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Human Reproduction: Target of Endocrine Disruptors

György Csaba*

Department of Genetics, Cell and Immunobiology, Budapest, Hungary

***Corresponding author:** György Csaba, Department of Genetics, Cell and Immunobiology, Budapest, Hungary

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ABSTRACT

Endocrine disruptors are natural or man-made hormone-like molecules, which after entering into the human organism are bound by hormone receptors (similarly to physiological hormones) disturbing the normal (endogenous) hormonal regulation. Their effects are depending on the timing of exposure: in adults they can cause an acute reaction (disease), while in the perinatal (late fetal and early postnatal) period they are provoking faulty hormonal imprinting with late manifested symptoms: inclination to diseases, diseases, or alteration of certain functions (functional teratogenicity with the prolongation of teratogen-sensitive period). The developmentally originated diseases (DOHAD) can be explained by the provocation of perinatal hormonal imprinting. The effect of faulty hormonal imprinting - as an epigenetic process- is inherited also to the progeny generations. As the amount and variations of man-made endocrine disruptors (plasticizers, agrotechnical materials, pharmaceuticals etc.) and also the consumption of phytoestrogen- containing foods (soy-products) are increasing, the growing number of disruptor-caused diseases can be observed and is expected in the future. This could be manifested in sub- or infertility as well, as other functional teratogenicity which are qualitatively and quantitatively influencing human reproduction and demographical indexes.

Introduction

As a result of human activity many artificial, synthetic molecules appeared in the environment which are similar to the regulators of human life functions (hormones). These are named endocrine disruptors, as they have steroid characters mimicking the structure of steroid hormones, produced by endocrine glands of mammals (consequently human beings). Among them there are anti-estrogenic, estrogenic, anti-androgenic, and androgenic types [1]. These molecules are entering into the human organism by air, water and foods, or by medical treatments and cosmetics [2] and compete with the physiological hormones, stimulating or inhibiting different organs or cells. Because of their structural similarities they are able to inhibit the binding of physiological hormones to their receptors or in contrast, by binding to the receptors they transmit faulty messages. This action disturbs the normal, well balanced function of the human endocrine system in the target cells (organs) of the given hormone or in general, as many organs (cells) have steroid or steroid-reactive receptors without being direct targets of steroid hormones.

However, the main targets of the endocrine disruptors are the reproductive organs and also cells which have a role in sexually influenced actions and considering this the fertility and fecundity are deeply touched by the presence of endocrine disruptors. As fertility is a main factor in the amount and distribution of people, endocrine disruptors (their quality and quantity) basically influence demography of people generally and regionally alike. Hormones do not affect cell functions without receptors which bind them and transmit the message, transported by the hormone. The receptors develop independently of hormones. These latters are produced by endocrine glands, while receptors are present in (on) any cells of the organism (glands included). However, The development and maturation of the two components are coordinated, and by this the normal (physiological) function is secured.

Physiological and Faulty Hormonal Imprinting

Perinatally (in the late fetal and early postnatal period) the developing receptor and its target hormone meet each other, and normal hormonal imprinting takes place, which determines the binding capacity of receptor for life [3]. Without imprinting the receptor-hormone complex cannot co-operate physiologically [4]. However, in the critical period of perinatal development the window for imprinting is open and not only the physiological target

molecules can be bound by the receptors but similar (related) molecules as well [5]. These molecules could be related members of the same hormone family, steroid-like molecules in food (baby formulas with soy components, phytoestrogens [6], molecules of air pollution (benzopyrene, dioxin), medicaments etc. [7]. These are endocrine disruptors, causing faulty hormonal imprinting, also with lifelong consequences [8].

This latters could be late-manifested diseases, or inclination to diseases (which requests a further provocateur for manifestation in adult age), or mild or strong alterations of hormone production etc. [9]. Many diseases of adult or senile age have the origin (DOHAD) in the defects of hormonal imprinting as cardinal or metabolic diseases, sexual, immune and bone deficiencies, psychiatric diseases etc. [10]. While large dose or repeated exposure by endocrine disruptors needed for the acute manifestation of alterations in adult age, the exposure to a minimal single dose of endocrine disruptors in the perinatal (late fetal, early postnatal) period can cause late-manifested problems in adult age. As there is a long distance between the disruptor exposure and disease manifestation, it is difficult to prove the connection. However, animal experiments help to justify them.

The faulty hormonal imprinting, caused by endocrine disruptors is inherited to the members of the given cell line as well, as to the progeny generations, without causing mutation. This means that it is an epigenetic phenomenon [5]. The methylation pattern of genes (DNA) is altered by it, determining gene expression in the given cells (organs), and this serves the late manifestation of the change as well, as the transmission to the offspring generations [5,11]. The strength of expression is also determined by the alteration of methylation. However, in man only up to the third generation was observed the inheritance because of the long change of generations, while in the unicellular model it was observed up to the 1000th generation [12].

