INTRODUCTION

Recently, sufficient reproductive abilities of farm animals and other mammals including humans have been the object of current reproductive biotechnologies. The quality of fertilized oocytes is a key factor for adequate interaction between an oocyte and a spermatozoon, which results in successful embryonic development and progress in reproductive biotechnology. However, reproductive disorders, based on faults in hormonal release, transport, metabolism and interactions, affect the quality of gametes. Endocrine disrupting chemicals (EDCs), occurring ubiquitously in the environment, are frequently suspected as the cause of these failures (Colborn, 2004) resulting in decreases in reproductive potential in animals and humans exposed to EDCs (Huang et al., 2014; Romaní et al., 2014). The origin of EDCs has various sources including pesticides, plastic compounds, medicines, and heavy metal residues.

The assignment of advanced reproductive biotechnologies involves relieving the EDCs’ negative effect. A complete understanding of the reproduction physiology of both male and female is a necessary condition for reproductive biotechnology success. In this review, a summary of known mechanisms in female reproduction focusing on oogenesis is submitted. A comparison of common reproductive models stressing their utilization for the study of the effect of potential endocrine disruptors has been performed.
Oogenesis and meiotic maturation

Generally, oogenesis is female gamete production and it begins as early as during female embryonic development. Oocyte progression takes place throughout meiotic maturation, and is blocked in dictyotene of the first meiotic prophase in the germinal vesicle stage (GV). This state is established in the follicle of the female embryonic ovary as the first meiotic arrest. The blocked oocyte persists into puberty onset without significant changes. Under hormonal stimulation in adult females, the oocyte is stimulated to grow as necessary for oocyte maturation (Wasserman, 1988; Yanagimachi, 1988).

In growing oocytes, increasing amounts of cell organelle such as mitochondria, endoplasmic reticulum, Golgi complex, and cortical granules occur. Moreover, zona pellucida, a glycoprotein membrane covering the oocyte, separating it from the surrounding follicular cells, is created. The cell organelles of the growing oocyte are important for the synthesis of key meiosis regulators (Wasserman, 1988; Yanagimachi, 1988). Key regulators of meiotic division are accumulated as pro-enzymes and they are necessary for meiotic competence acquisition, complete meiotic progress, and correct chromosome segregation (Wasserman, Albertini, 1994).

Meiotic division of the fully grown oocyte predestined for ovulation and fertilization is known as oocyte maturation, which begins with germinal vesicle breakdown (GVBD). After that, the oocyte achieves the first meiotic metaphase (MI) and the meiotically component oocyte undergoes the 2nd meiosis. The 2nd meiosis of fish, amphibian, and some mammalian oocytes, including mouse, pig, bovine, and human, is spontaneously blocked in the metaphase (MII). Meiosis completion occurs after fertilization by sperm or spontaneous parthenogenetic activation (Wasserman, 1988; Yanagimachi, 1988). Oocyte maturation takes place in a tertiary follicle just before ovulation. Meiotic maturation of oocytes is also inducible under in vitro conditions and usable for cell cycle study. Oocyte maturation is a key process for the acquisition of developmental competence and thus for a successful early embryonic development (Han et al., 2006; Aucelair et al., 2013).

One of the key regulators of oocyte meiotic maturation is M-phase/maturation promoting factor (MPF), consisting of regulatory and catalytic subunits – cyclin B and cyclin-dependent kinase 2 (CDC2), respectively. Both compounds are synthesized, aggregated and accumulated in an inactive form of proenzyme called pre-MPF. Inhibitory phosphorylation of Thr14/Tyr15 of CDC2 by WEE1 and MYT1 kinases is
responsible for the maintenance of inactive pre-MPF (Tai eb et al., 1997). MPF activation depends not only on CDC2 dephosphorylation, but also on activating phosphorylation of cyclin B on Ser-94/Ser-96 (Izumi, Maller, 1991).

Biochemical changes of MPF leading to meiosis re-initiation and completion are induced by hormonal stimuli. The hormonal stimulus is 17α,20β-dihydroxy-4-pregnen-3-one (17α,20β-DP) for fish such as zebrafish (Brachydanio rerio) and goldfish (Carassius auratus), progesterone (PG) for frogs Xenopus sp. (Masui, Market, 1971; Nurse, 1993; K obayashi et al., 2000), 17β-estradiol and gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH) for mammals (De kel, Be ers, 1978; Fuku i et al., 1982; Mattioli et al., 1991; Funahashi et al., 1994) (Fig. 1). Oocyte receptors are sensitive to certain hormones. Hence, estrogen receptors in maturing oocytes are responsible for regulating second messengers and key kinase pathways (Pro ssni tz et al., 2007; Pang et al., 2008). Therefore, the above-mentioned hormones induce concentration changes of second messengers, simple molecules with signal transduction ability, including cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Metabolites of follicular cells flow through gap junctions into the oocyte and influence various enzymes with kinase activity, such as cAMP-dependent and cGMP-dependent protein kinases (PKA, PKG) (Le vesque, Sir ard, 1995; Mori et al., 2000; Zhang et al., 2005).

