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Alpha-linoleic acid enhances mitochondrial activity in cumulus cells and improves developmental capacity of bovine oocytes matured under lipotoxic conditions

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Dietary omega-3 (*n-3*) fatty acids (FAs) can enhance fertility in human and farm animals. We have shown that supplementation of cumulus oocyte complexes (COCs) with alpha-linoleic acid (ALA), the parent *n-3* FA, reduces oxidative stress, supports mitochondrial activity in bovine oocytes, and induces a MAPK-mediated improvement in nuclear oocyte maturation and subsequent *in vitro* embryo development. In contrast, saturated (SFAs) and mono-unsaturated FAs (MUFAs), which are typically elevated in certain metabolic lipolytic conditions, exert lipotoxic effects on oocytes. This involves oxidative stress, increased apoptosis, and hampered development. In the present study, we hypothesized that these lipotoxic effects can be attenuated or alleviated by ALA. Bovine COCs were supplemented *in vitro* during maturation with either: 1) ALA (50 µM), 2) a mixture of the most predominant lipotoxic SFAs and MUFAs in the follicular fluid (palmitic, stearic and oleic acids, PSO, 425µM), or 3) a combination of both (PSO+ALA). 4) A standard FA-free control and 5) a solvent control (SCONT) were included. In Exp. 1, treated COCs (n=198, 3 repeats) were partially denuded at 22h of maturation, stained with JC1 and examined under a confocal microscope to determine mitochondrial activity (intensity of J-aggregates) in oocytes and surrounding cumulus cells (CCs) separately. In Exp. 2, treated COCs (1529 COCs, 5 repeats) were fertilized and cultured in FA-free and serum-free conditions until day 8 post-fertilization to examine embryo development and quality. Compared with the controls, ALA significantly enhanced mitochondrial activity only in CCs ($P<0.05$) but not in the oocytes. PSO-FAs reduced mitochondrial activity in both CCs and oocytes ($P<0.05$), an effect that was alleviated by ALA only in the CCs. Compared with SCONT, PSO-FAs resulted in higher fragmentation rates (16.8% vs. 9.5%, $P<0.05$) and lower blastocyst rates on day 7 ($P<0.05$), either expressed as a proportion from the total number of fertilized oocytes (15.6% vs. 22.8%) or from cleaved embryos (20.4% vs. 30.6%). Moreover, hatched and expanded blastocysts produced from PSO-exposed oocytes had higher apoptotic cell indices. In contrast, these negative effects were alleviated by ALA supplementation. In the PSO+ALA group, fragmentation (6.9%), blastocyst rate on day 7 (21.4% from total fertilized oocytes and 28.7% from cleaved embryos), and apoptotic cell index were similar to the SCONT. In addition, PSO+ALA group had significantly higher total cell numbers in expanded and normal blastocysts compared with those from PSO group. In conclusion, ALA supplementation enhanced mitochondrial activity in CCs during maturation under lipotoxic conditions, which was associated with a significant improvement in developmental potential of the oocytes. These results may have clinical implications to improve fertility through dietary interventions in animals and humans suffering from metabolic disorders associated with lipolysis.