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Modeling sex differences in the renin angiotensin system and the efficacy of antihypertensive therapies

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ABSTRACT

The renin angiotensin system is a major regulator of blood pressure and a target for many antihypertensive therapies; yet the efficacy of these treatments varies between the sexes. We use published data for systemic RAS hormones to build separate models for four groups of rats: male normotensive, male hypertensive, female normotensive, and female hypertensive rats. We found that plasma renin activity, angiotensinogen production rate, angiotensin converting enzyme activity, and neutral endopeptidase activity differ significantly among the four groups of rats. Model results indicate that angiotensin converting enzyme inhibitors and angiotensin receptor blockers induce similar *percentage* decreases in angiotensin I and II between groups, but substantially different *absolute* decreases. We further propose that a major difference between the male and female RAS may be the strength of the feedback mechanism, by which receptor bound angiotensin II impacts the production of renin.

1. Introduction

The renin angiotensin system (RAS) is an important regulator of blood pressure. The RAS consists of an enzymatic cascade that produces the bioactive peptide angiotensin II (Ang II) (Sparks et al., 2011). The cascade starts with angiotensinogen (AGT), which is cleaved by renin and later angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP) into different forms of angiotensin (see Fig. 1) (Chappell, 2012; Chappell et al., 2014; Sparks et al., 2011). The enzyme renin catalyzes the first reaction in the RAS and is often thought as the driving force in the cascade. The products of the RAS are major biologically active products includes angiotensin (1–7) (Ang (1–7)) and Ang II. These bind to receptors and impact the brain, heart, kidney, vasculature, and immune system (Sparks et al., 2011). Ang II has two different types of receptors. When bound to angiotensin II type 1 receptor (AT1R), Ang II stimulates renal vasoconstriction, raises sodium reabsorption, and promotes inflammation and fibrosis (Chappell, 2012). When bound to angiotensin II type 2 receptor (AT2R), Ang II induces vasodilation and natriuresis. Ang (1–7) binds to the angiotensin type 7 receptor (AT7R), also known as the MAS receptor, to cause vasodilation and natriuresis and increase production of nitric oxide to reduce inflammation and fibrosis (Chappell, 2012; Chappell et al., 2014).

AT1R-bound Ang II regulates overall blood pressure via its effects on the kidney. The kidney is responsible for filtering blood into urine to remove waste from the body. Through the glomerulus, blood is filtered leaving all proteins, such as hemoglobin, behind in the body. Attached to the glomerulus is the nephron, which is the kidney's functional unit and is responsible for reabsorption and secretion. As the filtrate travels through the nephrons, essential solutes and water are reabsorbed or secreted. In particular, the reabsorption of sodium by the nephron is critical for blood pressure regulation (Guyton et al., 1972). AT1R-bound Ang II regulates blood pressure by increasing sodium and fluid reabsorption in the proximal tubule, which is a key segment of nephron that normally reabsorbs about 2/3 of the filtered salt and water (Sparks et al., 2011).

The relation between the RAS and the kidney is two-way with the kidney influencing the RAS by providing the first two essential components of the RAS: AGT and renin. The proximal tubule, as well as the liver, are the primary places of production for AGT, whereas renin is produced in the juxtaglomerular apparatus, a microscopic structure in the kidney. When blood pressure is low, renal blood flow decreases and kidney function may become impaired. To compensate, the kidney elevates renin production, causing an increase in AT1R-bound Ang II, which raises blood pressure.

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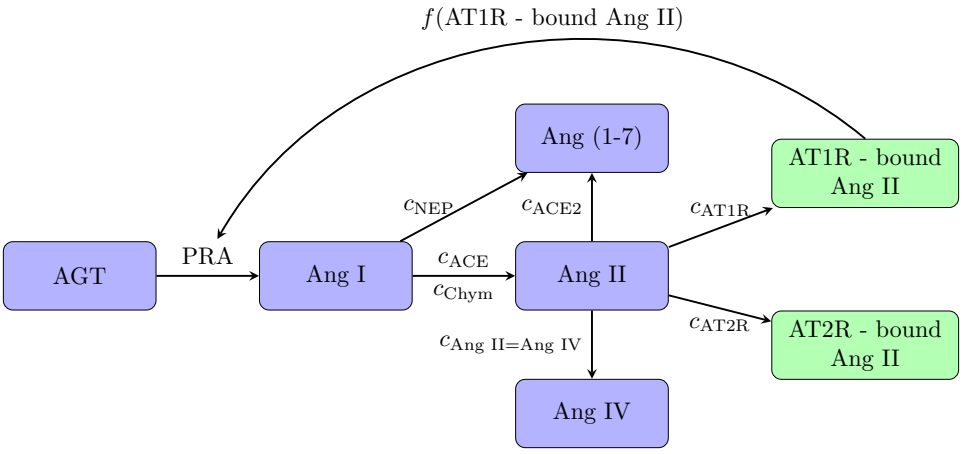

Fig. 1. Schematic diagram depicting the RAS reaction cascade.

