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Impact of endocrine disruptors on sexuality: A pediatric aspect

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Abstract

Endocrine disruptors(EDs) can act and disturb the function of endocrine system during the whole life however, their impact is outstanding during childhood, as the effects in this period could lifelong influence different processes, mainly in the sexual area. The endocrine disruptors can directly influence the development of sexual organs, as teratogens, during the fetal life (cryptorchidism, hypospadias, micropenis), and late (pubertal, adult) sexual events as faulty imprinters (functional teratogens, when the exposure happens perinatally or later). The perinatal period is not the last, when endocrine disruptors can influence the development of sexuality as the system is very sensitive during adolescence and continuously dividing cells can also be imprinted during the whole life. Pubertal hormonal imprinting is also inherited to the progeny generations. The number and amount of EDs are extremely increasing and their importance as inducers of sexual alterations became outstanding. There is not drugs against them (many drugs are EDs themselves) only the information on them and on their effects can help to diminish the danger. It must not forget the DES-catastrophe, when mass vaginal cancers were recognized decades after the exposure to diethylstilbestrol and other serious alterations afterwards in both genders, and must know that EDs are DES-like molecules with very long-time effects.

Endocrine disruptors (EDs) are arteficial or natural molecules, which are similar to the steroid hormones or without this, can be bound by nuclear hormone receptors and are able to mimic or influence the effect of physiological hormones introduced to the human organism. These molecules are prepared (and used) by the industry (e.g. bisphenol A ,which is a component of all plastic objects, dental seals or cosmetics), or utilized by the agrotechnic (as pesticides, herbicides, fungicides etc), are produced by communal tools (e.g. benzpyrene, dioxin) or are present in plants (phytoestrogens, which are consumed by us). A special group of arteficial EDs are the drugs (medicaments) prepared for curing different diseases however, because of their chemical structure behave as EDs. The number and amount of EDs are extremely increasing and their effects are unavoidable in any time of life. However, the most sensitive periods of human life are the fetal, perinatal phases and early childhood, in which their effect influences physiological parameters for life. Because of this, in these periods the effect of EDs is different from the effect in adult age and deserves outstanding consideration.

EDs, being similar to steroid hormones can disturb the normal hormonal functions by binding to steroid hormone receptors, activating the response of the receptor-bearing cell. However, there is also a possibility to block the effect of physiological hormone, occupying its place on the receptor, without activating it. There is also a possibility of inhibition of receptor- or hormone-production. An ED can act on different receptors, provoking an extensive activation[1].

As it was mentioned, the number of EDs is enormous and impossible to study all of them. However, there are some groups which deserve special attention, and some members of them are studied supposing that other (realated) members of the group have similar effects. So bisphenol A (BPA) represents phtalates and phenols, DDT is a representative of pesticides, dioxin and benzpyrene as pollutants of the air, genistein and daidzein as representatives of phytoestrogens and diethylstilbestrol (DES) and vitamin D as representatives of drugs.

Selection of data on prenatal (fetal) ED- effects

The endocrine disruptors are mostly steroid hormone-like molecules , so they can act as steroid hormones. This means that they are able to disturb the normal development, where hormonal effects are the provocator or influencer of the process. Considering the sexual development they can not influence the determination of sex, as it is done by genes however, the sex ratio between male and female newborns is influenced by them. The normal (male/female) sex ratio in man is 106/100 at birth with the adventage of boys and it was observed in case of an industrial ED, dioxin, that this shifted the adventage to girls in the children of male workers of insecticide factories, without touching female workers [2,3] . The explanation of this phenomenon is unknown presently.

There are such malformations, the manifestation of which are strongly influenced by EDs. These are the cryptorchidism, the hypospadias and the length of the penis. The first two common genital birth defects affect 2-9% or 02-1 % of the male human newborns [4-8]. Measuring the presence of bisphenol A (BPA) and propyl-parabene in the human placenta,, significant association was found between them and the presence of hypospadias and cryptorchidism [9]. Phtalates in general have an outstanding role in the change of semen quality and fertility rates [10]. They are participating as causal factors in the decrease of sperm count[11]. 92% of newborns with cryptorchidism, hypospadias and/or micropenis presented fetal contamination with EDs (DDT) and their mother (80.36%) and father (58,63%) were involved in works with EDs [12].

