Council's Corner: Hypertension Issues - a personal view

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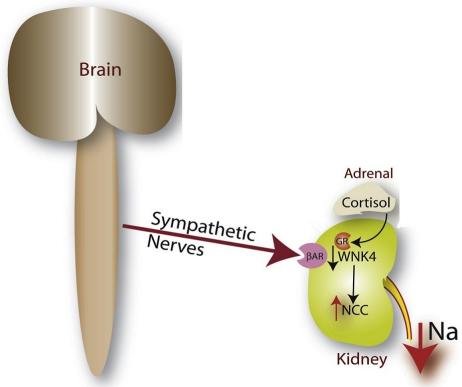
Salt-sensitive hypertension –what does the future hold?

Hypertension represent a global health epidemic that is predicted to affect over 1.5 billion individuals by the year 2025 and salt-sensitive hypertension is a significant component of hypertension. Salt-sensitivity affects approximately 50% of hypertensive patients, leading to a 3-fold increase in the risk of adverse cardiovascular events compared to salt-resistant hypertensive patients. It is well established that integrated neural, humoral, and renal mechanisms are implicated in the pathogenesis of salt-sensitive hypertension. Interest in enhancing our understanding of the neural mechanisms involved in hypertension, and salt-sensitivity in particular, has been renewed by 1) the elegant work of Dr. Fujita who demonstrated a direct role of renal sympathetic innervation in the dysregulation of the renal sodium chloride co-transporter as a key event in the pathophysiology of salt-sensitive hypertension (1) and 2) the conflicting results of the SYMPLICITY HTN trials in which renal nerve ablation produced both persistent blood pressure reduction (HTN 1 & 2) and a lack of effect versus placebo (HTN-3). Despite decades of pioneering work enhancing our knowledge of the neural control of the kidney (2) and recent insights into the regulation of renal sodium transporters, as illustrated schematically, the central mechanisms regulating sympathetic nerve traffic to the kidney remain to be defined.



(Adapted from Ellison and Brooks, 2011 Cell

Here in Boston, in the Department of Pharmacology & Experimental Therapeutics and the Whitaker Cardiovascular Institute, we have been investigating the integrated neural control of blood pressure, with a particular focus on the central regulation of the renal sympathetic nerves. These investigations have revealed the presence of an endogenous central molecular signal transduction pathway, Gαi2 subunit proteins (which facilitate signal transduction following GPCR activation), that is required to mediate the acute renal sympathoinhibitory, hypotensive, and natriuretic responses to both pharmacological and physiological stimuli. Significantly, endogenous up-regulation of hypothalamic PVN Gαi2 proteins in salt-resistant animal models in response to increased salt-intake is required to potentiate endogenous renal nerve dependent sympathoinhibitory sodium excreting mechanisms to counter the development of salt-sensitive hypertension (4). We postulate that this central molecular pathway compliments the ground breaking research of the Fujita lab and provides a potential mechanism in the central nervous system through which renal nerve activity is regulated to influence renal regulation of the sodium chloride co-transporter in both salt-resistant and sat-sensitive rat phenotypes.

Owing to the increasing worldwide prevalence of hypertension, and the role of dietary salt-intake in the pathophysiology of this disease (5), it is clear that increased understanding of the central mechanisms involved in blood pressure regulation, in both normotensive and salt-sensitive hypertensive animal models and humans is required. A significant number of key questions pose barriers to our understanding of the pathophysiology of salt-sensitivity including; how and where is salt-sensed by the body? What mechanistic responses are activated to maintain salt-resistance and do these represent future therapeutic targets? How can you rapidly and reproducibly assess salt-sensitivity in human patient populations? Can non-invasive biomarkers of salt-sensitivity be identified? I look forward to the answers to these issues being addressed by the global hypertension community in the coming decades to enhance to our ability to understand and combat the global hypertension epidemic.

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