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Modeling of angiotensin II–angiotensin-(1-7) counterbalance in disease progression in spontaneously hypertensive rats treated with/without perindopril

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ABSTRACT

Angiotensin II (Ang II) and angiotensin-(1-7) (Ang-(1-7)) are biologically active effectors in the renin–angiotensin system (RAS) and have been demonstrated to have potential function in predicting cardiovascular diseases. We developed mechanism-based mathematical models to characterize the up/down-regulation of Ang II/Ang-(1-7), and the effects of perindopril on hypertension progression in spontaneously hypertensive rats (SHR). SHR were randomly assigned to the control group ($n = 6$) and treatment group ($n = 6$). Rats in the treatment group received oral perindopril (5 mg kg^{-1} day^{-1}). Systolic blood pressure (SBP) was measured by the tail-cuff method. Serum Ang II and Ang-(1-7) concentrations were determined by enzyme-linked immunosorbent assay (ELISA). Three linked turnover models were developed to describe Ang II, Ang-(1-7) and SBP profiles. All parameters were estimated using nonlinear mixed-effects modeling. The results showed that Ang II, Ang-(1-7) and SBP gradually increased in the control group. These counterbalance mechanisms were reflected in the models with two feedback cycles. It was assumed that the Ang-(1-7) production rate constant (K_{in_Ang17}) was stimulated by Ang II, and the Ang II output rate constant (K_{out_Ang2}) reflecting Ang II degradation was stimulated by Ang-(1-7). The decrease in Ang II and increase in Ang-(1-7) were observed in rats treated with perindopril. The models described the counterbalance relationship of Ang II and Ang-(1-7) well, and provided insights into ACE inhibition using perindopril. The models could be extended to incorporate other biomarkers and the effects of various ACE inhibitors (ACEIs).

1. Introduction

Hypertension is the one of the most important public health problems worldwide. It is well established that hypertension is a leading risk factor for mortality from both cardiovascular disease (CVD) and all-cause comorbidity [1]. The renin–angiotensin system (RAS) is one of the most studied enzyme–substrate systems in the body, in part, due to its role in regulating cardiovascular function. It plays a major physiological role in the regulation of blood pressure and volume homeostasis in the pathogenesis of cardiovascular-related diseases, such as hypertension and diabetes [2].

In previous studies, the RAS was shown to be a complex system involved in many physiological and pathophysiological conditions. It is composed of two opposing arms (Fig. 1). The pressor arm is mainly constituted by renin, angiotensin-converting enzyme (ACE), angiotensin II (Ang II) and Ang II type 1 receptor (AT1R). In this arm, Ang II is considered the key effector molecule in the RAS due to its central role in the up-regulation of blood pressure [3,4]. In addition, the depressor arm is composed of angiotensin-converting enzyme 2 (ACE2), angiotensin-(1-7) (Ang-(1-7)) and the Mas receptor. Ang-(1-7) is a vasodilator and opposes the actions of increasing Ang II in pathological states [5–8]. The normal levels of Ang II and Ang-(1-7), both in tissues and in the circulation, may be disturbed in many disease states such as

Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; ACEI, angiotensin-converting enzyme inhibitor; Ang II, angiotensin II; Ang-(1-7), angiotensin-(1-7); AT1R, angiotensin II type 1 receptor; FOCE, first order conditional estimation method; OFV, objective function value; PK-PD, pharmacokinetic and pharmacodynamic; RAS, renin–angiotensin system; RSE, relative standard error; SBP, systolic blood pressure; SHR, spontaneously hypertensive rats.

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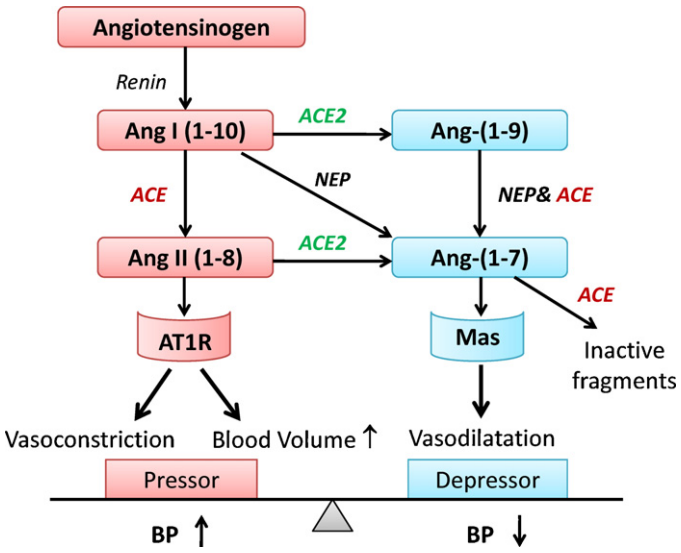

Fig. 1. Schematic diagram of the renin–angiotensin system (RAS) pathway. It shows that renin, angiotensin-converting enzyme (ACE) and ACE2 contribute to the formation of angiotensin peptides. The pressor arm of RAS (left), shows that Ang I is converted by ACE to Ang II. Ang II mainly mediates the pressor effect via the AT1 receptor. The depressor arm of RAS is shown on the right, and demonstrates that Ang-(1-7) can be generated both from Ang II by ACE2 and from Ang I by neutral endopeptidase (NEP). The pathway from Ang I to Ang-(1-9) by ACE2 and then Ang-(1-7) by NEP and ACE represents alternative steps in this pathway. Ang-(1-7) mediates these effects via the Mas receptor.

hypertension, cardiac fibrosis, and myocardial infarction. Thus, a better understanding of the balance between the two peptides will be helpful in unraveling the ways in which these disease states can best be treated.

