interact with AT_1-and AT_2– receptors. The Ala1-Ang-(1–7) compound, known as alamandine, has its receptor, called the Mas-related G-protein-coupled receptor D (MrgD) [6].

2.1. Location and effects of RAAS peptides

Continued research revealed that the RAAS not only exerts systemic effects, but can also act on specific organs; it can be regarded as an endocrine, paracrine, and intracrine system depending on the target tissue and the current metabolic conditions. Thus, the existence of a circulating (systemic) and a local RAAS was proposed. Both systems contribute to the levels of RAAS peptides in blood [7]. The location and effects on different tissues and organs of two major RAAS peptides: AngII and Ang-(1–7) are shown in Fig. 2.

The first evidence of the existence of a local RAAS was reported in 1971 in dog brains [8]. The presence of tissue-specific RAAS has been described in the heart, blood vessels, kidney, adipose tissue, adrenal gland, pancreas, liver, reproductive system, lymphatic tissue, placenta, and eye [9]. As shown in Fig. 2, some RAAS peptides, mainly AngII and Ang-(1–7), are involved in proinflammatory modulation, insulin secretion, and beta-cell apoptosis, as well as in the reduction of gluconeogenesis and hepatic glucose output [10,11].

3. ACE inhibitors on vascular diseases

ACE is a zinc carboxypeptidase enzyme with two catalytic domains, the N-domain and the C-domain, the latter being responsible for hydrolyzing AngI to produce AngII [12]. ACE inhibitor drugs target these domains and are used to treat diseases such as arterial hypertension, congestive heart failure, left ventricular dysfunction, and myocardial infarction, as well as renal diseases [2].

In 1961 Rocha e Silva discovered that the venom of a Brazilian snake: *Bothrops jararaca*, contributed to the formation of a substance with hypotensive and smooth muscle spasmogenic functions, which was called “bradykinin”. Ferreira, a laboratory Colleague, found that some compounds in snake venom inhibited bradykinin degradation, potentiating its actions both *in vitro* and *in vivo* [13]. Shortly

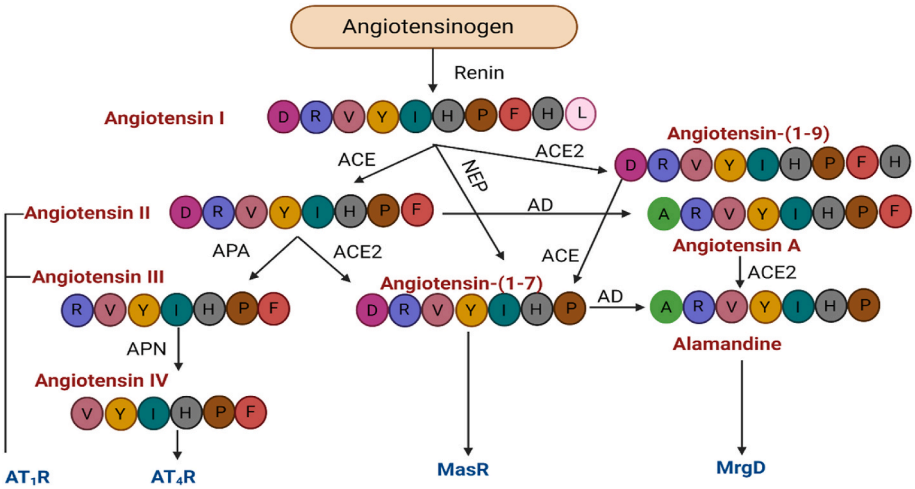

Fig. 1. Representative schematic showing the synthesis of the peptides associated with the renin-angiotensin-aldosterone system (RAAS). ACE: angiotensin-converting enzyme, ACE2: ACE type 2, AT1R: angiotensin II type 1 receptor, AT4R: angiotensin IV receptor, MasR: Mas receptor, MrgD: Mas-related G protein-coupled receptor D, APA: aminopeptidase A, APN: aminopeptidase N, NEP: neutral endopeptidase, AD: aspartate decarboxylase.

