Journal of Bioequivalence & Bioavailability
ISSN: 0975-0851

Ayrapetyan, J Bioequiv Availab 2015, 8:1
DOI: 10.4172/jbb.10000e70

Editorial Open Access

The Dysfunction of Camp-Dependent Na^+/Ca^{2+} Exchange in Reverse Mode as a Primary Mechanism for Age-Dependent Cardio-Muscle Failure

Sinerik Ayrapetyan*

UNESCO Chair-Life Sciences, International Postgraduate Educational Center, 31 Acharyan St, 0040 Yerevan, Armenia

Heart muscle failure, the risk of which is increased by aging, remains as a major cause of mortality and morbidity. The cardio-myocyte is made up of approximately 50% of myofibrils, and the remainder consists of mitochondria, nucleus, sarcoplasmic reticulum (SR) and the cytosol [1]. Therefore, the cytoskeleton and myofibril contractility have their essential roles in metabolic regulation of myocyte volume, which could be considered as a marker for myocyte contraction. As Ca^{2+} has a key role in the process of muscle contractility, at present all precautionary and therapeutic methods, aimed at decreasing age-dependent heart muscle failure, are based on the concept that the elevation of SR stress-induced intracellular Ca^{2+} ($[Ca^{2+}]_i$) leads to the generation of a number of pathological changes of heart muscle [2,3]. However, the primary mechanism dysfunction of which brings to the increase of $[Ca^{2+}]_i$ is not clear yet. Though myocyte dehydration is one of the essential hallmarks for aging, our knowledge on its role in heart muscle failure, particularly in increase of $[Ca^{2+}]_i$ is rather limited. As water is a dominant component of cells and serves as a common medium for metabolic reactions, its physicochemical properties has determining role in regulation of cell metabolism. The regulatory role of intracellular water on cell metabolism is realized by controlling intracellular macromolecules, including DNA activities through the "folding –unfolding" mechanisms [4], by surface-dependent changes of a number of functionally active proteins, having enzymes [5], receptors [6] and ionic channel properties [7]. The facts that water structure is extra sensitive to physical and chemical factors [8] and cell membrane is highly permeable for water [9], make the water molecules as primary messengers between cell bathing medium and intracellular metabolism [10]. As intracellular osmotic pressure exceeds the extracellular one, water influx is osmotically driven into cell, which is balanced by metabolism-dependent water efflux. It has been shown that depending on their directions water fluxes through the membrane have activation or inactivation effect on ionic currents: water influx has activation effect on Na^+ (I_{Na}) and Ca^{2+} (I_{Ca}) currents and inactivation effect on K^+ (I_k) current, while water efflux has the opposite effect on these currents [7,11-14]. From these data it is predicted that metabolism-dependent water efflux has a great physiological meaning as it inhibits the electrochemical driving of Na^+ and Ca^{2+} influxes into myocyte.

There are minimum three enzyme systems that are actively involved in metabolic controlling of cell hydration and heart muscle contractility: transporting ATP-ases, having anti-gradient ions transporting functions through the membrane; kinases, regulating contractility of myofibrils; and enzyme systems involved in intracellular oxidation processes, producing water molecules in cytoplasm. It is known that among the aforementioned enzyme systems controlling cell hydration, Na^+/K^+-ATPase has a central role, which is due to the following properties of Na^+/K^+-ATPase: a) being working molecules for Na^+/K^+-pump, Na^+/K^+-ATPase generates Na^+ gradient on membrane, serves as an energy source for a number of secondary ionic transporters in membrane, including Na^+/Ca^{2+} and Na^+/H^+ exchange [15]; b) being the highest ATP energy utilizing mechanism, it determines the rate of oxidative phosphorylation processes resulting the ATP synthesis and the release of H_2O in cytoplasm; [16] c) having electrogenic character, it pumps water from the cells [17-19] and d) besides the transporting function, Na^+/K^+-ATPase has also multisided intracellular signaling functions, including controlling of $[Ca^{2+}]_i$ and phosphorylation and dephosphorylation processes [20,21]. It is known that Na^+/K^+-pump functions with higher rate in pacemaker cells because of high permeability for Na^+ [22]. Therefore, all above mentioned mechanisms are active and Na^+/K^+-pump serves as a central membrane mechanism through which the metabolic controlling of pacemaker activity of cells, including pacemaker of heart muscle is realized [23-25]. Previously it has been shown that Na^+/K^+-pump regulates membrane excitability not only by membrane hyperpolarization but also by potential-independent mechanisms such as water efflux-induced inactivation of I_{Na+} and I_{Ca} and surface-dependent decrease of a number of ionic channels in membrane [7,11].

