Unscrambling a role of a newly characterized splice-variant NaCl cotransporter in the regulation of arterial blood pressure

Clinical relevance

Hypertension affects up to 25% of the adult population in industrialized countries. It contributes importantly to morbidity and mortality. The kidney plays a key role in chronic blood pressure homeostasis by maintaining appropriate renal Na^+ reabsorption. The thiazide-sensitive NaCl cotransporter (NCC) is a major salt transporter in the distal convoluted tubule (DCT) of mammalian kidneys. The role of NCC in the regulation of arterial blood pressure has been firmly established by the clinical effects of reduced or augmented activity of the cotransporter. The thiazide diuretics that act by blocking NCC are considered the first line pharmacological treatment of hypertension.

Background

The NCC is a membrane protein responsible for reabsorbing 5-10% of the filtered load Na^+ in the kidney. The NCC is regulated via phosphorylation; the amino (N)-terminal domain of NCC contains several phosphorylation sites being of critical importance for NCC functioning. NCC has three isoforms that differ in length of amino acid chain. Despite the presence of all isoform in the human kidney, the longest splice variant (NCC-Sv) has been neglected in the majority of the NCC studies. Recently, a novel phosphorylation site at a serine 811 has been demonstrated in NCC-Sv providing novel insights into complex machinery regulating salt reabsorption.

Goals

The aim of the present proposal is to address molecular, functional, and clinical implications of NCC-Sv activity and the regulation of blood pressure. The rational is that NCC-Sv plays a key role on the Na^+ reabsorption and blood pressure regulation. The network of signaling proteins connected to the mechanism of NaCl reabsorption in DCT will be dissected using cell and animal models as well as human urinary samples in a collaborative study involving the departments of Nephrology and Physiology. The following key objectives will be investigated:

I) Molecular mechanism of NCC-Sv regulation using mammalian cell lines.
II) Dissect the role of NCC-Sv in development of pathological conditions (especially hypertension) by implementing urinary exosomes analysis.

The results of the present study will increased the understanding of the molecular pathways on Na^+ reabsorption and will enable us to formulate a rational guideline for the treatment of hypertension.

Techniques

This internship will allow you to learn and apply several techniques, such as:

- Molecular cloning
- Cell culture
- Immunohistochemistry
- Exosome isolation
- Western Blot

Contact

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