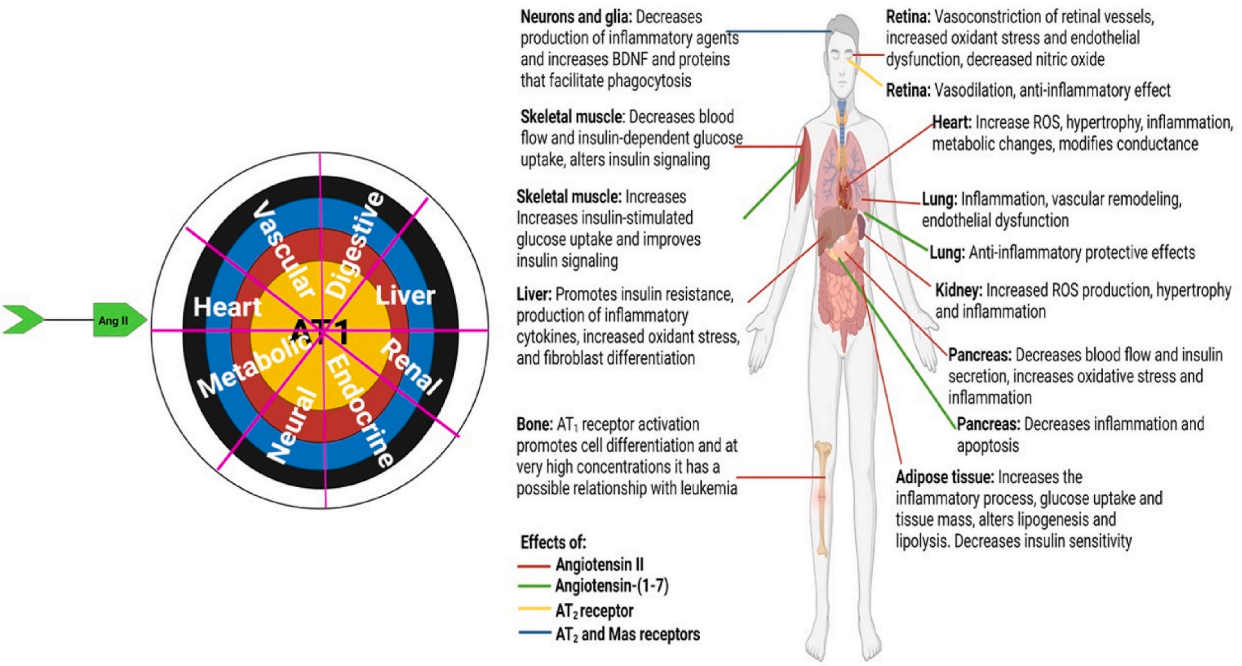

Fig. 2. Effects of the peptides angiotensin II and angiotensin-(1–7) on some organs of the body. BDNF: brain-derived neurotrophic factor, ROS: reactive oxygen species.

thereafter it was found that the enzyme inhibiting the action of bradykinin was a carboxypeptidase very similar to ACE [14,15].

Since bradykinin's effects are opposite to those of AngII, its discovery opened new avenues to develop ACE inhibitors (ACEi). In the 1970s, Cushman, Ondetti, and Colleagues studied the structure-activity relationship of components in *B. jararaca* venom and discovered the first ACEi known as captopril, which was approved by the U.S. Food and Drug Administration (FDA) in 1981 [16,17].

Captopril discovery was followed soon by analogs like enalapril, lisinopril, benazepril, perindopril, quinapril, ramipril, trandolapril, and moexipril [18]. They are used to treat diseases such as hypertension, heart failure, and diabetic nephropathy [19].

