

Lifelong Impact of Perinatal Endocrine Disruptor Exposures (Faulty Hormonal Imprinting)

Gyorgy Csaba*

Department of Genetics, Cell and Immunobiology, Semmelweis University, Hungary

Abstract

Perinatal hormonal imprinting is taking place when the developing hormone receptors meet the target hormone at first occasion. This is needed for the normal function of receptor-hormone complex and valid for life. However, when the developmental window is open, related molecules, as endocrine disruptors also can be bound, causing life-long distortion (faulty hormonal imprinting) which could be manifested as diseases in any period of life (adult age), even it is transgenerationally inherited by an epigenetic route. The nervous system, sexuality and immune system are touched first of all however, some alteration can be observed in the whole human organism. At present most of the well-known endocrine disruptors are man-made steroid hormone-like molecules, utilized in the industry, agrotechnics and medical treatments. The effect of endocrine disruptor molecules seems to be noxious in any period of life however, most deleterious perinatally, causing late manifested faulty imprinting. Nevertheless, faulty imprinting can be provoked also later, at weaning, at adolescence and in continuously differentiating cells in the whole life, with less decisive however important consequences. The recognition of faulty hormonal imprinting changed our picture on teratogenesis, as a mass of functional teratogens appeared in the form of endocrine disruptors, and the period of teratogenicity has been prolonged over birth. The industrial, communal or agrotechnical endocrine disruptors are very difficultly avoided however, medical disruptors (hormones, lipid-soluble vitamins etc.) must be observed and omitted in the critical periods. The hereditary transmission of faulty hormonal imprinting seems to be dangerous for the future of mankind, although positive effects by the adaptation of endocrine system to the present and future circumstances can be imagined.

Keywords: Hormones; Functional teratogenicity; Critical developmental periods; Epigenetics; Early development; Diseases; Sexuality; Immunity

Introduction

During early human development the sensitivity to harmful molecules is dependent on the time of exposure. In the period of embryonal development (first three months in man) under the effect of teratogens malformations are manifested, which can be observed and recognized at birth. Near to the zygote stage the teratogenic effect could be so grave that the embryo dies, while in the late embryonic stages systematic malformations are produced [1]. In the fetal period the malformations are not systematic however, they are restricted to one certain organ and in late fetal period as well, as in the early postnatal period functional teratogenicity can be observed, which means that the alteration is not appreciable at birth however, it is manifested as a disease in adult age. During the development of the endocrine system receptors and hormones developed independently of each other, in different organs or cells however, they must be tuned for the normal function of the system. This tuning was named by us perinatal hormonal imprinting, which is absolutely needed for the later (adult) normal endocrine functions [2]. However, in this critical developmental period of the endocrine system the developing receptors are rather sensitive to some alterations of the organism or to certain hormone-like materials which are introduced into the

organism, the actions of which can cause faulty hormonal imprinting [3-5]. The impact of normal (physiological) imprinting, as well, as the faulty imprinting is lifelong. However, while the physiological hormonal imprinting is necessary, in case of faulty imprinting such pathological alterations are provoked, which are manifested later in adult age, in the immune and nervous systems, in the skeletal system, in sexuality, and in any organs of the organism [6-14]. In addition, though faulty imprinting does not influence the base sequence of genes (not mutagenic) as it is an epigenetic process, there is a hereditary transmission of it, consequently its effects are manifested in the progeny -at present justified -up to the third generation [5,15,16]. Faulty imprinter could be the physiological hormone in a higher dose, or members of the same hormone family, but in our present time the most likely faulty imprinters are the endocrine disruptors, which can be bound by the hormone receptors in each period of life with pathological consequences however, their presence is the most dangerous in the developmentally critical periods of life, outstandingly at the perinatal period [17-22]. This is proved in many selected observations and experiments.

