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Physiological relevance of nitric oxide in ovarian functions: An overview

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ABSTRACT

Nitric oxide (NO, nitrogen monoxide), a short-lived, free radical carrying an unpaired electron, is one of the smallest molecules synthesized in the biological system. In addition to its role in angiogenesis, neuronal function and inflammatory response, NO has wide-spread significance in regulation of ovarian function in vertebrates. Based on tissue-specific expression, three different nitric oxide synthase (NOS) isoforms, neuronal (nNOS) or NOS1, inducible (iNOS) or NOS2 and endothelial (eNOS) or NOS3 have been identified. While expression of both inducible (iNOS) and constitutive NOS (eNOS) isoforms varies considerably in the ovary at various stages of follicular growth and development, selective binding of NO with proteins containing heme moieties have significant influence on ovarian steroidogenesis. Besides, NO modulation of ovulatory response suggests physiological significance of NO/NOS system in mammalian ovary. Compared to the duality of NO action on follicular development, steroidogenesis and meiotic maturation in mammalian models, participation of NO/NOS system in teleost ovary is less investigated. Genes encoding *nos1* and *nos2* have been identified in fish; however, presence of *nos3* is still ambiguous. Interestingly, two distinct *nos2* genes, *nos2a* and *nos2b* in zebrafish, possibly arose through whole genome duplication. Differential expression of major NOS isoforms in catfish ovary, NO inhibition of meiosis resumption in *Anabas testudineus* follicle-enclosed oocytes and NO/sGC/cGMP modulation of oocyte maturation in zebrafish are some of the recent advancements. The present overview is an update on the advancements made and shortfalls still remaining in NO/NOS modulation of intercellular communication in teleost vis-à-vis mammalian ovary.

1. Introduction

Nitric oxide (NO) is a heteronuclear, diatomic, short-lived, free radical messenger molecule that freely diffuses through biological membranes and participates in diverse physiological functions (Knowles and Moncada, 1994; Moncada et al., 1991). The spectrum of cellular events regulated by NO and/or reactive nitrogen species (RNS) includes protein nitrosylation, phosphorylation at tyrosine residues, DNA deamination and activation of transcription factors (Hanafy et al., 2001; Martínez-Ruiz and Lamas, 2007; Mohr et al., 1996). Moreover, NO displays high reactivity to heme proteins leading to the formation of stable chemical species (Grisham et al., 1999).

Physiologically, NO is produced by the oxidation of L-arginine in an NADPH-dependent mechanism catalyzed by a heme-containing enzyme nitric oxide synthase (NOS) (Palmer and Moncada, 1989). Tissue-specific expression of three different NOS isoforms, namely neuronal (nNOS) or NOS1, inducible (iNOS) or NOS2 and endothelial (eNOS) or NOS3, has been correlated with development and differentiation of neuronal tissues, angiogenesis as well as inflammatory response (Knowles and Moncada, 1994). Additionally, reduction of nitrate and nitrite can spontaneously generate NO in hypoxia or acidic environment independent of NOS action (Lundberg and Weitzberg, 2010). Moreover, xanthine oxidase and cytochrome oxidase mediate in catalytic conversion of nitrite to NO (Basini and Grasselli, 2015 and references therein; Godber et al., 2000). Even microbial reduction of nitrate to nitrite, nitric oxide and ammonia under physiological condition highlights importance of gut bacteria in mammalian nitrate/nitrite/NO metabolism (Tiso and Schechter, 2015). The present review seeks to explore mechanisms by which NO/NOS system can modulate ovarian function in vertebrates, including speculation, based on limited study, about its function in teleost fishes.

2. General background: NO/NOS modulation of female reproduction

Production of viable eggs principally relies upon pituitary-derived gonadotropins and ovarian steroids (Nagahama and Yamashita, 2008). Nitric oxide modulation of hypothalamo-pituitary-gonadal (HPG) axis has pivotal influence in reproduction in general, and regulation of ovarian function in particular. NO from hypothalamic neurons

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facilitates LHRH secretion that in turn promotes LH release from the anterior pituitary and induces ovulatory response in female rats (Pinilla et al., 1998). Elevated nNOS expression corroborates well with kinetics of LH surge. While NO donor, sodium nitroprusside (SNP) stimulates GnRH release, inhibition of NOS activity abrogates pre-ovulatory LH surge in female rats (Lamar et al., 1999; Rettori et al., 1993). Besides, nNOS positive gonadotroph cells have been localized in rat anterior pituitary (Ceccatelli et al., 1993; Lloyd et al., 1995). Compared to studies conducted in mammals, relatively few or no information is available on NO/NOS regulation of HPG axis in fish. Detail discussion on this aspect, however, is beyond the scope of the present review.

In addition to systemic endocrine regulators, ovarian autocrine/paracrine and oocyte-derived local factors influence follicular growth, maturational potential as well as ovulatory response across vertebrate classes, albeit in a manner sensitive to specific reproductive strategies (Clelland and Peng, 2009; Ge, 2005; Reis et al., 2000). NO/NOS modulation of female reproduction, principally events like follicular development, steroidogenesis, granulosa cell apoptosis in atretic follicles, alteration of maturation potential and most importantly NO modulation of cyclooxygenases (COX-1, COX-2) action and prostaglandin synthesis prior to ovulation have received intense attention since last few decades (reviewed in Basini and Grasselli, 2015; Rosselli et al., 1998; Tamanini et al., 2003). NO binding to heme containing soluble guanylyl cyclase (sGC) – a heterodimer of α and β subunits, catalyzes formation of cyclic guanosine 3′, 5′-monophosphate (cGMP). NO-sensitive sGC (GUCY1) present in mammalian granulosa cells increases cGMP load and maintains prophase-I arrest in mammalian oocytes (Sela-Abramovich et al., 2008; Shi et al., 2004). Besides, binding of peptide hormone ligands (natriuretic peptide type C, NPPC) to natriuretic peptide receptor 2 (NPR2)-the major membrane bound or particulate guanylyl cyclase (pGC) in granulosa cell membrane, elevates cGMP within ovarian follicles (Robinson et al., 2012; Vaccari et al., 2009; Zhang et al., 2010). Relative importance of cGMP in intercellular communication within ovarian follicle includes modulation of cyclic nucleotide-mediated signaling events, phosphodiesterases (PDEs) and protein kinases (Egbert et al., 2018; Jaffe and Egbert, 2017; Norris and Carr, 2013; Norris et al., 2009).

