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Cardiac aquaporin-1 mediates transmembrane transport of hydrogen peroxide and modulates myocardial fibrosis and hypertrophic remodeling

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Aquaporins are a family of transmembrane water channels known to mediate rapid water movements following osmotic gradients. Some isoforms may be permeable to small molecules (H2O2 in plants) although such function in mammalian Aqp’s is undefined. We identified Aqp1 in peripheral membranes of both capillary endothelial and cardiac muscle cells. Subcellular fractionation showed that Aqp1 co-segregated with caveolin 1 in cardiac membranes. We observed that genetic deletion of Aqp1 in mice produces a microcardia, with smaller cardiac myocytes. Isolated adult myocytes from Aqp1 KO mice failed to build a normal hypertrophic response to pro-hypertrophic stimuli such as phenylephrine (PE). By analogy with plant aquaporins, we hypothesized that Aqp1 facilitates transmembrane transport of extracellular H2O2 generated by, and mediating the hypertrophic response to alpha1-adrenergic activation. Indeed, genetic deletion of Aqp1 reduced the intracellular detection of ROS (by H2-DCFDA) or H2O2 (with the specific HyPer3 sensor targeted to caveolae through infection with a recombinant AAV9) in adult cardiac myocytes exposed to graded concentrations of extracellular H2O2, demonstrating a role for Aqp1 in transmembrane transport of H2O2. Incubation of WT myocytes with PE increased ROS/H2O2 signals, but co-treatment with PE and cell-impermeable catalase abrogated both the intracellular ROS signals and the hypertrophic response. Decreased ROS/H2O2 signals were observed upon exposure of myocytes from Aqp1 KO mice to PE (normalized fluorescence, X103; 102+/−34 vs 400+/−16 in WT; P<0.05), suggesting that Aqp1 mediates the import of H2O2 produced extracellularly upon alpha1-adrenergic stimulation. Downstream phosphorylation of ROS-sensitive protein kinases involved in hypertrophy (p38 MAPK, ERK) was similarly reduced in membrane fractions of adult cardiac myocytes from Aqp1−/− mice treated with graded concentrations of PE. To test the functional importance of Aqp1 deletion on cardiac remodeling, we treated Aqp1 KO mice (and WT littermate) with minipump infusion of angiotensin II for 14 days. To control for loading conditions, blood pressure was continuously measured in all mice by implanted telemetry. Ang II resulted in similar increases in BP in both genotypes. WT mice developed cardiac myocyte hypertrophy and fibrosis, which were significantly attenuated in Aqp1 KO (myocyte area : 462+/−13µ2 vs 702+/−23 µ2 in WT; P<0.01). Similar reductions in hypertrophy and fibrosis were observed in Aqp1 KO mice after TAC (myocyte area : 454+/−15µ2 vs 762+/−14 µ2 in WT; P<0.01). Hypomorphic Aqp1+/− showed an intermediate response in both Ang II and TAC models.

We conclude that cardiac AQP1 mediates transmembrane transport of H2O2 and critically modulates the development of myocardial hypertrophy and fibrosis in response to physiologic and pathologic stimuli.
Pharmacologic inhibition of AQP1 could be exploited therapeutically to attenuate stress-induced myocardial remodeling.