Selected Facts

Reproduction and sexual behavior

Malformations caused by endocrine disruptors: These malformations are less conspicuous, and sometimes has to be sought. These are the cryptorchidism, hypospadias and micropenis as well as (in case of animal observations) the differences in anogenital distance, time of vaginal opening, number of nipples, preputial separation and nipple-like areoles of males [23]. In an area of Brazil where pesticides were intensively used 2710 male newborns were explored for cryptorchidism, hypospadias and micropenis. The 80% of mothers and 59% of fathers reported such works which was in connection with the use of pesticides [24]. Penile length in Egyptian male newborns at birth was found 34 mm. Micropenis (less than 25

Citation: Csaba G. Lifelong Impact of Perinatal Endocrine Disruptor Exposures (Faulty Hormonal Imprinting). *Ann Genet Genom.* 2019; 1(1): 1003.

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Publisher Name: Medtext Publications LLC

Manuscript compiled: June 26th, 2019

***Corresponding author:** Gyorgy Csaba, Department of Genetics, Cell and Immunobiology, Semmelweis University, Budapest, Hungary, E-mail: csaba.gyorgy@med.semmelweis-univ.hu

mm) and hypospadias were found in 1.8% of cases, which had a linear relationship with free testosterone level in the blood [25]. In France (Andalusia) (studying 45.000 pathological and 950.000 normal cases), hypospadias, cryptorchidism and micropenis was significantly higher in the areas, where higher uses of pesticides was employed [26]. In a French study (529 families) demonstrated the hereditary effect of DES exposure to hypospadias [27]. Prenatal exposure to diethylstilbestrol (DES) or pesticides increased the number of cryptorchidism [28]. A literature-search pointed to the role of endocrine disruptors in the worldwide increase of hypospadias [29].

Functional alterations: Environmental xenoestrogens (herbicides, pesticides, polychlorinated biphenils, etc.) and antiandrogens disturbed male sexual differentiation. In the last decades the amount and quality of human sperm decreased and the incidence of male genital defects, testicular, prostate and breast cancer has increased. Endocrine disruption can be responsible for these problems [30,31]. Perinatal exposure to bisphenol A (BPA) negatively impact both male and female reproduction [32]. In other experiments perinatal administration of it inhibits the sexual behavior of male rats, while for females it was indifferent [33]. Fipronil, an insecticide in case of perinatal exposure provoked shorter estrus cycle and reduced number of cycles in rats [34]. Polychlorinated biphenils (PCBs) given in late pregnancy of rats skewed the sex ratio toward females and caused dysregulation of reproductive physiology [35]. Increase of postimplantation loss and a decrease in litter size as well as decrease of sperm count and motility were observed after BPA exposure perinatally [36]. Advancement of reproductive senescence is caused by perinatal exposure to methoxychlor of rats [37]. However, it is also provoked by the exposure of mixtures of endocrine disrupting chemicals, as phthalates, pesticides, uv-filters, BPA, butylparaben and paracetamol [38]. Human infertility is caused by endocrine disruptors in general [39]. Neonatal inhalatory exposure of endocrine disruptor influences the fertility and sexual behavior of male rats. The transgenerational passage of sexual alterations by endocrine disruptors can be observed [40,41]. Perinatal exposure to BPA modulates the hypothalamic-pituitary-testis axis of the progeny generations [42]. Dramatically disrupts ovarian and reproductive functions in females which could participate in the induction of polycystic ovary syndrome [43]. Perinatal BPA treatment by the route of breastfeeding caused lower expression of androgen receptors of growing follicles, which shows that folliculogenesis is a target of BPA in the ovary [44]. Secular trends towards earlier puberty is observed worldwide, and endocrine disruptor effects are surmized in it [45]. Mate preference is influenced by transgenerational epigenetic imprinting of endocrine disruptors [46].

Metabolic syndrome and obesity

Perinatal exposure to BPA have a dose- and sex-dependent effect on body weight of adult rodents. In addition BPA has effect on adipocyte differentiation, lipid accumulation and adiponectin secretion in *in vitro* experiments [47]. Diethylstilbestrol (DES) which is known by its carcinogenic effect in young women, increases the incidence of obesity in a sex-dependent manner and can act as a potential chemical stressor for obesity and obesity related disorders [48]. Endocrine disruptors employed during the critical phases of development can be responsible for the increasing number of obesity and metabolic syndrome. Perinatal BPA exposure could play a role in the increased risk of diabetes and obesity.

