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Review

Endocrine disrupters—A threat to women's health?

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ABSTRACT

Endocrine disruption has been a topic of public concern for many years and its study remains high on the scientific agenda. Endocrine disrupters (EDs) are compounds which may be of industrial or natural origin and which act to dysregulate steroid function and metabolism. As well as their actions on nuclear steroid receptors, EDs can inhibit the pathways of steroid synthesis and degradation. They not only affect reproductive function but also affect a range of tissues which are steroid sensitive such as the central nervous system and thyroid. Results from the latest studies suggest that EDs may also affect the immune system, glucose homeostasis and can act as epigenetic modulators resulting in transgenerational effects. Research in this area has led to the development of drugs used in the treatment of several types of hormone-sensitive cancer. However, despite many years of effort, the effects on human health of long-term environmental exposure to EDs, whether singly or as mixtures, remain unknown.

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Contents

1. Introduction

Endocrine disruption remains one of the 'hot topics' of our time and is still unresolved despite the expenditure of so much time and money. Endocrine disrupters (EDs) are chemicals that alter steroid metabolism or function and so might have effects on the human population that could be long-term. Public perception is often that EDs consist solely of manufactured chemicals (sometimes referred to as "xenoestrogens") such as bisphenol A, phthalates, polychlorinated and polybrominated biphenyls, some pesticides and fungicides and that they are associated wholly with adverse effects. However, the phytoestrogens, which are erroneously perceived as wholly beneficial, are also members of the group. Currently, EDs have been re-branded as 'endocrine active' substances to allow for the fact that their effects may not necessarily be deleterious and to avoid the negative connotations associated with the word "disrupter." In this paper we outline the sites and mechanisms of action of EDs and discuss the implications for women's health of both medical and environmental exposure to these chemicals.

2. Mechanisms of action

EDs exert their effects at both the receptor and metabolic levels. It was originally thought that EDs worked by acting as agonists or antagonists at nuclear receptors (estrogen, androgen, thyroid, progesterone and retinoid). However, it became apparent that this view was too simplistic and that in many cases their affinity for the receptors *in vitro* did not correlate with their hormonal potency *in vivo*. It is now known that EDs can act via non-nuclear steroid membrane receptors, and non-steroid receptors such as those for serotonin, dopamine and noradrenalin which are found in the central nervous system [1]. EDs also have non-receptor mediated actions, controlling the production and break-down of endogenous steroids [2]. Modulation of these pathways (see Fig. 1) has now

Abbreviations: BPA, bisphenol A; ED, endocrine disruptor; SULT, sulfotransferase.

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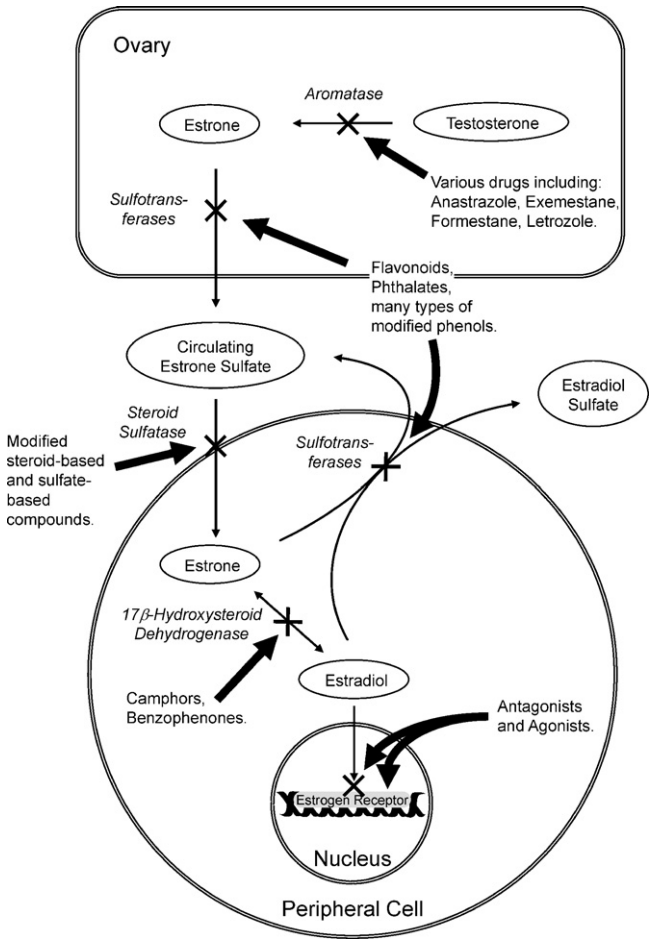

