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A role of xenoestrogen in endocrine disruptions: A review of mechanism and consequences

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Abstract
Xenoestrogens are chemicals that mimic our body's natural hormone estrogen, acting as endocrine disruptors by disrupting the normal functioning of the endocrine system. Chemicals which mimic endogenous hormones or interfere with endocrine processes are collectively called endocrine disruptors. These xenoestrogen are broadly categories into natural and synthetic xenoestrogen. Natural xenoestrogen consist phytoestrogen, mycoestrogen, and alkaloid substance that are present in plants. Synthetic xenoestrogen contain chemicals that are present in UV filters, food preservatives, personal care products, coolant, pesticides etc. These chemicals are mainly present in plastic bottles like plastic food container, sunscreen bottle, lotion bottles, and pesticide also. In addition to this paraben is also a chemical that is also present in cosmetics bottles as preservatives which also cause same health disorder like xenoestrogen. These compounds are structurally or functionally related to human sex hormone 17β-estradiol. Due to the presence of these chemical in our body, our body's estrogen receptor get confused because it can bind to estrogen receptors in the body, leading to a cascade of effects that disrupt normal hormone function and cause several health disorders like hormonal imbalancement, metabolic disorders, irregular periods, decrease sperm count, obesity, early puberty, insulin resistance, thyroid dysfunction and risk of cancer. The rate of the effect of these chemicals is also depends upon the concentration of these chemical present into the body of living beings. Sometime these chemical can show their adverse effect in minimum concentration also. The true risk to humans is a controversial issue; to date, little evidence exists for clear cut relationships between xenoestrogen exposure and major human health concerns. However, because of the complexity of their mechanism and potential for adverse effects, much interest remains in learning how xenoestrogens affect normal estrogen signaling. These disorders are the major issue of concern now. To minimize exposure to xenoestrogens and their potential side effects, prioritize organic foods, avoid plastic containers, filter water, and choose safer personal care products.

Keywords: Xenoestrogen, paraben, plastic, hormone receptor, endocrine

Introduction
The chemicals that are used in manufacturing of consumer products like plastics, surfactants, pesticides, resins) exhibit estrogenic activities, called as Xenoestrogen. In few past years a large number of natural and synthetic chemicals have been identified those are interfering with the endocrine system they are collectively termed endocrine-disrupting chemicals (EDCs) or endocrine disruptors. These endocrine disruptors are also known as exogenous compounds, which modify the signaling pathways of their specific receptors [1]. According to the definition given by Environmental Protection Agency (EPA), an endocrine disruptor is "an exogenous agent that alters the synthesis, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis, reproduction, regulation of developmental processes and behavior [2]. These Xenoestrogens (XEs) or EDC are chemically similar with some steroid hormone like estrogens and are one of the major categories of synthesized compounds that disrupt endocrine actions. Potent rapid actions of XEs contribute significantly to their disruptive effects on functional endpoints (e.g. cell proliferation/death, transport, peptide release).

Adverse effects by endocrine disrupting chemicals (particularly xenoestrogens) include a number of developmental anomalies in wildlife and humans XEs like obesity, thyroid, PCOD etc. and can also cause disruptions of non-genomic signaling pathway represent by endogenous estrogens [3]. Mixtures of XEs, commonly found in contaminated environments, disrupt the signaling actions of physiological estrogens even more severely than do single XEs. And their mode of action is also depends upon the concentration of XE [4].

Different Cateogories of xenoestrogen

Several kind of XE are reported which can be divided into natural compounds (e.g. from plants or fungi), and synthetically derived agents including certain drugs, pesticides and industrial by-products Endocrine disruptors comprise more than 100.000 synthetic chemical compounds that belong to different classes [5].

