ROLE OF STRIATIN AND MINERALOCORTICOID RECEPTOR (MR) IN CARDIOVASCULAR DISEASES

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ABSTRACT

Cardiovascular (CV) disease has been implicated as the leading cause of death and remains one of the most complex disease due to its pathophysiology involving multiple organs systems. One of the many causes of hypertension, the most common CV disease, is activation of mineralocorticoid receptor (MR) by aldosterone (ALDO). MR is a well-studied steroid hormone receptor and our laboratory has recently shown that MR co-immunoprecipitates with striatin, a novel scaffolding protein. Striatin potentially modulates MR's non-genomic functions. Furthermore, striatin polymorphism in humans is associated with salt sensitivity of blood pressure. Therefore, we investigated the role of striatin in modulating blood pressure along with modulation of MR's non-genomic functions using a genetically modified mouse model.

Striatin heterozygous knock-out mice ($Strn^{+/-}$) were generated by KOMP Repository Knockout Mouse Project at UC Davis. Sixteen-week old male $Strn^{+/-}$ and aged-matched littermate wild-type (WT) mice were randomized in a crossover intervention to liberal salt diet (HS, 1.6% Na^+) or restricted salt diet (LS, 0.03% Na^+) for 7 days on each diet. At the end of each diet intervention blood pressure (BP) was measured by tail cuff plethysmopraphy. At the end of the second week, mice were placed in metabolic cages to assess food and water intake and collect 24 hour urines. Mice underwent cheek bleeding and subsequently were euthanized to collect heart, kidney and adrenal tissue.

Reduction of striatin in mice leads to increased salt sensitivity of blood pressure. Plasma and stimulated ALDO and MR levels are not affected by striatin levels. Interestingly the non-genomic downstream MR transcription targets such as, pAkt/Akt and pERK/ERK in heart tissue were downregulated in the $Strn^{+/-}$ mice. Thus, striatin may be a novel factor influencing cardiovascular risk by mechanisms that remain to be elucidated.

In WT mice, no significant blood pressure changes were observed from a LS diet to HS diet (105.3±2.6mmHg vs 109.6±2.6mmHg). On contrary, $Strn^{+/-}$ mice showed a significant rise in systolic (104.2±2.8 vs 112.6±3.2) and diastolic blood pressure from a LS to HS diet. Our data provides evidence that striatin regulates the non-genomic effects of ALDO/MR signalling pathway as shown by significant reduction in expression of pAkt/Akt, a component of non-genomic signalling pathway.

INTRODUCTION

Cardiovascular (CV) disease is caused by disorders of the blood vessels and heart. Hypertension, myocardial infarction, peripheral artery disease and heart failure are the major disorders leading to morbidity and mortality among patients suffering from CV diseases (WHO, 2008) .In the US, CV disease remains the leading cause of death. An estimated 8.7 million adults in the US have one or more types of CV disease (Rosamond, 2008). According to the World Health Organization (WHO) report in May 2012, one in three adults worldwide suffer from hypertension and it is a major contributing factor towards morbidity and mortality as a result of heart disease and stroke (WHO, 2012).

The mineralocorticoid receptor (MR) is a member of the steroid-thyroid receptor superfamily and is a ligand dependant transcription factor (Fejes-Tóth G, 1998). MR is a well-studied steroid hormone receptor and has been linked to numerous cardiovascular (CV) functions and diseases. MR plays an important role in the regulation of salt and water homeostasis that in turn leads to regulation of the blood pressure. MR exerts its function through activation by aldosterone (ALDO). ALDO is the principal human mineralocorticoid synthesized from cholesterol in zona glomerulosa of the adrenal cortex (Scott M. MacKenzie, 2006).

ALDO regulates the genomic as well as non-genomic pathways of MR activation. Genomic pathway of MR activation involves the translocation of MR from cytosol into the nucleus after activation by ALDO. Translocation of ALDO-MR complex to the nucleus leads to regulation of specific gene transcription, which leads to production of specific proteins that exert biological responses. This process usually takes hours to complete. On the other hand, non-genomic response of MR activation occurs within minutes and involves the phosphorylation of certain biological molecules including ERK and AKT (RALF M. LOSEL, 2003).

Abnormalities in ALDO/MR signalling has significant effects on CV function particularly the vasculature and the kidney. Several studies have demonstrated that MR is expressed in the heart, blood vessels and brain (Young M, 1994). This evidence suggests that the activation of MR by ALDO in the vasculature may have adverse effects on the vasculature and contribute to the development of hypertension. However, the mechanism(s)