Hypertension is a polygenic condition that characterizes one of the most common and relevant cardiovascular complications that contributes to approximately 650,000 deaths per year in the United States. The Renin-Angiotensin-Aldosterone system (RAAS) plays a significant role in systemic and neurogenic hypertension [1, 2]. Angiotensin II (Ang II), an octadecapeptide, is a key hormonal peptide that interacts with AT1 and AT2 G protein-coupled receptors (GPCRs). The effects of AT1R mediate excitatory responses, and AT2, serves as the protective arm of RAAS at the level of cardiomyocytes. Angiotensin-converting enzyme-2 (ACE2) converts AngII into Ang-(1–7) mediated by MAS receptor, a GPCR for Ang-(1–7), to mitigate myocardial ischemia and regulate blood pressure. Angiotensin 1–7 (Ang 1–7) has been shown to reduce blood pressure [3], cardiac contractility [4, 5], and reactive oxygen species (ROS) [6], mediated via MAS1 proline-40-glycoprotein protein (MAS). The objective is to study the expression of RAAS receptors on ventricular myocytes isolated from hypertensive rodents to assess the implication of the AngII in the presence or absence of antihypertensive drugs. There was a correlation in the circulating plasma AngII with blood pressure in hypertensive rodents. The blood pressure was reversed with angiotensin receptor blocker (ARB) suggesting the impact of RAAS. Cardiac expression for AT1R showed a significant increase compared to the control group (p<0.01) but was abolished in the treated group with angiotensin receptor blocker (fmlfHED) and the control group. Conversely, AT2R expression in hypertensive group was significantly lower compared to control group (p<0.01). However, the antihypertensive drug treatments did not reverse AT2 response to control level suggesting a non-reversal of AT2 expression when blood pressure is returned to normal. Furthermore, there was a significant decrease in the protein expression of MAS receptors for angiotensin-1 (Ang-(1–7)) peptides but was returned to control levels in the treated group. These results suggest that while AT1R mediates excitability and enhancement of cardiac contraction in hypertensive condition, MAS receptor mediates the metabolism of AngII, through Ang1–7 and, along with AT2R, to serve as the protective arm of angiotensin peptides. This work implies that changes in the expression of the receptors on the surface of the cells are a key mechanism involved in the signaling pathways that lead to the manifestation of hypertensive. It also suggests that treatments for hypertension works by restoring receptor expression to basal level.

Introduction

• Hypertension, is a condition characterized by a systolic pressure of ≥140 mmHg or greater and diastolic pressure of ≥90 mmHg. Older age is a major factor that increases the odds of developing hypertension.

• Hypertension is a major risk factor for the development of stroke, heart attack, heart failure, kidney disease, and other cardiovascular complications.

• The cascade of physiologic events which lead to hypertension are not fully elucidated.

• However, treatment with angiotensin converting enzyme (ACE) inhibitors or AngII receptor antagonists is extremely efficient.

• Recently, the importance of AT2R and MAS receptor in sympathetic nerve transmission has been speculated to attenuate ROS activities. It is speculated Ang1–7 would reduce ROS production.

• The objective of this study is to test the expression of RAAS receptors on ventricular myocytes isolated from mRen227 transgenic hypertensive rodents to assess the implication of the AngII peptide in the presence of antihypertensive treatment.

Methods

(a) Mouse Ren227 gene inserted into genome of rat – mRen227 transgenic hypertensive model

(b) Plasma assay for Ang and Ang 1–7 before and after antihypertensive drug treatment

(c) Isolation of left ventricular cardiomyocytes before and after antihypertensive drug treatment

(d) Protein and RNA isolation from the HnSD and mRen227/AT2 transcardiomyocytes

(e) SDS PAGE-Western blotting and qRT-PCR analysis of RAAS receptor protein expression.

Results

• Blood pressure in this model of hypertension was reduced by normal cardiomyocytes and dihydropyridine treatments suggesting that the angiotensin receptor blockers (ARBs) and vasodilators are effective in RAAS-mediated hypertension (Figure 1).

• There is a decrease in circulating AngII in the mRen2 animals compared to the HnSD, however the antihypertensive treated group showed a significant increase in plasma AngII suggesting ARBs–AngII competitive binding on AT2 receptor (Figure 2A&B).

• There is an increased protein expression for AT2 receptor in hypertension but was abolished in the mRen2 rodents treated with anti-hypertensive drugs. This suggests a reversal of AT2R protein expression when blood pressure was returned to normal (Figure 3A).

• Protein expression for AT2 receptor showed a significant decrease in cardiomyocytes isolated from the mRen2 animals compared to the HnSD. However, the anti-hypertensive drug did not restore the protein expression for AT2 receptor (Figure 3B).

• There was a decrease in Mas protein expression in the cardiomyocytes isolated from mRen2 animals compared to HnSD. However, those treated with anti-hypertensive drug restored the MAS receptor expression which further suggested that the protective arm of RAAS protein expression (i.e., MAS) may reappear when blood pressure is normalized (Figure 3C).

• Expression of the receptors on the cells are a key mechanism involved in the signaling pathways that lead to the manifestation of hypertension.

Conclusion


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Reference

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