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Critical review

Human

Endocrine disruptors: a gender affair

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Abstract

Introduction

The increase in non-communicable diseases in humans and wildlife over the past 40 years indicates an important role of the environment in disease aetiology. In particular, a huge amount of literature demonstrates the role of environmental endocrine disrupting chemicals in the pathogenesis of several diseases. Nowadays, it is clear that fundamental principles of endocrinology must be applied to the design and execution of studies on endocrine disrupting chemicals to be cognizant that the specific actions of individual hormones often change with development and ageing, they may be different in males and females, and may be mediated by different receptor isoforms expressed in different tissues or at different life stages. These statements are particularly true when assessing the hazard of endocrine disrupting chemicals against oestrogen and androgen actions in that these hormones are crucial determinants of sex-related differences in anatomical, physiological, and behavioural traits which characterise male and female physiology.

This review aims to dissect the role exerted by endocrine disrupting chemicals in modulating androgen and oestrogen receptor activities to define the possible sex-related responses to these compounds. Data discussed here lead to a paradigm shift that challenges the concept that female organs are sensitive only to oestrogens (and anti-oestrogens), and male organs are sensitive only to androgens (and anti-androgens) because the pathways of sex steroid hormone biosynthesis as well as androgen and oestrogen response elements are found in both sexes. Thus, an overall estrogenic effect would occur in males exposed to endocrine disrupting chemicals, which could change the male hormonal milieu assured by a characteristic high ratio of androgen signals with respect to oestrogen signals. The opposite could also be envisioned in females.

Conclusion

Data on endocrine disrupting chemical action mechanisms are still unclear, confused and sometimes contrasting. Molecular studies *in vitro* and with *in vivo* animal models of both sexes are needed to identify pathways for endocrine disrupting chemical influence on sex steroid target tissues. In addition, studies on endocrine disrupting chemicals on several of these systems are much underrepresented, and these fields need to be expanded. These experimental approaches can surely highlight endocrine disrupting chemical disrupting action mechanism(s) in the future.

Introduction

Endocrine disruption has a long historical background starting in the early 1900s when pig farmers in the USA complained of fertility problems in swine herds fed on mouldy grain and in sheep grazing on certain clovers in Western Australia[1]. Over the following two decades, endocrine disruption was evidenced in birds and in mammals, while feminisation of fishes was observed in UK rivers in the presence of estrogenic components in sewage effluent[1]. These observations prompted the scientific community to develop the idea that xenobiotic chemicals could inappropriately modulate the endocrine system, in particular, sex steroid hormones, thereby causing detrimental effects in wildlife and human life[2].

Currently, more than 100 chemicals, containing halogen groups, have been identified as endocrine disrupting chemicals (EDCs). They include: (a) synthetic chemicals used in industry, agriculture and consumer products; (b) synthetic chemicals used as prescription drugs and (c) chemical components of human and animal food. Exposure to EDCs can occur from a number of different sources: water, air, food, soil or even in the workplace. EDCs have very low water solubility, extremely high lipid solubility and long environmental half-life resulting in a continuous increase in their global concentration in the environment even at great distances from where they are produced, used or released. However, even when present in minute amounts, EDCs could interfere with the synthesis, secretion, transport, metabolism, binding, action or elimination of sex steroid hormones interfering with the homeostasis maintenance, reproduction and developmental processes regulated by these hormone systems[1].

In recent years, the American Endocrine Society published two scientific statements[3,4] supporting the existence and detrimental effects of EDCs, underscoring them as a significant concern for public, and stating the need of more focused mechanistic research. Moreover, fundamental principles of endocrinology must be applied to the design and execution of studies on EDCs to be cognizant that the specific actions of individual

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FOR CITATION PURPOSES: *Pellegrini M, Acconcia F, Marino M.* Endocrine disruptors: a gender affair. OA Biology 2013 Dec 01;1(1):5.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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hormones often change with development and with ageing; they may be different in males and females and may be mediated by different receptor isoforms expressed in different tissues or at different life stages[3,4]. These statements are particularly true when assessing the hazard of EDCs against oestrogen and androgen actions in that these hormones are crucial determinants of sex-related differences in anatomical, physiological and behavioural traits which characterise male and female physiology[5,6]. While sex hormone-dependent reproductive behaviour and physiology are known to be altered by EDCs[7], less is known about the effects of these chemicals on other sex differences[8]. This review aims to dissect the role exerted by EDCs in modulating androgen and oestrogen receptor activities to define the possible sex-related responses to these compounds.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Animal care was also in accordance with the institution guidelines.

