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Endocrine Disruptor—A threat to the animal world

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Abstract

Various types of naturally occurring and artificially made chemicals cause disruption of endocrine processes among animals. They mimic biochemically with hormones and interfere with the normal signaling and activity of the endocrine system, causing enormous changes at the cellular level of animals from lower to higher organisms, including human being. These modified regulations of cellular activities as a result of endocrine disruptors have severe implications at the organismal level. Types and adverse effects of these natural and synthetic agents, especially estrogenic compounds causing biological threats have been discussed in details in this review.

Keywords: Ecology, endocrine disruptor, human health, phytoestrogen, xenoestrogen.

Introduction

Rachel Carson's Silent Spring (1962) warned us regarding the adverse-effects of chemicals, especially that of DDT (Dichloro-diphenyltrichloroethane), which might be responsible for the reduced number of birds by natural contamination. These natural and artificial chemicals can harm the natural endocrine processes and other cellular functions. They interfere with the synthesis, storage, transport and release mechanisms and also of metabolism and receptor binding of endogenous hormones. These are collectively called as endocrine disruptors and act at pharmacological doses. There are various types of endocrine-disrupting chemicals (EDCs), such as DDT, diethyl-stilbesterol, phyto-estrogen, xeno-estrogen, organo-chlorines, polychlorinated bisphenols, bisphenol-A etc. These materials interfere with normal endocrine processes and mimic the functions of endogenous hormones. These disruptions can cause various physiological and psychological disorders. Fishes are exposed to these chemicals naturally in rivers, ponds, etc., where these chemicals are released regularly through sewerage as a result of household and industrial use. Gallons of detergents, pesticides etc. are released into various water bodies.

The occurrence of hermaphrodite fish was found in the lagoons of sewage treatment works (Purdom et al., 1994). These chemicals can potentially alter the reproductive physiology of fishes (Folmar et al., 1996). These chemicals (especially xenoestrogens) exert their effects by binding through the estrogen receptors (Singleton and Khan, 2003). The effect of these endocrine disruptors in human health are adverse and life threatening.

The review contains a list of the chemicals currently termed as endocrine disruptors and a summary of the effects of xenoestrogens with an ecological perspective and also of their direct/indirect impact on human health. The role, mode of action, adverse-effects of endocrine disruptor are also focused in this review.

Various types of EDCs

Various types of EDCs are now in everyday use like epoxy resins, plastic ware, cans, dental sealants (Goodman and Peterson, 2014; Rathee et al., 2012) as all these materials contain bisphenol-A. Astrazine, another EDC, used as herbicide throughout the world to control the leaf weeds grow in corn, sugarcane etc. (Kyle et al., 1996). Now a days polybrominated biphenols are widely used in plastic, foam textile, computer monitor making industries (Agency for Toxic Substances and Disease Registry, 2004). Roeder et al. (1998) described that pulp and paper industries discharge dioxin (toxic chemical) into the water bodies, which is accumulated in animal fat.

Phthalates are plasticizers used in flooring, wall covering, medical devices such as intravenous bags and tubing to make them more durable and flexible (high molecular weight). Low molecular weight phthalates are used in manufacturing perfumes, lotions, cosmetics, varnishes, coating etc. (Huber et al., 1996, Staples et al., 1997).

Occurrence

1) Phytoestrogen

The main sources of estrogenic compound from the natural origin are phytoestrogens. They occur in plants and fungi. It comes through soya products which contains isoflavones (genistein and daidzein). Other than soy products, they are present in legumes of plants, grains etc. (Liggins et al., 2000), fruits and nuts; lignans, enterolactone, enterodiole etc. (Bingham et al., 1998).