Several reports have documented that ACEi promote ACE2 expression [20]. Due to the role of ACE2 mediating the entrance of SARS-CoV-2 into the cells to cause COVID-19, concerns arose regarding the safety of the patients being treated with ACEi. In this regard, arguments in favor of continuing treatment with ACEi showed that AngII is a potent activator of the ADAM17 enzyme, a protease that cleaves ACE2, once it binds to the spike protein of the virus it favors the entry of the virus into the cell, so that inhibition of AngII production would thereby reduce the possibility of infection. Furthermore, in a hypoxic state, AngII is activated to restore ventilatory pressure; however, as AngII levels increase, as well as its side effects, including proinflammatory activity. Given these arguments, adherence to ACEi treatment was recommended in patients with cardiovascular disease infected with SARS-CoV-2 [21,22].

3.1. Arterial hypertension

The first therapeutic use described for ACEi was to treat arterial hypertension. The reduction in AngII production promoted by ACEi improves natriuresis and prevents vascular smooth muscle cells and myocytes remodeling. In addition, ACEi block the degradation of bradykinin, which produces vasodilatory effects. These actions preserve the balance between vasoconstriction and vasodilatation [23].

3.2. Congestive heart failure

ACEi promote 1) decreased afterload, preload, and systolic wall stress, which enhances cardiac output; 2) an increased renal blood flow; 3) a reduced production of aldosterone and antidiuretic hormone; and 4) a reduction in cardiac myocyte hypertrophy [23]; actions that improve the cardiac condition in patients with heart failure (HF). The benefits of their use include a reduction in mortality, primarily in patients with heart failure with reduced ejection fraction (HFrEF) [24,25].

It has been described that captopril (2 g/L water, p.o.) in experimental models alleviates cerebrovascular alterations during exercise in rats with HFrEF [26]. The overexpression of RAAS metabolites may impair cerebral blood flow and vascular conductance in skeletal muscle during HF [27–29]. Therefore, the treatment with drugs modulating RAAS is also effective.

3.3. Stroke

The participation of ACE in the development of stroke has been highlighted in different ethnic groups exhibiting genetic alterations

in the enzyme. Particularly, polymorphisms in intron 16 have been found to contribute to the risk of stroke [30–32]. In this regard, it has been reported that stroke patients who received ACEi reduced the risk of suffering from this disease by 14 % [33].

3.4. Migraine

The effects of RAAS on the cerebrovascular and cardiovascular systems suggest that ACEi could be useful in treating migraine. They have been shown to have fewer side effects and are less expensive than FDA-approved anti-migraine drugs [34].

According to Schrader et al. lisinopril reduced both headache and migraine pain [35], while enalapril reduced the severity and duration of headache [36], and captopril reduced the frequency, duration, and severity of headache episodes [37]. Among other potential mechanisms, ACEi have been proposed to act in migraine through 1) Regulation at the brain level; the intrinsic blood-brain barrier RAAS affects cerebral vascular tone by regulating nitric oxide production and the levels of the calcitonin gene-related peptide (CGRP) [38], increase local bradykinin concentrations, thus enhancing its vasodilatory effects [39], 2) Genetic factors; the ACE-DD polymorphism has been found to occur more frequently in migraine patients with respect to controls [40], 3) ACE plays a role in the production of AngII and AngIII as seen in Fig. 1; therefore ACEi reduce AngIII levels and AngIII-induced activation of NF-κB alleviating migraine [41,42].

3.5. Renal diseases

3.5.1. Chronic kidney disease (CKD)

CKD is associated with diabetes, arterial hypertension, obesity, and cardiovascular disease and it is characterized by changes in the morphology of the glomeruli where the podocyte process is lost, the expression of diaphragm slit proteins is decreased, and there is thickening of the glomerular basement membrane; all of this leads to a significant alteration in kidney function known as albuminuria and later as proteinuria. Structural changes at the level of the renal tubules cause the loss of molecules and electrolytes into the urine, as well as the accumulation in the blood of degradation products such as creatinine. The success of using ACEi as a treatment to prevent the progression to chronic kidney disease has been reported in both clinical studies and experimental models.