Influence of locally-produced NO/cGMP in teleost ovary has also emerged as an area of active research in recent past. Differential expression of all three NOS isoforms at various stages of ovarian folliculogenesis correlates well with annual breeding cycle in catfish, *Heteropneustes fossilis* (Tripathi and Krishna, 2008) and *Claraias batrachus* (Singh and Lal, 2015). While multiple sGC subunits has been reported earlier in medaka ovary (Yao et al., 2003), dual role of NO/sGC/cGMP pathway in either activation or inhibition of meiotic maturation in zebrafish oocytes has been proposed (Li et al., 2018). Our recent data demonstrate that NO inhibition of meiotic G2-M1 transition in *Anabas testudineus* follicle-enclosed oocytes involves cyclin adenosine 3′,5′-monophosphase (cAMP)/protein kinase (PKA) activation (presumably through the cGMP-PDE3 cascade) and down regulation of Cdc25 and Mos-MAPK signalling events (Nath et al., 2018).

3. Nitric oxide synthase variants: The enzyme responsible for NO production

3.1. Mammalian NOS

Based on regulation of enzymatic activity, tissue-specific expression, inhibitor sensitivity and physiological functions, three major NOS enzymes, nNOS, iNOS and eNOS have been identified as the product of three distinct genes in mammals (Knowles and Moncada, 1994). All the NOS enzymes contain an N-terminal oxygenase domain and a C-terminal reductase domain linked by a central calmodulin (CaM) binding sequence. The reductase domains of the NOS proteins have the binding sites for nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD) and flavin-adenine mononucleotide (FMN) and are related to many other flavoprotein reductases. On the other hand, NOS oxygenase domains do not show significant sequence similarity with other proteins and has highly conserved heme (Fe), tetrahydrobiopterin (H_4B) and arginine (arg) binding sites (Bredt et al., 1991; Chen and Wu, 2000 and references therein).

Activation of constitutively expressed NOS isoforms, nNOS and eNOS, is dependent on intracellular Ca^{2+} concentration. In contrast, iNOS expression is independent of Ca^{2+} and induced by endotoxic or inflammatory responses (Alderton et al., 2001; Bredt et al., 1991; Campbell et al., 2014). Dimerization of NOS monomers gives rise functionally active NOS enzymes (Hemmens et al., 1998). After translation, heme-free monomer binds to CaM, FMN and FAD to form a functional reductase domain. Heme binding allows two monomers to form a loose dimer. Subsequently binding of H_4B and arg gives rise to the generation of an active “tight dimer” (Stuehr, 1999). Further, cellular NO can block heme incorporation into iNOS monomer which has earlier been implicated in duration-dependent accumulation of heme-free iNOS monomer in cytokine triggered cells (Albakri and Stuehr, 1996). Collectively, considerable information is available on assembly of reductase and oxygenase domains, involvement of heme, H_4B, Zn^{2+} or even cellular NO level in dimerization and stabilization of functional NOS enzymes from studies in mammalian cells (Campbell et al., 2014). However, no such mechanistic study has yet been initiated for any NOS variants in fish models requiring active research initiatives in near future.

3.2. Evidence of NOS in fish

Previously *nos1* and *nos2* have been identified in various fish species including goldfish, carp, rainbow trout, channel catfish, zebrafish and tilapia; however, presence of *nos3* is still ambiguous and possibly first appeared in reptiles (Donald and Broughton, 2005; Laing et al., 1996; Lepiller et al., 2009; Reddick et al., 2006; Saeij et al., 2000; Wang et al., 2001; Yao et al., 2014). In zebrafish, the ortholog of *nos1* (*nnos)* is well conserved, sharing almost 82–86% sequence similarity with human, murine and fugu nNOS (Poon, 2003). Expression of *nnos* (*nos1*) during embryogenesis and in the adult brain suggests its involvement in neurogenesis, organogenesis and neuronal differentiation in zebrafish (Holmqvist et al., 2000; Poon, 2003). Interestingly, genome duplication has potentially given rise two *nos2* variants, *nos2a* and *nos2b* in zebrafish (Force et al., 1999; Lepiller et al., 2009; Robinson-Rechavi et al., 2004). Expression of *nos2a* is predominant in immune tissues like spleen and pathogen-invading organs such as gills, skin and gut (Lepiller et al., 2009). Conversely, *nos2b* expression is constitutive and specifically detected surrounding the oral cavity throughout developmental stages and almost in all the adult tissues of zebrafish (Holmqvist et al., 2000, 2004; Poon, 2003).