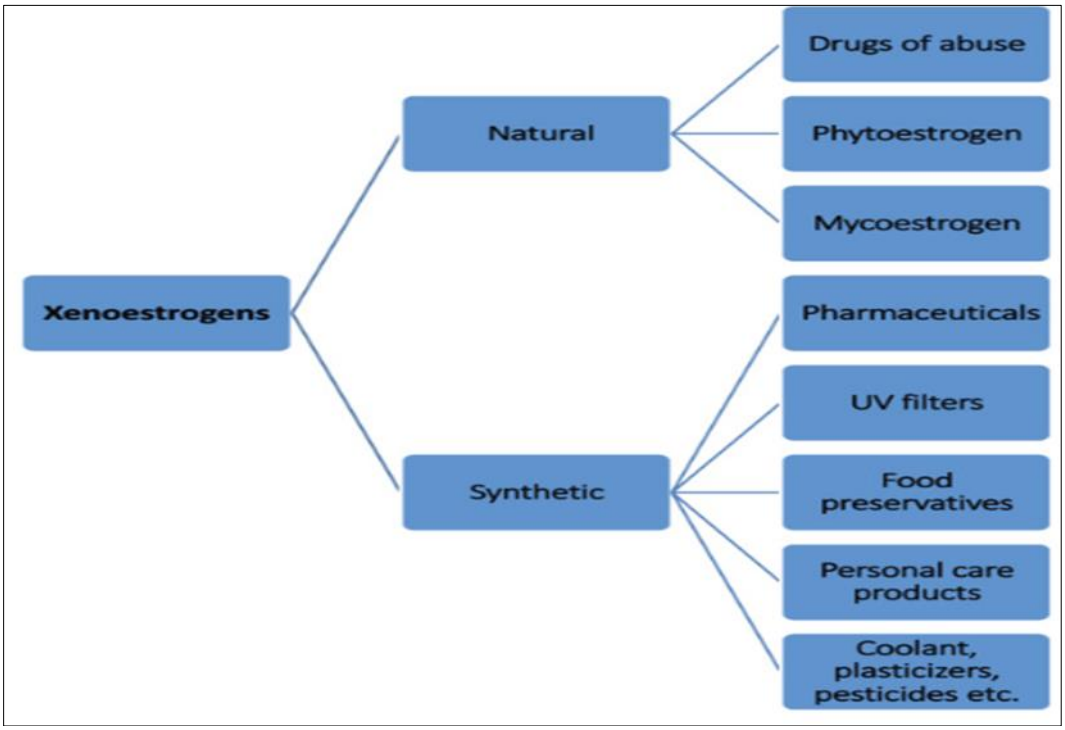

Fig 1: Shows types of Xenoestrogen that are of two kinds that is natural and synthetic chemicals, natural xenoestrogen is categories as drugs of abuse, phytoestrogen, mycoestrogen and synthetic estrogenis categories as UV filters, food preservatives, personal care products, coolant, plasticizers and pesticides etc.

Natural Xenoestrogen: The chemicals those possess estrogenic activity and obtained fromnature or plants are known as Phytoestrogens**.** The most common estrogenic compounds obtained through dietary sources containing phytoestrogens are soy supplemented diets such as infants taking soy-based formulas, the isoflavones (genistein and daidzein), found mainly in soy products, but also present in fruits and nuts act as phytoestrogens such which are increasingly marketed as over-the-counter, natural products, for use as an alternative to hormone replacement therapy in post-menopausal women.

Synthetic Xenoestrogens: These chemicals are mainly found in pharmaceutical, UV rays, Food preservatives, personal care products, coolant, plasticizers and pesticides**.** Some common synthetic xenoestrogen are DDT, PCB, phthales, bisphenol-A. Organochlorines such as PCB are extremely resistant to biological transformation and are known to accumulate in the food chain cause several side effects to the aquatic and terrestrial organism. Plasma levels of PCBs and the DDT metabolite DDE were approximately 20 nM in U.S. women identified from various geographical areas. Along with this PCBs and DDT are persistent in nature, but in recent survey in Germany has suggested that their environmental and endogenous burden rate is declining. There is some thought that these contaminants may be related to an increasing incidence of breast cancer, however, epidemiological evidence has not supported this [6]. Phthalates, also reported as XE is found in cosmetics and personal care products which can be extremely persistent in the environment. Bisphenol-A (BPA) It is an industrial monomer used in production of polycarbonates and epoxy resins has potential to leach from the lining of food cans, plastic ware, and from dental sealants and cause adverse effects on development Estimates of oral exposure to BPA are 90-930 mg during the first hour following administration of dental sealant and up to 6.3 mg per day from food cans, which illustrate its potential for endocrine disruption.