In addition to cyclic nucleotides, gasotransmitters are another group of signalling molecules involved in the regulation of oocyte maturation (summarized in S m ele cová, Tichovská, 2011). Nitric oxide, which is enzymatically released directly in the oocyte, is the most commonly observed gasotransmitter with a physiological role in oocyte maturation. Nitric oxide signalization is essential for meiosis re-initiation and the completion of oocyte maturation (J a b lonka-Shariff, Olson, 2002; C hmelíková et al., 2010; Tichovská et al., 2011).

Another second messenger, a Ca²⁺ ion, acts outright in the oocyte. The signal pathway of Ca²⁺ includes down-stream regulated kinases: calmodulin-dependent kinase (CaMKII) (Fan et al., 2003) and some Ca²⁺-dependent protein kinase (PKC) isoforms (Fan et al., 2002a; Fan, Sun, 2004). These kinases cause the activation of Cell Division Cycle 25 phosphatase (CDC25) with dephosphorylating activity responsible for removing inhibitory phosphates of CDC2 (Tai eb et al., 1997). Changes of MPF phosphorylation pattern and auto-accelerating positive feedback lead to an intense increase in MPF activity, resulting in GVBD (Lee et al., 1999; Fan et al., 2002b; Kishimoto, 2003).

Increasing MPF activity in the oocyte reaches a maximum in the MI stage, and MPF decreases together with the arrival of anaphase I and telophase I (Ver hac et al., 1993, 1994). Decreasing MPF activity is up-regulated by anaphase promoting factor/cyclosome (APC/C), degrading the regulatory subunit of MPF – cyclin B. This degradation is based on polyubiquitination, and cyclin B is destined to proteolysis in proteasome S26 (Peters, 2002; Yi et al., 2008). APC/C inactivation in meiosis II is followed by re-activation of MPF (Tai eb et al., 1997; Kubelka et al., 2000).

Another key meiotic regulator is activated around GVBD – mitogen-activated protein kinase (MAPK), a member of Ser/Thr protein kinase family (In oue et al., 1998; Fan et al., 2002b; Ohashi et al., 2003; Tao et al., 2005). The MAPK signal pathway includes a few up-stream factors – Mos and MEK (Kyriakis, Av ruch, 2001). In addition, G protein estrogen receptors are involved in MAPK activity (Li et al., 2013).

Due to the action of these factors, MAPK activity is nearly constant over the whole oocyte maturation (Lee et al., 2000; Villa-Diaz, Miyano, 2004). This activity profile is necessary for meiosis I followed immediately by meiosis II without an interphase between them (Kishimoto, 2003; Fan, Sun, 2004; Sasaki, Chiba, 2004).

Maturation signal pathways and the correct MPF dynamics with interaction with Mos-MEK-MAPK determine chromatin condensation, nuclear lamin phosphorylation and depolymerisation, correct chromatid segregation, and extrusion of homologous chromosomes in first polar body (Lüscher et al., 1991; Hampl, Eppig, 1995; Inoue et al., 1995, 1998; Lee et al., 2000; Takakura et al., 2005). Persistent high MPF and MAPK activity in MII maintains the haploid oocyte in the so-called second meiotic arrest (Tai eb et al., 1997).

Multi-enzyme complex cytostatic factor (CSF) is accountable for second meiotic arrest maintenance (Li et al., 2002; Reimann, Jackson, 2002). The above-mentioned Mos is one of its compounds. The role of CSF is suppression of cyclin B proteolytic degradation, MPF stabilization, and maintaining constant MPF and MAPK activity in a matured MII-oocyte (Maller et al., 2001, 2002; Kyriakis, Av ruch, 2001; Fan, Sun, 2004). A fall in CSF activity follows the release and oscillation of Ca²⁺ ions after fertilization and oocyte activation (Fan et al., 2002b; Fan, Sun, 2004).