Time-Dependence of Disruptor Effects

Morphological and Functional Teratogenicity

Endocrine disruptors can influence sexuality and sexuality can influence demography. If the endocrine disruptors impact in the very early (embryonal) period, malformations of the reproductive system are observed, as micropenis, hypospadias, cryptorchidism, which can be observed already at birth [13]. In the early perinatal (fetal) period functional teratogenicity [9] is observed, with late, adult consequences. However, in a presently unknown route, the sexual male/female ratio is also altered [14]. Earlier, in this ratio at birth males were preferred, more boys were born, than girls (1.06/1 ratio). At present the ratio is advantageous for girls [15,16]. The sex (gender) of man is dependent on the sexual chromosomes (X,Y) and spermatozoa contain X or Y sex chromosome, while ova always contain X. The chance of being fertilized by one of the spermatozoa is equal, so being for boys and girls is also equal. However, at present more girls are delivered in case of parents working in agricultural areas where pesticides or herbicides are sprayed as well as in factories, where plasticizers are used.

As the new gender ratio is valid since the time of the enhanced presence of man-made endocrine disruptors (first of all bisphenol A, a plasticizer, or paraben, used in cosmetics, as well as atrazine and vinclozolin (used in agronomy), the effect is imputed to them. In the late fetal period of development, the chance for direct, morphological teratogenicity decreases however, the chance for functional teratogenicity is growing. This means that the time of effects by endocrine disruptors is prolonged and partly translocated to the extrauterine period. While the destroying strength of a teratogen substance is modified and filtered by the mother's defense mechanisms, after birth these latters are disclosed and the effect evolves without them. In addition, such molecules became teratogen, which were not earlier in this category and also such diseases are believed the consequences of (functional) teratogenicity, which previously had not been listed among them.

As endocrine disruptors are mainly steroid hormone-like molecules, they bind to sexual-steroid receptors in any organs but first of all by reproductive organs, which have basic role in the formation of the population, chipping on the demography of a given population. As in this life period the sensitivity to endocrine disruptors is very high, it must be considered also the immaturity of degradation enzyme-system [17]. The above-mentioned facts show that there is a difference in the effects of endocrine disruptors, depending on the period of life, when the disruptors' effect and also in the life-period when their effects are manifested. There are outstanding (special) periods of human life, when the result of the perinatal effect (faulty imprinting) is especially manifested, and this also can be observed in puberty.

Special Problems of Puberty

Puberty (adolescence) starts in girls about between 8 and 12 years and in boys between 9 and 14 years, depending on races (individually inside) and its duration is about three years in girls and 4 years in boys. This is the situation at present. However, in the United States the mean start of puberty at 1860 was at 16.6-year-old girls, at 1920, 14.6, at 1950 13.1, at 1980 12.5, and at 2010 10.5 years [18]. Similar decreasing data was observed in boys, with the difference that one year later appear the signs. This means that a continuous decrease can be observed. However , the sign which is considered could be different. If the first menstruation (menarche) is considered as the start of puberty in girls, the difference in the start of puberty between the old and present times is only few months, while considering the breast development the difference is higher (about one year). In Afro-American girls the first signs of puberty one year earlier were observed than in white and Asian populations. In the earlier appearance of pubertal signs not only human-made substances have a role, but the progression of soy-food

consumption [19]. In addition, there are also some contradictory data, when endocrine disruptors prolonged the start of puberty in girls, while forwarded in boys, so the process is rather complicated.

Puberty is not a simple 3-4 years period of life, without further consequences, but a determining life-period, which has an impact on further life, consequently influencing further sexuality and demographical indexes. This period is rather sensitive to hormones which are present in the developing organism or entering from the environment in the form of endocrine disruptors. Faulty imprinting can develop, transforming or overwriting the effects of perinatal hormonal imprinting. So, the endocrine system and the endocrine-regulated organs and systems will not be the same, as they were before puberty, and this influences later sexual ability and intention for family planning. In addition, the earlier maturation of sexual system (without considering faulty imprinting) related to brain-maturation also could cause (sometimes criminal) problems. Puberty is not only a life-period when the results of faulty perinatal hormonal imprinting are manifested but also a sensitive period for non-perinatal imprinting.