3.5.2. Diabetic nephropathy

The components of RAAS are expressed along the nephron; therefore pharmacological inactivation of this system exerts significant effects on renal function. Besides electrolyte homeostasis, blood pressure and volume control, and metabolite filtration, the kidney also regulates glucose levels. However, the kidney may be unable to reabsorb glucose due to excessive plasma concentrations, a condition leading to the irreversible onset of type 2 diabetes mellitus (T2DM) and the onset of diabetic nephropathy. The loss of glomerular and tubular function characterized by the collapse of podocytes, mesangial expansion, thickening of the basement membrane, and dysfunction of tubular epithelial cells has been treated with ACEi [43]. Kojima et al. reported that the combined treatment of ACEi and an inhibitor of SGLT2, in diabetic rats, exerts renoprotective effects [44].

Among the mechanisms proposed to explain nephroprotection by ACEi in diabetic nephropathy are.

a. Improvement of muscular blood flow
b. Decrease in sympathetic activity
c. Adequate exchange of ions, mainly potassium and magnesium
d. Increased insulin signaling
e. Effects on adipose tissue

3.5.3. Scleroderma renal crisis

Pathological features of scleroderma renal crisis (SRC) include malignant arterial hypertension (secondary to overactivation of RAAS), oligoanuric acute renal failure, hypertensive encephalopathy, congestive heart failure, and/or microangiopathic hemolytic anemia [45,46]. Being the role of RAAS that important, it is expected that treatment with ACEi would be effective. Woodworth et al. reported a reduced incidence of SRC from 5-15 %–2.4 % in patients treated with ACEi [47]. Additionally, captopril has shown beneficial effects in patients with SRC [48]. Observational and clinical studies have reported that ACEi like captopril or enalapril could reduce renal crises and help to decrease short-term mortality [49,50].

4. ACEi on metabolism of glucose and lipids

Glucose oxidation is the primary source of energy in the human body. The liver is one of the main organs involved in glucose metabolism, and about 90 % of endogenous glucose is produced there [51]. Glucose enters hepatocytes via glucose transporters (GLUT), mainly GLUT2, and can be released into the blood during fasting [52]. The liver, which receives dietary carbohydrates via the portal vein, participates in the processes of glycogenesis, glycogenolysis, glycolysis, and gluconeogenesis [53].

Glucose metabolism contributes to the energy supply required for blood and oxygen delivery from the heart to other organs. Glucose uptake in cardiomyocytes is regulated by GLUTs, mainly GLUT1 and GLUT4 isoforms, which predominate in the fetal and adult heart, respectively [54–59]. In cardiomyocytes, glucose can activate different metabolic pathways: 1) polyol, 2) glycolysis, 3) pentose phosphate, and 4) hexosamine biosynthetic pathway [60].

4.1. Diabetes

Under physiological conditions, glucose levels in the liver and heart are regulated by the action of enzymes and hormones such as insulin. However, alterations in the homeostasis of these processes lead to the onset of pathologies for which pharmacological treatment is being actively sought and ACEi have shown encouraging results. In this regard, studies in the 1990s demonstrated a hypoglycemic effect of ACEi in adult diabetic patients [61,62].

In 2004, Pepine and Cooper-Dehoff reported that non-diabetic patients who received ACEi treatment showed a lower risk of developing diabetes with respect to patients receiving beta-blockers or diuretics [63]. In addition, the evidence showed that in patients with a high risk of cardiovascular events, ramipril reduced the incidence of diabetes (34 % reduction) [64]. In the Captopril Prevention Project randomized trial, there was a 14 % reduction in the risk of developing diabetes mellitus [65]. Contrary to this, it has been reported that captopril may have an inverse relationship between reducing blood pressure and regulating glucose levels [66]. Similarly, the effects of ACEi on glucose metabolism have been reported in experimental models. For example, in a model of T2DM in male KK-Ay/Ta mice, administration of temocapril (1 mg/kg/day) for 14 days significantly decreased glucose and insulin concentrations in plasma with respect to the control group [67]. In a murine model of obesity induced by consumption of a 60 %-fat diet for eleven weeks, treatment with captopril (50 mg/L) in drinking water for the last three weeks of the obesogenic diet improved insulin sensitivity [68]. On the other hand, oral administration of ramipril (10 mg/kg) for five weeks decreased blood glucose levels in male Wistar rats [69]. However, one report noted that the use of ACEi could lead to a serious risk of hypoglycemia [70].