We can assume that endocrine disruptors influence the above-mentioned signal pathways (Fig. 1). However, their molecular mechanisms still remain unclear and certain common model organisms are sufficient for the preliminary elucidation of endocrine disruptor action.

**Xenopus oocytes: a traditional model for cell cycle study**

The reasons for introducing *Xenopus laevis* as a biological model are its especially easy keeping and
10

SCIENTIA AGRICULTURAE BOHEMICA, 46, 2015 (1): 7–20

handling, resistance to disease, short reproductive cycle, and constant response to hormonal stimulation regardless of the season (Kay, Peng, 1991). Another advantage is simple preparation and manipulation with a large amount of fairly big oocytes.

The mitotic division of amphibian oogonies occurs throughout the whole lifetime. Primary oocytes enter first meiosis, which is physiologically disrupted in the diplotene of first prophase, in first meiotic arrest. The arrested oocytes grow intensively, accumulating organelles and proteins, acquiring meiotic competence and encapsulating in the thin-walled follicle closely surrounding the oocyte. Follicular cells communicate with the oocyte throughout gap junctions, participating in egg yolk cumulation and meiosis regulation (Brown et al., 1979). Oocyte growth is not a fully synchronized process and oocytes in various developmental stages occur in both ovary lobes. The stage of oocyte growth is evaluable and classifiable into one of six growth stages (Dumont, 1972).

Fully grown oocytes in final stage VI achieve 1.3 mm in diameter with visible animal and vegetative poles. The non-pigmented equatorial band is enclosed by both of the poles. The germinal vesicle is situated in the middle of oocyte and includes a few nucleoli with a large amount of mRNA. Just fully grown oocytes are meiotically competent and able to re-initiate and finalize meiotic maturation (Rasar, Hammes, 2006).

The oocyte maturation of Xenopus laevis (hereafter referred as Xenopus) is regulated by epiphyseal gonadotropins. They give an incentive to progesterone production by follicular cells. Progesterone is in usage for in vitro maturation of Xenopus oocytes. Under in vitro conditions, only fully grown oocytes respond to progesterone treatment (Smith, Eck, 1970).

Progesterone acts as a ligand for receptors enclosed in the oocyte cytoplasmic membrane as well as for soluble receptors in ooplasm. By binding to both receptors, it inhibits adenylyl cyclase (AC) activity and reduces the intracellular concentration of cAMP suppressing meiosis re-initiation. Therefore, a decrease in cAMP-dependent protein kinase (PKA) activity responsible for the first meiotic arrest takes place in the oocyte. Low PKA activity is an adequate inducement for GVBD (Palmer, Nebra, 2000).

G-protein coupled receptors are one of the progesterone membrane receptors. They are able to activate factors leading to oocyte maturation re-initiation – Mos, MEK, and subsequently mitogen activated protein kinase (MAPK) (Blumer, Johnson, 1994). The Mos-MEK-MAPK signal pathway induces activity of p90 ribosomal protein s6 kinase (Eriksson, 1991). This protein is responsible for MYT1 inhibition and dephosphorylation of inhibiting phosphate residua on CDC2, the catalytic subunit of m-phase/maturation promoting factor (MPF) (Palmer et al., 1998).

Moreover, the activation of other regulating factors of MPF occurs there: polo-like kinase 1 (PLK1) and CDC25 (Karaiskou et al., 1998).

Subsequently to this, MAPK and MPF activity increases. The activation of the mentioned signal pathways leads to GVBD induction and re-initiation of oocyte maturation, also called M-phase for Xenopus oocytes. While MPF is essential for GVBD and meiosis, MAPK is dispensable and its lack causes at most MAPK dynamics and meiotic maturation disruption (Schmitt, Nebra, 2002).

The meiotic division of Xenopus oocytes has become a process appropriately describing biochemical changes of MPF, a key factor in cell cycle regulation. The G-phase to M-phase transition in Xenopus oocyte offers an opportunity for MPF activity and dynamics understanding as background for the further study of somatic cells’ cell cycle and also for meiosis study in higher vertebrate biological models more similar to farm animals and human.

Mus musculus: mammalian model with Xenopus advantages

Mouse (Mus musculus) represents a more human-like genetic and biological model than amphibians, including Xenopus. Mice have a high reproductive ability and there are also a number of options for genetic modifications and the study of their influence on reproductive efficiency.