As shown in Fig. 1, all the piscine Nos isoforms reported so far, possess conserved N-terminal domains for heme (Fe) binding followed by BH4, CaM, FMN, FAD and a C-terminal NADPH binding domain. As in higher vertebrates, structural diversity of Nos1 protein reveals an additional PDZ domain at N-terminal region (Fig. 1) in fish (Yao et al., 2014). PDZ domain of nNOS binds to the C termini of target proteins with very low affinity and has significant influence in sub-cellular targeting (Merino-Gracia et al., 2016; Stricker et al., 1997 for review). Moreover, N-terminal myristoylation (Myr) site and its expression in adult heart suggest functional homology of zebrafish Nos2b with mammalian NOS3 (Fig. 1). However, endotoxic stimulation promotes both *nos2a* (*iNOS*) and *nos2b (eNOS)* expression, albeit with differential intensity, indicating comparable promoter sequences and similarity in expression regulation of two *nos2* variants in this species (Dudzinski et al., 2006; Förstermann et al., 1998; Lepiller et al., 2009).

Presence of a *nos3* gene has never been reported in fish (Andreakis et al., 2011; Holmqvist et al., 2007). In contrast, NOS3 immunoreactive protein has been identified in heart, kidney, retina, endothelium and gills of various fishes using heterologous antibodies. However; still

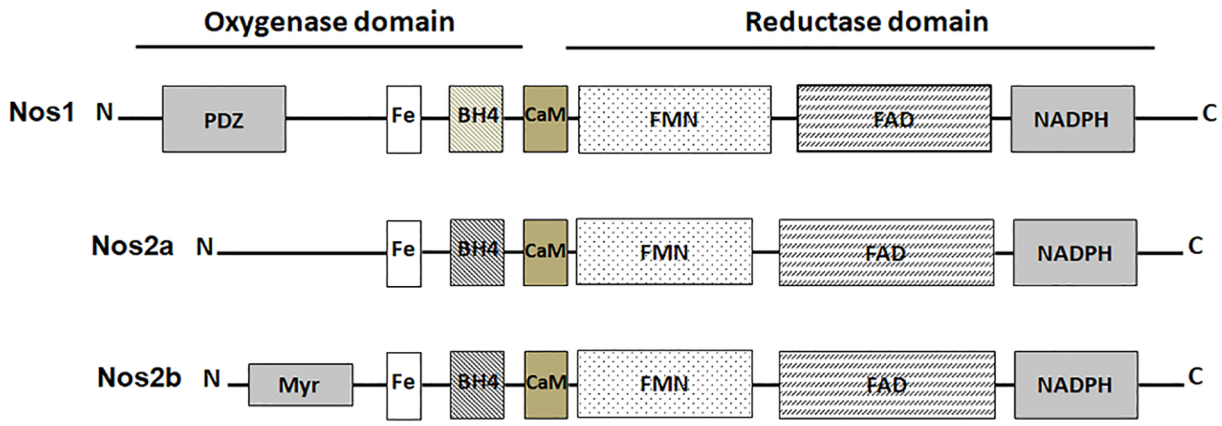

Fig. 1. Schematic representation of zebrafish Nos isoforms on the basis of data represented elsewhere (Lepiller et al., 2009; Yao et al., 2014). Zebrafish *nnos* (the *nos1* ortholog) is located on chromosome 5 and has been cloned to a 4552 bp cDNA sequence (AY211528), encoding a peptide consisting of 1432 amino acids (Poon, 2003). Localized in chromosome 5, the 3382 bp cDNA (accession number AM749801) of *nos2a* encodes a protein with 1079 amino acid residues. The *nos2b* gene is located in chromosome 15, the 3435 bp cDNA (accession number AM749802) encodes a protein of 1077 amino acids (Lepiller et al., 2009). Consensus binding sites for heme (Fe), tetrahydrobiopterin (BH4), calmodulin (CaM), flavin-adenine mononucleotide (FMN), flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide phosphate (NADPH) are indicated from N-terminal end of the mature peptide. The N-terminal PDZ domain in Nos1 and N-terminal myristoylation site (Myr) in Nos2b are also shown.

others have failed to detect presence of NOS3 in endothelial cells of fish and amphibians either through NADPH-diaphorase activity or immunocytochemistry. Collectively functional relevance of NOS3-derived NO in endothelial cell functions in fish is still ambiguous (Andreakis et al., 2011; Donald and Broughton, 2005 and references therein).

3.3. Expression of nitric oxide synthase in the ovary

Table 1 shows expression of NOS, specifically that of eNOS and iNOS, during various stages of folliculogenesis in mammalian ovary. While all three functional NOS enzymes are present in rat ovary before puberty, nNOS expression has not been detected in the ovary of any adult mammalian model studied so far (reviewed in Basini and Grasselli, 2015; Jablonka-Shariff and Olson, 1997; Tamanini et al., 2003). Primarily expression of eNOS is predominant in mural granulosa cells, theca layer, ovarian blood vessels and stroma in rats (Jablonka-Shariff and Olson, 1997; Nakamura et al., 1999; Yamagata et al., 2002; Zackrisson et al., 1996). However, iNOS expression is restricted to the follicular cells of primary, secondary and small antral follicles as well as in corpus luteum (Jablonka-Shariff and Olson, 1997; Yamagata et al., 2002). Importantly, expression of iNOS predominates over eNOS in both granulosa and theca layers in mouse ovary (Mitchell et al., 2004; Tamanini et al., 2003). Moreover, significant variations in NO load during follicular growth and development may be due to variations in intra-follicular NOS expression (Basini et al., 1998; Grasselli et al., 2002; Nakamura et al., 2002).

