"Zależny od białek transportu cholesterolu StAR mitochondrialny import wodoronadtlenków cholesterolu w komórkach Leydiga i jego biologiczne konsekwencje"

ABSTRACT

Proper distribution of intracellular cholesterol (Ch) plays a key role in maintaining cellular homeostasis. Trafficking of Ch to and into mitochondria of steroidogenic cells is required for steroid hormone biosynthesis, which is initiated in the inner mitochondrial membrane by cleavage of Ch side chain to give pregnenolone. The reaction is controlled by availability of Ch as a substrate. Proteins of the StAR family, particularly STARD1 and STARD4 play a key role in transport and delivery of CH to mitochondria inner membrane. They contain START domain which securely binds Ch and facilitates its translocation. In the previous studies we have shown that START domain can bind and deliver not only Ch but also its oxidation product – cholesterol-7-hydroperoxide (7-OOH).

Here, studies of possible link between cytotoxic properties of 7-OOH, and testosterone output, are described. Two glioma models were used, MA-10 (carcinogenic) and TM3 (normal immortalized) cells along with primary Leydig cells freshly isolated from rat testis. Treatment of Leydig cells with small unilamellar vesicles containing POPC/Ch/7-OOH results in transfer of Ch along with 7-OOH to mitochondria. Introducing 7-OOH results in peroxidation of mitochondrial membranes, loss of membrane potential, and decreased steroidogenesis. These effects are strongly dependent on the presence of StAR proteins. When comparing cytotoxicity, 7-OOH was much more toxic than phospholipid hydroperoxides at the same concentration range. That is most likely due to presence of sterol-specific carrier proteins of StAR family delivering 7-OOH to the vital target. Introduction of RSL3 – specific inhibitor of GPx4 results in exacerbation of 7-OOH toxicity, while Ebselen – synthetic mimetic of GPx4, decreases negative consequences of inhibiting GPx4. Central role of GPx4 in detoxifying 7-OOH and protecting testosterone output, was confirmed in knock-out experiments in which silencing of *gpx4* expression resulted in greatly increased sensitivity to 7-OOH. Observations made during described studies are consistent with high content of GPx4 in testis.

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