The role of ACEi as a treatment against the coexistence of arterial hypertension and hyperglycemia in patients with cardiovascular disease and diabetes has been widely documented [71,72], highlighting that patients treated with ACEi have better insulin sensitivity, therefore, better regulation of plasma glucose, thus reducing the incidence of diabetes in patients with cardiovascular dysfunction [66,73]. ACEi also promote insulin-dependent transport of glucose through increasing GLUT4 expression in obese rats. Therefore, glucose utilization becomes more efficient in the muscle [67–74].

4.2. Pancreatitis

Various organs express RAAS components, suggesting that changes in the expression and activity of this system are related to the pathophysiology of the organs or tissues where it is expressed, so the inhibition of RAAS components could have a therapeutic effect on disorders that are not specifically cardiovascular [75]. The finding of an active RAAS in the pancreas [75,76] confirms that the benefits obtained with the treatment of ACEi in diabetic patients with cardiovascular disease are not only obtained through the decrease in vasoconstriction and proinflammatory and proapoptotic signaling; also, by promoting insulin release and improving dilation of the pancreatic ducts to facilitate insulin transport (Fig. 3) [75].

The pancreas is an exocrine and endocrine organ. The exocrine function is carried out by the pancreatic acini, which are responsible for the release of hormones to carry out digestion. While the endocrine function, which is carried out in the islets of Langerhans, refers to the secretion of factors such as insulin – by beta cells- and glucagon –by alpha cells-. The release of hormones depends on several factors and one of them is the activation of the endogenous RAAS. Regarding the system expressed in the islets, it was found that stimulation by exogenous AngII is capable of inhibiting glucose-dependent insulin release [77]. The morphology of the islets is

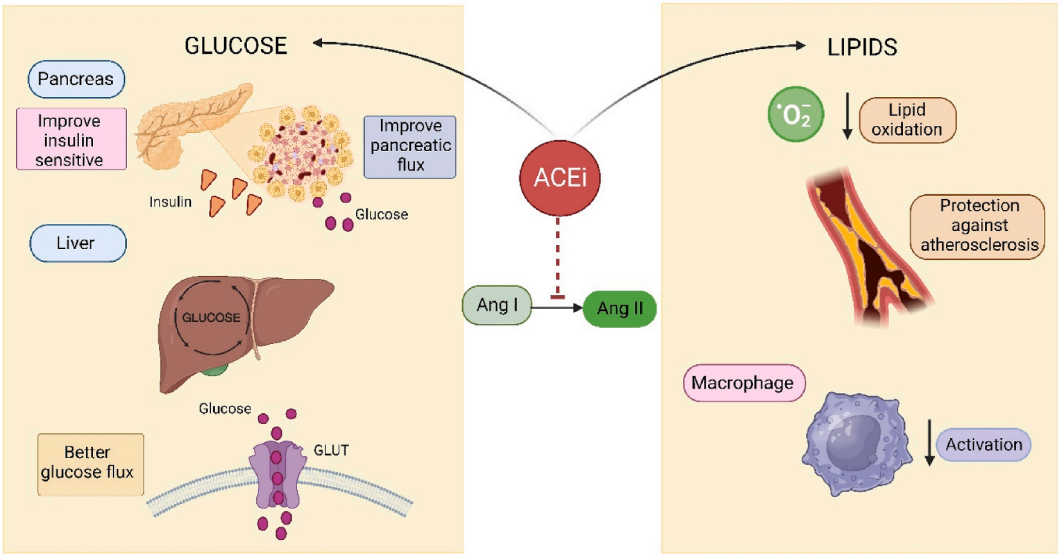

Fig. 3. Effects of ACEi on glucose and lipid in some organs. ACEi can promote insulin release and improve vasodilatation of the pancreatic ducts to facilitate insulin and glucose transport. In the liver, ACEi can contribute to glucose production processes and increase GLUT expression, which improves glucose transport. In addition, ACEi can reduce lipid oxidation and protect against diseases such as atherosclerosis.

important to maintain their function. In diabetic rats, it was observed that treatment with perindopril maintained the structure of the islets, preventing the loss of beta cells and reducing fibrosis, these findings being independent of glycemic control [78].