Estrogen receptor pathways

Estrogen which is steroid molecule has the ability to cross the plasma membrane of cell due to their lipid soluble ability. Most of the estrogen shows their effect by binding, in the cell cytoplasm or at nuclear membrane receptor known as to estrogen receptors (ERs) which shows numerous cell types. ER, ERα (ESR1, NR3A1), and ERβ (ESR2, NR3A2) that were identified in mammals [7].

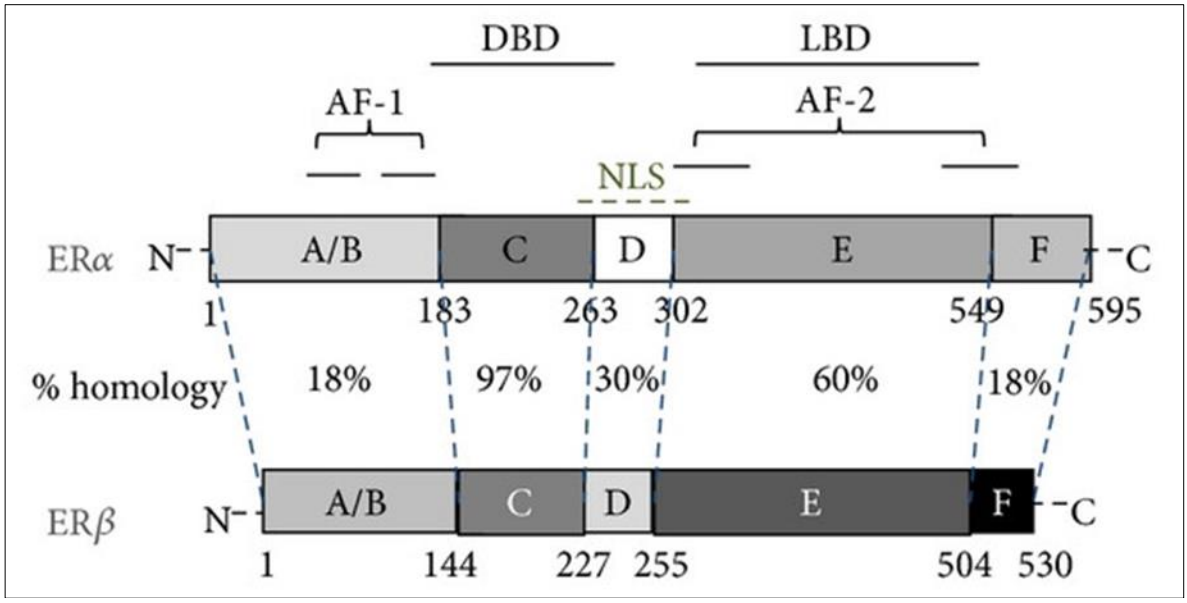

Fig 2: The pattern and pathway of estrogen receptors. ER is present in dimer form that is ERα and ERβ contain evolutionary conserved modular structure. Some homologous sequences are present between them. The sequences of ligand-binding domain (LBD) is present in E domain and the DNA-binding domain (DBD) is present in C domain are also presented. ERs contain two transactivation functions factor that is AF-1 and AF-2 that is singly divided into two subdomains which control the expression of target genes which exhibit a nuclear localization signal (NLS). (b) Due to the lipid soluble ability character of estradiol (E2) it can cross plasma membrane of cell passively. E2 is binds with ERs in the cytoplasm or the nucleus forms ER dimmers, then bind to the chromatin material to modulate target gene expression. This mechanism accelerates the genomic expression of ERs, however ERs can also modulate the signaling pathway rapidly into the cytoplasm