Oocyte capability of GVBD and meiosis I to II transition is conditioned by age and puberty achievement (Wasserman, 1988). During all post-partal stages of ontogenesis, ovarian follicles and oocytes are developing. During the growth stage, oocyte attains 30, 60, and 80 μm in diameter in 5, 15, and 21 days after the birth of the female, respectively. Only 60 μm oocytes are able to initiate meiotic maturation. A rapid increase in the number of oocytes capable of GVBD takes place in ovaries around the 17th day of age (Sorensen, Wasserman, 1976). Oocytes with less than 60 μm in diameter are retained in the dictyate stage unable of meiosis. However, small and meiotic incompetent mouse oocytes are able to mature into fully-grown competent oocytes (Fulk Jr. et al., 1985).

A fully grown mouse oocyte is maintained in the first meiotic arrest by a high concentration of cAMP (Schultz et al., 1983). The molecules of cAMP are generated by 3-adenyl cyclase in the oocyte (Horrer et al., 2003) or follicular cells followed by cAMP flow into the oocyte (Dekel et al., 1981). Follicular cells closely surrounding the oocyte, which are known as cumulus cells, are stimulated by gonadotropins LH and FSH to produce a large amount of extracellular matrix compounds and mucify, a process known as cumulus expansion (Dekel et al., 1988). As such, gap junctions connecting cumulus cells and oocyte are
disrupted and cAMP flow into the oocyte is prevented (D e k e l , 1988). However, a transient rise in cAMP concentration in mouse cumulus-oocyte complexes occurs due to FSH action (S a l u s t r i et al. , 1985; W e b b et al. , 2002; E d r y et al. , 2006; C h e n et al. , 2009). Thereafter, enzymatic cAMP degradation by phosphodiesterase (PDE) follows (S h i t s u k a w a et al. , 2001). The PDE activity is stimulated by phosphorylation through protein kinase b (also called akt) participating in oocyte maturation (H a n et al. , 2006). The metabolic product of PDE-induced cAMP degradation, adenosine monophosphate, is an important regulating factor of AMP-activated protein kinase (AMPK), supporting GVBD and oocyte maturation (C h e n et al. , 2006). Before this process, a sufficient amount of cAMP in oocytes determines adequate stimulation of meiosis resumption by AMPK (C h e n et al. , 2009).

One of the cAMP-dependent factors regulating meiosis in oocytes is protein kinase A (PKA). PKA maintains a high activity of WEE1 and MYT1, responsible for enzymatically inactive pre-MPF maintenance. The fall in cAMP concentration and PKA activity enables CDC25 activation, a further regulating kinase activating MPF (H a n , C o n t i , 2006; P i r i n o et al. , 2009; O h et al. , 2010). In addition to MPF activation, cyclin B proteosynthesis is ongoing throughout the whole meiotic maturation (W i n s t o n , 1997). The result of MPF activation is GVBD occurring at around 3 h of oocyte maturation (S z ö l l ö s i et al. , 1972; J u n g et al. , 1993). With meiosis I to II transition, MPF activity decreases and re-achieves an activity peak in MII-oocytes (A b r i e u et al. , 1991).

The high cAMP concentration in immature GV-oocytes suppresses MAPK activity. When MAPK activity increases, MAPK remains active and independent of further concentration of cAMP (S u n et al. , 1999). MAPK is necessary for spindle formation, correct chromosome segregation, and MPF reactivation in meiosis II; rather, MAPK signal pathway is not essential for GVBD and first polar body extrusion in the mouse oocyte (A r a k i et al. , 1996).

Endocrine disruptors likely affect key signal pathways of oocyte maturation. Published data regarding bisphenol A point to the influence of estrogen receptors in mouse oocytes (C h a o et al. , 2012). Subsequently, DNA methylation and epigenetic inheritance, as well as nitric oxide production, are regulated (C h a o et al. , 2012; T r a p p h o f et al. , 2013; P a n d e y , D e s h p a n d e , 2015). Oocyte signalization failure results in failure spindle microtubular organization and an increased incidence in aneuploidy (H u n t et al. , 2003; C a n et al. , 2005). However, current knowledge lacks the complete explanation of EDCs action.

Obtaining and cultivating mouse oocytes are less difficult than in some other models (e.g. cows, pigs), and for this reason they have been utilized as a suitable biological model for the study of factors involved in MPF activation and meiosis resumption, such as PLK1, MYT1, WEE1, and CDC25. On the other hand, following maturation, mouse oocytes have a few differences in comparison with bovine, porcine, and human oocytes. The application of endocrine disruptor studies based on mouse model seems to be less suitable for human. For greater resemblance, porcine oocytes are used as a more appropriate biological model offering applications in human transplantation and reproductive medicine.