Nervous system and behavior

Soy phytoestrogen, genistein in the diet of rats during lactation impaired spatial learning of male offspring. In other experiments perinatal exposure to low-dose BPA specifically impaired spatial learning and memory in male offspring. Sexual behavior was also touched. Perinatal BPA exposure also perturbs the basal and stress-induced activity of Hypothalamic-Pituitary Axis (HPA) in a sexually dimorphic manner at adolescence [49-52]. Organochlorine pesticides in case of infant exposure causes learning disabilities, low intelligence quotient, attention deficit and hyperactivity [53]. The role of BPA is suspected in case of Autism Spectrum Disorder (ASD) as BPA is not metabolized well in children with ASD and decreased serotonin transporter and serotonin receptor binding have been reported in case of autism [54]. Perinatal administration of BPA causes instability, nervousness, twitching of head, agitation, reduction of food intake, and reduction of body weight also could be observed [55]. DNA methylation and sex steroid hormone receptor expression is reprogrammed by endocrine disruptors [56].

Immunity

Perinatal exposure to BPA weakens protective and regulatory immune functions in the intestine and at systemic level in adult offspring. An increased susceptibility to inflammatory response is observed [57]. Perinatal phytoestrogen (genistein) exposure seriously influences immune cells [58].

Other systems

Faulty imprinting by different endocrine disruptors cause pathological development of the bones, which could be responsible for later osteoporotic fractures [59]. Perinatal exposure to BPA causes hepatic tumors in adult mice [60]. Neoplastic transformation of prostate is also observed [61-63]. Perinatal exposure to lipid soluble vitamins (A,D,E,K) provokes faulty imprinting and consequently altered receptor binding, altered sexuality, and brain function, immunity, which is epigenetically inherited to the progeny generations [64,65]. Transmaternal BPA exposure in utero and during lactation accelerated the manifestation of type 1 diabetes in mice [66].

Discussion

The facts selected from the mass of literature unanimously demonstrate the profound and compromise effect of faulty hormonal imprinting caused by endocrine disruptors [67]. The selection is arbitrary and can be absolutely concluded, that all systems and organs of the human organism are touched. However, it is not accidental that reproductive and sexual alterations are dominated in the list, as most of the endocrine disruptor molecules have steroid character, consequently sexual steroid hormone receptors are influenced principally. However, most of the cells of the organism have steroid receptors or their overlapping receptors (immune cells, HPA-cells, adipose cells etc.), so endocrine disruptors expose a general effect and the selection into Facts is indeed, peremptory. The endocrine disruptors' interaction with the developing steroid receptor is taking place during the development of the target system, and the realization of its effect is late, in the adult age, so the verification of their interrelation is difficult. Considering this fact, in human cases mainly the most conspicuous alterations are observed and registered, while alterations in the less important organs or systems are remaining hidden. In addition some alterations can be measured easily, others not or not at all [68]. Nevertheless, the presence of the most popular endocrine disruptors in the list of more systems mentioned points to

