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Hypothetical mechanism of sodium pump regulation by estradiol under primary hypertension

Emina Sudar[a], Jelena Velebit[a], Zoran Gluvic[b], Zorica Zakula[c], Emilija Lazic[a], Ljiljana Vuksanovic-Topic[a], Biljana Putnikovic[b], Aleksandar Neskovic[b], Esma R. Isenovic[a,*]

[a]*Laboratory for Molecular Genetics and Radiobiology, Institute Vinca, P.O. Box 522, 11001 Belgrade, Serbia*
[b]*Department of Endocrinology and Cardiology, Clinical Hospital Center—Zemun, Vukova Street 9, 11080 Zemun, Serbia*
[c]*Laboratory for Molecular Biology and Endocrinology, Institute Vinca, P.O. Box 522, 11001 Belgrade, Serbia*

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Abstract

Causal relationship between sodium and hypertension has been proposed and various changes in Na^+,K^+-ATPase (sodium pump) activity have been described in established primary hypertension. A number of direct vascular effects of estradiol have been reported, including its impact on the regulation of sodium pump activity and vasomotor tone. The effects of estradiol involve the activation of multiple signaling cascades, including phosphatydil inositol-3 kinase (PI3K) and p42/44 mitogen-activated protein kinase ($p42/44^{MAPK}$). In addition, some of the effects of estradiol have been linked to activity of cytosolic phospholipase A_2 ($cPLA_2$). One possible cardioprotective mechanism of estradiol involves of the interaction between estradiol and the rennin–angiotensin system (RAS). Elevated circulating and tissue levels of angiotensin II (Ang II) have been implicated in the development of hypertension and heart failure. The aim of our investigation was to elucidate the signaling mechanisms employed by estradiol and Ang II in mediating sodium pump, in vascular smooth muscle cells (VSMC). The aim of our investigation was to elucidate the signaling mechanisms employed by estradiol and Ang II in mediating sodium pump activity/expression in VSMC, with particular emphasis on $PI3K/cPLA_2/p42/44^{MAPK}$ signaling pathways. Our primary hypothesis is that estradiol stimulates sodium pump activity/expression in VSMC *via* $PI3K/cPLA_2/p42/44^{MAPK}$ dependent mechanism and, that impaired estradiol-stimulated sodium pump activity/expression in hypertensive rodent models (i.e. SHR), Ang II-mediated vascular impairment of estradiol is related to a decrease ability of estradiol to stimulate the $PI3K/cPLA_2/p42/44^{MAPK}$ signaling pathways. An important corollary to this hypothesis is that in hypertensive state (i.e. SHR rats) the decreasing in ACE enzyme activity and/or AT1 receptor expression caused by administration of estradiol is accompanying with abrogated ability of Ang II to decrease IRS-1/PI3K association, and consequent $PI3K/cPLA_2/p42/44^{MAPK}$ activity and associated sodium pump activity/expression.

A clear characterization of how Ang II attenuates estradiol signaling may lead to a better understanding of the molecular mechanism(s) underlying pathophysiological conditions such as hypertension and to understanding how certain pathophysiological situations affect sodium pump activity/expression in VSMC.

Keywords: Estradiol; Vascular smooth muscle cells; Hypertension; Kinase; RAS

1. Introduction

The Na^+,K^+-ATPase (sodium pump) is a highly conserved integral membrane protein that is expressed in virtually all cells of higher organisms. It has been estimated that roughly 25% of all cytoplasmic ATP is hydrolyzed by sodium pumps in resting humans. Abnormalities in the number or function of sodium pump are thought to be involved in several pathologic states, particularly in heart diseases and hypertension.

Hypertension is the major cardiovascular risk factor and is associated with significant morbidity and mortality worldwide (Ezzati et al., 2002). Primary hypertension that accounts for up to 95% of all cases of hypertension (Kaplan, 2006) results from the complex interplay of

*Corresponding author. Tel./fax: +381 11 2447485.
E-mail address: isenovic@yahoo.com (E.R. Isenovic).

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internal derangements (primarily in the kidney) and the external environment. Sodium, the main extracellular cation, has long been considered as pivotal environmental factor in hypertension. Numerous studies have demonstrated an adverse effect of surfeit of sodium on arterial blood pressure (Iwamoto and Kita, 2006; Williams and Hollenberg, 1991; O'Shaughnessy and Karet, 2004; Elliott, 2003). By contrast, potassium, the main intracellular cation, has usually been viewed as a minor factor in the pathogenesis of hypertension. However, it has been indicated that potassium deficit may also have a role in hypertension and its cardiovascular sequelae (Whelton, 2003). Thus, it appears that interaction of sodium and potassium, as compared with an isolated surfeit of sodium or deficit of potassium, is the dominant environmental factor in the pathogenesis of primary hypertension.