It is known that the dysfunction of Na^+/K^+-pump, is a common consequence of any pathology, including age-induced heart muscle failure. However, the dysfunction of which properties of Na^+/K^+-pump is a primary mechanism for generation of age-induced cardio-muscle dehydration and failure of muscle contractility is not clear yet.

At present it is well established that Na^+/K^+-ATPase in membrane of cardio-myocyte has three catalytic isoforms, having different affinities to cardio glycosades: low(α_1), middle (α_2) and high (α_3) [26]. Among them α_3 isoform has only signaling function [20,21]. Earlier we have shown that $\leq 10^{-9}$M ouabain (agonist for α_3 receptors) stimulates Na^+/Ca^{2+} exchange in reverse mode (R Na^+/Ca^{2+}) by increasing intracellular contents of cAMP, which leads to membrane hyperpolarization and inhibition of pacemaker activity [27]. Based on the literature data, that cAMP-activated Ca^{2+}-ATPase in SR membrane pushes Ca ions from cytoplasm into SR [28], the aforementioned data on nM ouabain-induced activation of R Na^+/Ca^{2+}exchange can be explained by the decrease of $[Ca^{2+}]_i$.

Our recent study has shown that in spite of the affinities of α_1 and α_2 isoforms to ouabain, the affinity of α_3 isoform to ouabain has pronounced age-dependent depressing character, which is due to the dysfunction of R Na^+/Ca^{2+}exchange [29].

The most essential discovery was that in spite of the fact that R Na^+/Ca^{2+} exchange functions in stoichiometry of 3Na:1Ca [26,30] its activation by $\leq 10^{-9}$M ouabain leads to muscle hydration which has

***Corresponding author:** Sinerik Ayrapetyan, UNESCO Chir-Life Sciences, International Postgraduate Educational Center, 31 Acharyan St, 0040 Yerevan, Armenia, Tel: 74-10-624170; E-mail: info@biophys.am

Received December 17, 2015; **Accepted** December 19, 2015; **Published** December 26, 2015

Citation: Ayrapetyan S (2015) The Dysfunction of Camp-Dependent Na^+/Ca^{2+} Exchange in Reverse Mode as a Primary Mechanism for Age-Dependent Cardio-Muscle Failure. J Bioequiv Availab 8: e70. doi:10.4172/jbb.10000e70

strong metabolism-dependent and age-induced weakening character [29,31,32].

Thus, based on the above mentioned data it is suggested that the dysfunction of the pathway through which cAMP-dependent R Na^+/Ca^{2+} exchange stimulates the release of intracellular water molecules (water efflux from the myocyte) can be considered as a primary mechanism for age-dependent increase of membrane permeability for Na^+ and Ca^{2+} leading to heart muscle failure. Therefore, the elucidation of the mechanism(s) through which cAMP-dependent R Na^+/Ca^{2+} exchange stimulate(s) the rate of glycolysis (H_2O-release) could serve as a novel therapeutic target for age-dependent heart muscle failure.