Fig. 1. Sites of action for endocrine disrupters showing the enzymes affected by these compounds. Inhibition of the sulfotransferases can be unpredictable as this can reduce the concentration of circulating hormone-sulfates while increasing the concentration of free hormone in the peripheral cells. Effects at the estrogen receptors are also extremely complex as a molecule that acts as an agonist in one tissue can act as an antagonist in another. For example, the drug Tamoxifen acts as an antagonist in the breast, an agonist in the bone and a partial agonist in the endometrium; while it can alleviate breast cancer and osteoporosis, Tamoxifen treatment can also lead to the development of cancer of the uterus.

been demonstrated with several different types of environmental EDs and has also been exploited medically to control a variety of hormone-based conditions. For example, the sulfotransferase (SULT) enzymes, once thought to be confined to a minor role in the detoxification of phenols, have been shown to play a key role in the transport and breakdown of estrogens which are also phenolic compounds. Estrogen sulfonates, unlike the parent compounds, are inactive so that this pathway removes the pharmacological and physiological effects of steroids from the biological system. Compounds which inhibit SULTs therefore increase the levels of the endogenous estrogens (rather than acting as exogenous agents at receptors). Our own studies have shown that enzymes from this group are vulnerable to inhibition by flavonoids, alkylphenols and phthalates and that relatively small differences in structure can make huge differences to potency [3–7]. Interestingly, although the synthetic chemicals are the ones that arouse the greatest public concern, it is the naturally occurring flavonoids which are the most potent inhibitors.

In mammals, androgens such as the masculinising hormone testosterone are converted to the feminising estrogens such as estradiol by the enzyme aromatase. Aromatase is an isoform (CYP19) of the cytochrome P450 family of enzymes. These are heme-containing proteins that catalyse oxidation reactions, adding an atom of oxygen (derived from molecular oxygen) or removing hydrogen atoms. Cytochromes P450 are found in the microsomal fraction of cells (where substrates are usually drugs or other xenobiotics) and also in the mitochondrial fraction (where substrates are usually endogenous such as steroids). Aromatase acts as a 'gateway' enzyme, the only entrance to the pathway for estrogen synthesis and any inhibition of its action results in increased levels of androgens and hence masculinisation. Aromatase inhibitors are effective in the treatment of tamoxifen-resistant hormone-sensitive breast cancer in postmenopausal women [8]. These drugs are also abused by some body-builders who use them to prevent the gynecomastia caused when the enzyme converts testosterone supplements to excess estrogen [9]. Other metabolic blocks are known to exist—17β-hydroxysteroid dehydrogenase is inhibited by camphors and benzophenones used in sun-screen preparations [10] while steroid sulfatase inhibitors are used to treat skin disorders such as androgen-dependent acne [11] and hormone-dependent endometrial [12] and breast cancers [13].

The effects of EDs were originally observed in non-mammalian species. Feminisation occurs in fish (manifested by the production of the egg protein vitellogenin) when they are exposed to ED-containing sewage effluent [14,15] and in the amphibian *Xenopus laevis* exposed to octyl- and nonyl-phenols, bisphenol A and butylhydroxyanisole at sub-micromolar concentrations [16]. Masculinisation can also occur. The compound tributyltin, once used to prevent fouling of ships' timbers, is an aromatase inhibitor which not only causes significant masculinisation of female zebra fish at concentrations as low as 100 pg l^{-1} but also causes sperm damage (lower levels of motility or loss of flagella) at similar concentrations [17]. Mammals are also affected. A variety of conditions have been observed in rats and mice exposed to EDs including hypospadia, cryptorchidism, microphallus and prostate cancer in males, and abnormalities in the mammary glands and reproductive tracts (including increased risk of cancers) in females. In some cases, e.g. for the insecticide methoxychlor, the fungicide vinclozolin and the drug diethylstilbestrol (which, ironically, was prescribed to prevent birth complications), these effects are heritable and appear to be transmitted *via* epigenetic mechanisms.

3. Effects on women

Given that so many EDs have been shown to affect reproduction in vertebrates, the question must now be whether this also occurs in human beings. There are many species differences in the relevant biological systems and of course EDs usually occur in complex combinations from environmental exposure. Reproduction is less easily evaluated in humans than in laboratory rats; the evidence is not clear-cut and there are many contradictory reports. In women, the incidence of cancers of the reproductive organs (breast, ovary) seems to be increasing although other cancers are slightly less common. It is probable that intrauterine influences can affect the initial processes which lead to the growth of tumours many years later. Evidence from epidemiological and dietary studies suggests that there are 'critical windows' in fetal and neonatal development where the organism is particularly sensitive to the levels of steroids and also to the estrogen/androgen ratio [18]. Factors interfering with ovarian formation (germ cell migration to yolk sac in the first trimester, differentiation into oocytes in the second and third trimesters) will obviously impact on reproductive outcomes decades later, as will any post-natal dysregulation of uterine formation. In both animals and women, the exact developmental stage at which exposure to EDs occurs will determine the physiological effects; polycystic ovarian syndrome, premature ovarian failure, ectopic pregnancy, fibroids and endometriosis have all been

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