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Review Article

Endocrine Disruptors Stress Responses in Aquatic Environment: Consequence on Fish Reproductive Physiology: A Review

Sunayana Goswami[1], Himabrata Chakravarty[2*], Sangeeta Dey[3]
[1]*Department of Zoology, Biswanath College, Biswanath Chariali– 784176, India*
[2]*Department Zoology, Srikishan Sarda College, Hailakandi– 788151, India*
[3]*Department of Ecology, Gurucharan College, Silchar, – 788001, India*

ABSTRACT

Endocrine disruptor chemicals (EDCs) are mostly synthetic molecules from industrial origin that are present in the environment and promote adverse modifications of endocrine homeostasis in animals. EDCs raise serious concerns about their potential health impact. Endocrine-disrupting compounds can alter biological function in organisms at environmentally relevant concentrations and are a significant threat to aquatic biodiversity. At the molecular level, the EDCs can affect the expression of steroid and sex hormone related enzymes by binding to the nuclear receptors. Fishes are generally considered to be the most feasible organisms for pollution monitoring in aquatic systems. Fish carrying high loads of EDCs in their body tissue potentially suffer impaired health. The fish endocrine system is fundamentally similar to that of mammals, and fish reproduction may be a relevant indicator on the mechanism of endocrine disruption by chemical compounds. Fish are good indicators of the toxicity of endocrine disrupting chemicals. In the present communication, a detailed analysis of endocrine disruptors in aquatic systems, their impact on animals has been done through the literature available in recent years.

Keywords: Endocrine disruptors, Aquatic animals, Hormone receptor, Fish reproduction.

INTRODUCTION

Endocrine-disrupting chemicals (EDCs) are a heterogeneous group of substances that are ableto interfere with the hormonal-signalling pathways and alter metabolic and reproductive functions. Endocrine disruption chemical is an exogenous substance or mixture which can be natural or manmade that alters functions of the endocrine system in an organism or its progeny or its sub populations (Söffker and Tyler, 2012; Schug and Birnbaum, 2020; Meli *et al*., 2020). The group of molecules recognised as EDCs are highly heterogeneous and includes synthetic chemicals such as Polychlorinated biphenyls (PCBs), Polybrominatedbiphenyls (PBBs), Polycyclic aromatic hydrocarbons (PAHs), plastics, pesticides, Dichlorodiphenyltrichloroethane (DDT), fungicides and pharmaceutical agents. The US Environmental Protection Agency (US-EPA) has defined Endocrine disruptor Compound as ‘‘exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes.’’. Many

*Corresponding author's Email: himabratac@gamail.com

animal studies provided evidence that several of these chemicals can disturb sexual development and differentiation. Natural chemicals found in human and animal food (*e.g*., phytoestrogens, including genistein and coumestrol) can also act as endocrine disruptors (Söffker and Tyler, 2012; Dickerson and Gore, 2007; Diamanti-Kandarakis *et al*., 2009; Schug and Birnbaum, 2020; Gassman, 2017).

Exposure to Endocrine-disrupting chemicals is associated with deleterious health effects for animals and humans and affects not only endocrine and reproductive organs but also immune and central nervous systems through several mechanisms, including *oxidative* stress (Diamanti-Kandarakis *et al*., 2009; Söffker and Tyler, 2012; Meli *et al*., 2020). EDCs enable an organism to develop and reproduce. Widespread use of pesticides for agriculture or domestic purposes damage the non-target organisms, including fish of commercial importance. The investigation of the effects of pesticide on fish has diagnostic significance in evaluation of adverse effects of pesticides to human health since fish have an important role in food chain (Porte *et al.*, 2006; Diamanti-Kandarakis *et al.*, 2009; Patisaul *et al.*, 2017).

Chemical Nature of Endocrine Disrupting Chemicals

The source of exposure to EDCs is diverse & globally very wide. Both natural & man-made EDC's are considered to cause endocrine disruption. The group of endocrine disruption (EDCs) is diverse, and this can be classified into different categories and have different sources.

The group of known EDs is extremely heterogeneous. The EDs can be classified in two categories:

1) Those that are synthesized. These can be grouped as follows:

a) synthetic substances used as industrial lubricants and solvents, and their by-products: e.g. polychlorinated biphenyls (PCBs), Polybrominated diphenyl ethers (PBDE) and dioxins e.g. 2,3,7,8tet-rachlorodibenzo-p-dioxin (TCDD), decabromodi- phenylethane (DBPDE).

b) plastics: bisphenols – e.g. bisphenol A (BPA) and bisphenol S (BPS)

(c) plasticizers: e.g. phthalates

(d) pesticides: e.g. atrazine, cypermethrin, dichlordiphenyltrichlorethane (DDT), dieldrin, methoxychlor (MTX) and its metabolites e.g. 2,2-