Immunohistochemical localization of NOS isoforms has been correlated with seasonality of reproduction in teleost ovary. Negative correlation between follicular growth and expression of eNOS/iNOS has been observed in the ovary of two catfish species *C. batrachus* and *H. fossilis*, both of which breed during the monsoon (Table 2). While peak levels are observed during recrudescence phase, expression of both eNOS and iNOS undergoes progressive attenuation before reaching the basal level prior to ovulation. Although its functional relevance in ovary is still unclear, in *H. fossilis* expression of nNOS immunoreactivity reaches its peak during ovulatory phase (Tripathi and Krishna, 2008). Contrary to the situation in mammals, evaluation of NOS expression in fish ovary has been carried out using heterologous antibodies specific for mammalian NOS isoforms. Availability of the fish-specific antibodies can provide important breakthroughs to identify functional NOS isoforms in fish ovary. At the mRNA level, expression of *nos1, nos2a* and *nos2b* was reported in zebrafish ovary (Li et al., 2018). Moreover, our recent data demonstrtate significant variation in *nos2a* and *nos2b* expression at early-, mid-, and late-vitellogenic stages of follicular growth in this species (manuscript under preparation).

3.4. Hormonal regulation of nitric oxide synthase in mammalian and fish ovary

Sharp decline in follicular iNOS expression in PMSG and/or hCG stimulated immature rat ovary was reported earlier (Matsumi et al., 1998; Nakamura et al., 2002; Yamagata et al., 2002). In PMSG-induced rat ovary, follicular growth is closely connected to the elevated eNOS, but not iNOS expression (Jablonka-Shariff and Olson, 1997; Van Voorhis et al., 1995). In cultured porcine granulosa cells, harvested from small follicles, FSH stimulation promotes expression of eNOS mRNA and NO synthesis (Takesue et al., 2001). Moreover, E2 promotes eNOS enzyme and NO production by cumulus oocyte complexes in porcine ovary (Hattori et al., 2004). In porcine cumulus-enclosed oocytes, contrary to the situation in granulosa cells, exogenous FSH administration attenuates eNOS protein in dose-dependent manner and suppresses NO production (Hattori et al., 2000). In contrast to the situation in mammals, direct evidence on endocrine modulation of Nos expression in fish ovary is still lacking. However, recently we observed significant alteration in *nos2a* and *nos2b* expression in hCG-treated zebrafish follicles *in vitro* (manuscript under preparation). Thus possibility of close association between differential expression of Nos enzymes in teleost ovary and pituitary-derived gonadotropins (FSH/LH) and/or ovarian steroid hormones (E2/MIH) cannot be ruled out. Collectively, hormonal regulation of NOS expression in fish ovary might appear as an area of intense research initiative in upcoming years.

4. Nitric oxide regulation of ovarian function

4.1. Folliculogenesis and granulosa cell apoptosis

Substantial increase in ovarian vascular system is necessary to satisfy the need for nutrient deposition, elevated oxygen consumption and incorporation of other maternal determinants during folliculogenesis in mammals. Increase in nitrite/nitrate (NOx) concentration shares a positive correlation with follicular size as well as estradiol concentration in human and porcine ovarian follicles (Hattori and Tabata, 2006;

Table 1
Localization of NOS isoforms in mammalian ovary.

Model organisms	Follicular phage	NOS Isoform			Cell/ tissue type		Reference	Method
		nNOS	eNOS	iNOS	oocyte	follicular layer		
Rat	Before puberty	+ + +	+ +	+ +	Nucleus and cytoplasm of primordial, primary, secondary, tertiary and atretic follicles	–	Zhang et al. (2011)	Immunohistochemistry and NADPH-diaphorase reactivity
	Pre-ovulatory	–	+ + + (*)	+ + + (#)	–	(*) mural granulosa cells, thecal layer, ovarian blood vessels, stroma (#)follicular cells of primary, secondary and small antral follicles	Jablonka-Shariff and Olson (1997); Nakamura et al. (1999); Van Voorhis et al. (1995); Yamagata et al. (2002); Zackrisson et al., 1996	
	Ovulatory	–	+	+	Cells of the corpus luteum			
Mice	Pre-ovulatory	–	+ +	+ + +	Cytoplasm	Granulosa cells, theca cells	Mitchell et al. (2004)	Immunohistochemistry and *in situ* hybridization
Bovine	Pre-ovulatory	–	+ + +	+ + +	Cytoplasm of primary, secondary and tertiary oocyte	Theca, granulosa layer of primary, secondary and tertiary follicles	Basini et al. (1998); Pires et al. (2009)	Immunohistochemistry, fluorescence microscopy andquantitative real-time PCR
	Ovulatory	–	+ +	+ +	Corpus luteum, corpus albicans, surface epithelium and stroma			
Porcine	Pre-ovulatory	–	+ + + (*)	+ + (#)	(*) antral follicle and increasing from small, medium to large follicles (#) primordial and early antral follicle, decreased in large follicles	*, # granulosa cells of small and medium follicles	Grasselli et al. (2001); Tao et al. (2004)	Immunohistochemistry
	Ovulatory	–	+ + +	+ +	Corpus luteum and parenchymal cells in corpus albicans			
Human	In women undergoing in vitro fertilization	–	–	+ +	Cultured granulosa-luteal cells		VanVoorhis et al. (1994)	Immunocytochemistry

Table 2
Nitric oxide synthase localization in fish ovary.

