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Review

Are the endothelial mechanisms of ACE-Is already established?

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Abstract:
The endothelial mechanism of ACE-Is action is multifaceted. On the one hand, by inhibiting ACE, ACE-Is diminish Ang II synthesis, one of the best known active peptides. On the other hand, they modify synthesis and release of PGI_2 and NO *via* increasing production of other biologically important peptides like bradykinin, Ang-(1-7) or Ang-(1-9). Thus, ACE-Is play a crucial role in the function of endothelium and are effective and important tool for therapy of range of cardiovascular system disorders. Moreover, they are sensitive pharmacological instrument to elucidate and expand our knowledge about the role of RAS in human patophysiology.

Key words:
angiotensin converting enzyme, angiotensin converting enzyme inhibitors, bradykinin, angiotensin, prostacyclin, nitric oxide.

Abbreviations: ACE – angiotensin converting enzyme, ACE-Is – angiotensin converting enzyme inhibitors, Ang – angotensin, $AT_{1,\ (1–7)}$ – angiotensin receptors, B_2 – bradykinin receptor type 2, BK – bradykinin, $[Ca^{2+}]i$ – intrinsic calcium signaling, CAL – calmodullin, CHD – coronary heart disease, COX – cycloxygenase, CPP – carboxipeptydase P, E – endopeptidase, e-NOS – endothelial nitric oxide synthase, G – G-signalling protein, IP – inactive peptides, LDL – low density lipoproteins, LOX-1 – oxidative stress-lectin-like oxidized LDL receptor type 1, MAPK – mitogen-activated protein kinase, MCP-1 – monocyte chemoattractant protein type 1, MI – myocardial infarction, MP – metalloprotease, NEP – neprylisin, NO – nitric oxide, PAI-1 – plasminogen activator inhibitor type 1, PGI_2 – prostacyclin, PKC – phosphokinase C, PLA_2 – phospholipase A_2, TF – tissue factor, t-PA – tissue-type plasminogen activator

Introduction

In 1898, Tigerstedt and Bergman published their observation that kidney extracts produce pressor effects [42]. Although this was the beginning of understanding the role of the kidney in hypertension and the renin-angiotensin system (RAS), their discovery lay dormant for nearly 40 years. Then, two research groups, working independently, using the Goldblatt technique to produce experimental hypertension, demonstrated renal secretion of a pressor agent similar to renin. In the following years, both teams described the presence of a new compound in the renal vein blood of ischemic kidneys. The final conclusion was that renin acted enzymatically on a plasma protein to produce the new substance. In Buenos Aires, it was called hypertensin; in the United States, angiotonin. In 1958, Eduardo Braun Menéndez from Argentina and Irving H. Page from the United States agreed to name it angiotensin. It was proposed that renin cleaves angiotensinogen to form angiotensin I (Ang I) and then Angiotensin I Converting-Enzyme (ACE) converts Ang I to angiotensin II (Ang II). This hypothesis became the basis of RAS system. The main effects of Ang II on cardiovascular system, like pressor activity and altering vascular and cardiac

structure was identified. Later, in 1968 Ng and Vane showed that peptides from the poison of *Bothrops jararaca* inhibit the conversion of Ang I to Ang II [31]. This extremely important finding led to the discovering of new antihypertensive drugs – specific inhibitors of ACE (ACE-Is) [32]. In next years it has been shown that endothelium is the main target organ of many cardiovascular drugs, including ACE-Is [11].

Diminishing of Ang II production by ACE-Is

Since the beginning of ACE-Is discovering, diminishing of Ang II production was thought to be the main mechanism of their antihypertensive and antiproliferative action. It explained the effectiveness of ACE-Is in the treatment of hypertension and congestive heart failure, proved in many clinical studies. In the last decade many new findings appear, indicating that, beside systemic, Ang II exerts also local activities and the main target organ is endothelium. It has been demonstrated that Ang II contributes to endothelial dysfunction by inducing oxidative stress [7], promoting atherosclerosis [45], inhibiting nitric oxide (NO) synthesis [47] and enhancing leukocytes infiltration and adhesion to vascular wall [33, 37, 43]. All the findings summarized on Figure 1 suggest that Ang II may be one of the risk factors for the thrombosis development.