**Sus scrofa: just like a human**

Pig (*Sus scrofa domestica*) is a multiparous species with high fertility and its ovaries are well available immediately after slaughter. Pig is a more advisable model for research result applications in human medicine than frogs or mice.

Early oogenesis in pigs occurs in a similar manner to mouse. In the prenatal stage of ontogenesis, meiotic division of oogonies and their entry to meiosis take place in ovarian follicles. Meiosis is arrested in the first meiotic block consisting of prophase I maintenance until sex maturity is achieved. Ovaries of newborn gilt contain about 210 thousand immature oocytes with the established first meiotic arrest (P r a t h e r , D a y , 1998). Oocytes of matured gilts and swines are destined to re-initiation of growing and meiosis as a result of hormonal stimuli.

The duration of meiotic maturation under *in vitro* condition is comparatively long (44–48 h), and thus the porcine oocyte is suitable for the study of GVBD and particular meiotic stages. The meiotic maturation of fully grown GV-oocyte arrested in prophase I with 120–125 µm in diameter is initiated by GVBD. This process includes four different stages: GV I, GV II, GV III, and GV IV. In GV I, the nucleoplasm is intact and chromatin is established in a ring. The GV II is specified by recognizable nucleus containing heterochromatin missing its ring shape. The chromatin of the GV III oocyte is fully diffused and not recognizable by staining. Chromatin of the GV IV oocyte is highly condensed in bivalents and the nuclear envelope is disaggregated and not visible. Under *in vitro* condition, completed GVBD takes 16–24 h (M o t l i k , F u l k a , 1976; M e i n e c k e , M e i n e c k e - T i l l m a n n , 1979).

GVBD is immediately followed by the MI stage. Anaphase I and telophase I are difficult to distinguish and they are jointly evaluated as AI/TI stage where homologous chromosomes are segregated and diverged to spindle poles. Meiosis I continuously passes into meiosis II when the first polar body is extruded, meiotic division is stopped in MII and 2nd meiotic arrest is established. MII achievement is considered the termination of oocyte maturation. Meiosis completion is allowed after fertilization and oocyte activation by sperm where the sister chromatids are excluded as second polar body (T h i b a u l t et al. , 1987; W a s s a r m a n , 1988).
GVBD in in vivo matured oocytes occurs after hormonal stimulation by gonadotropins – follicle stimulating hormone (FSH) and luteinizing hormone (LH). Gonadotropins cause suppression of meiosis inhibiting factors, such as cAMP and cAMP-dependent kinase (PKA), in cumulus cells and oocytes (Mattio li et al., 1994). Under in vitro conditions, usage of gonadotropins and their synthetic analogs commonly used with blood serum proteins and growth factors is possible for the induction of oocyte maturation (Singh et al., 1997; Uhm et al., 1998).

The cAMP/PKA signal pathway in cumulus cells and the oocyte is responsible for the first dictyate arrest in porcine oocytes. The cAMP generation is enzymatically catalyzed by adenylate-cyclase localized in the oocyte cytoplasmic membrane (Liang et al., 2005). Falling cAMP concentration is a result of inhibited adenylate-cyclase activity and concurrent activation of phosphodiesterases cleaving cyclic bounds of cAMP (Mattio li et al., 1994). In addition to cAMP role, another cell second messenger participates in meiosis regulation, cyclic guanosine monophosphate (cGMP), followed by cGMP-dependent protein kinase (PKG) activity decreasing. Falling amounts of cGMP in cumulus cells allow phosphodiesterase activation and decrease of cAMP concentration in the oocyte (Lapol t et al., 2003). Further concentration of cAMP in the oocyte also decreases due to the gap junction disconnecting between the oocyte and cumulus cells following meiosis induction (Liang et al., 2007). The initial cAMP and PKA suppression is essential for meiosis re-initiation and GVBD (Racowsky, 1983; Mattio li et al., 1994). Low cAMP concentration persists throughout oocyte maturation (Mattio li et al., 1994).

At the same time as the decrease in the concentration of inhibitory factors, Ca2+ ions are released from endoplasmic reticulum by inositol-triphosphate receptors (IP3R) and ryanodine receptors (RyR) into the oocyte cytoplasm (Machat y et al., 1997). The Ca2+ ions activate protein kinases calcmodulin-dependent kinase (CaMKII) (Fan et al., 2003) and some isoforms of Ca2+-dependent protein kinases (PKC) (Fan et al., 2002a; Fan, Sun, 2004). Together with CDC25 (Taeib et al., 1997), PLK1 (An ger et al., 2004), and phosphatidylinositol 3-kinase (PI3K)-up-regulated AKT (Kalous et al., 2009), these kinases are involved in the regulation of key maturation factors, MPF, and MAPK (Motlik, Kubelka, 1990).

