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Review

Potential role of polyunsaturated fatty acids, with particular regard to the signaling pathways of arachidonic acid and its derivatives in the process of maturation of the oocytes: Contemporary review

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ABSTRACT

Oocyte meiotic maturation is one of the significant physiological requirements for ovulation and fertility. It is believed that Cyclic Adenosine Monophosphate, protein kinase A and protein kinase C pathways along with eicosanoids, particularly prostaglandin E_2, and steroids are the key factors regulating mammalian oocyte maturation. The aim of the current study was to highlight the molecular events triggered by arachidonic acid during oocyte meiotic arrest and resumption at the time of gonadotrophin surge. It should be noted that arachidonic acid release is tightly regulated by Follicle-stimulating and Luteinizing hormones during oocyte development.

Contents

1. Introduction

Arachidonic acid (AA), as a member of omega-6 (n-6) polyunsaturated fatty acids (PUFAs) family, is one of the most important fatty acids (FAs) in cell behavior and responses. Its release from membrane phospholipids and subsequent conversion into its metabolites, particularly eicosanoids, influences the quality

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of oocyte and fertility. AA, among other long-chain PUFAs, namely docosahexaenoic acid (DHA; omega-3) and eicosapentaenoic acid (EPA; omega-3) are crucial components of all cell membrane phospholipids [1].

The role of AA in steroidogenesis is important for cell function; notably, steroid hormones are essential for critical steps of gametogenesis and remarkably in oocyte maturation [2]. Still, more importantly, the amount and type of dietary PUFAs affect not only ovarian steroid synthesis but also oocyte maturation, pregnancy, and uterine function. The PUFA composition of cell membrane impacts signaling pathways and susceptibility to oxidative damage. All of these factors might influence reproduction. Although studies' results are inconsistent among some experiments, it seems that AA is an essential fatty acid for the biology of oocytes and its optimum levels in normal oocyte growth and fertility must be defined appropriately [3,4]. Animal models are widely used to study the dynamic of ovarian tissue or oocyte physiology instead of human counterpart since ethical concerns prohibit frequent sampling or any manipulation which might have side effects or even may affect fertility rate. In line with this statement, the bovine model is most preferred due to the great similarities with a female reproductive system such as ovary size and morphology, gestation period and physiology of the folliculogenesis [5].

2. The role of PUFAs in oocyte maturation

PUFAs play a key role in oocyte maturation, development, and fertility in the mammalians' reproductive system [6]. It seems that they act as a reservoir of energy, structural components of membranes and the precursors of steroidogenesis. Additionally, they participate in different signaling cascades via their metabolites as biologically active molecules [7].

According to available data, neighboring cumulus cells (CCs) support oocyte by the expression of numerous genes involved in FAs metabolism [8]. Saturated and monounsaturated fatty acids, mainly palmitic (PA 16:0) and oleic acids (OA 18:1n9), are abundant in the immature oocyte of porcine and bovine. However, PUFAs are also considered as a reservoir of ATP for the oocyte [9]. In addition to the potential role of PUFAs in meeting energy demand, each PUFA family of omega-3 (n-3) and omega-6 (n-6) families produces its own derivatives due to distinct metabolic pathways resulting in different eicosanoids synthesis, which are precursors for important signaling molecules such as prostaglandins (PGs), leukotrienes (LTs), thromboxanes (TOX) and lipoxins (LXs). Similar to other tissues, every substantial inflammatory response is modulated by these active molecules in the ovary [10]. For instance, it has been shown that n3 PUFAs such as EPA and DHA have anti-inflammatory properties through producing the second series of PGs, which promote follicular growth. However, n-6 type PUFAs, particularly linoleic acid (LA 18:2) or AA (20:4), generally produce proinflammatory eicosanoids, namely the third series of PGs, which down-regulate NF-KB and contribute to the inflammatory reactions of ovulation [11]. They also improve oocyte maturation through activation of prostaglandin E_2 (PGE_2), Cyclic Adenosine Monophosphate (cAMP) and mitogen-activated protein kinases (MAPK) signaling in cattle cumulus-oocyte complexes (COCs) [6].