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The fungicid vinclozolin inhibit fetal testosterone production and demasculinizes male mice [13]. Phytoestrogens, as genistein causes hypospadias, by altering the expression of genes which are participating in the pathways of morphogenesis [14]. The dietary phytoestrogens (genistein, daidzein) can be demonstrated in 96.2 % of human amniotic fluid tested in the second trimester [15]. Increased serum bioactivity was also demonstrated in case of male pseudohermaphroditism where the mother was exposed to EDs during pregnacy [16]. Coumestrol (a fungal phytoestrogen) and equol (a metabolite of phytoestrogens) also have deleterious effect on gonadal development [17].The effects to gonadal development during the fetal life are transmitted to the progeny generations, epigenetically [18,19].

Perinatal effects

As long, as the fetus is living in the womb, mostly maternal hormones are regulating its life functions. From this point of view birth is a milestone of the life, as after it the hormones produced by the infant command the life functions , accepting the signals and directing the responses. For this process the setting of receptor-hormone coupling is needed which does happen in case of the first encounter between the developing receptor and the infant's hormones. This provokes the physiological hormonal imprinting, which is absolutely needed for the normal function of receptor-hormone connection. This connection which is established by the imprinting is long-lasting and determines the binding capacity of receptor for life [20,21]. However, though the binding of receptor is almost specific for the hormone, perinatally it can be misdirected by hormone analogons [22], related or synthetic hormones, members of a hormone family , hormone-like vitamins [23,24], drugs, or environmental pollutants, as the endocrine disruptors. This leads to faulty hormonal imprinting, the effect of which is also prolonged for life and could cause differences in hormone binding and sexual hormone levels [25], consequently inclination to diseases or manifest diseases (e.g. tumours). As sexual functions are also dependent on hormones, faulty perinatal hormonal imprinting can cause different alterations in sexual behavior [26], in fertility etc. This means that the perinatal effect causes late manifestation as was in the case of diethylstilbestrol (DES), (it is worth mentioning that DES was prescribed for avoiding spontaneous abortions in case of endangered pregnancies, but later without prescription for more beautiful babies) when decades were passed between the exposition (of the drug) and the manifestation of diseases (clear cell vaginal carcinoma, behavioral sexual differences, etc)[27] . A special property of perinatal imprinting is the low dose of imprinter and the short exposition: only a single dose of imprinter is enough for the provocation of imprinting. An other very important property is the heritabilty of imprinting [28] by an epigenetic route [29]. While in the case of fetal ED exposures the interrelation between the long lasting exposure and anatomical malformation in men is clear, in the case of hormonal imprinting in men the interrelation between the single encounter between the receptor and the faulty imprinter hardly justifiable. Considering this, there are only animal experiments which justifies the hormonal imprinting, except the DES-case however, in the time of DES-catastrophe the concept of hormonal imprinting was not known, consequently the explanation of it by imprinting is subsequent.

The polycyclic hydrocarbon, benzpyrene is present in different concentrations in the air, polluting first of all the urban air. It is a very important and hardly avoidable endocrine disruptor, acting to human beings from birth to death. The perinatal exposure in rat experiments caused a profound increase in sexual activity of male rats, while that of females a dramatic decrease was observed [30]. The binding capacity of uterine estrogen receptors were also significantly decreased [31]. The effect of imprinting was transmitted to the progenies [32].

One of the most dangerous EDs, is bisphenol A (BPA). In male rats a depotentiation of sexual behavior was observed after perinatal exposure, while in females a potentiation [33]. Studying two sexually dimorphic regions of the brain the faulty imprinting with BPA altered sex-specific hypothalamic morphology [34,35]. Phtalate/adipate esters caused decreased copulatory behavior in males and also decreased lordosis quotient [36]. The demasculinization of males was outstanding.