Table 1. List of some Common Endocrine-Disrupting Chemicals with their source and use

ECDs (compound)	Source /Use
Polychlorinated Biphenyl (PCB)	Electrical coolant andother uses
Polybrominated Diphenyl Ethers (PBDE)	Flame retardants
Polycarbonate Plastics, Bisphenol A(BPA) & Bisphenol S(BPS)	Plastics, thermalreceipts
Decabromodiphenyl Ethane (DBPDE)	Industrial lubricants and solvents
Polyvinyl chloride (PVC), Phthalates	Plastics, fragrances
Vinclozolin (VCZ), Dicarboximid, Hexachlorbenzene (HCB)	Fungicides
Atrazine, Dichlordiphenyltrichlorethane (DDT), Endosulphan	Pesticides
Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin)	Formed in industrialprocessing
Ethinyloestradiol (EE), Diethylstilbestrol (DES), Anti- inflammatory drugs (NSAID) & Acetaminophen.	Drug industry
Phytoestrogens (Genistein)	Naturally prevail

bis(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE), endosulphan

e) fungicides: e.g. vinclozolin (VCZ), dicarboximid, hexachlorbenzene (HCB)

f) and drugs: e.g. diethylstilbestrol (DES) and ethinyloestradiol (EE) as well as non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen

2) Those that occur naturally.
a) natural chemicals such as a phytoestrogens e.g. genistein (Diamanti-Kandarakis *et al.*, 2009; Chmelíková *et al*., 2018; Schug and Birnbaum, 2020).

Some potent Endocrine disrupting chemicals along their sources are represented in Table (Diamanti-Kandarakis *et al.*, 2009; Chmelíková *et al*., 2018; Schug and Birnbaum, 2020; Buoso *et al*., 2020; Hamid *et al*., 2021).

Mode of action of Endocrine Disruptors

Endocrine-disrupting chemicals (EDCs) are a special group of compounds that can bind to the endocrine receptors to activate, block, or alter natural hormone synthesis and degradation by a number of mechanisms resulting in abnormal hormonal signals that can increase or inhibit normal endocrine functioning. EDCs are structurally similar to many hormones and function at extremely low concentrations, and many have lipophilic properties (Schug and Birnbaum, 2020; Whirledge and Cidlowski, 2019; Buoso *et al*., 2020). EDCs are capable of mimicking natural hormones and exerting similar modes of action, transport, and storage within tissues. EDCs have high tendency and potency to activate or antagonize nuclear hormone receptors family. Endocrine-disrupting chemicals were originally thought to exert actions primarily through nuclear hormone receptors, including estrogen receptors (ERs), androgen receptors (ARs), progesterone receptors, thyroid receptors (TRs), and retinoid receptors, among others. The estrogens are a group of steroid hormones produced by enzymatic modification of cholesterol. EDCs can mimic the estrogens and alterthe signalling pathways of estrogen hormone by binding to estrogen receptors and either activating or inhibiting transcriptional response. They disrupt normal development via interaction with estrogen receptors. Some Endocrine-disrupting chemicals act as estrogen mimics, others have variable estrogenic activity, and some act as selective estrogen receptor modulators. They may interrupt sexual development and modification or alteration (Porte *et al*., 2006; Welshons *et al*., 2013; Buoso *et al*., 2020; Whirledge and Cidlowski, 2019; La Merrill *et al.*, 2020).

Impacts of Endocrine disruptors on aquatic ecosystem

Endocrine disrupting chemicals are a ubiquitous issue of concern in our aquatic systems. The potency of EDCs varies considerably, to persist and move in the environment. Current research indicates that EDCs are found in complex mixtures in surface, ground, and finished water. Endocrine disrupting chemicals enter aquatic ecosystems through discharged effluents, mainly from wastewater treatment plant and diffuse run off from land, and affect a wide range of aquatic biota, including fish.Fish play an integral role in the aquatic ecosystem food web, and any effects that change the population structure of fish may also alter community and food web dynamics (Kavlock *et al*., 1996; Johnson *et al.*, 2000; Diamanti-Kandarakis *et al.*, 2009; Söffker and Tyler, 2012). Fishes can biomagnifiy contaminants, fishes are potentially useful sentinels of aquatic environmental degradation. Fishes are a major protein food source for humans, with a high economic value in the aquaculture industry. The use of pharmaceuticals, pesticides, and fertilizers for maintaining and increasing fish health and growth also contributes to EDCs pollution in the water body .Fish carrying high loads of EDCs in their body tissue potentially suffer impaired health and can deliver high concentrations of EDCs to their consumers. Fish are particularly vulnerable to exposure to EDCs and the uptake occurs via multiple routes including directly from the water via the gills, skin and drink-

ing (gut), through the diet and by means of sediment contact.[1,14,15,17] Some EDCs have been shown to bio-concentrate in fish and to bio-accumulate in fish species that occupy higher trophic levels. Effects of EDCs have been studied on many aspects of fish physiology, most commonly on features relating to growth, development and reproduction. EDCs can also have effects on fish behavior (Welshons *et al.*, 2003; Porte *et al.*, 2006; Clark and Grant, 2010; Söffker and Tyler, 2012).