Model organisms	Reproductive phage	NOS isoform			Cell/ tissue type		Reference	Method
		nNOS	eNOS	iNOS	Oocyte	Follicular layer		
Indian walking catfish (*Clarias batrachus*)	Late quiescence	+ +	–	–	Nucleus and cytoplasm of *peri*-nuclear and stage I oocytes	–	Singh and Lal (2015)	Immunohistochemistry
	Recrudescence	+ + +	+ + +	+ + +	–	thecal and granulosa cells of stage II and III oocytes		
	Late recrudescence and spawning	+	+ +	+ +	–	thecal and granulosa cells of the stage III oocytes		
	Ovulatory	–	–	+	Zona radiata of ovulated oocyte	–		
Asian stinging catfish (*Heteropneustes fossilis*)	Early recrudescence	+ + +	+	+	Nucleus and/or cytoplasm of primordial oocyte	–	Tripathi and Krishna (2008)	Immunohistochemistry and Western blots
	Early and mid previtellogenic	+ +	+ + +	+ +	nNOS in nucleus and cytoplasm of stage I and II oocyte	moderate iNOS but intense eNOS in granulosa and theca cell layer of stage I and II follicles		
	Vitellogenic	–	–	–	–	–		
	ovulatory	+ +	–	–	Nucleus and cytoplasm of resting phase oocyte	–		
Zebrafish (*Danio rerio*)	At any time point of the year (daily spawning fish)	+ + +	+ +	+ +	*nos* positive ovary tissue		Lepiller et al. (2009)	RT-PCR analysis
Channel catfish (*Ictalurus punctatus*)	–	+ +	+ +	+	*nos* positive ovary tissue		Yao et al. (2014)	RT-PCR analysis

The intensity of NOS expression is represented as: − absence; + weak; + + modest; + + + intense presence.

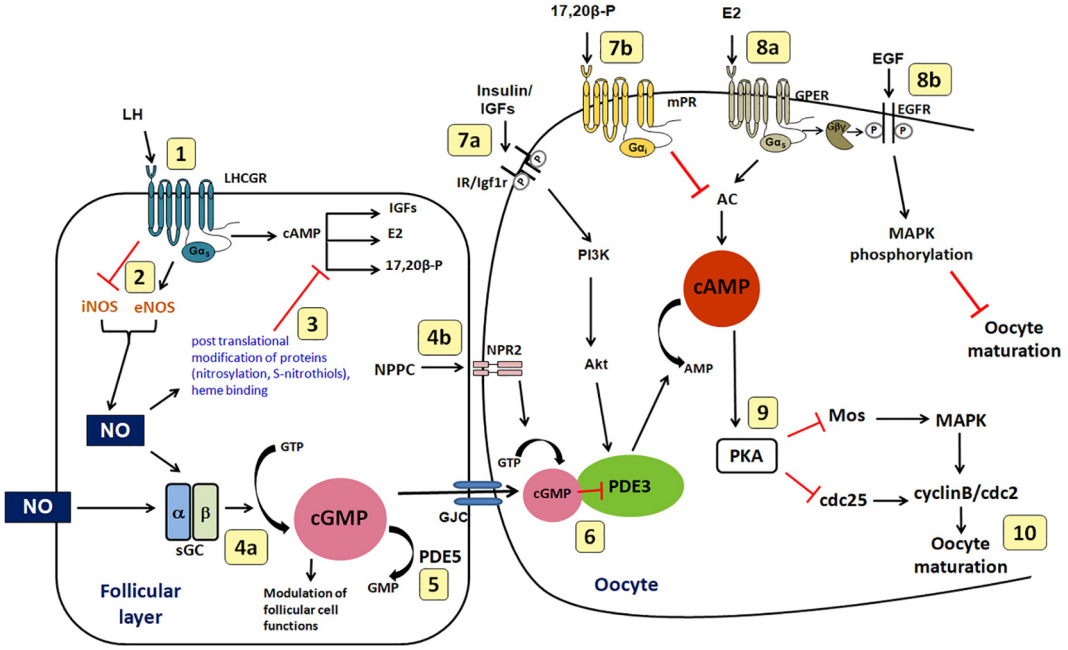

Fig. 2. A snapshot on complex intercellular communication within ovarian follicle highlighting functional significance of NO/cGMP modulation of diverse signaling events. LH binding to its cell-surface G-protein coupled receptor (LHCGR) promotes follicular steroidogenesis and synthesis of IGFs potentially through $G\alpha_s$/adenylyl cyclase (AC)/cAMP signaling (1) (Li et al., 2015; Mehlmann, 2005; Nagahama and Yamashita, 2008). While it inhibits iNOS expression, LH-induction of eNOS expression promotes endothelial cell function in the mammalian ovary (2) (Matsumi et al., 1998; Nakamura et al., 2002). Exogenous NO administration or endogenous NOS-mediated NO synthesis in the ovary can modulate diverse effector functions which includes *inter alia* post-translational modifications of protein structure such as nitrosylation, phosphorylation at tyrosine residues, formation of S-nitrosothiol and binding to heme-containing enzymes (3) (Hanafy et al., 2001; Jablonka-Shariff and Olson, 1997; Nakamura et al., 1999; Tamanini et al., 2003). Additionally, NO/sGC interaction and/or binding of granulosa cell-derived peptide ligand, NPPC to its cognate receptor, NPR2, at the oocyte surface promotes cGMP accumulation in both mammalian and fish ovary (4a,b) (Li et al., 2018; Pang and Thomas, 2018; Shi et al., 2004; Zhang et al., 2010). Though various PDE isoforms have been reported in ovarian follicle, PDE5 localized in follicular layer have crucial influence on cGMP accumulation (5). Moreover, cGMP can enter the oocyte through gap-junction complex (GJC), prevents oocyte-specific PDE3 (6) which in its turn may allow cAMP accumulation (9) and prevents meiosis resumption in mice (Jaffe and Egbert, 2017; Norris et al., 2008; Shuhaibar et al., 2015). Although details on NO/cGMP modulation of intra-oocyte cAMP accumulation has not yet been worked out in any teleost model, our recent results showed for the first time elevated cAMP/PKA activation in SNP-treated folliculated perch (*A. testudineus*) oocytes has negative influence on MPF activation and oocyte GVBD, in a manner sensitive to activation of Cdc25 and Mos/MAPK (ERK1/2) signaling (10) (Nath et al., 2018). Besides, our earlier data reveals functional importance of PDE3 downstream to PI3K/Akt activation during insulin/IGF-induction of oocyte maturation in zebrafish oocytes *in vitro* (7a) (Das et al., 2013). 1720β-P action at the oocyte surface, through mPRα, activates $G\alpha_i$ which in turn attenuates AC activity (7b) and prevents cAMP synthesis as well as PKA activation (9) prior to resumption of meiosis in zebrafish and majority of other fish species studied so far (Zhu et al., 2003; Nagahama and Yamashita, 2008). Conversely, E2 action through GPER/$G\alpha_s$/AC promotes significant increase in cAMP concentration to ensure maintenance of prophase arrest (8a) (Pang and Thomas, 2010). Also, E2-mediated transactivation of epidermal growth factor receptor (EGFR) and MAPK activation has been implicated in maintenance of meiotic arrest in zebrafish oocytes (8b) (Peyton and Thomas, 2011). Additionally, the importance of cGMP signaling in zebrafish ovary stems out from recent evidence showing NPPC/NPR2-mediated cGMP accumulation within the oocyte prevents meiosis resumption in this species (4b) (Pang and Thomas, 2018).