2) Xenoestrogen

Many artificially manufactured chemicals mimic estrogen. These chemicals are known as xenoestrogen. They are man-made compound with estrogenic effect but differ in structure from natural estrogen. They are present everywhere like plastic material, food preservatives, sunscreen lotion, insecticides, paint, cosmetics, soaps, shampoos, fabric, laundry detergents, toothpaste, body wash, shaving cream, Mascara, mouth wash etc. They are also found in water supply and in ocean (Paterni et al., 2017; Costet et al., 2015). The esrogenic property of these chemicals allows them to act like estrogenic hormones. (Roy et al., 1997). They exert additional load to the biological system. Xenoestrogens like ethinyl estradiol, diethyl stilbestrol (DES), β-hexachloro-cyclohexane, polychlorinated biphenyls, DDT, isoflavones or lignans etc. are more stable and remain in the system specially in adipose tissues longer than natural estrogens (Tapiero et al., 2002). Singleton and Khan (2003) demonstrated that DDT and polychlorinated biphenyls have possibilities to be transferred to humans from other animals.

Exposure to natural estrogen

Endocrine disruptor is no doubt a global problem now. It is present in various food chains and food webs of this contaminated environment and are used everywhere in food, air, water, cosmetics etc. (Gore et al., 2014).

The most common source of estrogenic compound is found in various food, such as soy product, fruits, vegetables etc. These products are sometimes prescribed for hormone replacement therapy of post-menopausal females (Liggins et al., 2000). Xenoestrogens also used as protective measure of certain type of cancers, osteoporosis and also cardiovascular disorders (Bingham et al., 1998). Natural estrogenic compounds are balanced in such a way that these compounds may not have any adverse effect on animal system.

Exposure to artificial estrogen

Synthetic xenoestrogens like DDT metabolites, polychlorinated biphenyls (PCB) are widely available in modern life style. They are accumulated in non-human animal system and are the main source of synthetic xenoestrogen for human consumption. Bio-magnification of such components may also take shelter in human blood, adipose tissue and milk, the effect of which ultimately may be carcinogenesis and contamination in new born babies with adverse effects.

Bisphenol-A contamination may take place through food containers, plastic wares, dental sealants, which are good sources of endocrine disruptions. Sewage effluents contain huge amount of nonylphenol and octylphenols that affect aquatic animals (Clark et al., 1992). DDT exposure may cause oligospermia (Singer, 1949). Diethyl-stilbestol is a potent synthetic estrogen analogue with side effects of significant morbidity in males and females due to carcinogenesis and teratogenesis (Chia, 2000).

Mode of action

Tributyltin (TBT) and Triphenyltin (TPT) act through hormone receptors called PPARϒ (Peroxisome proliferator activated receptor gamma) (Kirchner et al., 2010; Janesick and Blumberg, 2011). PPAR (Peroxisome proliferator activated receptor) is a class of ligand-dependent transcriptional regulators with three subtypes—PPARα, PPARβ and PPARϒ. These are important transcriptional factors that regulate metabolic balance in humans. PPARϒ regulates the transcription of multiple genes involved in differentiation of adipose precursor cells, mediates insulin mediated uptake of glucose (Wilbanks et al., 2014; Wang et al., 2015). The PPARϒ gene is located on chromosome 3p25. Once activated by binding to the ligand PPARϒ binds to the retinoid X receptor (RXR) to form a heterodimer and then recruits a series of synergistic factors. The promoter region binds to the heterodimer and regulates transduction; it can also (PPARϒ) directly activates specific genes. PPARϒ can inhibit JAK-STAT pathway. PPAR is associated with many diseases like liver cancer, fatty liver disease (Huang et al*.,* 2018; Wagner and Wagner, 2010).

Estrogen Receptor (ER)

Estrogen receptors (ERs1) are ligand-activated transcription factors that belong to the nuclear hormone receptor super family which binds intracellular 17β-estradiol as demonstrated by Jensen and Jordan (2003). As reported till date (Green et al., 1986; Greene et al., 1986; Kuiper et al., 1996), there are two classes of receptors known as ERα and ERβ. They have been detected in a

broad spectrum of tissues, where both receptor subtypes are expressed at similar levels, or, either of the subtype predominates. Both receptor subtypes can also be present in the same tissue but in different cell types. Tissues where ERα is mainly expressed are uterus, prostate (stroma), ovary (theca cells), testes (Leydig cells), epididymis, bone, breast, various regions of the brain, liver, and white adipose tissue, whereas ERβ is mainly expressed in colon, prostate (epithelium), testis, ovary (granulosa cells), bone marrow, salivary gland, vascular endothelium, and certain regions of the brain (Dahlman-Wright et al., 2006). Thus, xenoestrogens, targeting these receptors, can create a serious effect on physical and mental health.