In this phase of life, the developmental (critical) window for imprinting is open, as this is requested for the adaptation of later, adult life and this makes possible the effect of faulty imprinters with life-long and inheriting consequences. In this period faulty imprinters can transform the state suited perinatally, causing such alterations in the sexual system which are later influencing sexual behavior or demographical problems. This means that men's fertility and women's fecundity are touched by endocrine disruptor effects at puberty [20]. In animal experiments the effects of bisphenol A, which is one of the most effective endocrine disruptors influenced female's fertility, (reproductive capacity) by affecting the morphology, and function (estrus cyclicity, implantation and hormone secretion [21]). Dioxin (TCDD) reduced the Y chromosome containing sperms in mice (and less of the X containing spermatozoa (7). In human cases male reproductive diseases in pesticide-rich areas were observed [13]. Higher rates of miscarriages also occurred [22].

The endocrine disruptors -causing the problems- were phthalates, polychlorinated biphenyl, aromatic hydrocarbons, dioxins, alkylphenols and perfluorinated chemicals [23]. The pollution of human organism is rather widespread, for example in the South-Korean population most people are exposed to parabens [24]. If a pair was infertile, earlier always women were accused and studied, now first of all males are believed to be responsible. While the fecundity of women did not change during the passing time, the fertility of men was basically influenced [25]. The number and motility of spermatozoa decreased. Between 1940 and 1990 the mean amount of semen reduced with 18% in France and Scotland (in 50 years) however the number of spermatozoa in the seminal fluid decreased with 42% [26].

In Paris between 1973 and 1992 (in 20 years only) there was not difference in the amount of semen, but important differences were observed in the number and motility of spermatozoa [27]. The number of testicular cancers is increasing [26,27]. Whilst the fertility seemingly the problem of man at present, it is a common problem of the pair and also a demographical problem (about 10-15% of the population is infertile [28]) in economically developed countries). However, although male infertility is easier studied, female infertility in correlation with endocrine disruptors not to be neglected [29,30]. It can be manifested in improper hormone production, estrus and menstrual cycle abnormalities and early reproductive senescence, however endometriosis, breast cancer, ovarian misdevelopment is also not disclosed [31,32], as in some opinions the female reproductive system is particularly susceptible to the effects of endocrine disruptors. Mainly consumption of endocrine-disruptor contaminated water and food is responsible for the problem [33].

Role of Mother

In the womb, fetus is saved from external effects, and maternal (placental) defense mechanisms does not permit the entrance of strange, earlier unknown molecules into the fetus. However, these defense mechanisms had been developed during the evolution, recognizing such molecules which were present in earlier times, and the defense system was adapted to them. These molecules,(e.g., aromatic hydrocarbons, food phytoestrogens, mold toxins) are familiar to the evolutionarily formed defense tools and these are able to mostly neutralize them. However, the mass of new industrial, agrotechnical and medicinal molecules are unfamiliar, and the defense system is not able to easily recognize and decompose them, or new forms of them appear in the attacked organism by insufficient decomposition.

The yet incomplete maturity of the developing enzyme system also contributes to the problem. These complete or incomplete molecules permeate the placental barrier and are represented as endocrine disruptors in the time of openness of the critical developmental window for imprinting. A similar situation occurs in the case of lactating mother: breastmilk could be reach of hormone-like molecules (endocrine disruptors could be concentrated in mother-milk), which are also present in yellow-labelled 'artificial' nutriments of the baby (phytoestrogens: genistein or daidzein) or in cow system formula.

The Routes of Contamination by Endocrine Disruptors

The Communal Contamination

Without human contribution endocrine disruptors were and is present in the environment, as consequences of volcanic eruptions (in the air and water), biological waste products in waters, phytoestrogens and mycotoxins in foods, forest fires, etc., and as general side products of human presence, as heating, smoking,

traffic and transportation etc. However, there are specific areas of human activity which cause specific endocrine disruptor effects.

The Medicinal Contamination

Anticoncipient pills are synthetic hormones with the duty of inhibiting gravidity. During this (in general successful) action they are recognized and bound by steroid receptors of other -non-sexual- organs, disturbing these latter's normal function. In addition, if their targeted effect is not successful, the delivered infant had been falsely imprinted by strange (synthetic) steroid hormones, causing incalculable consequences, manifested in adult age. These synthetic estrogens and their waste products can enter into the urine and finally into the surface waters. However, not only anticoncipient are dangerous from this point of view, as there are other medicaments which have faulty imprinting effects [34,35]. Certain lipid soluble vitamins (first of all vitamins A and D) are not really vitamins, as they are bound by steroid hormone receptors, similar to steroid hormones. These molecules are exohormones, with endohormonal effects.