Characteristics of ERs

These receptors are the members of nuclear receptor superfamily that also include other receptor like glucocorticoid receptor (GR), progesterone receptor (PGR), & androgen receptor (AR). These receptor activity is depend upon the ligand binding then they act as transcription factor which is the basic characteristics of nuclear receptor superfamily. ERs have special structural and functional domains that are present in modular proteins. The AF-1 which is a ligand independent transactivation factor is present inA/B domain. The zinc finger DNA-binding domain (DBD) are the conserved sequences that is present in C domain. The nuclear localization signals (NLSs) sequences are present on D domain. And in last AF2 transactivation factor those activity is ligand dependent is exhibited by E/F domain of ERs. In general estrogen or estradiol E2 shows their effects by binding with ER, and cause the expression of genes. These effects are known as "genomic" actions that may cause adverse effects and these actions are opposed as to the non-genomic actions of estrogens that involve cytoplasmic signaling pathways. These non-genomic signaling pathway has rapid effects, which result in the activation of various intracellular signaling pathways of some transcription factor like MAPK or PI3K.

Mechanisms of Xenoestrogen Actions

Most of the EDC are structurally and chemically similar to steroid hormone like estrogen (E2) and can bind with estrogen receptor (ER). Like E2, these agents are thought to exert their actions by promoting an active ER conformation, which regulates target genes accordingly. The action of xenoestrogens is also depend upon the amount of concentration that present in our body that require 100-1000 fold greater concentration to show a similar biological effect relative to endogenous estradiol. Ligand dependent activation of ER involves dimerization and conformational changes within the receptor allowing recruitment of coactivators. Paige and co-workers showed that structurally diverse peptides that bound to ER could promote different conformations leading to recruitment of various sets of coactivators. These structurally different compounds induced ER dimer formation as well as stimulating ERE mediated transcription. Binding of the coactivator RIP-140 enhance the effects of the xenoestrogens illustrating the potential for tissue specific actions. Some endocrine disrupting agents can interfere with binding of endogenous hormones to plasma transport proteins. This process is studied for thyroid hormone which is also a steroid is replaced from its receptor by dioxin and organochlorines cause low level production this and cause various metabolic disorder [8]. Also, it is important to note that EDCs may affect more than one component of the endocrine system, with different potencies.

Endocrine signaling pathway is followed by cascade of events so these XE can affects at every level of the pathway. Firstly these disrupt the synthesis of this endocrine substances then modify the activity of enzymes that play role in the metabolism of this endocrine substances. This can be seen by alteration the activity of aromatase enzyme change the synthesis of estrogen that further affect the development of reproductive organ and menstrual cycle in case of women. As like aromtase another enzymes that involved in production or synthesis of steroid hormone can also be modified by these health hazards chemicals. Sulfotransferase enzyme which is responsible for the increased production of estradiol is also inhibited by PCB. The transport of endocrine substances from one site to another is occur with the help of some target site like SHBG (sex hormone binding globulin), is also inhibited by these chemicals.