MPF activity decreases with entry into Al/TI. This decrease is important for meiosis I to II transition, chromosome segregation, and first polar body extrusion (Gl o t z e r et al., 1991). Particular MPF inactivation is based on proteolytical degradation of cyclin B, the regulator compound of MPF. Ubiquitination through anaphase-promoting complex/cyclosome (APC/C) is required for cyclin B proteolysis by proteasome S26 (Peters, 2002). As such, ubiquitin-proteosome system (UPS) is necessary for the correct progression of porcine oocyte maturation (Yi et al., 2008). Subsequent to this, MPF activity increases again and achieves maximum activity in MII where it is essential for the 2nd meiotic arrest maintenance (Yanagimachi, 1988).

The signal pathway of Mos-MEK-MAPK is involved in porcine meiotic maturation through FSH (Li et al., 2002), cAMP (Liang et al., 2005), and MPF action (Fan et al., 2002b). WEhrend, Meinecke (2001) observed increasing MAPK activity immediately before MPF-induced GVBD. In spite of MPF, MAPK activity during oocyte maturation persists almost constantly (Lee et al., 2000; Villa-Diaz, Miyan o, 2004). The important target of MAPK is ribosome S6-kinase p90<sup>srk</sup> (Fan et al., 2002b; Kishimoto, 2003; Fan, Sun, 2004; Roux, Blenis, 2004) and MAPK participates in cyclin B re-synthesis and MPF re-activation through this target molecule during meiotic maturation (Ohashi et al., 2003). In addition, MAPK suppresses MYT1 activity through PLK1 and prevents inhibitory phosphorylation of Cdk2 and MPF to pre-MPF conversion (Fan et al., 2002b; Kishimoto, 2003; Ohashi et al., 2003). Moreover, MAPK is required for CDC25 to remain stable and thus ensures MPF activity (Kishimoto, 2003). Regulatory factors, such as the above-mentioned PKA, PKC, and CaMKII are other MAPK target systems (Kishimoto, 2003; Fan, Sun, 2004).

MAPK has a non-essential role in GVBD induction (Fan et al., 2002b), however it participates in meiosis resumption through MPF activation (Ohashi et al., 2003). Active MAPK induces spindle migration in the ooplasm during meiosis II, asymmetric cytokinesis, and excluding of the first polar body (Tong et al., 2003). MAPK remains active until MII achievement and holds 2nd meiotic arrest through highly active CSF keeping (Fan et al., 2002b; Maller et al., 2002; Kishimoto, 2003; Ohashi et al., 2003).

CSF is an important factor for 2nd meiotic arrest maintenance in the matured MII oocyte because CSF inhibits APC/C activity and cyclin B degradation. Concurrently, active MPF promotes CSF activity through Emi1, one of the CSF compounds, activating phosphorylation (Kishimoto, 2003). The second compound of CSF – Mos, is involved in Mek and MAPK activity keeping (Kyriakis, Avruch, 2001).

The comprehensive and exact mechanism of oocyte maturation is key for the so-called developmental competence acquisition, determining success following early embryogenesis (Li et al., 2002; Reimann, Jackson, 2002). Understanding regulatory mechanisms under in vitro conditions will be of help in studying various artificial substances possibly present in the environment and endangering the reproductive health of farm animals and humans, including their gametogenesis and oocyte maturation.

Regulatory mechanisms of porcine oocyte maturation are largely similar to the human oocyte. For long onset of GVBD, the porcine oocyte offers a suitable
way to study the dynamic regulatory factors responsible for meiosis reinitiation. In addition to GVBD study, a long duration of further meiosis is convenient for understanding meiosis I to II transition. Moreover, porcine meiosis is an appreciated model for testing the antioxidant or negative effect of environmental pollutants on oocyte maturation and embryonic development. Recently there have been developments in research of pollutants occurring at very low concentrations. Findings include the fact that EDCs are able to negatively influence human health, manifested especially in reproduction failures (Machtiger et al., 2013; Machtiger, Orvieto, 2014).