ERα and ERβ in different nucleus directly binds to DNA and regulates gene expression indirectly binding to other transcription factors. It activates PI3K (Phos-phati-dylinositol-3-Kinase) signaling pathway. Estrogen can also work through G-protein mediated action (GPR30, G protein-coupled receptor 30) and activates PI3K and MAPK (mitogen-activated protein kinase) signalling pathways (Velarde, 2013; Obiorah et al., 2014).

Various diseases are associated with the activation of estrogen receptor. Breast cancer is an estrogen –depended tumour. ER-α 36 and ER-α 66 mRNA are related with gastric cancer. Deposition of fatty substances in the inner wall of arteries is also associated with ER (Obiorah et al., 2014; Ticconi et al., 2013; Li et al., 2013).

EDCs

EDCs have low binding affinity with ERα / ERβ, these chemicals are widely used throughout the world. They may have a phenolic structure which can act as endogenous hormone. They can interact with steroid hormone receptors to act as agonist or antagonist (Shanle and Xu, 2010). They can alter the activities of ERα or stimulate G-protein mediated activities (Watson et al., 2007; Manavathi and Kumar, 2006). EDCs have found to affect the target cell in a dose-dependent fashion, owing to their ability to bind ERs (Li et al., 2012; Moral et al., 2011). DDT binds ERα and induces transcriptional activity in ERα positive breast cancer MCF-7 cells (Lemaire et al., 2006).

Phytoestrogens found in soybeans, genistein, isoflavonoids can have agonistic or antagonistic activities (Sotoca et al., 2010; Penza et al., 2006). Genistein inhibits cell proliferation in breast and prostate cancer and controls gene expression (Watson et al., 2007). Exposure to various EDCs (phytoestrogen) have synergistic effect on human health.

Effects and adverse-effects

Good effects of phytoestrogen include protective effect against some cancers, osteoporosis, cardiovascular disorders etc. (Bingham et al., 1998). In Japan, there are incidences that soy-supplemented diets contain 50-500nM daidzein and up to 900nM genistein, which may be related to be protective to certain cancers (Setchell et al., 1998). Although the presence of estradiol(Ohnishi et al., 1985; Das and Ray, 2007; Keshan and Ray, 2001; De, 2007; Roy, 2007) and its role in the alteration of female specific protein (Das and Ray, 2014; Das, 2016) and the development of female characteristics (Shen et al., 2015) has been established in invertebrates like silkworm, *Bombyx mori* but its role as endocrine disruptor is not known. Environmental estrogens may work by mimicking or by blocking the natural estrogenic action or

altering the effect of estrogen (Tapiero et al., 2002).

From various studies it has been established that Bisphenol-A (BPA) is a potential endocrine disruptor and can exert adverse effect on development (Singleton and Khan, 2003). DDT and polychlorinated biphenyls accumulate in various food chain and can be transferred to humans where it is bio-accumulated in blood, fat and milk. These may be one of the reasons behind breast cancer. Various surfactants like nonyphenol, octylphenol are formed in sewage effluents and other sources, which may be dangerous for aquatic life (Singleton and Khan, 2003). People working in the production of oral contraceptives have adverse effects of xenoestrogen as it is absorbed through their skin. Clinical use of diethylstilbestrol (DES) may cause morbidity in human males and females (Singleton and Khan, 2003). DES produces several changes which may lead to carcinogenesis in the kidney in Syrian hamsters (Roy et al., 1997). Bio-magnification of such chemicals may cause serious problems to these animals.

