Topic 25 – Heart failure, cardiomyopathy – E

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0307
QSOX1 has a protective role in the myocardium face to acute stress

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Introduction: QSOX1 was identified as a plasma biomarker of acute heart failure (AHF). QSOX1 being a sulfhydryl oxidase, our aim was to decipher the role of QSOX1 in the heart face to an AHF event.

Methods: AHF was provoked by IP injections of Isoproterenol (ISO, 300mg/kg/12h) for 2 days in mice (C57Bl/6 J) whereas control (C) received NaCl 9%. Mice were killed at day 3, after echocardiography. QSOX1 KO (C57Bl/6 J) mice were generated using a Y.XO1tm1a embryonic stem cell clone (KOMP). The KO construct contains a promoter-less lacZ gene under the control of the QSOX1 regulatory sequences. The mRNA levels were analyzed by RT-qPCR. The cellular level of oxidative stress was detected by using DHE. Fibrosis was analysed by Sirius red and collagen mRNA.

Results: At baseline QSOX1+/- adult mice did not display any cardiac or vascular phenotype. After ISO, lacZ expression dramatically increased in QSOX1+/- hearts with the strongest β-galactosidase staining in the atria. In mice receiving ISO, a pulmonary congestion, BNP (x2 p<0.001) and CD68 (x3, p<0.001) increases were observed only in QSOX1+/-, whereas Galectin 3 increased in both groups. After ISO, the severe cardiac dysfunction in QSOX1+/- hearts with the strongest β-galactosidase staining in the atria. An early fibrosis was observed by Sirius red analysis and associated with an increase of collagen 1 and 3 mRNAs without difference between WT and QSOX1+/- mice.

Conclusion: We provided evidence that the absence of QSOX1 leads to a more serious cardiac dysfunction in response to acute cardiac stress by ISO than in WT counterparts. Hence, our data indicated that QSOX1 protects the heart in response to acute stress.

0310
Effects of connexin 43 inhibition on mitochondrial function in cardiac skinned fibers and isolated mitochondria

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Connexin 43 (Cx43) is a main component of intercellular gap junction channels in cardiomyocytes. The presence of Cx43 in heart mitochondria has been also reported, where it may participate in energy metabolism and protection against ischemia. Given the key role for mitochondria in pathogenesis of heart diseases, we examined how mitochondrial function could be altered in case of Cx43 pharmacological inhibition by carbenoxolone (CBX). Oxygen consumption rates under various substrate conditions were determined either in ventricles from pig hearts using saponin-permeabilized fibers, or in isolated mitochondria from rat hearts. Measurements of mitochondrial membrane potential (ΔΨ) and reactive oxygen species (ROS) by fluorescence, as well as calcium-induced matrix swelling by light scattering were recorded in cardiac mitochondria exposed to increasing CBX concentrations. At high dose (100μM), CBX substantially decreased the ADP-stimulated respiration while increasing mitochondrial protons leak in permeabilized ventricular fibers. In isolated mitochondria, we found a similar response accompanied by a collapse of ΔΨ and ROS production. At lower CBX concentrations (52.5μM), the substrate oxidation rates by mitochondria were not changed (except for ADP-stimulated complex I respiration which was slightly reduced), but ΔΨ remained stable. More interestingly, low CBX concentrations increased calcium sensitivity of mitochondria when incubated in a KC1 versus sucrose medium. This phenomenon was partly prevented by cyclosporin A, an inhibitor of the permeability transition pore (PTP) involved in apoptosis. These data suggest a possible interaction between the function of Cx43 and the mitochondrial PTP. Further investigations will resolve the impact of Cx43 on bioenergetics in order to better understand some mitochondrial disorders in failing hearts.