In contrast, there are case reports where the use of lisinopril promotes pancreatitis [79], but not the treatment with captopril or enalapril. In a model of acute pancreatitis, the use of ramipril increased pancreatic damage, observed as edema, increased secretion of alpha-amylase, and increased lipase activity [80].

The exact mechanism by which ACEi can regulate glucose metabolism is not clear, but the effects described above could be due to: 1) an increase in insulin sensitivity which may occur because ACEi interfere with the generation of AngII and consequently glucose metabolism is improved [68], 2) enhanced insulin receptor substrate (IRS-1) tyrosine phosphorylation and phosphatidylinositol-3-kinase activity; it has been reported that AngII can use the IRS-1 to activate signaling, therefore ACEi promote insulin activation [81], 3) increases GLUT4; due to an improvement in the insulin signaling pathway [3], and 4) improved ionic balance (K^+), it has been described that hypokalemia can affect the secretion of insulin and glucose, an effect that can be reversed by the action of ACEi [82].

4.3. ACEi on lipid-related metabolic diseases

Along with carbohydrates, proteins, and nucleic acids, lipids are essential biological molecules for humans. Among the functions of lipids are energy storage, chemical messengers, the formation of cell membranes, and the transport of liposoluble vitamins [83].

Lipids can either be obtained from the diet or synthesized in the liver; therefore, two pathways should be considered in lipid metabolism, exogenous and endogenous [83]. Lipids from the exogenous pathway are absorbed by the small intestine [84]. Most works on lipid metabolism focus on the liver or adipose tissue, with relatively few studies addressing the involvement of the heart in lipid metabolism [85].

There is evidence of the effect of ACEi on lipid metabolism [86]. In hypercholesterolemic rabbits that were administered with captopril (25–50 mg/kg), cholesterol levels and atherosclerosis were reduced [87]. Furthermore, in patients with T2DM, administration of benazepril (10 mg/day) in combination with a calcium-channel blocker (amlodipine, 5 mg/day) was reported to significantly decrease the percentage expression of lipid subfractions HDL2 and HDL3 [88].

Recent studies have reported that treatment with captopril (50 mg/kg/day, i.p.) for six weeks in male Wistar rats with hypercholesterolemia, induced by a cholesterol-rich diet for eight weeks, significantly decreased the levels of total cholesterol, triglycerides, and LDL [89]. Supporting these results, a decrease in triglyceride levels and in the expression of lipogenesis-related markers, particularly the marker for fatty acid synthesis, acetyl coenzyme-A carboxylase, and the peroxisome proliferator-activated receptor isoform gamma (PPARγ) was reported in male Swiss mice receiving enalapril (10 mg/kg/day) plus resveratrol (30 mg/kg/day) orally for 60 days. Those authors attributed such effects to an inhibition of adipocyte differentiation and proliferation, and a prevention of fatty acid release from adipocytes [90]. In contrast to these reports, in a study made with adolescents with type 1 diabetes mellitus (T1DM), treatment with an ACEi showed no significant effects on lipid or HDL levels [91].

Among the potential mechanisms by which ACE inhibitors act on lipid metabolism, the following have been proposed: 1) Blocking the synthesis of AngII; the expression of this peptide is directly related to cholesterol levels [92,93]. 2) AngII has been identified as a participant in diseases such as atherosclerosis, due to its involvement in the processes of inflammation, fibrosis, increased vasoconstriction, and fluid retention (Fig. 3) [94,95]. 3) Inhibition of LDL oxidation [96], the oxidized form of LDL increases the expression of AT_1 receptor mRNA through the NADPH oxidase and MAPK pathways [97]. 4) Prevention of endothelial dysfunction [98].

