The Na/K-ATPase as an Amplifier for Oxidant Signals: Brief Historical Review and Possible Implications

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Our laboratories have focused their efforts over the past 20 years on elucidating the role of the sodium potassium adenosine triphosphatase (Na/K-ATPase) in the cardiovascular disease associate with renal failure. Before I briefly summarize some of our insights, let me first reassure the reader that we understand that this is not a novel topic. In fact, one could argue that the Na/K-ATPase has been the most (or certainly one of the most) studied protein(s) in biomedical science since its discovery by Jens Skou in the late 1950s. Moreover, the endogenous ligands of this protein, referred to historically as "3rd factor", digitalis like substances and more recently cardiotonic steroids have been studied by a virtual who’s who of nephrology including Hugh de Wardner, Robert Schrier, Vardaman Buckalew, and Neal Bricker as well as other scientific luminaries such as Mordecai Blaustein, John Hamlyn and Alexei Bagrov [1].

The concept that these workers developed was based on the critically important pumping function of the Na/K-ATPase which, in mammalian systems, extrudes 3 Na molecules from the intracellular milieu and brings 2 K molecules into the cytosol, both actions working against established concentration gradients. The Post-Albers model of the sodium pump involves cycling between E1 and E2 states to allow for energy dependent pumping of Na and K against their concentration gradients [2]. Up until the late 1990s, all signaling function attributed to the pump involved either augmented or inhibited pumping function producing changes in cytosolic Na and K to initiate the postulated signal cascade. A detailed description of the shortcomings of this ionic model for sodium pump signaling is beyond the scope of this editorial but is discussed in several recent reviews [1-4]. While some effects of cardiotonic steroids may, in fact, be mediated through alteration of the pumping function of the Na/K-ATPase, a different role of this protein probably explains quite bit more.

In the late 1990s, Dr. Zijian Xie and collaborators from our laboratories uncovered evidence supporting a scaffolding function for the Na/K-ATPase [5,6]. Specifically, it was observed that in higher animals, a portion of the N domain of the alpha1 subunit contained a sequence which bound the kinase domain of sarcoma related kinase (Src) [7,8]. When the conformation of the Na/K-ATPase was altered by binding a cardiotonic steroid or oxidation (vita infra), Src was able to modify the epithelial growth factor receptor (EGFR) and trigger a signal cascade which leads to the generation of reactive oxygen species (ROS) and widespread downstream effects ranging from increases in cytosolic calcium to changes in gene transcription [9]. Additional work from our laboratories established that these ROS fed back to the alpha1 subunit with specific carbonylation sites, allowing the Na/K-ATPase signal cascade to function as a feed forward amplifier whose signal appears to be terminated by endocytosis. This endocytosis of the basolateral Na/K-ATPase in renal proximal tubular cells appears to be coordinated with a redistribution of the apical sodium proton antiporter (isoform 3, NHE3) allowing for a meaningful decrease in net sodium reabsorption by the kidney [10-14]. However, additional work speaks to a role for the Na/K-ATPase as a promiscuous amplifier of oxidant signals, potentially relevant to a number of cardiovascular conditions including renal fibrosis and hypertension, uremic cardiomyopathy and obesity/metabolic syndrome [15-21].

The concept that emerges from this body of work is the Na/K-ATPase signal cascade as an amplifier system with the endogenous cardiotonic steroids serving as a biological rheostat to this amplifier. Although not all hormone and cytokines signal via oxidants, many do, and the Na/K-ATPase signal cascade essentially amplifies the signal produced by those that do. That stated, if this scenario is correct, it offers a novel and potentially safe targets for a number of biomedical conditions. In some cases, stimulating this oxidant amplification in target tissues might be appropriate (e.g., organ differentiation and development in premature infants, muscle hypertrophy in post-traumatic rehabilitation) whereas blocking this pathway could potentially ameliorate maladaptive growth and scarring (e.g., cardiomyopathy associated with renal failure, scleroderma). To date, some agonists of the Na/K-ATPase signal cascade have been identified as have some antagonists. We have also specifically developed classes of peptides which serve as signal complex disrupters as well as signal terminators [17,20,22-25]. It is our hope and expectation that pharmacological agents useful in the clinic will be developed from Professor Xie’s insights which have reinvigorated the study of this important system.

References


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