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REVIEW PAPER

How endocrine disruptors affect fish reproduction on multiple levels: A review

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Abstract. This review paper presents fish reproductive toxicology studies with a specific focus on endocrine-disrupting chemicals (EDCs) present in the aquatic environment. These substances, including bisphenols, heavy metals, pesticides, phthalates, and polychlorinated biphenyls (PCBs), act as hormone mimics, receptor blockers, or enzyme inhibitors that affect hormonal regulation in the hypothalamic-pituitary-gonadal (HPG) axis. In this review, we provide an overview of the adverse effects of these pollutants on both female and male fish reproduction (i.e., hormonal disruption in the HPG axis, gametogenesis disorders, disturbed embryogenesis, etc.). Even at low concentrations, EDCs can exhibit reproductive toxicity in fishes. They can affect the functioning of certain systems within the hypothalamus (Kiss/GPR54, GnRH) and can also impact luteinizing hormone (LH) secretion in the pituitary. These compounds have negative impacts on gonads, oocyte maturation, steroidogenesis, and gametes. Early-life exposure to these substances not only affects embryonic development, resulting in increased mortality and body malformations, but this also induces genetic changes in newly hatched larvae. All these observations underscore the need for monitoring the aquatic environment for EDCs and implementing protective measures to preserve the health and welfare of fishes and safeguard water ecosystems.

Keywords: pesticides, fish, reproduction, xenobiotic, embryos dysfunctions

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Introduction

Fish reproductive toxicology studies focus on endocrine disrupting chemicals (EDCs) present in the aquatic environment. EDCs act as hormone mimics, receptor blockers, or enzyme inhibitors that affect the hormonal regulation at the hypothalamic-pituitary--gonadal axis (HPG axis) (Leet et al. 2011, Golshan et al. 2016, Gárriz et al. 2017, Golshan and Alavi 2019, Smith et al. 2019, Davico et al. 2021, Socha et al. 2021b). The HPG axis plays the central role in the reproductive cycles in fishes and other vertebrates. The key neuroendocrine hormone, kisspeptin (Kiss), binding to its receptor, GPR54, initiates the production of gonadotropin-releasing hormone (GnRH) in

the hypothalamus. GnRH activates the synthesis and release of gonadotropins, including follicle-stimulating hormone (FSH) and luteinizing hormone (LH), from the pituitary (Levavi-Sivan et al. 2010, Zohar et al. 2010, Gárriz et al. 2017, Nakajo et al. 2018). Gonadotropins and their receptors (FSHr, LHr) play important roles in gametogenesis and in regulating the production of sex steroid hormones such as testosterone (T), 11-ketotestosterone (11-KT), 17β-estradiol (E2), and progestogens, such as 17α,20β-dihydroxy-4-pregnen-3-one (17,20β-P) (Gárriz et al. 2017). In female fishes, E2 promotes oogonial proliferation, vitellogenesis, and choriogenesis. Known as maturation inducing steroid (MIS), 17,20β-P promotes the initiation of germ cell meiosis and follicular maturation and ovulation (Nagahama and Yamashita 2008, Biran and Levavi-Sivan 2018). In male fishes, androgens, mainly 11-KT, are responsible for stimulating spermatogonial proliferation and spermatogenesis, while 17,20β-P initiates the meiotic division of spermatogonia and controls spermatozoa maturation and spermiation (Biran and Levavi-Sivan 2018).

There are data showing the adverse effects of aquatic contaminants (e.g., bisphenols, heavy metals, pesticides, phthalates, and polychlorinated biphenyls – PCBs) that can disrupt hormonal regulation at different levels of the HPG axis and exhibit estrogenic and/or anti-androgenic actions (Khan and Thomas 2001, Khan et al. 2001, Tokumoto et al. 2005, Hatef et al. 2012a, 2012b, Golshan et al. 2014, 2016, Gárriz et al. 2017, Smith et al. 2019, Wang et al. 2019, Davico et al. 2021). This review presents the current state of knowledge on the impact these compounds have fish reproduction at the specific levels of the HPG axis and on gamete formation and embryogenesis.

