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Primary Research Interest:	Internal Medicine
Description of Research:	The aim of this grant application is to investigate the molecular mechanisms underlying WNK4's inhibitory effect on Maxi K. Studies have shown that WNK kinase affects ROMK function and protein expressions. However, little is known about the regulation of Maxi K channel by WNK kinase. The central hypothesis of this application is that WNK4 kinase requires a specific interaction with Maxi K (or BK) in order to modulate Maxi K activity either through affecting Maxi K protein processing or through altering the phosphorylation of Maxi K. Further exploration of ion transport regulation by WNK kinase in the distal nephron, as well as the elucidation of the underlying pathophysiologic mechanism of PHA II caused by mutations of WNK kinases, will give us a better understanding of essential hypertension, a prerequisite for development of therapeutics for millions of hypertensive patients. In addition, the goal of new VA merit award is to investigate the novel role of BK channel in renal fibrosis underlying CKD progression. Using combination of cell culture, different renal fibrotic mouse models in WT and BK knock out mice and renal biopsy samples we will explore the mechanism underlying the pathogenesis of renal fibrosis and development and progression of CKD.
Relevance to VA:	Hypertension is one of most common diseases in the world. Elderly population including Veteran in USA has very high prevalence in hypertension. Kidney plays an important role in the regulation of potassium homeostasis. WNK kinase is a novel serine/threonine kinase that represents a novel signaling pathway in the regulation of blood pressure and electrolyte homeostasis. Mutations in this kinase member cause pseudohypoaldosteronism type II (PHA II) featuring hypertension, hyperkalemia and metabolic acidosis. Further exploration of potassium channel regulation by WNK kinase in the distal nephron, as well as the elucidation of the underlying pathophysiologic mechanism of PHA II caused by mutations of WNK kinases, will give us a better understanding of essential hypertension, a prerequisite for development of therapeutics for millions of hypertensive patients. In addition, PI also investigates the novel role of BK channel in Renal fibrosis using both cell culture, animal and renal biopsy sample. Renal fibrosis is the hall marker for the progression of chronic kidney disease (CKD) which is one of the most common diseases in Veteran population. Exploration of potential therapeutic target on novel BK channel is highly clinical relevant.