Vitamin A is not produced by the human organism at all, however it is very needed for a lot of life-important functions, though it is imported from outside. Vitamin D can be produced by men's largest endocrine organ, the skin under the effect of solarization, however the amount of it is insufficient north from the Equator [36]. Because of this fact, the absence of both yellow labelled hormonesare causing serious problems in a lot of organs, brain included [37,38]. The other known lipid soluble vitamins (vitamins E and K) also could be hormones however, the thorough study of them from this aspect not yet happened up to now [39-41]. In addition, there are other molecules in medicinal use, which also could have hormone-like effects (e.g. antihormones), which could be faulty imprinters, without lightly knowing their such effects at present. Outstandingly, oxytocin, which has an important role for starting delivery also is a faulty imprinter in animal experiments and its harmful effect (provoking autism or ADHD) is under discussion [42,43]. Many medical devices and packaging materials for tablets and solutions are made of plastics. This means that bisphenol A and other plasticizers could be come into the content and increases the multitude of disruptors.

The Food and Water Contamination

Soybean contain genistein and daidzein phthalates, which are strong faulty imprinters. Soy have a very important role in Asian cuisine since millennia, seemingly without any harmful effects and now it is propagated in the European and American cuisine. It seems to be unavoidable as it is present in many nutritive components: from bred to ice creams, from meats to dairy products. The absence of harmful effects in Asia does not mean that it is not responsible for the basically differences between the Asian and European populations, in mean blood tension, reproduction etc. Mycotoxins also could be faulty imprinters and they are present in many foods. However, not only phytoestrogens and mycotoxins can be effective, but food contact materials. Kitchen wessels and bottles as well as nursing bottles are made from plastics, so plasticizers can be solved into the foods [44].

This is contributed by the communal water, which arrives through plastic tubes and contains agricultural and medical waste products (originated from the pharmaceutical industry, hospitals and medicaments-using people (such as, partly degraded anticoncipients) as well, as plasticizers [45]. In the groundwaters as well as in the surface waters the organic contaminants (endocrine disruptors included) are emerging [46], and this is caused first of all by geotechnics, industrial wastes and pharmaceutical products [47-49]. The amount of synthetic estrogens entering to the adult human organism could be insignificant compared to the physiological production however, enough at the perinatal period for provoking faulty imprinting [50].

The Industrial Contamination

Environmental pollutants, as polychlorinated biphenyls, dioxins, polycyclic aromatic hydrocarbons, phthalates (bisphenol A), alkylphenols are used in and propagated by the industry and can be found in industrial waste waters, which is after thorough purification appear in surface waters and ground waters alike. Minute quantities of pollutants can be found in this water, which seems to be harmless for adults however, they are present in such amount, which can participate in faulty imprinting processes [51,52]. As millions of tons of plastics are produced in the world every year, phthalates in them can cause a lot of health problems (cardiovascular and reproductive included [53]).

Agricultural Contamination

Most of materials used in agrotechnics (herbicides, pesticides etc.) have steroid hormone-like structures (e.g. vinclozolin, atrazine, and can be bound by human steroid receptors [54-56]. People, who are working in agriculture can be touched by these disruptors. In addition, the sprayed materials are getting into the surface and ground waters, contaminating them.

Conclusion

Endocrine disruptors are seriously influencing human reproduction. As steroid hormone-like molecules, they are bound by sexual-steroid hormone receptors transmitting faulty messages in adults, provoking altered reactions from sterility to cancers. They are causing faulty hormonal imprinting in the perinatal period influenced by the placenta and lactation [57] and at puberty provoking far-exposing alterations (disturbances) in the endocrine system as well, as in the endocrine system-influenced organs . This could cause the appearance of certain known reproductive diseases in higher amount as well, as the appearance of up to now not known reproductive diseases in the future. Although endocrine disruptors attack the whole human organism, the sexual (reproductive) sphere is their main target, considering the general distribution of sexual-steroid receptors and their sensitivity to any endocrine disruptors.

At present only the shifting in gender ratio at birth and decrease in semen quality as well, as morphological teratogenicity can be observed as objective and direct signs of disruptor activity in the reproductive system, however its diseases in the frame of DOHAD can be deduced to faulty hormonal imprinting and without considering faulty hormonal imprinting, DOHAD cannot be explainable. There are also not exactly measurable demographical alterations however, these are expected as a consequence, in the future. Apart from the individual aspects, endocrine disruptors are causing burden and disease costs which have to be considered [58]. As faulty hormonal imprinting is an epigenetic process, its results are inherited to the offspring's. This means that the problems in the future will be accumulating [59] and together with social problems (e.g. deliveries in later parental ages) will cause demographic alterations in the economically developed populations. By this, the cultural evolution [60] basically influences the general (biological) evolution of man in a gradually broader and wider form [61].

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