Because of its central role in fluid homeostasis, the RAS, in particular ACE and AT1R, are often targeted in hypertensive treatments. Given that AT1R-bound Ang II causes vasoconstriction and higher blood pressure, antihypertensive drug treatments seek to lower the amount of Ang II bound to AT1R. Given also that ACE converts Ang I into Ang II, by lowering the level of ACE activity through ACE inhibitors (ACEI), the total amount of Ang II that is available to bind to AT1R can be reduced. Angiotensin receptor blockers (ARB) are AT1R antagonists that reduce vasoconstriction by preventing the binding of vasoactive peptides (i.e. Ang II).

The RAS is similar in mammals, as are the sex differences. Females have been shown to have lower blood pressure than males in humans, rats, dogs, and birds (Sandberg and Ji, 2012). Major sex differences in the RAS have been identified, including how much substrate is produced and how angiotensin interacts with receptors. For example, in both rats and humans, females have greater circulating levels of AGT (Fischer et al., 2002), causing an overall greater amount of angiotensin to be flowing through the system. Also, male rats have been shown to have greater Ang II levels (Sandberg and Ji, 2012) while female rats have greater levels of Ang (1–7) (Zimmerman and Sullivan, 2013). However, a greater level of ACE2 activity (which converts Ang II to Ang (1–7)) has been measured in male rats (Zimmerman and Sullivan, 2013).

Interestingly, males and females exhibit differing responses to Ang II. Changes in Ang II levels produce smaller changes in blood pressure in female rats (Fischer et al., 2002; Sandberg and Ji, 2012). That discrepancy may be attributed to differences in receptor expression, inasmuch as male rats have greater AT1R expression and lower AT2R expression than female rats (Bubb et al., 2012; Sandberg and Ji, 2012; Zimmerman and Sullivan, 2013). Estrogen also reduces the half life of AT1R-bound Ang II (Thompson and Khalil, 2003).

Given the above observations, it should come as no surprise that males and females respond differently to antihypertensive treatments that target the RAS. In one study, women who were prescribed ARBs had better survival rates than women prescribed ACEIs, while the opposite was true in men (Sullivan, 2008). Studies have provided evidence that the effectiveness of ACEIs in women decreases over time and offers less benefit to women as determined by total mortality (Sullivan, 2008). While these trends have been observed in multiple studies, the underlying mechanisms are not well understood. Thus, the goal of this study is to obtain a better understanding of the RAS of the rat and the functional implications of the sex differences. To achieve that goal, we develop mathematical models of the RAS for four groups of rats: normotensive male, normotensive female, hypertensive male, and hypertensive female rats. The models are formulated using ordinary differential equations based on a published RAS model for normotensive humans, presumably males (Lo et al., 2011). Other studies have modeled the RAS within the larger context of the circulatory system, but none of these have looked into how sex differences within the RAS affects the circulatory system and blood pressure (Ford Versypt et al., 2017; Guillaud and Hannaert, 2010; Hallow et al., 2014). A goal of this study is to identify individual parameter sets that correspond to the different types of rats (normotensive and hypertensive rats, male and female). Our focus on the rat is motivated by its role as one of the most commonly used animal models in experiments and drug trials. Following the successful determination of the model parameters, we apply the models to elucidate the mechanisms by which the known differences between the sexes contribute to the sex-specific responses to anti-hypertensive therapies. Since the rat and human share many of the known sex differences in the RAS, conclusions from this study should be applicable to humans.

2. Methods

2.1. Model equations

A schematic diagram that depicts the RAS reaction cascade can be found in Fig. 1. As previously discussed, AGT is catalytically cleaved by renin to produce Ang I. The rate of change of [AGT] is given by the production rate k_{AGT}, the conversion to Ang I catalyzed by renin, and the decay based on its half life h_{AGT}:

$$\frac{d[AGT]}{dt} = k_{AGT} - PRA - \frac{\ln(2)}{h_{AGT}}[AGT] \tag{1}$$

where PRA denotes plasma renin activity. PRA is assumed to follow Michaelis-Menton kinetics, characterized by the maximum rate V_{max} (Lo et al., 2011). The Michaelis constant is taken to be the [AGT] value at which PRA reaches half of its maximum value (denoted $[AGT]_{EQ}$). PRA also depends on the feedback effect of AT1R-bound Ang II (Hallow et al., 2014).

$$PRA = \frac{V_{max}[AGT]}{[AGT] + [AGT]_{EQ}} * f([\text{AT1R-bound Ang II}]) \tag{2}$$

$$f = \left(\frac{[\text{AT1R-bound Ang II}]_{EQ}}{[\text{AT1R-bound Ang II}]}\right)^{B_{AT1}} \tag{3}$$

Because the exponent B_{AT1} is taken to be positive (0.95), when [AT1R-bound Ang II] is above its equilibrium value ($[\text{AT1R-bound Ang II}]_{EQ}$), PRA decreases.