Sex steroid hormones play vital roles in almost all aspects of reproduction, including mediating sexual differentiation, gonadal growth, and reproductive behaviors. Some of the most potent sex steroids EDCs are receptor agonists and they include the synthetic estrogen. EDCs disrupting sex steroid action and affecting sexual development and reproduction in fishes. Natural steroid estrogens are widespread in the aquatic environment and they too (obviously) are potent as estrogen receptor agonists.[19,20,21]

In fish evidence for endocrine disruption in both male and female populations is extensive. Fish carrying high loads of EDCs in their body tissue potentially suffer impaired health and can deliver high concentrations of EDCs to their consumers. The validity of molecular biomarkers of stress and exposure to different types of pollution in fish is proved in a broad number of studies. EDCs have been implicated in the complete or partial feminization of male fish, induction of vitellogenin or other egg-related proteins in male fish and juveniles, decreases in gamete quality or quantity (fecundity) and changes in sexual and mating behaviors (Tollefsen *et al.*, 2007; Coe *et al.*, 2008; Hamid *et al.*, 2021). Endocrine disrupting chemicals induces production of female proteinsin males – vitellogenin (VTG), and alterations in germcell development – production of oocytes in the testis of fish exposed to EDCs. In female population EDCs induces androgenic responses include masculinized secondary sex characters in female fish exposed to industry effluents. Widespread feminization of fish in the United Kingdom has been attributed to the estrogenic properties of municipal sewage effluent (Ankley and Johnson, 2004; Coe *et al.*, 2008).

Numerous compound having EDCs properties that are found in the environment cause abnormalities in growth and development in fishes. In the reproductive system, chlorinated pesticides can result in abnormal stimulation of reproductive tract development and function in females and decrease overall fertility. One of the most efficient and important agents, organophosphorous pesticides have been used throughout the world to control pests in agricultural crops, forests, and wetlands for more than four decades. DDT is a persistent pesticide, whose compound structure permit and several different isomeric forms have been implicated as a potent endocrine disrupting chemical. Observed effects of DDT on fish reproductive physiology have ranged from subtle changes in basic physiology of species to permanently altered sexual differentiation (Welshons *et al.*, 2003; Ankley and Johnson, 2004; Porte *et al.*, 2006; Coe *et al.*, 2009; La Merrill *et al.*, 2020; Schug and Birnbaum, 2020).

In fish many laboratory studies have shown effects of EDCs on reproductive behaviour in individuals, with a predominant focus on estrogen in males. Examples include disruption of nest building in adult male three-spined stickleback exposed to EDCs, where a reduced gluing frequency, delayed onset of nest building or reduced care for the nest (Coe *et al.*, 2009; Clark and Grant, 2010). In sand gobies exposure of adult fishto industrial effluents was shown to reduce the ability of malesto gain and keep a nest and reduced their display ofsexual behaviours (Coe *et al.*, 2009; Daley *et al.*, 2009; Clark and Grant, 2010; Johnson *et al.*, 2020). Similarly, adult male fathead minnows exposed to EDCs showedreduced care for the spawning site (Coe *et al*, 2009; Daley *et al.*, 2009). Recent studies on female Zebra fish exposed to EDCs showeddiminished courting response towards males and hadlower reproductive success than unexposed females.[17,20,23]These findings suggest that changes in sexual behaviour of fishes exposed to endocrine disrupting compounds

canhave important consequences on the dynamics of thepopulation, as female reproductive capability plays a keyrole in its maintenance.

CONCLUSION

Endocrine-disrupting substanceis a compound, either natural or synthetic, which, through environmental or inappropriate developmentalexposures, alters the hormonal and homeostatic systemsthat enable the organism to communicate with and respondto its environment. Endocrine disruptors; when enters the aquatic ecosystem; not only interfere with the aqua fauna but also with terrestrial and aerial animals linked directly or indirectly with water for food and other ecological interactions. The food chain and food web are responsible for transferring these chemicals to animals of different trophic levels. Several developmental, neurological, reproductive, metabolic, and immune disorders are the consequent effect of EDCs exposure to animals and humans. Endocrine-disrupting chemicals can alter biological function in organisms at environmentally relevantconcentrations and are a significant threat to aquatic biodiversity, but there is little understanding of exposureconsequences for populations, communities and ecosystems.

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