During oocyte nuclear maturation, gap junctions (GJs) are vital systems of communication between cumulus granulosa cells (CGCs) and oocytes, which mediate a rapid transfer of small metabolites and regulatory molecules among them. Furthermore, GJs appear to have an important role in chromatin remodeling in fully developed oocytes from early antral to half of antral folliculogenesis at the late stages [11], GJs communication among CGCs and oocyte is required for the oocyte maturation [12]. Nevertheless, GJs irruption coincides with the meiotic resumption in the oocyte [13]. Particularly, PUFAs and AA exert impressive effects on the dynamics of GJs. Marandykina et al. investigated the effects of different amounts of AA on HeLa cells in in vitro experiments by activating or inhibiting the cytosolic phospholipase A_2 (cPLA2). They concluded that elevated levels of AA decrease number of the membrane channels. More interestingly, inhibition of AA production could enhance the expression of GJs [14]. Concurrently, Jin et a confirmed that AA-induced activation of protein kinase C (PKC) and MAPK signaling pathways promoted the production of extracellular matrix glycoprotein laminin and GJ protein connexin-43 in cultured granulosa cells (GCs) of laying hens [15]. It seems that the balance of AA pathway and kinase activity are essential in direct cell-to-cell cross-talk by engaging GJs to contribute synergistically to the modulation of paracrine signaling [16].

PUFAs play a critical role in maintaining membrane biogenesis. In this process, desaturase and elongases enzymatic activities determine the abundance of monounsaturated fatty acid (MUFA) and PUFA in membrane phospholipids. PUFAs' participation in the oocyte membrane not only influences the ability of sperm fusing with egg but also impacts the quality of oocyte freezing or chilling in in vitro fertilization (IVF) [17]. At the gonadal level, folliculogenesis is tightly under the supervision of neuroendocrine, endocrine and paracrine factors tailored by steroids. Previous experiments showed that the concentration of estradiol (E_2) and the 17-estradiol/progesterone (E_2/P_4) ratio could be a reliable indicator for assessing follicles status [18]. Recent studies have confirmed that all of these hormonal fluctuations, specifically in E_2 levels which are related to the increased number and size of preovulatory follicles and were beneficial for ovarian function [19,20]. Since elevated levels of E_2 leads to full expression of aromatase and follicle growth through the inhibition of anti-Müllerian hormone, but higher concentrations could hinder progression to metaphase II during in vitro maturation [21,22]. Ovarian theca cells (TCs) along with granulosa cells (GCS) synthesize and secrete oocyte maturation inducing steroids (MIS) like estrogens and progestins [23]. In vivo experiments showed that in female mammals, diets enriched with n-3 PUFA enhance plasmatic levels of E_2 [24]. Although the exact mechanism, by which E_2 synthesis is enhanced through PUFAs, is still unclear, it appears that PUFA supplementation could increase plasma steroid concentrations directly by increasing availability of substrates for steroidogenesis or indirectly by its derivatives like PGs. These changes, in turn, activate the expression of substantial enzymes or proteins required for steroidogeneses such as aromatase, peroxisome proliferator-activated receptors (PPAR) or steroidogenic acute regulatory protein (STAR). PPARs are a family of transcription factors related to numerous processes such as steroidogenesis. PUFAs act as potent ligands for PPARs [25,26]. Both n-3 and n-6 PUFAs increase STAR expression and steroid secretion in cows [27]. In another study, steroid hormones were elevated in the preovulatory follicles of dairy cows after being supplemented with PUFA [28]. Also, a positive correlation was indicated between the concentration of PUFAs and circulating steroid hormones and slight increases in testosterone concentrations in women [29,30]. Steroid hormones, in turn, can modify PUFAs' production through the modulation of desaturase expression which will result in inflammatory responses through the PUFA metabolites [31].

Given diverse effects of the n-6 PUFA and n-3 PUFA on fertility, this issue should be discussed cautiously. It was suggested that high fertility rates in dairy cows during winter was related to elevated levels of the MUFA and PUFA in oocytes and surrounding GCs [32]. Furthermore, the consumption of MUFA and PUFA instead of SFA improved the risk of ovulatory infertility and