References

1. Nakano S, Muramatsu T, Nishimura S, Senbonmatsu T (2012) Cardiomyocyte and Heart Failure (Eds).
2. Pott C, Eckardt L, Goldhaber JI (2011) Triple threat: the Na^+/Ca^{2+} exchanger in the pathophysiology of cardiac arrhythmia, ischemia and heart failure. Curr Drug Targets 12: 737-747.
3. Goldwater DS, Pinney SP (2015) Frailty in Advanced Heart Failure: A Consequence of Aging or a Separate Entity? Clin Med Insights Cardiol 9: 39-46.
4. Parsegian VA, Rand RP, Rau DC (2000) Osmotic stress, crowding, preferential hydration, and binding: A comparison of perspectives. Proc Natl Acad Sci U S A 97: 3987-3992.
5. Ayrapetyan SN, Suleymanyan MA, Saghyan AA, Dadalyan SS (1984) Autoregulation of the electrogenic sodium pump. Cell Mol Neurobiol 4: 367-383.
6. Ayrapetyan SN, Arvanov VL (1979) On the Mechanism of the Electrogenic Sodium Pump Dependence of Membrane Chemosensitivity. Comp Biochem Physiol, part A Comp Physiology 64: 601-604.
7. Ayrapetyan SN, Rychkov GY, Suleymanyan MA (1988) Effects of water flow on transmembrane ionic currents in neurons of Helix pomatia and in squid giant axons. Comp Biochem Physiol A Comp Physiol 89: 179-186.
8. Klassen VI (1982) Magnetized Water Systems. Chemistry Press 296 (in Russian).
9. Huang H, Lu FI, Jia S, Meng S, Cao Y, et al. (2007) Amotl2 is essential for cell movements in zebrafish embryo and regulates c-Src translocation. Development 134: 979-988.
10. Ayrapetyan S (2012) Cell hydration as a universal marker for detection of environmental pollution. Environmentalist J 32: 210-221.
11. Kojima M, Ayrapetyan S, Koketsu K (1984) On the membrane potential independent mechanism of sodium pump-induced inhibition of spontaneous electrical activity of japanese land snail neurons. Comp Biochem Physiol 77: 577- 583.
12. Ayrapetyan SN (1985) Activation and inactivation effect of the transmembrane water flows on the transmembrane currents squid giant axon. Biological Journal of Armenia 38: 245-250.
13. AÄrapetian SN, Rychkov GE, SuleÄmanian MA (1988) Modulation of calcium currents in the snail neuron membrane by osmotic gradient. Dokl Akad Nauk SSSR 300: 983-985.
14. Suleymanian MA, Ayrapetyan SN, Arakelyan VB, Ayrapetyan VY (1993) The effect of osmotic gradients on the outward potassium current in dialyzed neurons of Helix pomatia. Cell Mol Neurobiol 13: 183-190.
15. Lang F, Hoffmann EK (2012) Role of ion transport in control of apoptotic cell death. Compr Physiol 2: 2037-2061.
16. Lehninger AL (1970) Mitochondria and calcium ion transport. Biochem J 119: 129-138.
17. Ayrapetyan SN, Sulejmanian MA (1979) On the Pump-Induced Cell Volume Changes. Comp Biochem Physiol part A: Physiol 64: 571-575.
18. Saghian AA1, Ayrapetyan SN, Carpenter DO (1996) Low concentrations of ouabain stimulate Na/Ca exchange in neurons. See comment in PubMed Commons below Cell Mol Neurobiol 16: 489-498.
19. Hall JE, Guyton AC (2006) Textbook of medical physiology. St Louis Mo: Elsevier Saunders. ISBN 0-7216-0240-1.
20. Xie Z, Askari A (2002) Na(+)/K(+)-ATPase as a signal transducer. Eur J Biochem 269: 2434-2439.
21. Bai Y, Morgan EE, Giovannucci DR, Pierre SV, Philipson KD, et al. (2013) Different roles of the cardiac Na^+/Ca^{2+}-exchanger in ouabain-induced inotropy, cell signaling, and hypertrophy. Am J Physiol Heart Circ Physiol 304: H427-435.
22. Wachtel H, Wilson WA (1973) Voltage clamp analysis slow wave generation in bursting neurons. In: Neurobiology of Invertebrates. Mechanisms of Rhythm Regulation (Eds) by J. Salanki, Akademia Kiado, Budapest 59-80.
23. Ayrapetyan SN (1976) Involvement of Sodium Pump in Slow Oscillations Underlying the Bursting Patterns in Helix Neurons. In: Neurobiology of Invertebrates (Eds) by Salanki, Budapest: 353-370.
24. Azatian KV, White AR, Walker RJ, Ayrapetyan SN (1998) Cellular and molecular mechanisms of nitric oxide-induced heart muscle relaxation. Gen Pharmacol 30: 543-553.
25. Bueno-Orovio A, Sanchez C, Pueyo E, Rodriguez B (2014) Na/K pump regulation of cardiac repolarization: insights from a systems biology approach. Pflugers Arch 466: 183-193.
26. Blaustein MP, Zhang J, Chen L, Song H, Raina H, et al. (2009) The pump, the exchanger, and endogenous ouabain: signaling mechanisms that link salt retention to hypertension. See comment in PubMed Commons below Hypertension 53: 291-298.
27. Sagian AA, Ayrapetyan SN, Carpenter DO (1996) Low concentrations of ouabain stimulate Na/Ca exchange in neurons. Cell Mol Neurobiol 16:489-498.
28. Brini M, Carafoli E (2009) Calcium pumps in health and disease. Physiol Rev 89: 1341-1378.
29. Narinyan L, Ayrapetyan S (2015) Dysfunction of nM Ouabain-Induced Activation of the Signaling System Responsible for Age-Related Heart Muscle Failure. Advances in Life Sciences 5: 73-84
30. Baker PF, Blaustein MP, Hodgkin AL, Steinhardt RA (1969) The influence of calcium on sodium efflux in squid axons. J Physiol 200: 431-458.
31. Narinyan L, Ayrapetyan G, Ayrapetyan S (2012) Age-dependent magnetosensitivity of heart muscle hydration. Bioelectromagnetics 33: 452-458.
32. Narinyan LY, Ayrapetyan GS, Ayrapetyan SN (2013) Age-dependent magnetosensitivity of heart muscle ouabain receptors. Bioelectromagnetics 34: 312-322.