Sex steroid hormones

As other steroid hormones, sex steroids (i.e. oestrogens, progestins and androgens) are derived from cholesterol (Figure 1)[9].

Androgens (dihydrotestosterone (DHT), testosterone (Tes), androstanediol, androst-4-ene3, 17-dione, androsterone and deydroepiandrosterone) are all steroids with 19 carbons secreted by the testicular Leydig cells and in peripheral tissues by conversion[9]. In men, normal circulating Tes levels range from 10 to 30 nM, whereas much lower levels (0.6–2.5 nM) are found in women. Tes is converted to DHT by 5α-reductase, an NADPH-dependent enzyme (Figure 1). DHT and Tes bind to the same specific intracellular receptor, although with different dissociation affinity constants (DHT $K_d = 2$ nM; Tes $K_d = 8$ nM)[9].

Oestrogens (oestrone, estriol, and 17β-estradiol, E2) are all 18 carbons steroids, which derive from the aromatisation of A ring of either Tes to yield E2 or androst-4-ene-3,17-dione to yield oestrone (Figure 1). This reaction is mediated by aromatase present in the granulosa cells of the ovary, in the adrenal gland, placenta, brain and adipose tissue[9]. After puberty, the level of circulating oestrogens in females ranges between 250 and 1100 pM in dependence of ovary cycle, whereas much lower levels (50 pM) are found in men[9].

Androgens and oestrogens are pleiotropic hormones since they exert biological effects in male and female tissues including bone, skeletal muscle, adipose tissue, cardiovascular system and brain[9]. However, oestrogen effects have also been reported in male individuals. Testosterone conversion to E2 by aromatase is fundamental for the masculinisation of developing male brain, for prostate growth, for male bone mineralisation and for male fertility[10].

Sex steroid hormone receptors

The androgen (AR) and oestrogen (ERα and ERβ) receptors, expressed in all male and female organs, are members of the nuclear receptor

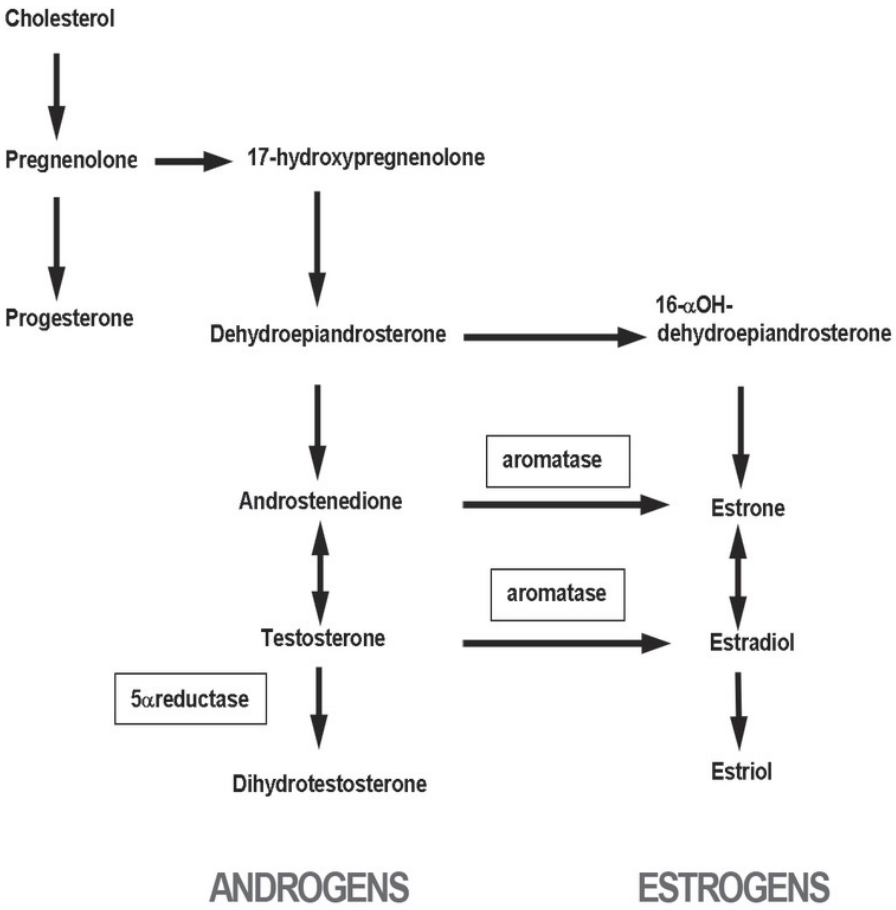

Figure 1: The biosynthetic pathway of sex steroid hormones. The involved enzymes are reported in the squares.