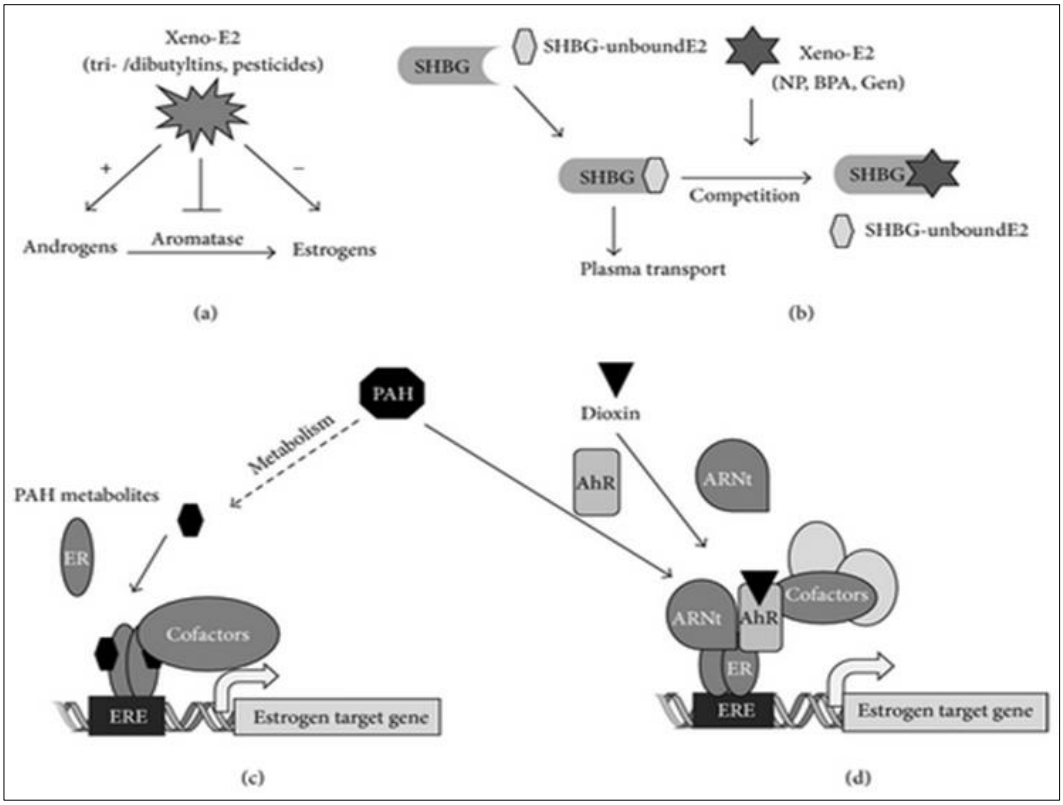

Fig 3: Represent the model of interaction between EDC and estrogen signaling pathway. (a) EDC such as tributyltins, inhibit activity of aromatase enzyme which is responsible for modification of androgens into estrogens, resulting in the improper androgen & estrogen ratio. (b) Some other EDC like BPA also compete with estradioal by binding with SHBG and modify the activity of estrogen receptor signaling ((c) Represent the interaction between PAH (polycyclic aromatic hydrocarbon) and ER that control the expression of Estrogen target gene by the addition of some coregulators and coactivatores (d) shows binding of chemical dioxin with aryl hydrocarbon nuclear trans locator (Arnt) cause heterodimerization of ER receptor, that cause unbounding of estradiol with ER and stop the expression of estrogen related target gene expression

These EDC has the ability to act as ligand for estrogen receptor and bind with this and activate the expression of target gene that disrupt the pathway of various biological process which leads to distinct biological effects in several mammalian tissue such as thyroid glands, ovary, testis, mammalian tissue, brain, kidney, bone, skin etc. ER dimmers that contain ERα and ERβ have control of various physiological functions of livings beings. If these get agonist or antagonist by these chemical then they can affect developmental process which leads to various anomalies. These chemicals binding can also leads to conformational structural change in tertiary structure of protein which helps in recruitment of coactivators and coregulators which leads to alteration in the expression of estrogen target gene expression.

Xenoestrogens generally act in 100-1000 folds greater concentrations than estradiol but can have additive or synergic effects with endogenous estradiol when they are present in combination. Furthermore, the ability of some xenoestrogens to act as agonists and as antagonists in certain tissue leads to the development and use of selective ER modulators (SERMs). Some XE like raloxifene and tamoxifen are used in some antihormonal treatments to avoid to inhibit the production of hormone.

Several mechanisms are also reported describe the antiestrogenicity of AhR ligands. These compounds bound with AhR start interference with transcriptionally active factor ER/AP-1 complex. They can also inhibit the binding of ER to ERE sites by direct association with ERα. However, AhR-mediated degeneration rates may vary according to the specific cellular context. Therefore, these interactions take into consideration by the interpretations of studies that investigate the estrogenic effects of AhR ligands, particularly in mixtures.