Rosselli et al., 1998). Although NO induces follicular blood flow in growing follicles, negative influence of NO action on angiogenesis may suggest significant correlation between ovarian NOS activity and follicular development (Grasselli et al., 2002; Mitsube et al., 2002; Zackrisson et al., 1996).

High level of NO helps in development of dominant follicles and induces granulosa cell apoptosis – A reliable marker for follicular atresia (Basini et al., 1998; Tamanini et al., 2003; Yamagata et al., 2002). However, at lower concentration NO positively influences granulosa cell proliferation in immature and pre-ovulatory follicles indicating it may act as both pro- and anti-apoptotic factor (Matsumi et al., 1998). Interestingly, NO donor, S-nitroso-N-acetylpenicillamine, could inhibit Fas/FasL system-induced apoptosis by suppressing caspase-3, -8, and -9 activities in rat granulosa cells suggesting potential cross-talk between Fas/FasL system-induced apoptosis pathway and NO-mediated anti-apoptotic pathway during follicular atresia (Chen et al., 2005).

Though comparable studies on relative importance of NO/NOS system in granulosa cell apoptosis and follicular atresia are still lacking in fish ovary, functional interplay between endocrine and/or locally-derive autocrine/paracrine growth factors has been studied extensively (reviewed in Clelland and Peng, 2009; Das et al., 2017; Ge, 2005). Follicular growth in fish can be divided into two distinct phases; gonadotropin-independent phase regulated by oocyte-derived factors and gonadotropin-dependent phase (Lubzens et al., 2010). Estradiol-17β (E2), synthesized under the influence of pituitary gonadotropins (FSH), promotes vitellogenesis that accounts for majority of growth of the secondary follicles in teleost ovary (Mommsen and Walsh, 1988; Nagahama and Yamashita, 2008). Additionally, local growth factors (specifically IGF-I and TGF-β family members) are associated with follicular growth (Ge, 2005). In addition to the localization of NOS immunoreactive proteins at various stages of folliculogenesis, NO concentration has been positively correlated with the secondary growth of follicles in the ovary of two seasonal breeder catfish species (Singh and Lal, 2015; Tripathi and Krishna, 2008). Elevated NO level coincides well with pre-vitellogenic follicular growth during recrudescence phase in *H. fossilis*. Conversely, NO level in either serum or ovary declines sharply during vitellogenin incorporation in this species (Tripathi and Krishna, 2008).

4.2. Ovarian steroidogenesis

Nitric oxide inhibition of ovarian steroidogenesis has wide-spread negative influence on growth and differentiation of reproductive tissues and fertility in mammals (reviewed in Basini and Grasselli, 2015; Hattori and Tabata, 2006). While it attenuates aromatase gene expression in human granulosa cells, NO binding to the prosthetic heme group inhibits aromatase activity and impairs ovarian steroidogenesis (Hanke et al., 1998; Van Voorhis et al., 1994). NO donor lowers E2 level in PMSG-treated rat ovaries (Dong et al., 1999). Nitric oxide attenuation of hCG action and down regulation of progesterone synthesis has been shown in pre-ovulatory follicles in rat (Dave et al., 1997; Mitsube et al., 2002; Yamagata et al., 2002). Elevated E2 level has been reported in eNOS knockout mice (Jablonka-Shariff and Olson, 1998). In female rats fed with NOS inhibitor, chronic NO inhibition results in elevated E2 production and constant estrus cycle (Dunnam et al., 1999). Besides, involvement of cGMP and cAMP has been reported in NO inhibition of E2 synthesis in rat granulosa cells (Ishimaru et al., 2001).

