MitoQ rescues early embryo development of metabolically-compromised bovine oocytes *in vitro*

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Maternal metabolic disorders e.g. obesity have been linked with reduced oocyte quality and subfertility. In these cases, upregulated lipolysis increases free fatty acid concentrations, predominantly palmitic acid (PA), in blood and ovarian follicular fluid, causing direct detrimental effects on oocyte quality and IVF results. Using proteomic analyses, we found that high cellular oxidative stress, mitochondrial dysfunction and unfolded protein responses (UPR) are key mechanisms explaining PA-linked lipotoxicity in bovine oocytes. Carryover of cellular stress to subsequent early embryonic stages increases the risk of embryo cell death and explains the reduced blastocyst rates observed *in vitro*. Mitochondria-targeted therapeutics are increasingly used to treat metabolic diseases, however, their efficiency in rescuing development of metabolically-compromised oocytes has not been examined. In the present study, oocytes matured in media containing high pathophysiological PA concentration (150µM) or solvent (Control) were cultured in the presence or absence of mitoquinone (MitoQ; a mitochondria-targeted antioxidant, 1µM) (from day 1 post-fertilization (D1) until D8, in serum-free FA-free SOF media). Embryo cleavage and fragmentation (at D2) and blastocyst rates (D8) were recorded. Gene expression patterns of markers of cellular stress were examined in the resultant D8 blastocysts. Numerical data were analyzed by ANOVA, and categorical data by binary logistic regression, followed by Bonferroni correction. At D2, PA had no effect (P>0.1) on embryo cleavage (63.6 vs. 70.2%) and fragmentation (14.2 vs. 12.9%) rates compared to control. However, PA significantly reduced blastocyst rate at D8 (16.9 vs. 25.7%, P<0.05). MitoQ supplementation during culture to PA-derived embryos significantly reduced embryo fragmentation (7.3 vs. 14.2%) and rescued embryo development to the blastocyst stage (25.0 vs. 16.9%) compared with PA-group cultured in the absence of MitoQ. Day 8 blastocysts derived from the PA group had significantly (*P*<0.05) higher mRNA expression of genes related to oxidative stress (*CAT*, 5.5±3.1 folds; *SOD2*, 3.4±0.4; but not *GPx*, 1.99±1.03); mitochondrial UPR (*HSPE1*, 4.2±1.6 folds, and *HSPD1*, 10.6±5.8 folds); and ER stress (*ATF4*, 2.2±0.29 folds; *ATF6*, 25.99±12.5 folds; and *HSPA5*, 10.7±4.7 folds). In contrast, MitoQ supplementation to PA-embryos during culture significantly reduced the expression of the affected genes to control levels (P>0.05). For oocytes matured in control conditions, MitoQ supplementation during culture had no significant effects on development and gene expression patterns (P>0.1). In conclusion, these results provide further evidence that mitochondria play a central role in the pathogenesis of reduced oocyte developmental capacity under metabolic stress. Mitochondrial-targeted therapy (MitoQ) during early development of embryos derived from metabolically-compromised oocytes may be an efficient tool to reduce cellular stress level and maximize embryo development to the blastocyst stage. Further investigations are in progress to examine the quality of the rescued embryos.