EDC can also alter hormonal signaling indirectly with the help of their metabolites. EDC metabolism should be taken into the consideration by the evaluation and identification of their mechanisms of action.

The Consequences of xenoestrogen exposure

Xenoestrogens attract much concern due to their adverse effect on the human endocrine system. The exposure of estrogenic compounds on organism in different periods of the life may facilitate the development of dysfunctions or even tumors of hormone-dependent tissues [9]. EDCs are characterized as they have deleterious effects on the health of living organisms and their descendant. Among the various sources of exposure, the ingestion of water or contaminated food, cosmetics, pharmaceuticals, industrial exposure, and contact with professional activities (e.g., pesticides) are the most common. The exposures to these compounds have critical effects at the fetal and postnatal stages. The development of the nervous system and the reproductive organs can be severely disrupted at these stages, because all these process are hormone regulated.

The human body is exposed to more than one particular substance, so the mixture of various substances may work synergically or antagonistically to each other. the potential effects of exposure of EDC is depends upon many factor like the age of the victim of exposure, type of substance, period of exposure, and size of the dose have to be taken into account. It also has to be taken into consideration that endocrine disrupting compounds will be active in smaller doses than the toxic dose threshold. Moreover, it needs to be

considered that a long time may elapse between the exposure to those compounds and the emergence of the first disease symptoms [10].

Over the years, various health complications reported in men, such as a higher incidence of testicle cancer, decrease in sperm quality or malformations of genital organs [11], as well as in women, such as a higher incidence of breast cancer, reproductive system tumors [12], were observed, which contributed to a significant increase of the interest in the cause of their origin. Multiple studies on the action of xenoestrogen show that these chemical exhibit estrogen like properties and affect the development of human reproductive system's organs [13].

With the less concentration of estrogen level in any organism body, cannot reproduce, and non-reproductive tissues also supported by estrogens (Es) cannot show proper function. Besides this high concentration of estrogenic substance in our body become responsible for the malfunction or development of some disease like cancers. Fetus or developing baby of a pregnant woman is exposed to xenoestrogen is more vulnerable to endocrine disruption process. EDCs can interfere with formation, metabolism and action of steroid hormones which cause to development various fertility problems like infertility and gonadial cancer in human beings. Some EDCs also cause obesity due to unproper production of enzymes and hormone that regulate Basal Metabolic Rate (BMR). These chemicals also affect the signaling pathway of hypothalamus pituitary axis that's indirectly affects all endocrine organs.

The insecticide DDT and its metabolite DDE (dichlorodiphenyldichloroethylene) are also characterized as weak estrogens in the environment which affect reproduction function in several animal species. DDE is a non-biodegradable pesticides has lipid soluble properties that is responsible for the stimulation of alligators to become feminize is reported from Lake Apopka. These effects are mediated by the inhibition of androgen signaling pathway during the critical developmental period.

Conclusion

Due to the production sector of economy, the industrial sector is much grown which release various health hazards chemicals in the environment. These chemicals act as EDC or commonly known as Xenoestrogen that disrupt the endocrine signaling pathway. Because the xenoestrogen are chemically similar with steroid hormone estrogen so these mimics the signaling pathway of this and cause various side effects in living organism. The action of these chemicals is depends upon the concentration of this chemical present in our body. Besides the concentration this is also depend upon age of living being and duration of exposure.

This chemical are lipophilic can rapidly cross the plasma membrane of the cell bind with ER that is present on nuclear membrane in dimer form i.e. ER alpha and ER beta, and alter the gene expression that is followed by estrogen that result in various adverse effects on human and other organism and their descendent like developmental anomalies, obesity, PCOD, thyroid gland dysfunction, infertility with low sperm count etc.

Perspective

Understanding the disruptive mechanism and signaling pathway of xenoestrogen and their adverse effect on living beings assist us to redesign the useful chemical those does not have estrogenic or antiestrogen activities. The most difficult aspect using this chemical is to assess the potential of their adverse effects on human bodies. So toxicological assessment takes into consideration while designing these chemicals. So that we can avoid the health hazards caused by these EDC.

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