There is a logical assumption that organisms living in water are permanently exposed to certain concentrations of substances that may act as endocrine disruptors. This is mainly due to the fact that aquatic environment (rivers, lakes, and seas) serve as recipient of sewage. Although the sewage treatment is a common practice in many countries, it does not influence many substances that may act as endocrine disruptors (Golovko et al., 2014).

Comeback to lower vertebrates

Aquatic lower vertebrates are confronted with a water environment usually over their whole life-time. In these conditions, pollutant accumulations take place. Therefore e.g. fishes are considered as an appreciated model for the study of EDCs and other pollutants since they may significantly influence their reproduction (Zhan et al., 2000; Tokumoto et al., 2004, 2005).

The zebrafish (Brachydanio rerio) is a traditional model for molecular and developmental biology. Its advantages include quick ontogenetic development and short life cycle, as well as embryonic development outside the female body and availability to observe organogenesis in \textit{in vitro} cultured embryos. Therefore, this model is utilized as a simple biological indicator for endocrine disruptor effects (Holbech et al., 2006; Santos et al., 2014; Kinch et al., 2015).

Goldfish (Carassius auratus) and common carp (Cyprinus carpio) are other fishes commonly used as model organisms suited for studies on the effect of EDCs (Wang et al. 2015). On the other hand, they are mainly utilized for the study of male reproduction disorders (Yan et al., 2013; Golshan et al. 2014) and female reproduction affection remains often unexplained.

Fish oocytes are maintained in the prophase of first meiotic division through high cAMP concentration just like in the previously mentioned mammalian model organisms. The cAMP concentration decline induces meiotic maturation. Meiosis regulation is determined by three key factors: gonadotropins, the maturation inducing hormone, identified as 17α,20β-dihydroxy-4-pregnen-3-one, and M-phase promoting factor (Yamashita, 1998). Pituitary gonadotropins act on thecal cells surrounding the oocyte. Hormone-induced thecal cells produce testosterone under receptor-mediated adenylate cyclase-cAMP control (Wang, Ge, 2003; Zhou et al., 2000). Testosterone production is regulated through other intracellular signal pathways such as Ca²⁺ions, calmodulin, and arachidonic acid. Testosterone is converted into estradiol-17β by aromatases directly in the thecal cells, where it is involved in oocyte growth. In addition to estradiol-17β production, 17α-hydroxyprogesterone is created by thecal cells and thereafter 17α,20β-dihydroxy-4-pregnen-3-one (17α,20β-DP) is produced by 20β-hydroxysteroid dehydrogenase. 17α,20β-DP is specific for fish females and the ooplasm is equipped with appropriate 17α,20β-DP receptors. After 17α,20β-DP binding onto its receptors, MPF activation and subsequent GVBD take place in the fish oocyte (Nagahama, 1997; Yamashita, 1998).

In contrast to the previously-mentioned species, pre-MPF is not present in fish oocytes (Tanaka, Yamashita, 1995). Meiotic incompetent oocytes do not include cyclin B, but these oocytes dispose of the inactive form of CDC2. Just before meiotic maturation, an increase in the amount of cyclin B and its conjugation with CDC2 and MPF creation is induced by 17α,20β-DP as a necessary condition of oocyte maturation. The cyclin B presence in a sufficient amount is an adequate stimulus for meiosis induction. For CDC2 activation, phosphorylation of CDC2 by p40MO15 is required, unlike cyclin B phosphorylation on serine residuum (Katsu et al., 1993; Tokumoto et al., 1997; Yamashita, 1998).

The incompetent oocyte has not enough Mos protein as an up-stream regulator of MAPK. Mos occurs around GVBD, and it achieves a peak in the MII-oocyte. MAPK is activated by Mos and is followed by MPF activity increasing. However, the Mos-MEK-MAPK signal pathway is not necessary for induction of meiotic maturation. The main MAPK action is based on participating in the 2nd meiotic arrest stabilization in matured oocytes by CSF (Yamashita, 1998; Kajira-Kobayashi et al., 2000; Khan, Maitra, 2013).

