Oxidative regulation of Na/K-ATPase in the cardiovascular system

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Background: The Na^+-K^+ pump's role in maintaining electrochemical gradients for Na^+ and K^+, indirectly regulating intracellular Ca^{2+}, gives it a particularly important role in cardiovascular pathophysiology. We have identified glutathionylation of its β1 subunit (β1-GSS), a reversible post-translational modification, as a regulatory mechanism of oxidative inhibition of the pump.

Methods and Results: We have used a combination of molecular biology and cellular electrophysiology to demonstrate the key role of β1-GSS in the regulation of the cardiac Na^+-K^+ pump by neurohormones, including Angiotensin II, adrenergic hormones, and atrial natriuretic peptide. Furthermore, the identification of increases in β1-GSS in heart failure, and under conditions of myocardial ischaemia-reperfusion, provides a novel link between the oxidative stress characteristic of these disease states, with pathophysiological dysregulation of Na^+ and Ca^{2+} in the cell. We have also explored the involvement glutathionylation of the Na^+-K^+ pump's β1 subunit in redox-mediated vascular dysfunction. β1-GSS, present at baseline in vascular smooth muscle, is increased by exposure to Ang II in rabbit aorta, primary rabbit aortic vascular smooth muscle cells (VSMCs) and human artery. This is associated with impaired K^+-induced vasorelaxation. The decrease in Na^+-K^+ ATPase activity is NADPH oxidase dependent. Given the known mediating role of ROS and $[Ca^{2+}]_i$ in growth signaling responses of VSMC, we next investigated the impact of redox regulation of the Na pump on VSMC proliferation. Silencing FXYD1, known to augment ROS-inhibition of the Na^+ pump, increased VSMC proliferation in a Src kinase-dependent manner. The proliferative response to silencing FXYD1 was similar in magnitude to that driven by the inflammatory cytokine TNFα, recognized as a key driver of growth signaling in VSMC in atherogenesis. Consistent with this, FXYD1 knockout *in vivo* resulted in increase in aortic medial thickness and perivascular fibrosis.

Conclusion: The Na^+-K^+ pump is inhibited by reversible glutathionylation of its β1 subunit in response to physiological and pathophysiological stimuli, with acute and chronic consequences. Collectively, these findings point to the Na^+-K^+ pump and associated regulatory molecules as promising targets for the treatment of ROS-mediated cardiovascular disease.