Recently, we confirmed that Ang II can enhance thrombosis in hypertensive rats [28]. From our results a complex but consistent picture emerges for the mechanism, in which Ang II promotes thrombus formation. Probably, Ang II directly enhances thrombosis by activation of AT_1 receptor. Furthermore, Ang II also possesses indirect prothrombotic activity mediated through one of its metabolites – Ang IV. Ang II exerts prothrombotic action by augmenting leukocytes adhesion to vascular wall and accelerating fibrin generation probably due to the increased synthesis of PAI-1. Taken together, these observations with many clinical data, indicating that Ang II plasma levels lowers during ACE-Is therapy, it is obvious that diminishing of Ang II production and its negative effects, like Ang II-induced endothelium dysfunction, is important part of the endothelial mechanisms of ACE-Is action.

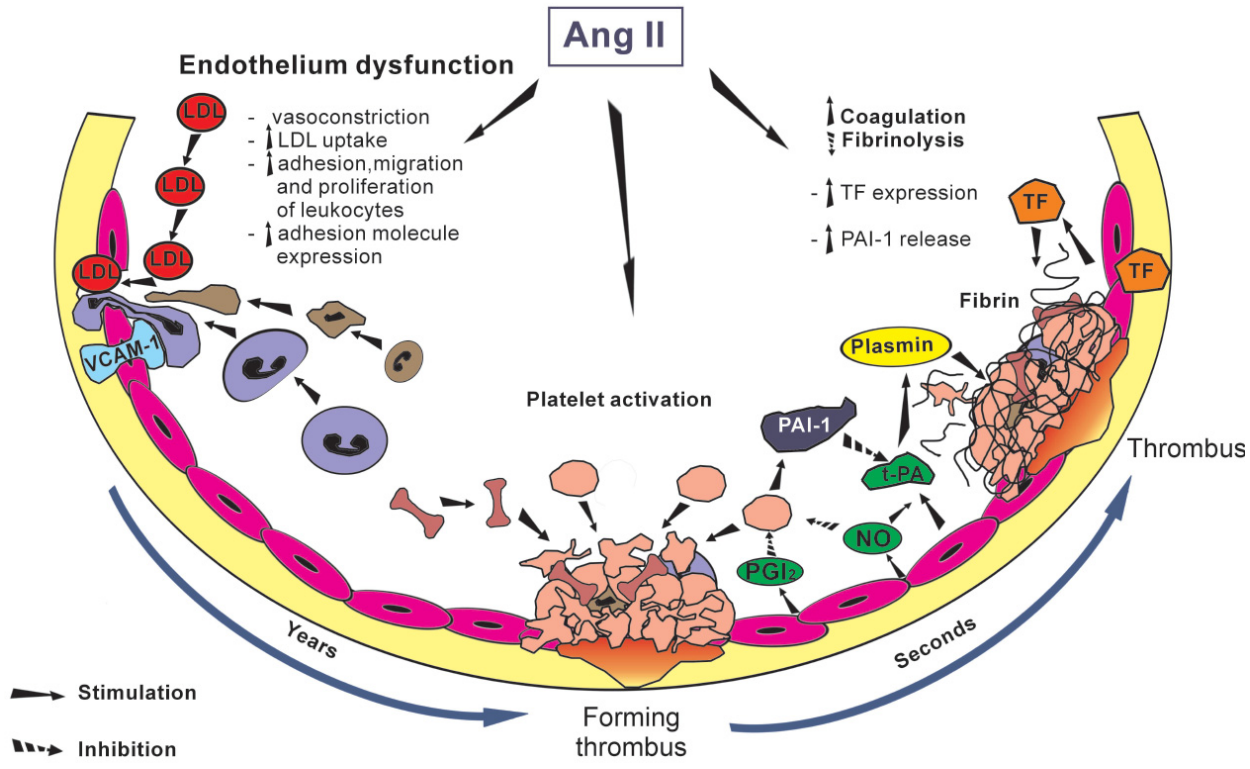

Fig. 1 Ang II induces thrombosis development

The role of bradykinin-NO/PGI_2 pathway in the endothelial effects of ACE-Is

In 1965 Ferreira [5] described for the first time bradykinin-potentiating factor in the poison of *Bothrops jararaca.* This observation made possible to know the second mechanism of ACE-Is action. ACE-Is reduce the degradation of bradykinin (Bk) which in turn release NO and prostacyclin (PGI_2), which results in the vasodilatation and blood pressure decrease. There are many data demonstrating that ACE-Is may release of NO and PGI_2 from endothelium [14, 17]. Since the NO and PGI_2 play an important role in the regulation of endothelium function, it is clear that ACE-Is possess many new therapeutic benefits over and above the treatment of hypertension and congestive heart failure, related to the endothelium function improvement. In 1992 it was demonstrated for the first time that long-term administration of captopril to patients with left ventricular dysfunction after myocardial infraction (MI) reduces the rate of recurrent coronary thrombosis [36]. Many of the following clinical trials, like HOPE, PROGRESS or EUROPA confirmed benefits of ACE-Is in reducing the rate of, deaths, MI, strokes, cardiac outcomes, diabetic complications, end-stage renal disease complications, hospitalizations in varying degrees of risk patients, such as, with chronic congestive heart failure, with MI, post MI and with stable coronary heart disease (CHD) without apparent heart failure [4, 13, 38]. MacMahon et al. [27] had previously showed that the overall morbidity or rate of cardiovascular events, such as stroke and CHD are related to the blood pressure values. Obviously, the hypotensive action of ACE-Is is partially responsible for the improvement of the patients survival. But, series of experimental data indicate that some local effects of ACE-Is, like inhibiting thrombosis, are independent on BP lowering. These observation are also in the line with our previous study, in which captopril inhibited thrombosis in rats when administered in non-hypotensive doses [34]. Therefore, it has been postulated that cardioprotective effects of ACE-Is are mediated by kinin-prostaglandin-NO pathway. Indeed, we have found that antithrombotic effect of ACE-Is is dependent on NO and PGI_2 release [2, 34, 35]. Our observation is in line with many others findings indicating that ACE-Is may release NO and PGI_2 from endothelium [9, 14]. Moreover, there is strong evidence that ACE inhibition causes selective and marked augmentation of BK-induced t-PA release due to the inhibition of BK degradation rather than enhancing of the capacity of endothelium to release t-PA acutely [25]. There are countless findings demonstrating the involvement of NO and PGI_2 in the various beneficial