Disruption of the hypothalamic-pituitary system

Smith et al. (2019) showed that the hypothalamic Kiss/Gpr54 system, which controls reproduction centrally, may be affected by early life exposure to Roundup in Japanese medaka (*Oryzias latipes* (Temminck & Schlegel)). This is probably related to the possible estrogenic action of this herbicide. Embryonic exposure to Roundup (at environmentally relevant concentrations) caused a significant decrease in Gpr54 mRNA levels in adult female medaka, which indicated the potential of this herbicide to modulate the function of neurons controlling reproduction at the molecular level (Smith et al. 2019). Changes in mRNA levels of kiss1 and gnrh3 were observed in adult male goldfish (*Carassius auratus* (L.)) after 10 days of treatment with vinclozolin, a fungicide that acts as an anti-androgen agent (Golshan et al. 2016). Furthermore, vinclozolin-related reproductive disorders at all levels of the HPG axis were detected in male goldfish. Vinclozolin caused stimulation in mRNA transcript abundance of kiss1 and gnrh3 in the hypothalamus, which in turn affected the pituitary and testes by increasing synthesis of LH and 11-KT, respectively, which resulted in reduced sperm quality and quantity (Hatef et al. 2012b, Golshan et al. 2014, 2016).

The disruption of the GnRH-LH system was observed after exposure to PCBs in Atlantic croaker (*Micropogonias undulatus* (L.)), Prussian carp (*Carassius gibelio* (Bloch)), and common carp (*Cyprinus carpio* L.) (Khan and Thomas 2001, Socha et al. 2013a, 2013b, 2021b). In Atlantic croaker, 30-day exposure to Aroclor 1254 (a PCB mixture) influenced the synthesis of GnRH at the level of hypothalamus and significantly lowered the number of pituitary GnRH receptors, which, in turn, affected LH secretion (Khan and Thomas 2001). An increase in spontaneous LH secretion was observed in female Prussian carp exposed for three days to Aroclor 1254, while a decrease in gonadotropin release was detected in GnRH-A-stimulated LH release (Socha et al. 2013a). The action of PCBs is sex-dependent. An in vitro study with male and female common carp pituitary cells incubated with Aroclor 1254 showed stimulation of basal LH secretion only in female pituitary cells (Socha et al. 2021b).

Changes in circulating LH levels in freshwater fishes were also observed after exposure to other

aquatic contaminants such as di-(2-ethylhexyl) phthalate (DEHP), vinclozolin, cadmium, and mercury (Szczerbik et al. 2006, Crump and Trudeau 2009, Golshan et al. 2014, 2015, Drąg-Kozak et al. 2018). Long-lasting, three-year dietary exposure to cadmium resulted in increased LH release and disruption of ovulation in Prussian carp (Szczerbik et al. 2006). In the same species, three-month aquatic exposure to cadmium impaired spontaneous LH secretion and impaired gonadotropin secretion during stimulated spawning (Drag-Kozak et al. 2018). A stimulation of LH secretion was also observed after 30 days of exposure to vinclozolin in goldfish (Golshan et al. 2014). However, di-(2-ethylhexyl) phthalate (DEHP) treatment led to a decrease in LH release (Golshan et al. 2015).

To sum up, numerous EDCs affect the hypothalamic-pituitary axis by modulating the functioning of the Kiss/GPR54 (Roundup, vinclozolin) and GnRH (vinclozolin, PCBs) systems at the level of hypothalamus and also influencing the secretion of LH (heavy metals, phthalates, PCBs, vinclozolin) at the level of pituitary.

Disruption of gonads and steroidogenesis

The impairment of fish reproduction at the hypothalamic-pituitary level (GnRH-LH system) may cause a cascade effect on gonads, changing the synthesis of important sex steroids (E2, 11-KT or 17,20β-P) and affecting the final maturation of gametes. In addition to such changes, many EDCs can influence gonads directly by changing ovary and testis morphology, affecting steroidogenesis. Thus, they cause various types of reproductive disorders in fishes (Coimbra and Reis-Henriques 2005, Tokumoto et al. 2005, Soso et al. 2007, Martinović et al. 2008, Berois et al. 2011, Hatef et al. 2011, 2012a, 2012b, 2013, Armiliato et al. 2014, Golshan et al. 2014, Maskey et al. 2019, Davico et al. 2021).