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superfamily being defined as ligand-activated transcriptional factors. AR and ERs are localised in the cytoplasm and in the nucleus of sex steroid hormone-target cells where they are associated, in the resting state, to heat shock proteins. A small pool of these receptors is palmitoylated and localised at the plasma membrane in association with caveolin-1 [11,12].

Like other nuclear receptors, the sex steroid receptors have five functional domains (Figure 2) including the *N*-terminal transcriptional activation domain (NTD), the central DNA-binding domain (DBD) consisting of two zinc finger motifs, a hinge domain, the ligand binding domain (LBD), and the *C*-terminal domain which can also modulate receptor transcriptional activities[11,13]. Binding to hormones induces a conformational change in receptor structure, its dimerisation and the nuclear translocation of the hormone-receptor complex. This complex binds to specific androgen response elements (AREs) or oestrogen response elements (EREs) localised in the upstream promoter of target genes and along with several co-regulator proteins (co-activators or co-repressors), leads to transcriptional activation of hormone-regulated genes (Figure 3)[11,13]. In addition to these slow genomic modes of action, sex steroid hormones as well as other steroid hormones exert rapid extra-nuclear effects (Figure 4) which have been implicated in several cellular effects, including regulation of survival/apoptosis balance, intracellular Ca^{2+}-homeostasis, plasma cholesterol homeostasis, aortic relaxation, neuronal plasticity and neurite outgrowth[14]. To further complicate this picture, several AR (e.g. AR 80 kDa) and ERs (e.g. ERα46, ERβ2) splicing forms have been discovered in hormone-related cancers (e.g. prostate cancer, breast and ovary cancers), even if many of them have also been identified in non-cancerous tissues (testis and vascular cells)[15,16]. In particular,

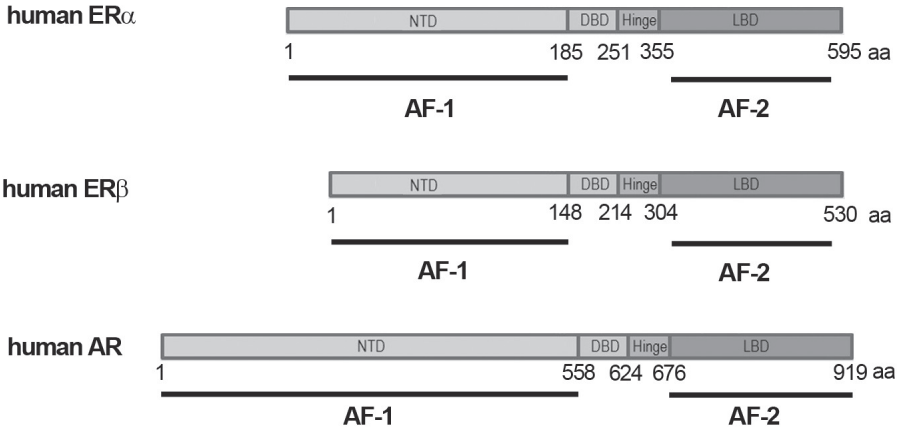

Figure 2: Schematic representation of sex steroid hormone receptors. AR, androgen receptor; ERα, oestrogen receptor α subtype; ERβ, oestrogen receptor β subtype; NTD, *N*-terminal domain; DBD, DNA-binding domain; LDB, ligand-binding domain; AF-1 and AF-2, activation function-1 and -2, respectively.