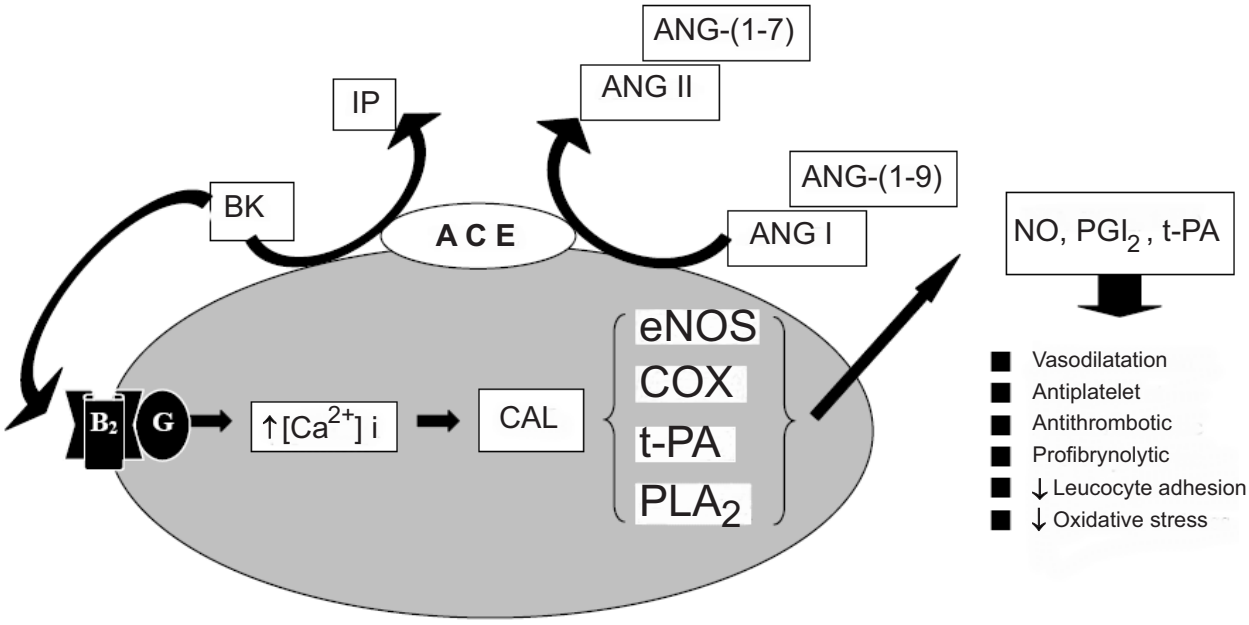

Fig. 2. Bradykinin pathway of ACE-Is mechanism of action

cardiovascular effects of ACEI-Is. These two endothelial mediators contribute to the antithrombotic, profibrynolytic, antiplatelet, antiadhesive, anioxidative effects of ACE-Is [6, 14, 18, 20, 29, 41, 44] (Fig. 2). It has been shown that in ACE-Is treated animals BK induces cAMP and cGMP to stimulate eNOS, resulting in increased NO availability [26, 46]. It is proposed that ACE-Is *via* BK dependent B_2 receptor increase intracellular [Ca^{2+}] concentration and activate PLA_2 [10]. This, in turn, supplies with the substrate COX-2 which results in PGI_2 release [8, 9]. The intracellular mechanism by which ACE-Is release NO/PGI_2 is presented on the Figure 2.

Enhanced production of active peptides by ACE-Is

Angiotenisin-(1-7)

Angiotenisin-(1-7) [Ang-(1-7)] is a biologically active component of RAS, produced either from Ang I, Ang II or possibly Ang-(1-9) [23]. It acts as a counterregulatory hormone to Ang II, limiting its pressor, proliferative and angiogenic actions [40]. Ang-(1-7) is a potent stimulator of NO and PGI_2 release [12]. Moreover, it is known that chronic treatment with RAS blockers results in 5- to 50-fold increase in the concentration of Ang-(1-7) [1, 15] (Fig. 3). Thus, high concentration of Ang-(1-7) acting on a putative Ang-(1-7) receptor and/or AT_1 receptors may facilitate the production and liberation of antithrombotic endothelial mediators – NO/PGI_2. Indeed, we have found that the antithrombotic effect of ACE-Is involves Ang-(1-7)-evoked release of NO and PGI_2 in experimental model of venous thrombosis in hypertensive rats [24].