5. Novel molecules that may inhibit ACE

As described in section 2, ACE inhibitors like captopril and enalapril are widely used in the clinic. However, adverse effects such as cough [99] eczematous reactions [100], arterial hypotension, hyperkalemia, and small bowel angioedema [101] make it mandatory to study more selective molecules with fewer adverse effects. Two techniques have been reported for the discovery of new drugs: 1) structure-based virtual screening (SBVS), which relies on the 3D structure of a molecule to determine its binding affinity to the receptor, and 2) ligand-based virtual screening (LBVS), which is used to identify the half-maximal inhibitory concentration of a ligand using structure-activity relationship (QSAR) models [102].

According to the QSAR model, an ACEi must meet the following criteria: 1) have a carboxyl group; 2) have a hydrogen bond acceptor; 3) have a functional group capable of interacting with the Zn^{2+} ion; and 4) have a hydrophobic character [103–105].

It was recently reported that the combination of an ACEi with a neutral endopeptidase inhibitor is effective in treating arterial hypertension in mice, without side effects such as alterations in vascular permeability and endothelial injury. These effects are due to the selectivity of current drugs for the C-terminal domain of ACE; therefore further study of the domains of this enzyme is necessary to design novel drugs [12].

Interestingly, it has been reported that circulating ACE can be inhibited by endogenous factors; for example, albumin contains amino acids that help inhibit active sites in circulating ACE [106,107].

On the other hand, in diseases such as HFrEF, it has been described that treatment with ACEi does not completely control the consequences of this pathology and interestingly it has been reported that the combined therapy of sacubitril, a neprilysin inhibitor, with valsartan, an ARA, could represent greater benefit; however, there is still a lot to study about these drugs [108–111].

6. Conclusions

The wide array of pathological situations where ACEi may exert a therapeutic effect highlight the relevance of local functions of ACE and AngII. The study of molecular/therapeutic targets of ACEi represents an area of opportunity to improve treatments and provide us with a deeper understanding of their use in metabolic diseases besides cardio-renal pathologies. It is crucial to continue investigating the effects on local tissues expressing ACE to understand the actions of ACEi and their therapeutic targets, which will allow us to design better treatments.

7. Future directions

To classify those ACEi that exert metabolic effects from the ones that do not, it is necessary to study them on a suitable experimental model. Due to the vasodilator effect promoted by ACEi, it would be interesting to determine to which extent this effect favors the hypoglycemic effect. The presence of comorbidities could modify ACEi pharmacological effects on metabolic pathways.

Although the use of ACE inhibitors was proposed as a therapy for already established cardiovascular pathologies, it has also been observed that their use has a protective effect that preserves the structure and function of the heart, brain, vascular endothelium, and kidney. Therefore, the use of ACEi can also protect the morphology and physiology of other organs where AngII production is not completely related to vasoconstriction, but rather to signaling that promotes and perpetuates some pathology. In this sense, the study of ACEi as a possible treatment in metabolic diseases would be interesting and would provide new therapeutic targets.

8. Search strategy

A literature search was carried out using Google Scholar and Pubmed, the search was limited to studies published in English. This systematic review followed PRISMA guidelines [112]. A total of 600 papers were analyzed and in the end, 112 papers were used for this review. Studies had to include ACE inhibitors and their effects on metabolism. The keywords for the article search were ACE inhibitors AND glucose, ACE inhibitors AND diabetes, ACE inhibitors AND pancreas, and ACE inhibitors AND metabolism glucose/lipids.

This review was carried out at the beginning of 2023 and includes articles considered pioneers on the topic up to the most recent advances. Articles describing effects induced by ARA, SGLT2 inhibitors, combination therapies, renal and cardiac studies, and studies whose abstract did not mention the use of ACEi were excluded. The authors reviewed all abstracts for inclusion.

Data availability statement

The information presented in the current paper was derived from a literature search using specific keywords detailed in the “Search strategy” section. No datasets were generated during the current study.

CRediT authorship contribution statement

Diana L. Silva-Velasco: Writing – review & editing, Writing – original draft, Software, Methodology, Conceptualization. **Luz G. Cervantes-Pérez:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Alicia Sánchez-Mendoza:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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