In female zebrafish (*Danio rerio* (Hamilton)), 15-day exposure to Roundup adversely affected ovarian maturation, leading to a decrease in late ovarian follicles with smaller diameter and the induction of ultrastructural alterations in oocytes (vacuolization in follicular cells, increase of perivitelline space, impaired mitochondria) and the vitelline envelope (reduction of thickness, increase of the vitelline protein content) (Davico et al. 2021). Similarly, the inhibition of maturation in zebrafish or crucian carp (*Carassius carassius* (L.)) oocytes after glyphosate or Roundup treatment were shown in in vitro studies (Armiliato et al. 2014, Maskey et al. 2019, Socha et al. 2023). Other aquatic xenoestrogens (i.e., genistein, endosulfan, and malathion) also inhibited the final maturation measured as germinal vesicle breakdown (GVBD) in zebrafish oocytes (Maskey et al. 2019).

The exposure of fishes to EDCs, particularly xenoestrogens (e.g., bisphenol A, nonylphenol, 2,4-dichlorophenol, and ethinylestradiol) increased feminization, abnormal development of the reproductive tract, and morphological changes in gonads and decreased gamete quality (Bennetau-Pelissero et al. 2001, Song et al. 2020, Hu et al. 2021). These reproductive disorders in fishes have been correlated with the disruption of sex hormone synthesis (Hatef et al. 2012a,b, Socha et al. 2013a, Golshan et al. 2014, 2015, Kroupova et al. 2014, Saravanan et al. 2019, Hu et al. 2021). A decrease in 17,20β-P secretion was observed in rainbow trout (*Oncorhynchus mykiss* (Wal.)) and Prussian carp after exposure to estrogenic endocrine disruptors, genistein, and Aroclor 1254, respectively (Bennetau-Pelissero et al. 2001, Socha et al. 2013a). Changes in 11-KT levels were observed in many fish species after exposure to nonylphenol (sea bream, *Sparus aurata* L.; black rockfish, *Sebastes melanops* Girard), 2,4-dichlorophenol (zebrafish), levonorgestrel (roach, *Rutilus rutilus* (L.)), vinclozolin (fathead minnow, *Pimephales promelas* Raf.; goldfish) (Martinović et al. 2008, Hatef et al. 2012b, Golshan et al. 2014, Kroupova et al. 2014, Saravanan et al. 2019, Hu et al. 2021). There is evidence that changes in important enzymes and/or their genes regulating steroidogenesis (cyp19a1a, cyp19a1b, 17β-hsd, and 11β-hsd) were involved in the imbalance of sex

hormones (Hu et al. 2021). The decrease in E2 concentrations in pubertal roach was observed after 28-day aquatic exposure to the progestin levonorgestrel (Kroupova et al. 2014). Forty-day exposure to glyphosate resulted in a decrease of 17β-estradiol in the neotropical fish *Rhamdia quelen* (Quoy & Gaimard) (Soso et al. 2007), while zebrafish treated with bisphenol A, bisphenol AF, or 2,4-DCP had elevated E2 levels and induced vitellogenin production (Yang et al. 2016, Zhao et al. 2017, Hu et al. 2021).

In conclusion, endocrine disruptors can affect gonadal function at multiple levels especially impacting ovarian maturation (glyphosate, Roundup, xenoestrogens) and steroidogenesis (glyphosate, PCBs, xenoestrogens).

