【Grant-in-Aid for Scientific Research(S)】

Biological Sciences (Medicine, dentistry, and pharmacy)

Title of Project : Salt stress-induced responses in health and disease: the role of WNK kinases and new therapeutic strategies

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Research Area : Hypertension, Kidney disease, Physiology
Keyword : With-No-Lysine (WNK) kinase, salt stress, transporter

【Purpose and Background of the Research】

The effects of high salt intake on blood pressure have been investigated for a long time. Recently, the adverse effects of high salt intake other than blood pressure, such as cancer, inflammation, and some types of neurological disorders, have been clarified. Identification of a key molecule such as WNK kinase have contributed significantly to our understanding of the molecular pathogenesis of salt-sensitivity. Considering that salt-sensitivity itself is a risk factor for cardiovascular events, it is an important task to investigate the molecular mechanisms and its consequences of increased salt-sensitivity in body.

The purpose of this study are to elucidate molecular mechanisms of salt-stress induced responses and injuries in cells and tissues within body and to establish new therapeutic strategies for the resultant disorders.

【Research Methods】

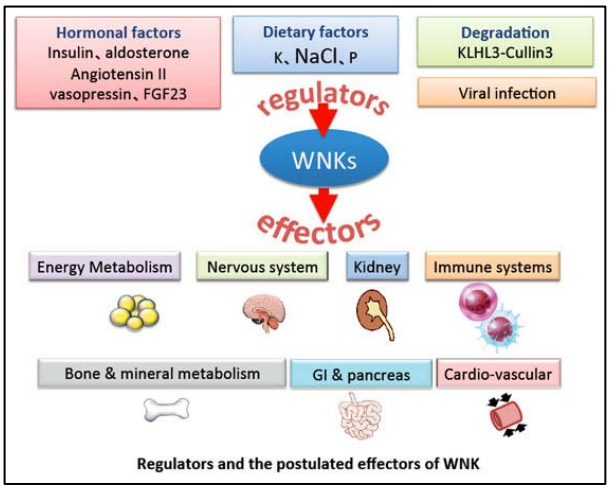
We have clarified the several upstream regulators and downstream effectors of WNK signal cascade, showing the involvement of WNK kinases not only in blood pressure regulation but also in other disorders in various organs (see Figure). In this study,

① We will identify more upstream regulators of WNK to elucidate factors inducing salt-sensitivity through the activation of WNK signal cascade. We have already clarified the mechanism of an increased salt-sensitivity in metabolic syndrome by identifying that hyperinsulinemia activates this cascade.

② To clarify the pathogenic effects of salt-sensitivity itself and salt stress-induced responses in organs, we will take advantage of our salt-sensitive hypertension model mouse ($Wnk4^{D561A/+}$ knock-in mouse). Comprehensive analyses of the mice under various salt diets will disclose biomarkers and new therapeutic targets in salt stress-induced disorders.

③ Several models of kidney dysfunction was made in our hypertensive model to clarify the alteration of salt stress-induced responses under the reduced kidney function.

④ Chemical library screening will be performed to search for drugs to modulate WNK signal cascade and newly identified targets involved in salt stress-induced responses.



Regulators and the postulated effectors of WNK

【Expected Research Achievements and Scientific Significance】

This study will provide new understanding of salt-sensitivity and new therapeutic strategy for salt stress-induced disorders.

【Publications Relevant to the Project】

1. Yang SS, Uchida S et al. Molecular pathogenesis of pseudo-hypoaldosteronism type II: generation and analysis of a Wnk4 D561A/+ knock-in mouse model. ***Cell Metab.*** 5:331-344, 2007.
2. Wakabayashi M, Uchida S et al. Impaired KLHL3-mediated ubiquitination of WNK4 causes human hypertension. ***Cell Rep.*** 3(3):858-68, 2013.

【Term of Project】 FY2013-2017

【Budget Allocation】 150, 200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.tmd.ac.jp/grad/kid/kid-J.htm