Growing evidence has shown that the vasoconstrictor effects of elevated Ang II concentration may be limited by increasing Ang-(1-7). This is most likely due to the increase in ACE2 activity as a counter-regulatory mechanism [9]. Ang II stimulates p-ERK1/2 and p-MEK1/2 via the AT_1 receptor, further up-regulates ACE2 and increases their hydrolysis through a negative regulatory feedback loop. Similar to Ang II, Ang-(1-7) enhances the stimulatory effect by activating Mas receptor, as a positive feedback loop (Fig. 2). These feedback loops may serve as a protective mechanism to maintain the static state of cardiac Ang II concentration [10–12]. Additional evidence suggests that the changes in circulating Ang II and Ang-(1-7) may be critical factors in mediating the progression of cardiovascular disease [13].

A preliminary insight into the effect of ACE inhibitor (ACEI) showed that the production of Ang II was reduced and blood pressure was decreased by inhibiting ACE [5,14,15]. Recent studies reveal that Ang-(1-7) levels, both in normotensive and hypertensive rats, increase during ACE inhibition, not only because ACE is one of the main Ang-(1-7)-degrading enzymes, but also because the up-regulated ACE2 expression during ACE inhibition results in enhanced Ang-(1-7) [16–18]. In addition, long-term ACEI therapy may lead to accumulation of Ang I, which result in enhancing Ang-(1-7) generation by neutral endopeptidase (NEP) (Fig. 1). These actions may contribute to the mechanism of controlling arterial pressure [19]. As a long-acting ACEI, perindopril, contributes to establishing treatment efficacy in hypertensive patients with different cardiovascular risk profiles [20,21]. Although classical pharmacokinetic–pharmacodynamic (PK–PD) modeling of ACEIs provided some information on the relationships between drug concentration and effects [22,23], the time-course of disease progression was ignored and the assumption of consistency was not realistic in long-term studies, as hypertension is a chronic progressive disease. Furthermore, the quantitative relationship between Ang II and Ang-(1-7) in long-term hypertension progression still remains unclear.

In this report, we used mathematical models to assess the longitudinal time-course of Ang II, Ang-(1-7) and SBP to improve our understanding of the RAS and facilitate the characterization of ACEI effects. Ang II/Ang-(1-7) homeostasis and their impact on blood pressure were quantified using an integrated model, and the model was extended to include changes in disease progression resulting from ACEI treatment. This may be helpful in validating the advanced mechanism in the RAS and evaluating ACEI effects.

2. Materials and methods

2.1. Animals

12 SHR aged 5 weeks, were purchased from the Vital River Laboratory Animal Technology Co. Ltd. (Beijing, China) and weight-matched to approximately 100 g. The rats were housed in an animal room under controlled conditions (temperature 22–24 °C, humidity 55–60%, 12-h light/12-h dark cycle). Rats had free access to food and water. This research adhered to the Principles of Laboratory Animal Care (NIH publication No. 85-23, revised 1996). All

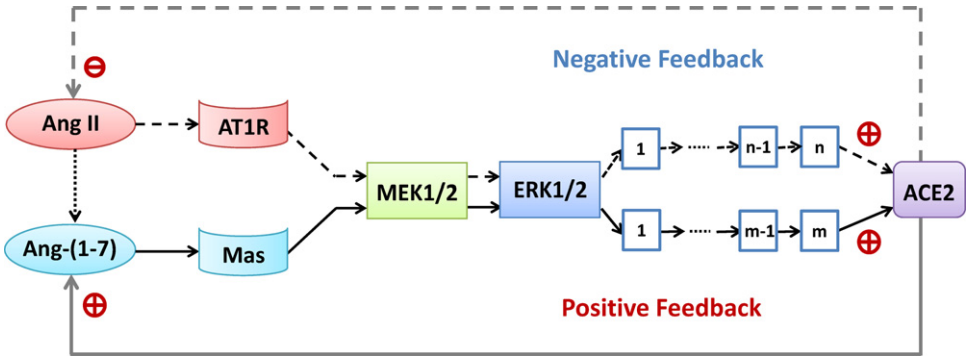

Fig. 2. Schematic diagram of Ang II-Ang-(1-7) interactions under cardiac ACE2 regulation. It shows that: (1) the generation of Ang-(1-7) can be stimulated by enhanced ACE2 through a positive feedback loop (solid lines). Components of the positive loop include ACE2, Ang-(1-7), Mas receptor, MEK1/2, ERK1/2 and other more complex signal-transduction pathway components (1,. . .,$n-1$, n). (2) The hydrolysis of Ang II can be stimulated by Ang II/Ang-(1-7) up-regulated ACE2 through a negative feedback loop (dashed lines). Components of the negative loop include Ang II, AT1R, MEK1/2, ERK1/2, other more complex signal-transduction pathway components (1,. . .,$m-1$, m) and ACE2.