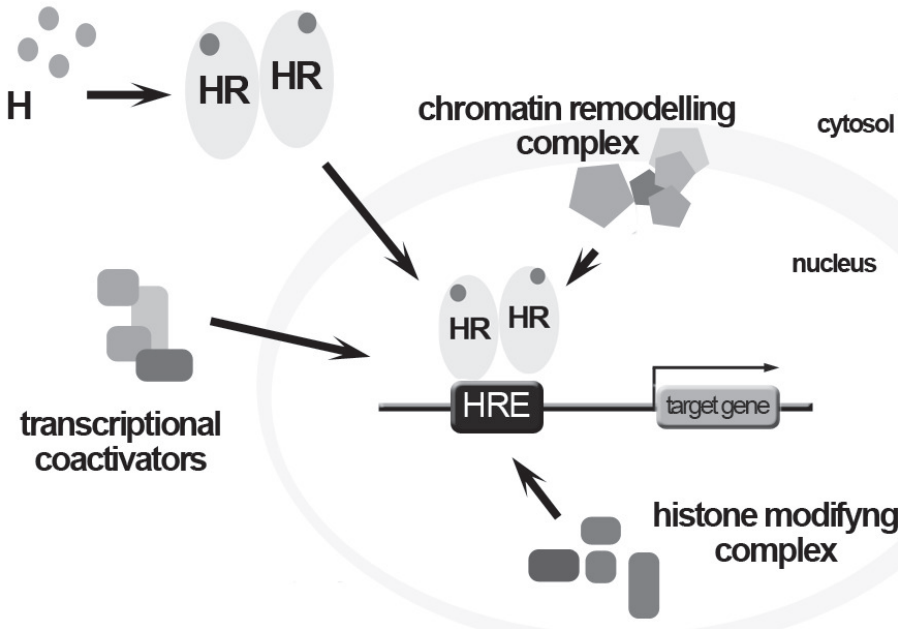

Figure 3: Transcriptional activity of sex steroid hormone receptors. Upon ligand (H) binding, receptors (HR) dimerise, translocate into the nucleus, and bind to hormone responsive element (HRE) present on DNA where transcriptional co-activators are also recruiting. Co-regulators support ligand-dependent transcriptional controls by HR through chromatin remodelling and histone modifications.

some AR isoforms retain NTD and DBD, but lack the LBD being constitutively active[15]; whereas, ERα46 and ERβ2 are principally localised at the plasma membrane and in the cytosol, respectively[16]. Thus, the pleiotropic effects elicited by androgens and oestrogens are obtained by different signal transduction pathways (i.e. genomic and extra-nuclear) for which activation depends on the cellular context of target cells, the receptor subtype and location within cells (i.e. membrane, cytosol, nucleus), as

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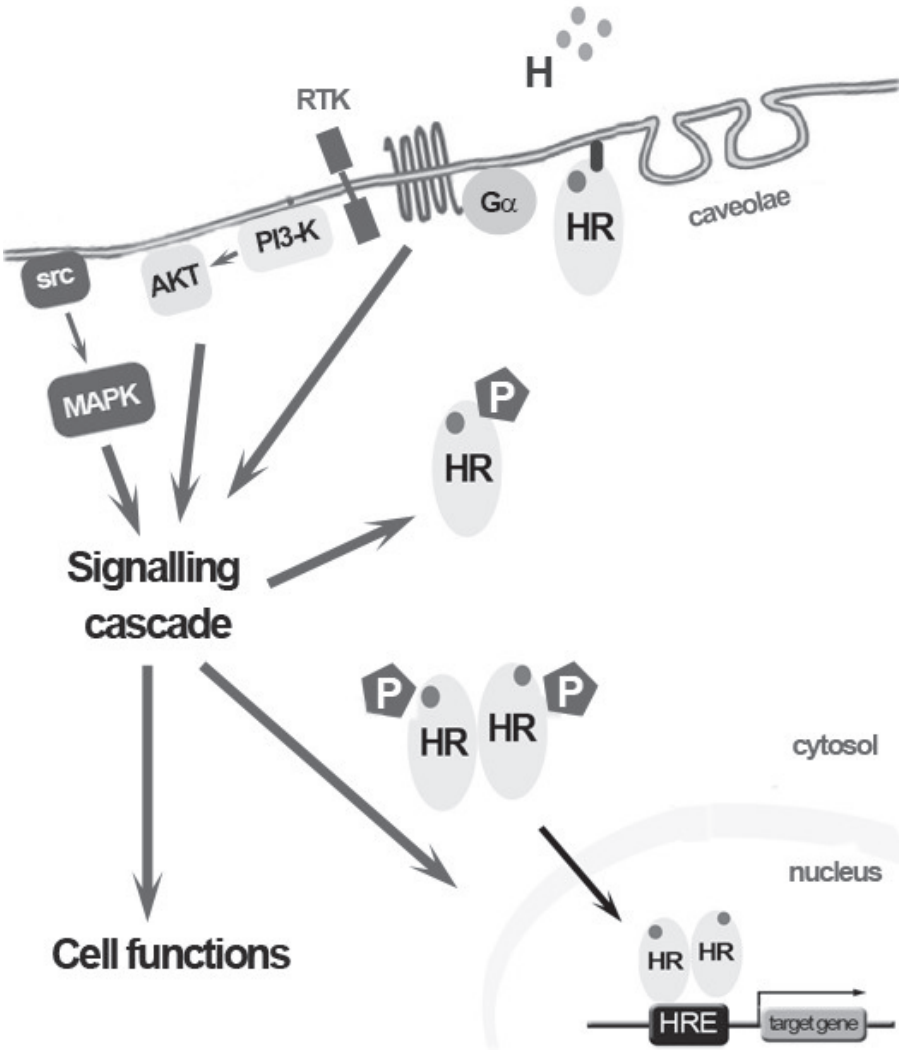