Fish culture in and around urban area are likely to get exposed to xenoestrogens and may cause induction of vitellogenin protein in male carp fish (Folmar et al., 1996). The artificial induction of vitellogenin protein in male fish by estradiol treatment is well established (Rose et al., 2002). Fishes cultured with sewage effluent caused induction of vitellogenin protein in male fish and reduction of their testosterone level (Folmar et al., 1996).

An Ecological Perspective

Xenoestrogens, like many other compounds are bioaccumulated and get biomagnified. Phytoestrogens (also found in many food items, like, rye, wheat, cabbage, sprouts, spinach, and soy- bean) do not bioaccumulate or get biomagnified, however, are easily metabolised (Adlercreutz et al., 1995; Verdeal and Ryan, 1979). Some organisms have been observed to be having reproductive abnormality as a result of consumption of phytoestrogens (Wocławek-Potocka et al., 2013; Verdeal and Ryan, 1979; Soto et al., 1992). The exposure to artificial xenoestrogens (like, organochlorine, alkylphenols, phthalate esters and bisphenol-A) can occur through pesticides, plastic materials etc., that can be accumulated into the animal system through food habits in human modified environment. Woodwell et al., (1967), studied the bioaccumulation and bio-magnification of DDT in the estuary ecosystem along south shore of Long Island, New York. Soto et al*.,* (1992) showed that among DDT isomers, o, p'-DDT was slightly more potent than p, p'-DDT and both are components of organo-chlorine fertilizer DDT. From these, the severity of DDT bioaccumulation can be understood. Impact on the ecosystem of these chemical components can be significant and can occur through changes in reproduction patterns in wildlife. Some of these effects include issues such as feminization, demasculinization, reduced fertility, reduced hatchability, reduced viability of offspring, impaired hormone secretion or activity, and altered sexual behaviour, including sexual reversal (Toppari et al., 1996; Colborn et al., 1993; Colborn et al., 1992; Kuhl et al., 2005). Adding to the concerns, human beings end up at the top of some of these food webs and the effect of bioaccumulation and bio-magnification of xenoestrogens can be proportionately estimated.

Most plastic products release estrogenic chemicals. In some cases, BPA (bisphenol A) free plastic products were found to be

leaching out more of chemicals having estrogenic activity (EA) than did BPA-containing products, when put under common-use and extracted by saline and ethanol solvents (Yang et al., 2011). Longer the half-life of a toxic agent, worse is its negative effect. Half-life of human steroidal estrogen was calculated to be 2 to 6 days in water and sediments in a test batch (Ying et al., 2002).

Human Health Issues

Since ERs can be detected in a broad spectrum of tissues, xenoestrogens, targeting these receptors, can create a serious effect on physical and mental health. They can stimulate signal transduction pathway for bringing about epigenetic changes (Crews and McLachlan, 2006; Hsu et al., 2009; Cheng et al., 2008; Nelles et al., 2011; Moore et al., 2016) that can lead to multiple gene repression (Huang and Esteller, 2010), causing cancer. They can also modulate the secretion of vascular epithelial growth factor (VEGF) (Buteau-Lozano et al., 2008), which is an important factor responsible for angiogenesis (Carmeliet, 2005). They play a pivotal role in many forms of cancer, like breast cancer (Hsu et al., 2009; Cheng et al., 2008; Huang and Esteller, 2010; Buteau-Lozano et al., 2008; Moore et al., 2016), prostate cancer (Li et al., 2012, 2013) etc. These suggest that xenoestrogens can have an adverse effect on reproductive health and reproductive cycle of human. In fact, Wocławek-Potocka et al*.,* (2013) had actually shown that phytoestrogens have an adverse effect in human and animal reproduction.

