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THE ROLE OF CAVEOLIN-1 IN MEDIATING THE EFFECTS OF ALDOSTERONE-MEDIATED MINERALOCORTICOID RECEPTOR ACTIVATION

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2. Abstract

Mineralocorticoid receptor (MR) activation by aldosterone (ALDO) in the endothelial cells of the vascular system has been recognized as one of the many causes of hypertension. Previous studies from this laboratory has recently demonstrated that MR is present and functional in endothelial cells, co-localizes and co-immunoprecipitates with caveolin-1 (CAV-1), suggesting a role of CAV-1 in modulating MR function. This is further supported by the presence of caveolin binding motifs on MR as well as evidence showing that CAV-1 KO has reduced ALDO-mediated vascular damage as compared to WT mice, implicating an interaction between MR and Cav-1. Despite the mounting evidence that MR and CAV-1 are associated in endothelial cells, the cross talk between the pathways mediated by these proteins remains vague. This study was designed to elucidate (1) the genomic effects of ALDO on MR and CAV-1 proteins, (2) the non-genomic effects of ALDO on CAV-1 and ERK1/2 phosphorylation, as well as (3) the role of CAV-1 in modulating these effects. Our data provides evidence that the genomic effects of ALDO include MR and eNOS downregulation, CAV-1 upregulation, ALDO-induced ERK1/2 phosphorylation and CAV-1 dephosphorylation. We were also able to show CAV-1's function in modulating the above mentioned proteins by knocking down CAV-1 (CAV-1 KD) in Ea.hy926 cells.

3. Introduction

According to WHO World Health Statistics 2012 Report, one out of three adults worldwide suffers from hypertension and this contributes largely to mortality as a result of stroke, renal insufficiency and heart disease. Inadequate management of a raised blood pressure leads to permanent, dire consequences for the cardiovascular system. Be that as it may, this disease is not only difficult to diagnose due to obscure physical symptoms, the etiology differs for each individual, ranging from primary causes such as diet, aging and stress to secondary causes as an effect of an underlying disease; making personal, specific treatment challenging (Kannel, 1996).

Caveolae, so called 'little caves'; are small flask shaped invaginations present mainly on the surface of plasma membranes. These organelles are expressed abundantly in various cell types, especially in adipocytes, endothelial and lung cells. Caveolae are believed to be mainly involved in receptor dependent and receptor independent endocytosis as well as signal transduction in endothelial cells. Caveolin-1 (CAV-1) is a major component of caveolae, supported by the fact that correct expression of CAV-1 is essential for proper caveolae expression on plasma membranes (Galbiati et al., 1998).

Mineralocorticoid receptors (MR) are found in epithelial cells lining the renal collecting tubules of the kidney, whereby they play an important role in salt and water regulation and thus, blood pressure homeostasis through its activation by the hormone ALDO (Arai et al, 1994; Farman & Rasfetin-Oblin). Derangements in this mechanism have been proposed as one of the causes of hypertension. Recently, MR was demonstrated to be expressed as well as being fully functional in both vascular smooth muscle and endothelial cells, inferring that it might have a role in the pathogenesis of hypertension directly through the vascular system in parallel to its effects on the kidney. Additionally, recent evidence supports a plasma membrane type of MR, which mediates ALDO's rapid effects on the vascular system. However, the MR mechanisms of action in the endothelial cells are yet to be fully understood. Some clarity came to this issue when it was determined that a steroid receptor binding motif - a definitive sequence of amino acids - exists on CAV-1. Because it has been documented that estrogen and androgen receptors bind to CAV-1, it is likely that there is a similar relationship between MR and CAV-1.

Based on this evidence, we theorize that CAV-1 modulates MR function in endothelial cells in both genomic and non-genomic pathways. To assess this hypothesis, we seek to clarify 1) the