Gamete and embryo dysfunctions

Disturbances in fish reproduction caused by EDCs are observed both in females and males, and the consequences of these disorders may be seen in the quality and/or quantity of gametes (eggs, spermatozoa) and finally, in reduced numbers of offspring. In fishes, external fertilization can lead to polluted water/medium having adverse effects directly on gametes. Exposure to heavy metals, pesticides, or PCBs was shown to suppress spermatozoa motility kinetics and fertilization ability in many fish species (Chyb et al. 2000, 2001, Kime et al. 2001, Socha et al. 2008, Hatef et al. 2011, 2013, Lopes et al. 2014, Gonçalves et al. 2018, Ługowska 2018, 2020, Mishu et al. 2020). In addition to direct effects on sperm, EDCs have negative effects even at the stage of spermatogenesis; these include, among others, abnormalities in sperm morphology and changes in their genome. Sperm morphology disorders result in reduced motility, an abnormal number of chromosomes, changes in DNA content, etc. Sperm DNA damage may cause fertilization failure and lead to genetic diseases in offspring (Alavi et al. 2021). The short lifespans of fish spermatozoa or eggs, as well as changes in environmental conditions caused by different EDCs, make reproductive success quite time-limited by sperm availability and strongly correlated with spermatozoa motility (Kholodnyy et al. 2020). Proper egg swelling is also very important for successful fertilization and further embryonic development of fishes. Some data indicate adverse effects from heavy metal or herbicide pollution on *Cyprinus carpio* L. and grass carp (*Ctenopharyngodon idella* (Val.)) egg swelling (Jezierska et al. 2009, Ługowska 2018, 2020). The changes observed in swelling may be due to disturbances in water uptake and ion exchange between the perivitelline fluid and the aquatic environment or to changes in the physical properties of the egg surface (Ługowska 2020).

The direct toxic effect of aquatic endocrine disruptors (heavy metals, PCBs, pesticides, xenoestrogens) on developing fish embryos was shown as decreased survival of fertilized eggs and/or increased frequency of body malformations in common carp, ide (*Leuciscus idus* (L.)), Japanese medaka, Prussian carp, Nile tilapia (*Oreochromis niloticus* (L.)), and zebrafish (Coimbra and Reis-Henriques 2007, Szczerbik et al. 2008, Socha et al. 2012, Uren Webster et al. 2014, Witeska et al. 2014, Bhandari et al. 2015, Ługowska 2018, Fiorino et al. 2018, Smith et al. 2019, Socha et al. 2021a). The most common developmental defects observed in fish embryos and larvae were abnormalities in yolk sac structure, pericardial edema, slow growth, and skeletal deformations. Additionally, premature or delayed larval hatching depended on the type and concentration of pesticide (Medkova et al. 2023, Kumar Bhardwaj et al. 2022, Meng et al. 2023, Lanzarin et al. 2023). Pompermaier et al. (2022) showed that glyphosate affects the behavior of zebrafish larvae by having an anti-anxiety effect. These authors demonstrated that glyphosate treatment caused excessive mobility and anti-predatory behavior, which may reduce chances of survival. Furthermore, Bhandari et al. (2015) showed that early developmental exposure of medaka to environmental estrogens (bisphenol A, 17a-ethinylestradiol) can lead to transgenerational reproductive abnormalities such as decreases in fertilization rates and reduced embryo survival two or three generations later. In

