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Editorial Open Access

On the Role of Aquaporins in Myocardial Injury

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Abstract

The presence of aquaporins in the cardiovascular system has been well documented, however our knowledge about their role in myocardial pathophysiology is now being elucidated. A brief overview of the presence, function and regulation of aquaporins in myocardial injury is here presented.

Keywords: Aquaporins; Myocardial edema; Cardiopulmonary bypass; Myocardial infarction; Cardiac ischemic injury; Diazoxide; Acetazolamide

Editorial Text

Cardiopulmonary bypass (CPB) renders the myocardium susceptible to water imbalance and subsequent Myocardial edema (ME) as a consequence of decreased cardiac energy supply [1]. Factors leading to ME include hemodilution, ischemia and reperfusion, as well as osmotic gradients arising from pathological changes of the physiological state.

Several members of the aquaporin (AQP) family have been described in the myocardium [2]. The mRNA expression of AQP -1, -3, -5, -7, -9, -10, and -11 was detected in human hearts, while AQP -1, -4, -6, -7, -8, and -11 were detected in hearts from mice and rats [3]. The protein expression of AQP6 was detected inside the myocytes in mice, while AQP4 was exclusively observed on the intercalated discs between cardiac myocytes [4].

Experiments with AQP1 knock-out mice showed microcardia, decreased myocyte dimensions and low blood pressure [5]. On the other hand, knock-out mice for AQP7 showed a conserved cardiac morphology, although low content of glycerol and ATP was observed [6].

Nowadays, research is focused on the role that aquaporins play in myocardial injury. AQP -1, -4, and -6 seems to play different roles in myocardial infarction (MI) in mouse hearts. While the time dependent pattern of the observed up-regulated expression of AQP4 in MI coincides with that of ME and cardiac dysfunction, the expression of AQP1 and AQP6 persistently increase [4].

One of the first reports of aquaporins in heart revealed that AQP1 colocalizes with Caveolin-3 at 20°C and 37°C in rats [7]. Interestingly, when rat cardiac myocytes were exposed to hypertonic media AQP1 was reversibly internalized [7]. In addition, a more recent report showed that AQP1 cosegragates with Caveolin-1 in mice [5]. Recent works demonstrated that the levels of AQP1 mRNA and protein increase 12 hours after global myocardial ischemia in goats following CPB [8]. Moreover, the treatment with HgCl2 reduced ME, indicating that AQP1 is involved in the development of edema [8]. Other works showed that AQP1 expression is inversely correlated with the protein expression of Connexin 43 in goats following CPB [9]. Altogether, these evidences suggest an important role of AQP1 in the regulation of Connexin 43 in the progression of ME, and a related localization of AQP1 and Caveolin-1.

In mouse hearts AQP1 was shown to be localized at caveolae but also in endothelial cell membranes. Cardioplegia, ischemia and hypoxia decrease AQP1 mRNA as well as total protein expression and glycosylation [10]. In endothelium, AQP1 does not regulate the endothelium-derived hyperpolarizing factor (EDH (F)) or NO-dependent relaxation, but its deletion increases prostanoids-dependent relaxation in resistance vessels [5]. AQP1 is involved in vascular angiogenesis in ischemic myocardium after myocardial infarction in rabbit hearts [11]. Acetazolamide (a carbonic anhydrase inhibitor) tempered the effects induced by AQP1 down regulating its expression [11].

The aquaporins expression in heart is regulated by changes of osmolarity. In this sense, it was demonstrated that hyperosmotic NaCl injections induce an up-regulation of AQP1 mRNA and the glycosylated fraction of the AQP1 protein in mice [12]. In the case of AQP4, it was demonstrated that both the mRNA and protein expression decreased in the mouse heart after hyperosmotic NaCl injections [12]. In rats AQP1 can be differentially regulated in response to hydration status [13]. By other side, experiments with AQP4 KO mice demonstrated that the cardiac weight index was increased after the treatment with Isoproterenol (a β-receptor agonist) and that the expression levels of FKBP12.6 (the cardiomyocyte subtype of the FK506 binding protein, which is essential for tight closing of the RyR2 channels during diastole), SERCA2a (sarcoplasmic reticulum Ca2+-ATPase2a), and CASQ2 (calsequestrin 2) were downregulated. In addition, the diastolic calcium concentrations increased [14]. According to the authors, these results indicate that AQP4 KO causes abnormalities of calcium modulating proteins leading to an exacerbation of risk for cardiac arrhythmias and failure. These changes are likely due to an increase in pro-inflammatory factors (ET_A, pPKCε, NADPH oxidase p67phox) which are exacerbated by stress [14]. Other works demonstrated that AQP4 KO mice undergoing global ischemia and reperfusion had reduced infarct size and attenuated left ventricular end-diastolic pressure during reperfusion after cardiac ischemic injury [15]. Also AQP4 KO cardio-myocytes were partially resisted to hypoosmotic stress in the presence of hypercontracture of the left coronary artery [15]. Other evidences indicate that Diazoxide (a mitochondrial KATP-channel opener) may have impact on myocardial water balance and

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glycerol uptake by decreasing the relative expression of AQP7 during coronary artery bypass grafting in patients with stable coronary artery disease [16].

The role that aquaporins play in myocardial injury is being studied at present. Recent research evidences the importance of AQPs in the development of edema following cardiopulmonary bypass. Changes of water balance and alterations of the calcium homeostasis are associated with the myocardial aquaporins function. Further research of AQP regulation will contribute important knowledge about myocardial injury and possible treatment.

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