Figure 4: Extra-nuclear activities of sex steroid hormone receptors. Hormone receptors (HR) are palmitoylated (black bar) and localised at the plasma membrane in association with caveolin-1. De-palmitoylation of ligand (H) bound HR allows receptor to interact with the tyrosine kinase c-Src to activate the mitogen-activated protein kinase (MAPK) pathway and to GDP-binding proteins (Gα) as well as tyrosine kinase receptors (RTK) to activate phosphatidyl-3 kinase (PI3-K)/AKT pathway and influence HR-mediated transcription via phosphorylation of HR and coactivator/receptor complexes. In addition, the HR-triggered signalling cascade can rapidly influence other cell functions (e.g. ion calcium pump, cell cycle progression, apoptosis, differentiation).

well as the ligand itself (e.g. Tes vs. DHT or E2 vs. estriol).

Intriguingly, the pathways of sex steroid hormone biosynthesis as well as AR and ERs are found in both sexes; therefore, circulating plasma concentrations of sex steroid hormones are representative of the relative conversion of androgens to oestrogens. Females have elevated plasma oestrogens compared with androgens, whereas males have the opposite ratio. Thus, as an example, the male versus female hormonal milieu will be generated by the ratio of androgen to oestrogen circulating levels and signal transduction pathways in target cells[17].

EDC interference of male and female functions

As expected, the largest body of literature reports the mimetic or disruptive effects of EDCs on oestrogen- and androgen-mediated regulation of reproductive organs. As examples (reviewed in[2–4,7,18]), exposure to EDCs reduced proportions of male births in the populations of a number of countries, increased the risk of cryptorchidism, hypospadias, and reduced semen quality in males[18]. Several studies in human, primates and rodents have found a relationship between adult exposures to EDCs and female reproductive disorders such as polycystic ovary syndrome, fibroids, endometriosis, premature ovarian failure and disorders associated with poor pregnancy outcomes[18].

Less information are available on other sex steroid hormone-dependent differences in male and female organisms. Sufficient data sets indicate that in utero exposure to EDCs (e.g. for polychlorinated biphenyl, PCBs, lead and methylmercury) cause deficits in oestrogen-dependent cognition and behaviour in humans. Moreover, epidemiological studies on humans also support a relationship between exposure to EDCs and decreased bone mineral density or increased risk of bone fractures. Obesity, diabetes and metabolic syndrome are due to disruption of the sex-specific energy storage–energy expenditure balance to which several endocrine systems including oestrogen contributes; thus, even this balance is sensitive to antioestrogenic chemicals. Remarkably, exposures of female animal models to a variety of chemicals (e.g. bisphenol A, BPA) have been shown to result in weight gain and in an 'android' fat deposition in the body. For this reason, these chemicals constitute a new class of endocrine disruptors called 'obesogens'.

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Finally, the role of endogenous and therapeutic sex steroid hormones in insurgence of breast, endometrial, ovarian and prostate cancers is well documented; this renders plausible that xenoandrogens and xenoestrogens could also contribute to the increased risk of these hormone-related cancers[18].

Moreover, it should be mentioned that EDC effects can act throughout life just as sex steroid hormones do. When exposure to EDCs occurs during development, they will affect programming of cell and tissue development and thus their effects are expected to be permanent, due to EDCs effects on programming of cell differentiation and tissue development, resulting in a tissue that has a different predisposition for disease in adulthood to that of a non-exposed tissue. When the same EDC is present later, in childhood or in the adult pre- and post-menopause or -andropause, the effects will be very different and could be transient[3,4,18].