Vinclozolin administered perinatally reduced erections of adult male rabbits [37,38]. The faulty imprinting effect of this fungicide was manifested transgenerationally when male infertility was also observed [40].The phytoestrogen, genistein given perinatally negatively influenced sperm and testosterone production and aggressivity decreased while defensive reactions increased in adult age [41]. Genistein also increases female and male rat's sexual activity [42]. Daidzein, an other soy isoflavone adversely affected penile erection in adulthood [43].

Lipid-soluble vitamins, as vitamin A and Vitamin D are not vitamins, but hormones (exohormones) which are bound by the members of nuclear hormone recepor family and can activate them [44]. Sexual activity of adult rats treated neonatally with vitamin A or D3 [45,46], as well, as with vitamins E and K , were depressed or completely inhibited in adult age [47,48]

Impact of endocrine disruptors on the onset of puberty (selection of data)

The time of puberty which is showed by menarche and thelarche in girls and penil erection and ejaculation in boys is determined by the individual endocrine system however, it has a mean which can be calculated. This mean (the secular trend of European and American youth) is becaming earlier related to the last centuries (96). The precocious puberty is more frequent and the change is supposed to be due of steroid- hormone like compounds in the human environment, in foods and waters [49-60].

The urinary BPA levels in girls having central precocious puberty (CPP) was higher than normal [61-63], and serum BPA concentration was also higher in girls with thelarche, aged 4 month to 2 year [64]. Peripheral precocious puberty was observed in 4-month-old girl,(whose father had a dramatic decrease of libido) and pesticides were found in the serum [65]. The serum genistein and daidzein concentrations were also higher in Korean girls having precocious puberty [66]. In premature breast development (thelarche, younger than 8 years) phtalate esters were higher in the serum [67,68]. The incidence of precocious puberty of children migrating into Belgium is higher with relation to their plasma level of DDT [69]. Different EDs and isoflavones were higher in the plasma of precocious puberty patients [70].

Higher serum testosterone concentrations were associated with higher phtalate and BPA concentrations in maternal urine during different phases of pregnacy [71].

Data on the effects during puberty

Tamoxifen treatment for 5+2 days at adolescent age dramatically reduced the sexual activity of rats (from 40 to 10 % immediately after treatments and 4-6 weeks after treatments [72]. Adolescent rats (sixth and sevent weeks after birth) were treated with retinol or retinoic acid, and serum testosterone and progesterone levels were measured in the

4th month. Retinol diminished testosterone level and was neutral to progesterone level. Retinoic acid decreased testosterone level and elevated progesterone level [73]. Pubertal benzpyrene imprinting caused a durable decrease in females' estrogen receptor density [74]. The effect of pubertal imprinting is inherited to the progeny generations epigenetically [74,75] similar to the inheritance of perinatal hormonal imprinting [76].

Conclusions

The above mentoned data clearly show that the endocrine disruptors strongly influence the sexuality in man and in animal experiments. There is a possibility of direct effects, when the hormonal exposure is teratogenic (if it is during the fetal life), which is manifested first of all in cryptorchidism or hypospadias or micropenis however an other possibility is the late effect, when the perinatal exposure (faulty hormonal impinting) does not provoke malformation however, later, during adolescence or in adult age pathological alterations appear, as early onset of puberty, obesity or changes in sexual capacity and behavior (functional teratogenicity). These alterations also can be observed in the progeny generations, which means that the effect of imprinting is inherited. In this case the inheritance does not mean a regular change of genetic material, but an inheritance by epigenetic route, which means the alteration in the expression of genes by the change of methylation of DNA or histones, which influences gene expression . Endocrine disruptors, as hormone-like materials are not neutral introduced into adults however, childhood exposure has deeper and wider effect as such structures are touched which are able to be transformed or are able to influence other structures. This means that childhood exposures to endocrine disruptors deserves outstanding attention. and not only the acute effects can be observed but also the presumable or not foreseeble, but possible consequences are taking into consideration. In the evaluation maternal and paternal transmission of ED contamination must be discriminated, as paternal risk factors are more transmissible [76].