In fish ovary shift in steroidogenesis occurs to maintain the normal ovarian function (Senthilkumaran et al., 2004). While elevated E2 in circulation promotes hepatic vitellogenin synthesis during ovarian growth phase, surge in LH triggers shift in steroidogenesis leading to synthesis of maturation inducing hormone (MIH) and resumption of final oocyte maturation prior to ovulation (Das et al., 2017; Nagahama and Yamashita, 2008). Information on nitric oxide regulation of steroidogenesis in fish ovary is relatively scarce. Our recent data demonstrate significant reduction in *StAR*, *cyp19a* and *20-β-hsd* expression in zebrafish full-grown follicles treated with SNP *in vitro* (unpublished observation). Conversely high dose of SNP, administered *in vivo,* promotes elevated testosterone and E2 production during the late-quiescence and mid-recrudescence phases in *C. batrachus* ovary (Singh and Lal, 2017). Although elevated 3β-HSD and 17β-HSD activity was considered as responsible for higher testosterone and E2 synthesis in this species, NO modulation of aromatase (*cyp19a*) gene expression remains to be seen.

4.3. Oocyte maturation

Based on literature available with us, molecular mechanisms underlying NO modulation of intrafollicular signaling events and potential NO targets in follicular theca-granulosa layer and/or maturing oocyte have been enumerated in Fig. 2. There is a large body of evidence showing participation of NO/NOS system in regulation of meiotic maturation in cumulus-oocyte complexes (Basini and Grasselli, 2015). Full-grown oocytes remain arrested at the diplotene stage of first meiotic prophase and resumption of meiosis depends on surge in pituitary-derived LH in almost all vertebrate species. In mammals, prior to ovulation, LH either removes an inhibitory, maturation arresting substance or provides a positive, maturation-promoting factor to the oocyte to undergo final oocyte maturation (Mehlmann, 2005).

Oocyte-derived elevated endogenous NO has pivotal influence in maintenance of meiotic arrest in mammalian models (Tripathi et al., 2010). Pre-ovulatory LH surge attenuates granulosa cell-specific iNOS expression and lowers NO synthesis prior to onset of maturational events in rat ovary (Yamagata et al., 2002). While NOS-inhibitor stimulates meiotic G2-M1 transition in rat folliculated oocytes *in vitro* (Nakamura et al., 2002); high NO could prevent or delay maturational response in variety of mammalian species (Bu et al., 2004; Nakamura et al., 2002; Schwarz et al., 2008; Sela-Abramovich et al., 2008; Tao et al., 2005).

Interestingly, the duality of NO action on meiotic maturation has also been suggested. While at low level it stimulates, NO at higher concentration prevents meiotic maturation in bovine and mouse oocytes (Bilodeau-Goeseels, 2007; Bu et al., 2003). Direct activation of ion channels, protein tyrosine kinases and G proteins, but not cGMP/PKG signaling, has been implicated in NO-induction of meiotic maturation in mice (Abbasi et al., 2009), rat (Tornell et al., 1990), bovine (Bilodeau-Goeseels, 2007) and porcine (Petr et al., 2006) oocytes. Conversely, high NO/cGMP attenuation of MAPK3/1 activation and interruption of gap junctional communication (GJC) prevents LH-induced meiosis resumption in rat oocytes (Nakamura et al., 2002; Sela-Abramovich et al., 2008).

In teleosts, binding of maturational steroid (MIH) to mPRα, at oocyte surface (Zhu et al., 2003), triggers downstream signaling events leading to activation of maturation promoting factor, MPF (a heterodimer of cyclin B and cdc2 protein), histone H1 kinase activation, chromatin condensation, nuclear membrane dissolution and first polar body exclusion (Nagahama and Yamashita, 2008). Additionally, insulin/IGF activation of meiotic maturation has been reported in many teleost species (Das et al., 2017, 2016, 2013; Li et al., 2015; Reinecke, 2010). Partial inhibitory action of NO on oocyte maturation was reported during late pre-spawning phase in the seasonal breeder catfish, *H. fossilis* (Tripathi and Krishna, 2008). Importantly, studies on identification of specific NO targets and potential involvement of nitric oxide/cGMP signaling in regulation of meiosis resumption in fish oocytes have been initiated very recently (Li et al., 2018, Nath et al., 2018). Li et al. (2018) have shown expression of all three NOS enzymes and four soluble sGC isoforms at mRNA level in zebrafish ovary. During oocyte maturation, NO levels increased in follicular cells but remained constant in oocytes, while cGMP levels increased in the follicular cell layer but decreased in oocytes in this species. Based on which dual role of NO/sGC/cGMP pathway in either activation or inhibition of meiotic maturation in zebrafish oocytes has been proposed (Li et al., 2018).

Our recent data demonstrate that congruent with elevated cAMP-dependent PKA activation, NO inhibition of p34Cdc2 (Thr-161) phosphorylation (a reliable marker for MPF activation) and meiotic maturation in perch (*A. testudineus*) oocytes, involves attenuation of Cdc25 activation, Mos (c-Mos proto-oncogene product) synthesis and MAPK3/1 (ERK1/2) phosphorylation (Nath et al., 2018). As PKA inhibitors [H89 or PKI-(6-22)-amide] alone in absence of MIH may promote oocyte maturation in this species (Khan and Maitra, 2013), involvement of high PKA activity in NO-inhibition of meiotic maturation was hypothesized. Even elevated cGMP accumulation in SNP-primed *A. testudineus* full-grown follicles shows positive correlation with robust increase in cAMP level (unpublished observation). Taken together, potential involvement of cyclic nucleotide signaling and activation of cAMP/PKA cascade has been proposed in NO attenuation of GVBD response in *A. testudineus* follicle-enclosed oocytes *in vitro* (Fig. 2) (Nath et al., 2018). Investigations on NO/cGMP modulation of PDEs and its impact on intercellular cyclic nucleotide signaling within fish ovarian follicles would be of prime importance in future.