Mechanistically, EDCs may disrupt sex steroid hormone actions in a number of ways. For example, EDCs can inhibit or induce the enzymes responsible for sex steroid hormone biosynthesis (e.g. aromatase) and/or influence the metabolic breakdown pathway[19,20]. Indeed, EDCs appear to lower foetal Tes and DHT levels which compel malformations of the male reproductive organs as a consequence. Furthermore, a chemical may mimic or block the action of the natural hormone by binding to its receptor or interfering with receptor activities in some other way[20]. This is the case of the interference of the synthetic (i.e. BPA) and natural (i.e. naringenin, Nar) EDCs on ERs. Although BPA binds to ERα and ERβ with a lower affinity than E2 (i.e. 10 μM BPA vs. 10 nM E2), it induces E2-responsive gene expression[20]. Moreover, BPA acts as an E2 agonist in the presence of ERα inducing cell proliferation via ERα-mediate extra-nuclear signal transduction pathway activation (i.e. extracellular regulated kinases and AKT phosphorylation); whereas, in presence of ERβ, BPA acts as a full E2 antagonist by blocking both genomic and extra-nuclear ERβ activities[20,21]. Quite the opposite effects are elicited by the plant-derived Nar which hampers ERα-mediated rapid activation of the above-mentioned signalling kinases and cyclin D1 transcription decoupling ERα with extra-nuclear signalling cascade activation. However, Nar is E2 mimetic on both genomic and extra-nuclear ERβ activities[20,22]. Thus, the same chemical could selectively prevent body functions induced by one ER subtype and stimulate the functions regulated by the other receptor subtype completely misbalancing the E2-dependent control of cell functions.

Although androgen and oestrogen receptors share similar action mechanisms, very few data are available on EDC impairment of androgen metabolism and AR transcriptional activity, while lack of knowledge is still present on the ability of these compounds to interfere with androgen dependent extra-nuclear signals[17,20,23]. In our laboratory, we used the xenoestrogenic EDCs, Nar and BPA, to evaluate their effects on mouse satellite cell differentiation, male rat vascular smooth muscle cells motility, and AR levels and transcriptional activity in human prostate cancer cells. All cell models used expressed AR wild type (i.e. 110 kDa), while only prostate cancer cells were positive for AR splicing forms (e.g. ARΔLBD, AR 75-80 kDa). Intriguingly, Nar and BPA acted as antiandrogens only when AR splicing forms were expressed. These data have been confirmed in HeLa cells transiently transfected with AR wild type (110 kDa) or AR mutants (i.e. AR ~80 kDa and AR ~28 kDa) (Marino M, unpublished data). These data, also established by other authors with different AR mutants[24], indicate that EDCs, such as BPA or Nar, could interfere with the therapy in patients with advanced prostate cancer via mutant ARs being ineffective in wild type AR expressing tissues[24,25].

On the other hand, both Nar and BPA maintained their ability to modulate ERs, which were also expressed in the same cells, impairing the ERα and ERβ activities as mentioned above (Marino M, unpublished data). Taking into account that ERs, principally ERβ, are mainly expressed in male reproductive system (e.g. testis, spermatozoa, prostate)[26], it is worth considering whether some, or even all, of the reported endocrine effects of EDCs are due not to their androgenicity, but rather to their abilities to interfere with the action of oestrogen receptors[17].

The increase in non-communicable diseases in humans and wildlife over the past 40 years indicates an important role of the environment in disease aetiology. EDCs are important components of the environmental influences on disease, along with nutrition and other factors. This statement is sustained by data obtained from epidemiologic evidence, *in vivo* and *in vitro* studies, which give us an alarming picture of the wide effect of EDCs on human health[7,18,20]. In particular, the literature demonstrates a role of EDCs in the pathogenesis of obesity, diabetes mellitus and cardiovascular disease, the major epidemics of the modern world[27].

Conclusion

The data reported here sustain the idea that oestrogen signalling is more prone to the EDCs interference. However, the presence of ERs in male tissues and of AR in female tissues oppose to the paradigm that female organs are sensitive only to oestrogens (and anti-oestrogens), and male organs are sensitive only to androgens and anti-androgens. Thus, an overall estrogenic effect would occur in males exposed to EDCs, which could change the male

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Acknowledgement

The authors thank former and present members of their laboratories who contributed data and discussions on the ideas presented here. The experimental work reported in this review was supported by grants of University Roma Tre to MM.

Abbreviations list

AR, androgen; AREs, androgen response elements; DBD, DNA-binding domain; DHT, dihydrotestosterone; EDCs, endocrine disrupting chemicals; EREs, oestrogen response elements; LBD, ligand binding domain; NTD, *N*-terminal transcriptional activation domain; Tes, testosterone.

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