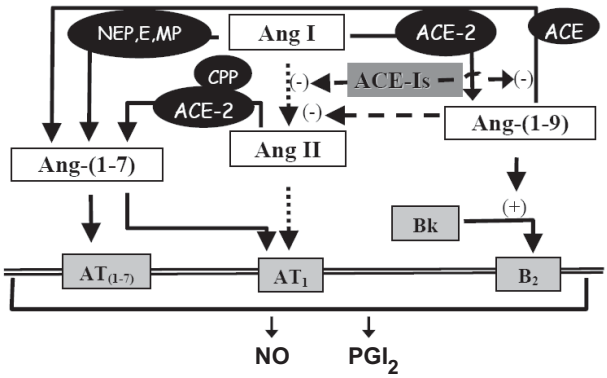

Fig. 3 Enhanced production of active peptides, Ang-(1-7) and Ang-(1-9)

Angiotensin-(1-9)

Angiotensin-(1-9) [Ang-(1-9)] is relatively poorly known element of RAS, so far considered as non-active peptide. Recently it has been demonstrated that Ang-(1-9) is generated by a newly described enzyme-ACE-2 from Ang I (Fig. 3) [3]. It has been demonstrated that Ang-(1-9) fully inhibits ACE by competitive mechanism [22]. Moreover, Ang-(1-9), like Ang-(1-7) potentiates BK action on the B_2 receptor by raising arachidonic acid and NO release [16]. Interestingly, Ang-(1-9) in rat plasma and kidney occurs only after ACE-Is administration [19]. Therefore the involvement of this peptide in mechanism of ACE-Is action can not be excluded.

Other possible endothelial mechanisms of ACE-Is action

Apart of BK-mediated beneficial properties, ACE-Is may suppress oxidative stress by decreasing the activities the NAD(P)H oxidase, PKC and MAPK [39] and by decreasing expression of oxidative stress-lectin-like oxidized LDL receptor-1 (LOX-1) [21]. Furthermore, ACE-Is decrease tissue factor (TF) and MCP-1 after 1-month therapy in patients with MI and downregulated TF synthesis *in vitro* by inhibition of endotoxin-induced nuclear factor-kappaB translocation to the promoter region of the gene encoding for TF [30].

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