The homeostasis of sodium and potassium plays an important role in endothelium-dependent vasodilatation, which is defective in primary hypertension (Panza et al., 1990). Sodium retention decreases the synthesis of nitric oxide, an arteriolar vasodilator elaborated by endothelial cells, and increases the plasma level of asymmetric dimethyl L-arginine, an endogenous inhibitor of nitric oxide production (Fujiwara et al., 2000). Sodium restriction has opposite effects. A high-potassium diet and increases in serum potassium, even within the physiologic range, cause endothelium-dependent vasodilatation by hyperpolarizing the endothelial cell through stimulation of the sodium pump and opening potassium channels (Amberg et al., 2003). Endothelial hyperpolarization is transmitted to the vascular smooth-muscle cells, resulting in decreased cytosolic calcium, which in turn promotes vasodilatation. Body deficit of potassium inhibits potassium channels in the cell membrane, depolarizing the membrane (the membrane potential shifts closer to 0). Because of its electrogenic nature, the inhibition of the sodium pump itself decreases the membrane potential. Membrane depolarization in the vascular smooth-muscle cells promotes a further rise in intracellular calcium by activating voltage-dependent calcium channels in the membrane, calcium channels in the sarcoplasmic reticulum, and the sodium–calcium exchanger (Iwamoto, 2006).

Estradiol is known to couse a sustained increase in sodium pump (Dzurba et al., 1997; Palacios et al., 2004). Although angiotensin II (Ang II) increases sodium pump in vascular smooth muscle cells (VSMC) (Brock et al., 1982; Isenovic et al., 2004a, b), it may interfere with estradiol mediated sodium pump activation. To our knowledge, there are no studies characterizing the interactions of the estradiol and Ang II signaling pathways involved in regulation of the sodium pump in VSMC. This information may serve as an important foundation for understanding the specific pathways by which the sodium pump activity/expression is selectively regulated in VSMC at a molecular level, which may have fundamental impact in both normal and pathophysiological conditions.

2. Role of the sodium pump in hypertension

Hypertension is a disease that provokes important alterations in cardiovascular system (Rose and Valdes, 1994). Causal relationship between sodium and hypertension has been proposed, and various changes in Na^+ pump activity have been described in established primary hypertension in the rat (David-Dufilho et al., 1984). Changes in the active and passive Na^+ and K^+ transport membrane and alterations in the Na^+-activation of cardiac sodium pump from SHR were reported (Godfraind and Noel, 1980).

Sodium pump (EC 3.6.1.37) is an important integral membrane protein that transports three Na^+ ions out of the cell and two K^+ ions into the cell using the energy derived from hydrolysis of one molecule of ATP. Structurally, the minimal units of the sodium pump are two major polypeptides, the alpha and beta-subunits. Also, the subunits have different isoforms, four alpha and three beta, which exhibit 85% and 45% identity, respectively (Blanco and Mercer, 1998). The alpha subunits are responsible for the catalytic and transport properties of the enzyme, as they contain binding sites for cations and ATP and a phosphorylation site (Terien and Blostein, 2000). The beta subunits are involved in docking with the sodium pump at the plasma membrane (Terien and Blostein, 2000). While multiple isoforms of sodium pump alpha (alpha1, alpha2, alpha3, alpha4) and beta (beta1, beta2, beta3) are expressed in a tissue-specific fashion, the alpha1 and beta1 subunits are constitutively expressed in most tissues (Crambert et al., 2000). Moreover, in primary cultures of VSMC alpha1 and beta1 represent the predominant isoforms (O'Donnell and Owen, 1994).

The sodium pump, represents the cellular transport system that controls Na^+ homeostasis (O'Donnell and Owen, 1994) and membrane potential (Hermsmeyer and Erne, 1990) and in this way can contribute to the regulation of the tone and contractility in the vasculature (Blaustein, 1993). The sodium pump is hypothesized to be involved in systemic vascular hypertension through its effects on smooth muscle reactivity and myocardial contractility (Herrera et al., 1988). It has been proposed that inhibition of the sodium pump in hypertensive patients leads to an increase in VSMC cytosolic Na^+, followed by elevation of free intracellular Ca^{2+} and resultant enhancement of contractility and blood pressure (Blaustein, 1993). Various recent studies showed that development of functional alterations of the sodium pump in response to hypertension induced complications in the cardiovascular system (Vrbjar et al., 1999a, b; Vrbjar and Pechanova, 2002; Vrbjar et al., 2002; Wu et al., 2003). Spontaneous hypertension was associated with cardiac hypertrophy as it is demonstrated by 71% increase of the heart weight/body weight ratio in male rats. This is in agreement with previous studies concerning the SHR (Godfraind and Noel, 1980; Jelicks and Gupta, 1994). The importance of sodium pump in the development and maintenance of hypertension was