There are such EDs, which are known and can be avoided and there are others, which are hidden in the air, the drinking water or food etc. Medicaments, as was the DES or are at present, as vitamin A or D, the fat soluble vitamins which are hormones really[44] , can be avoided. Can not be avoided benzpyrene or dioxin in the urban air, pesticides, herbicides, insecticides or contraceptive pill wast products in drinking water. And which are hardly avoidable are the phytoestrogens, components of soy (genistein and daidzein), which are present in clear or hidden forms in our food (soy formula as baby food, sausages, ice cream etc) which are consumed sometimes in extreme amount during childhood or by the nursing mother. Which can not be avoided it must be accepted however, we have to know that these molecules can be responsible for sexual alterations, inclination or manifestation of different diseases during late childhood and adult age.

Soy bean isofalvones are the most suspected EDs in the provocation of early onset of puberty [77]. Soy is used in different forms as food in Asian countries where the onset of puberty (menarche, thelarche) is different from that of European countries. However, in the last century soy foods are more frequently used in Europe and in the US than it was before, even than in Asian countries. Though they have some beneficial effects, their adverse effects could be dominant [78]. This alone would be enough for the increase of the number of precocious puberties. However, this is supplemented by the enormous amount of industrial and communal EDs. Precocious puberty used to be associated with other alterations, as e.g. malignant tumours, sexual disturbances, etc. This means that the manifestation of precocious puberty is a part of the general provocation of developmental potencies by the ED.

The long-lasting effect of EDs is not finished perinatally as there are periods of life, when the sensitivity to endogeneous or exogeneous imprinters –such as EDs- is also high. Adolescence is the main late period and as it was shown , in this period hormone-like factors can seriously influence sexuality for life at brain level, as well as in the level of sexual hormone receptors in general .

It seems to be very interesting and important the epigenetic inheritance of pubertal imprinting. It can be explained by the fact that during adolescence continously dividing (differentiating) cells can be imprinted and the male germ cells (spermatogonia) are also dividing.

Childhood obesity is very frequent in the countries where ED exposure is also frequent during childhood. The interrelation between the obesity and EDs seems to be clear [79-82] however, other factors (e.g. hyperfeeding) also can not be disclosed. Obesity is a part of the metabolic syndrome however, the interrelation between EDs and this latter is not completely cleared, but EDs are suspected in the dramatic increase of type 2 diabetes , especially in childhood [83-85].

The data mentioned above clearly show that the effect of endocrine disruptors is wide and very important areas are touched by them. The situation is aggravated by the cooperation of disruptor effects and by the transgenerational inheritance of inclinations caused by malformation (cryptorchidism etc) provoking fetal effects or functional teratogen faulty perinatal hormonal imprinting [74,86,87]. The cooperation can be resulted in such forms of diseases which can not be classified to the traditional ones and complicated by the long time between the disruptor exposure (in different periods of life by different cooperating chemicals) and the manifestation of disease, which hides the connection. The inheritance not only disturbs the health of the next generations but the disruptors of the future will effect on individuals sensitized to endocrine disruptors of the present time.

In the case of DES about two decades passed when the alterations of the sexual area appeared and the relation between the vaginal cancer and DES on the basis of fetal/perinatal exposure has been cleared. In the case of endocrine disruptors the recognition of interrelations will be more complicated, as not one substance can be suspected, but numerous molecules with different origin [88]. There is no time to pass without doing something against their effects.

There are not antidotes to endocrine disruptors. However, many of them can be avoided, and doctors must attend to not prescribe them, if they can be avoided. In addition it must call the parents' attention to the dangers of EDs, which is unknown by them, and hormone-like vitamins and soy foods can be bought without prescription . The first step in this fight against EDs is the convincing of medical doctors (the author hopes that it is done by this review), who try to avoid the prescription of EDs and transmit the informations to the parents after that.

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