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Protective effects of Mitoquinone during in vitro maturation of bovine oocytes under lipotoxic conditions

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Oxidative stress and mitochondrial dysfunction in oocytes play a central role in the pathogenesis of several conditions associated with infertility. Upregulated lipolysis during negative energy balance can directly increase oxidative stress and alter mitochondrial functions in oocytes. Furthermore, *in vitro* maturation (IVM) following ovum pick up has been shown to increase gene expression of markers of cellular stress in oocytes. This leads to reduced developmental competence and reduced production efficiency. Mitochondrial targeted treatments containing co-enzyme Q10 are used to increase the anti-oxidative capacity within the mitochondrial matrix and enhance mitochondrial activity, however their efficiency in assisted reproduction to enhance oocyte developmental competence has not been investigated. In the present study, we tested the effect of different concentrations of Mitoquinone (MitoQ; 0, 0.1, 0.5, 1.0 µM) during bovine oocyte IVM, then we tested the effect of MitoQ (0.1 µM) in the presence or absence of palmitic acid (PA)-induced lipotoxicity (150µM) as a model (Marei *et al.*2019, Sci. Rep. 9:3673). The effect of the carrier molecule of MitoQ, triphenyl-phosphonium (TPP) was also tested. A total of 2823 bovine oocytes from slaughterhouse ovaries were used. All data were derived from at least three replicates and were compared by linear logistic regression (categorical data) or ANOVA (numerical data) with Bonferroni post-hoc corrections. MitoQ supplementation at 1 µM significantly (P<0.05) reduced cleavage (50.8±6.81 vs. 78.7±5.17), and blastocyst rates (6.7±0.98 vs. 27.4±6.07) compared with solvent control (ethanol 0.01%). TPP (1 µM) also induced similar toxic effect (P<0.05). This was associated with, and probably caused by, a reduced mitochondrial inner membrane potential (J-aggregates: monomer intensity ratio of JC-1 staining) (P<0.05). Lower concentrations of MitoQ and TPP had no effects on developmental competence. PA increased the levels of oxidative stress in oocytes (43±2.39 vs. 28.4±2.36, CellRox Deep Red pixel intensity) and reduced cleavage (56.6% vs. 69%) and blastocyst (13.9% vs. 24%) rates compared with the controls (P<0.05). These negative effects were ameliorated in the presence of 0.1 µM MitoQ (CellRox, 30.5±2.30; cleavage, 69.4%; and blastocysts, 24.2%, P<0.05). In contrast, 0.1 µM TPP alone did not enhance cleavage (55.8%) and blastocysts rates (20.2%) compared to the PA group (P>0.1). In conclusion, low concentrations of MitoQ can protect against induced oxidative stress during oocyte IVM, and enhance developmental competence under lipotoxic conditions. These effects are specific to the CoQ10 content of MitoQ since the carrier molecule TPP had no protective effects. In contrast, higher doses of MitoQ and TPP are toxic for oocytes.