ROLE OF ENDOTHELIAL CAVEOLIN-1 IN RESPONSES TO ALDOSTERONE TREATMENT

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TABLE OF CONTENTS

ABSTRACT

Aims Cav-1 in the endothelium has a role in hemodynamic regulation. In the present study, we evaluate the role of endothelial cell Cav-1 in blood pressure regulation in response to dietary salt intake. We will also investigate the endothelial Cav-1 role in Aldosterone (ALDO)/mineralocorticoid receptor (MR) activation. As a secondary outcome, we will assess the role of endothelial Cav-1 in glucose and lipid homeostasis.

Methods and Results Studies were performed using endothelial cell specific Cav-1 knock-out (EC Cav-1 KO) mice and their wild-type (WT) littermates. Mice were maintained on a low salt (LS) diet (0.02% Na+) for a week, followed by another week on high salt (HS) diet (1.6% Na+), and continued with ALDO infusion via osmotic minipumps for 3 weeks. EC Cav-1 KO mice had higher pulse pressure on both LS and HS diets suggesting poor arterial compliance. EC Cav-1 deficient animals are also associated with increased heart rate, probably secondary to impaired baroreceptor reflex. ALDO infusion did not increase blood pressure but it caused organ damage as assessed by organ weight relative to body weight and albuminuria in both KO and WT animals. As compared to the WT, EC Cav-1 KO did not display overt insulin resistance (IR); however they display a trend for modified glucose tolerance curves and dyslipidemia.

Conclusion In conclusion, EC Cav-1 is necessary to maintain normal BP homeostasis on both LS and HS diet, possibly via regulation of eNOS. Normal endothelial function regulates arterial compliance and function. The present study does not suggest that EC Cav-1 modulate the effects of ALDO/MR activation on BP regulation. However, EC Cav-1 is likely to be a mediator for ALDO-induced cardiac

INTRODUCTION

A substantial portion of human diseases today are classified as multifactorial, caused by genetic and environmental factors. The genomic study of these diseases has attracted considerable attention during the past few years. The Genome Wide Association Study (GWAS) is one of the recently developed techniques that examine the association between Single Nucleotide Polymorphims (SNPs) and individual risks of developing a particular disease. In addition, knock-out animal models have been available since 1981 and these are useful to study the effect of eliminating a specific gene. Such models then gave the investigators a potential tool to understand the mechanisms responsible for the effects of gene variation in humans, thus allowing for better understanding of the pathophysiologic basis for these diseases. Another recent development in gene alteration includes using the Cre-Lox system of site specific recombination of bacteriophage P1, which enables us to see the effect of tissue specific gene knock-out.(Bedell et al., 1997)

Caveolae, discovered in the 1950s, are small invaginations on plasma membranes, measuring from 50-100nm.They are extremely rich in number on adipocytes, and are also found in endothelial cells, type I pneumocytes, and smooth muscle cells.(Cohen et al., 2004a) Structurally, they are visible as lipid rafts with striated coats, formed by proteins namely caveolins, for example, caveolin 1(Cav-1). (Sengupta (2012) Caveolae are involved in transportation of molecules (endocytosis, transcytosis and pinocytosis), and recently found to be involved in many signaling pathways as they contain several signaling molecules and enzymes. (Razani et al., 2002b) These signaling molecules are also believed to interact with Cav-1 itself. One of the most established interaction is with eNOS (endothelial nitric oxide synthase).