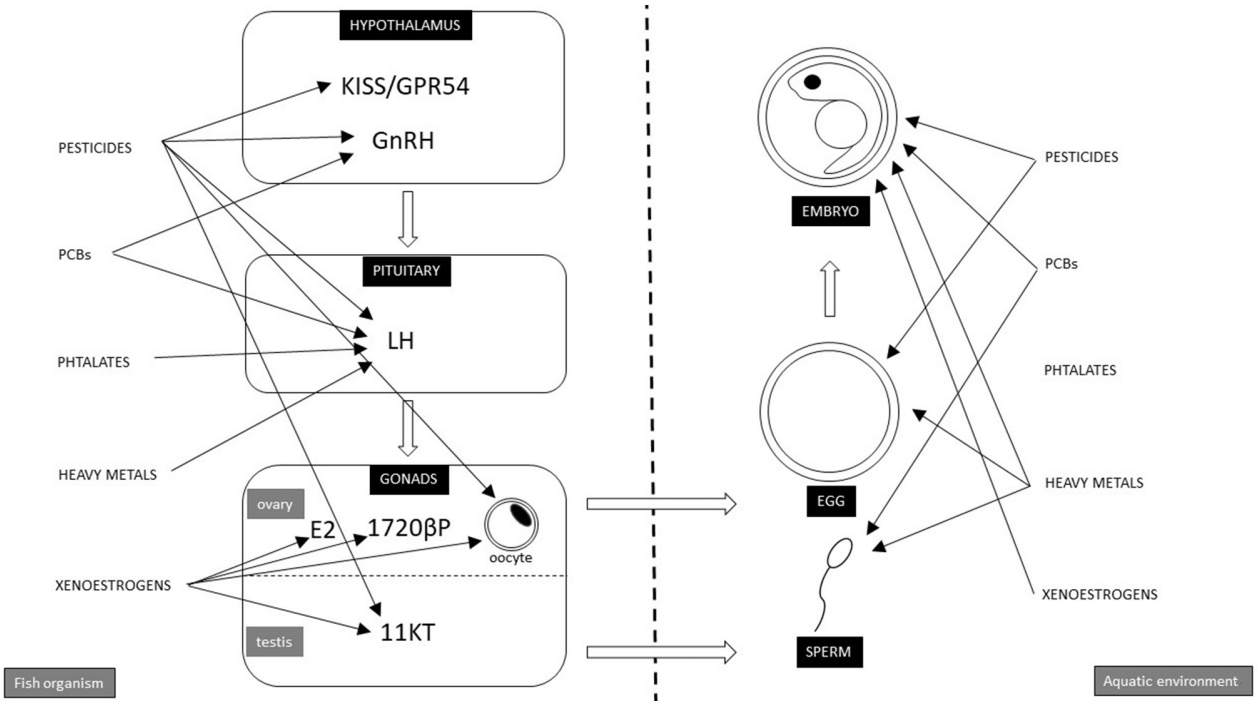

Figure 1. Schematic diagram showing possible points of action of endocrine disruptors.

a study conducted by Zhang et al. (2021), embryos exposed to fenbuconazole (a widely used fungicide) resulted in the inhibition of gametogenesis in adult zebrafish and reduced fertilization rates and embryo survival in the F1 generation. Short-term exposure of common carp or Japanese medaka to Roundup during embryogenesis may adversely affect not only the early stages of development and hatching success but also the transcription of genes responsible for proper development (Smith et al. 2019, Socha et al. 2021a). Smith et al. (2019) showed that embryonic exposure to Roundup and/or glyphosate caused reductions of mRNA expression of FSHR, Arα (androgen receptor alpha), and DMRT1 (DNA methyltransferase gene) in the testes of adult Japanese medaka. The studies cited above showed that the early impact of EDCs may have long-term consequences on fish reproduction as observed in changes in gene expression of epigenetic and reproductive-related genes.

In conclusion, endocrine disruptors can negatively impact gamete quality, gamete quantity, and embryonal development of fishes, which consequently leads to decreased numbers of high-quality larvae.

Summary and perspectives

Hormonally active xenobiotics (bisphenols, heavy metals, pesticides, phthalates, PCBs) present in the aquatic environment, even at low concentrations, act as reproductive toxicants on both the female and male reproductive systems. They can cause dysfunctional gametogenesis, endocrine disruption at the HPG axis, and may affect embryogenesis. Moreover, early life exposure to EDCs can affect not only embryonic development, resulting in body malformations and higher mortality, but it may also lead to changes in the genes involved in reproduction in newly hatched larvae as well as in sexually mature fishes. The schematic presentation of their possible points of action is shown in Figure 1.

The results discussed above indicate that EDCs can alter numerous hormonal paths regulating fish maturation and can impair subsequent stages

required for reproductive success. However, more detailed, complex approaches should be included in future studies to gain a fuller understanding of the roles of these compounds. Understanding the mechanisms of their action at the molecular level and complex interactions among them will contribute to a more detailed comprehension of the impact EDCs have on fish reproduction. It crucial to remember that endocrine disruptors entering the aquatic environment cause changes not only in single organisms, but they may affect entire populations. It is therefore necessary to develop reliable methods to assess the impact of EDCs on entire fish populations and to understand their impact on populations of aquatic organisms interacting with fishes.

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