Impaired neurogenesis is linked with many problems related to mental health, including schizophrenia, depression, memory loss, Alzheimer's disease (Grossman et al., 2003; Lazarov and Hollands, 2016; Sahab-Negah et al., 2020). It is well established that estrogen affect neuroplasticity in a number of brain regions, particularly modulating and mediating spine and synapse formation as well as neurogenesis in amygdala, hypothalamus and hippocampal formation (Sahab-Negah et al., 2020; Sheppard et al., 2019; Fowler et al., 2008; Spencer et al., 2008; Bless et al., 2016). It has also been found that estrogen impact energy homeostasis in humans and rodents, by acting in the hypothalamus. Postmenopausal women gain weight, increasing their risk for heart disease and diabetes were the effects seen as examples to this (Bless et al., 2016). Also, estrogen has been identified as a potential factor in age-related diseases. Although, it has been established that estrogens have cardio-protective (Baker et al., 2003; Murphy and Kelly, 2011) and neuro-protective (Green and Simpkins, 2000) roles, research on how excess estrogen and xenoestrogens affect cardiac and neural health is still lacking and needs to be done.

Implications with respect to the COVID-19 pandemic

The COVID-19 (Coronavirus disease 19) outbreak, which was first reported in China in December, 2019, is caused by the novel severe acute respiratory syndrome-related corona virus (SARS-CoV-2) and it is reported that this virus enters the human cell by binding to the human angiotensin-converting enzyme 2 (hACE2) receptor. (Wee and Wang, 2020; Zhang et al., 2020). The virus depends on the serine protease transmembrane protease serine 2 (TMPRSS2) for priming of the viral spike protein and also, the protease has been found to pre-activate the receptor binding domain (RBD) from a 'lying down' position to a 'standing up' position, which can then bind to the ACE2 receptor with a

higher affinity (Hoffmann et al. 2020, Shang et al. 2020). Bukowska et al., (2017), reported that there was a significant down regulation of ACE (Angiotensin-converting enzyme) expression and an increase in the ACE2 expression induced by (estradiol-17ß) E_2. This means that E_2 induces an anti-inflammatory, anti-oxidative, anti-atrophic, anti-fibrotic and vasodilatory effect, which results in tissue protection (Crackower et al., 2002, Imai et al., 2005). However, a recent study suggested that estrogen can regulate the expression of ACE2, but not TMPRSS2, in differentiated normal human bronchial epithelial (NHBE) cells. They have reported that 17β-estradiol (E_2) induced reduction of ACE2 mRNA concentration in NBHE cells and that there was no significant change in the levels of TMPRSS2 mRNA on E_2 treatment (Stelzig et al., 2020). However, the study lacks in terms of sample size and needs to be repeated in NHBE cells from multiple male and female donors. Stygar et al., (2020) demonstrated that the furin mRNA level in leukocytes was negatively regulated by estrogenic substances. Due to the global outbreak of this virus and its infectious nature, the World Health Organization guidelines along with other government guidelines have directed people to wash hand and other exposed body parts frequently with soap and water, or alcohol-based hand sanitizers in order to kill the virus and reduce viral transmissions (WHO guidelines, 2020). Triclosan, broad spectrum antimicrobial agent, similar to the xenoestrogens, is present in 75% of bactericidal hand soaps, toothpaste etc. (Hutz et al., 2014, Stoker et al., 2010; Yueh and Tukey, 2016). This means that there is a fair possibility of rise in health implications due to exposure of high levels of xenoestrogens as a result of such increased usage of soaps, mouthwash, toothpaste, detergents and sanitizers (Cullinan et al., 2015; Weatherly and Gosse, 2017). Also, these indicate that there is a requirement of further studies on the combinatorial health implications of xenoestrogens and SARS-CoV-2.

Interestingly, despite proposed safety limits to these EDCs, there are actually no threshold limits for them (Gaylor et al., 1988). The threshold is exceeded with exposure, automatically (Crews et al., 2000). Thus, further research needs to be done on this to identify a threshold range rather than a single threshold value and it needs to be ensured that the terrestrial, aquatic and human environments have EDC levels not beyond that range. More global data points, especially from the second and third world countries are required to narrow down to the threshold range as the larger percentage of population is located in these countries and thereare lack of studies in these places that fails to provide a very wide-view on these regions of the world. Similar concerns were also raised by Adeel et al., (2017).

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