4.4. Ovulatory response

Complex dialog of ovulation principally relies on cascades of follicular events mediated by some local ovarian factors and modulators of inflammatory response (Goetz and Garczynski, 1997). Nitric oxide regulation of ovulatory response is an area of active research since long in many mammalian species (Hattori and Tabata, 2006). In rat ovary, pharmacological inhibition of iNOS activity attenuates ovulation, an effect that could successfully be reversed by NO donor (Shukovski and Tsafriri, 1994). In addition, significant reduction in hCG-induced ovulation rate in eNOS-knockout mice indicates positive influence of eNOS on ovulation process (Jablonka-Shariff and Olson, 1998). Nitric oxide binding to the heme moiety of cyclooxygenases (COX-1, COX-2) modulates prostaglandin (PG) synthesis and ovulation (Hattori and Tabata, 2006 and references therein). NOS-2 derived NO stimulates PGF2α production and thus pharmacological inhibition of NOS activity prevents PGE2 and PGF2α synthesis (Dixit and Parvizi, 2001; Grasselli et al., 2001). Moreover, positive influence of NO on synthesis of prostaglandin-endoperoxide synthase (PTGS2), the key enzyme responsible for PG synthesis, has been reported during ovulation in human and

bovine models (Fang et al., 2015; Zamberlam et al., 2014). Interestingly, elevated COX-2 (*ptgs2)* expression in zebrafish ovary shows good temporal correlation with early morning ovulation in this species (Lister and Van Der Kraak, 2009). Although involvement of arachidonic acid (AA) and PGs synthesis was shown earlier during ovulation in teleosts (Goetz and Garczynski, 1997), NO/NOS action on ovulatory response warranting systematic research initiatives.

5. Ovarian cGMP signaling: At the cross roads of NO/sGC and NPPC/NPR2 cascades

In addition to NO/sGC mediated cGMP production (Basini and Grasselli, 2015), participation of natriuretic peptides in cGMP accumulation and regulation of meiotic maturation in mammalian models has received considerable attention (Norris and Carr, 2013). Expression of NPPC and NPR2 mRNAs was reported earlier in cumulus and mural granulosa cells (Gutkowska et al., 1999; Jankowski et al., 1997). Binding of NPPC to NPR2 elevates cGMP level within ovarian follicles (Robinson et al., 2012; Vaccari et al., 2009; Zhang et al., 2010). Inhibition of cGMP-specific PDE5 in follicular cells promotes cGMP accumulation leading to maintenance of prophase-I arrest in mouse oocytes (Jaffe and Egbert, 2017; Vaccari et al., 2009). Besides, elevated cGMP from the surrounding somatic cells prevents oocyte-specific PDE3, leading to cAMP accumulation and attenuation of meiotic maturation (Norris et al., 2009; Shitsukawa et al., 2001; Zaccolo and Movsesian, 2007). More importantly, pre-ovulatory LH surge or hCG treatment has negative influence on NPPC/NPR2/cGMP cascade allowing meiosis resumption in murine follicle-enclosed oocytes (Conti et al., 2012; Kawamura et al., 2011; Norris et al., 2008; Robinson et al., 2012; Shuhaibar et al., 2015). Accordingly, reduction in follicular cGMP level is considered as a pre-requisite for LH-induced meiosis resumption (Fig. 2) in mammalian models (Norris et al., 2008; Vaccari et al., 2009).

Recently, presence of NPPC and NPR2, at both mRNA and protein levels, as well as elevated cGMP synthesis in exogenous NPCC-treated follicle-enclosed oocytes were demonstrated in zebrafish (Pang and Thomas, 2018). Additionally, these authors have demonstrated involvement of E2-GPER pathway in cGMP-inhibition of meiotic maturation in this species. Even, we have hypothesized involvement of PDE3 in maintenance of high level of cAMP-dependent PKA during SNP-inhibition of meiotic maturation in *A. testudineus* folliculated oocytes (Nath et al., 2018). Collectively, conserved nature of NPPC/NPR2/cGMP-mediated inhibition of meiotic maturation and involvement of PDE isoforms in regulation of cyclic nucleotide signaling is most likely in mammalian and fish ovary (Fig. 2).

6. Conclusion

Though significant differences are there, differential expression of NOS enzymes at various stages of follicular growth, nitric oxide regulation of ovarian steroidogenesis, oocyte maturation and ovulatory response as well as NO/sGC/cGMP regulation of intercellular communication within ovarian follicle, are some of the major events which are relatively well conserved in mammalian as well as fish ovary. Though two distinct NOS isoforms, NOS1 and NOS2, have been identified in many fish species, presence of NOS3 is still in questionnaire. Though variations in the NOS expression at various stages of ovarian growth and development correlates with other reproductive parameters in fish models, the tissue-specific expression and functional characterization of these Nos isoforms are still in controversy and sometimes found as overlapping in action. In addition, localization of NOS isoforms in fish ovary using heterologous antibodies raised against mammalian NOS proteins has certain obvious limitations. Using modern gene editing tools, silencing of NOS genes identified till date in piscine organisms may facilitate the researchers to better understand their specific role in reproduction. Although involvement of NOS/NO/cGMP system during oocyte maturation in zebrafish has been reported, comparable studies in other fish models are still lacking. Importantly, our recent results demonstrate that NO attenuation of meiosis resumption in maturational-steroid induced perch oocytes involves down regulation of Cdc25 and MOS/MAPK activation, in a manner sensitive to cAMP/PKA activation; such studies may prove useful in identifying NO targets in fish oocyte in future.

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