Capability of a uniparental inheritance induced by gynogenesis or androgenesis is an advantage of fish model organisms (Komen, Thorgaard, 2007). Clonal lines of fish are of great interest since they can be used in a variety of research areas, including toxicology. Homozygous offspring in the first generation is the main benefit of gynogenetic reproduction (Sarder et al., 1999). Although the induction of gynogenesis requires human intervention, natural gynogenesis also appears sporadically within the fish taxa (Piferre et al., 2009). The Prussian carp (Carassius gibelio) as a related species to goldfish may reproduce by gynogenesis (Kalous, Knytl, 2011; Kalous et al. 2013) and such ability greatly facilitates the
availability of a great number of presumably clonal individuals. Moreover, the reproductive mechanism of Prussian carp is more complicated allowing also sexual reproduction when homologous sperm and egg meet (Gui, Zhou, 2010; Knytl et al., 2013). Such unique alternative system of reproduction comprising gynogenesis in combination with sexual reproduction determines this model organism for studying the alternative molecular pathways in meiosis regulations, which then could be used for more accurate research on the negative effects of pollutants acting in very low doses.

From the above mentioned reasons we consider oocytes of triploid Prussian carp as a potential model for evidence of negative effects of EDCs, which occur in the environment and could be potentially responsible for disorder in reproductive functions of humans.

CONCLUSION

The oocyte is an unrivalled material for reproductive biotechnology. The size, simplicity of manipulation, and opportunity to study the cell cycle and embryonic development are all advantages of oocyte use. For in vitro oocyte cultivation and usage of the organism as a biological model, an understanding of oogenesis regulatory signal pathways is important.

Re-initiation of oocyte meiosis is induced by hormones. Subsequently, second messenger molecules responsible for meiotic block are regulated and signal transduction requiring CDC25, MYT1, MPF, and MAPK is involved in oocyte meiotic maturation. MPF activity increases, resulting in lamin phosphorylation and subsequent GVBD. MPF and MAPK signal pathways are responsible for the complete and correct meiotic maturation and 2nd meiotic arrest maintenance.

For MPF activation and studying its function, Xenopus oocytes providing a lot of large oocytes are suitable. They supply a background for further research of the cell cycle of higher vertebrates including mammals. Mouse or pig biological models are used for the study of molecular reproduction. The great similarities of the pig model to humans are utilized for result applications in human disease healing, assisted reproduction, and xenotransplantation.

Besides regulatory mechanisms of gametogenesis, recent applied reproductive biology has focused on the negative effects of some environmental pollutants, such as phytostrogens, mycotoxins or endocrine-disrupting chemicals (EDCs). The act of the last appointed consists of very low and hardly-detectable concentrations expected in water environment. Recent understanding of endocrine disruptor action is often limited to hormonal failures (Caserta et al., 2014; Golshani et al., 2014; Pandey, Deshpande, 2015).

Due to simple way of obtaining eggs, natural gynogenesis, and alternative sexual reproduction, Prussian carp could be suggested as appropriate model for the study of key signal pathways of oocyte maturation. Anyway, the proper genetic identification of individuals taken to the experiments is essential due to different ploidy levels and various genome combinations within Carassius gibelio complex (Wouters et al. 2012; Ryková et al. 2013).

In the future the unique oocyte of Prussian carp could be an eligible object of reproductive biology studies focusing on pollutants dangerous for health and reproduction in humans due to its alternative mode of reproduction, which may unveil what still stays hidden in other animal models.

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LIST OF ABBREVIATIONS:

17α,20β-DP = 17α,20β-dihydroxy-4-pregnen-3-one, AC = adenylate cyclase, AMPK = AMP-activated protein kinase, APC/C) = anaphase-promoting complex/cyclosome, CaMKII = calmodulin-dependent kinase, cAMP = cyclic adenosine monophosphate, CDC2 = cyclin-dependent kinase 2, CDC25 = cell division cycle 25 phosphatase, cGMP = cyclic guanosine monophosphate, CSF = multi-enzyme complex cytostatic factor, EDCs = endocrine disrupting chemicals, FSH = follicle stimulating hormone, GV = germinal vesicle stage, GVBD = germinal vesicle breakdown, LH = luteinizing hormone, MAPK = mitogen-activated protein kinase, MI = the first meiotic metaphase, MII = the second meiotic metaphase, MPF = M-phase/maturation promoting factor, PG = progesterone, PI3K = phosphatidylinositol 3-kinase, PKA = cAMP-dependent protein kinase, PKA = protein kinase A, PKC = Ca2+-dependent protein kinase, PKG = cGMP-dependent protein kinase, PLK1 = polo-like kinase 1, UPS = ubiquitin-proteasome system.

Corresponding Author:

Ing. Ivona Weingartová, University of Life Sciences Prague, Faculty of Agrobiology, Food and Natural Resources, Department of Veterinary Sciences, Kamýcká 129, 165 21 Prague 6-Suchdol, Czech Republic, phone: +420 732 677 034, e-mail: weingartova@af.czu.cz