the probability of general effects, and call attention to the broadening of the list of the medically important endocrine disruptor effects in the near future. There are some signs that many neurological (behavioral) disease with growing presence in the today's population (autism spectrum disorder, ADHD) can be deduced to the perinatal hormonal imprinting by steroid-like endocrine disruptors. The revival of the medical approach, which is characteristic to our age requests the change of medical classification. Obesity, for example in earlier time was a sign of social welfare, presently a dangerous disease, part of the metabolic syndrome, which is also listed as endocrine disruptor-connected condition. Similarly, other conditions also will be changed and endocrine disruptors will be found as their reasons [69]. However, it is not sure, that always presently known disruptors will be found as responsive, because of the appearance of new endocrine disruptors sometimes having non-steroid structures. As faulty hormonal imprinting is an epigenetic process, its hereditary transmission to the given cell line and to progeny of the individuum, comes natural to us. However, this epigenetic transgenerational inheritance could cause dangerous problems, as next-generation interactions between the altered expression of genes in the further generations and new disruptors (imprinters) could cause such alterations which are not to be seen at present. Together with the growing amount and growing variations of endocrine disruptors increases the importance of faulty hormonal imprinting and this is dreadful [70-74]. However, positive process is also imaginable. Namely, in earlier ages there were not tools and intentions to measure the effects of natural endocrine disruptors (aromatic hydrocarbons, as benzopyrene or dioxin, phytoestrogens etc.) on the alteration of endocrine system and its influences, consequently it is not known what were the effects of them to the formation of the at present known endocrine system. So, this could have been a driving force in the shaping of the present endocrine system [75,76]. Considering this as a forming factor, it can be imagined that the present day endocrine disruptors are and will be the driving force to develop the present day human organism, which will be the most suitable for living in the future. However, doctors of present time have to cope with the dangers of our age and the optimistic idea is only some salvation for the medical soul [77-79]. It is obvious, that doctors - working in the prophylaxis or treatment of diseases - have the duty to fight against the proliferation of endocrine disruptors however, at present this is hopeless, as impossible to avoid them. Considering this pessimistic prognostication, the importance of the understanding of hormonal imprinting seems to be growing and this is manifested in the intensifying interest to DOHaD and other theories. The Thalidomid catastrophe in the sixties of the last century learned the medicine-oriented mankind to test the possible morphological teratogens and the DES-catastrophe did the same in case of functional teratogens [80]. Nevertheless, the employment of the teratogens did not stop in general, at most the use of the factual transgressors had been expelled. At present the bet is larger: not concrete (single) substance threatens the people, but a broad spectrum of materials (endocrine disruptors), which are favoured by the whole industry, agrotechnics, medical therapy, consequently the personal well being of people. This means that the personal comfort is confronted with the personal vulnerability. In addition, the money-hungrying of industry drives also the production of endocrine disrupting chemicals, so the decrease of their use can not be expected. The human evolution have been conveyed to the men-made equipments (tools) and new (more developed) products are prepared for the well-being of mankind by the utilization of tools. Some of

these products or materials for producing the tools (e.g. bisphenol A in plastic industry or vinclozoline and atrazine in agrotechnics), are the endocrine disruptors. Considering human evolution and the claim for prosperously living, these can not be avoided. This means that a durable coexistence between the endocrine disruptors and man must be tolerated. This has to be considered, and the medical mentality has to be adapted to it [81]. It seems to be likely, that more diseases can be deduced to the effects of endocrine disruptors than were discovered up to now. There are many cases which is suspected presently, the growing number of which is characteristic to our modern age and the reason of which is not recognized. These are first of all diseases of the nervous system (e.g. autism spectrum disorders, ADHD), the intestine (e.g. irritable bowel disease) and the immune system (e.g. autoimmune disorders). In a lot of these cases the endocrine disruptor can not be the cause of the disease, but it is the provocator, by which the number of these diseases are growing, as the perinatal exposure by them incline the manifestation and inhibit the normal (physiological) defense against them. In the study of endocrine disruptor effects the direct effects (to the adult organism) are in the frontline. The study of late-manifested effect, by perinatal exposure can be difficultly studied, as the interdependence between the perinatal exposure and the manifested disease is hard-provable, as long time used to be passed between them. However, while the direct effect can be more easily treated and valid for one occasion, the perinatal effect is valid for life and its treatment is uncertain. In addition, the perinatal hormonal imprinting's attack to the mentioned systems (especially the immune and nervous system) could set a chain of actions of other systems and organs, the prime mover is hardly recognizable. Although the most important period of faulty hormonal imprinting is the perinatal one, there are other periods of mammalian (human) life, when the developmental window for faulty hormonal imprinting is open. This are the weaning, the adolescence and in case of continuously differentiating (dividing) cells (e.g. in the bone marrow), the whole life [82-84]. This means that faulty hormonal imprinting can be provoked later in the life, and the effects are also durable. However, the main (deciding) imprinting is done perinatally, the later imprintings can modify their effects. Nevertheless, the later faulty imprintings also have to be seriously considered, especially in case of medicaments' prescription (e.g. anticoncipients, vitamins A or D), in the mentioned periods.

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