INTERNATIONAL JOURNAL OF PLANT, ANIMAL AND ENVIRONMENTAL SCIENCES
IJPAES
Volume-9, Issue-2 April-June-2019 Coden:IJPAJX-CAS-USA, Copyrights@2018 ISSN-2231-4490
Received: 24th Feb-2019 Revised: 25th Mar-2019 Accepted: 26th Mar-2019
DOI: 10.21276/Ijpaes http://dx.doi.org/10.21276/ijpaes Research Article

LIFELONG IMPACT OF PERINATAL ENDOCRINE DISRUPTOR EXPOSURES (FAULTY HORMONAL MPRINTING).

Csaba G

Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, 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 continously 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 transformation of endocrine system to the present and future circumstances can be imagined.
Key words: hormones, functional teratogenicity, critical developmental periods, epigenetics, early development, diseases, sexuality, immunity

*Corresponding autor: Csaba G, Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary

INTRODUCTION

During early human development the sensitivity to harmful molecules is dependent onthe 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 developingreceptors 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 [6], in the immune [7,8]and nervous [9-11] systems, in the skeletal system [12], in sexuality [13,14], and in any organs of the organism [6]. In addition, though faulty imprinting does not influence the base sequence of genes (not mutagenic) as it is an epigenetic process [5], there is a hereditary transmission of it, consequently its effects are manifested in the progeny-at present justified -up to the third generation [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 seeked. 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. 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 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 diethylstilbestrol(DES) exposure to hypospadias [27]. Prenatal exposure to DES or pesticides increased the number of cryptorchidism [28]. A literature-search pointed tothe 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 exosure 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 insecticid 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 phtalates, 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], and dramatically disrupts ovarian and reproductive functions in females [43] which could participate in the induction of polycystic ovary syndrome.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 .

Endocrine disruptors employed during the critical phases of development can be responsible for the increasing number of obesity and metabolic syndrome [48].

Nervous system and behavior

Soy phytoestrogen,genistein in the diet of rats during lactation impaired spatial learning of male offspring [49]. In other experiments [50] perinatal exposure to low-dose bisphenol A(BPA) specifically impaired spatial learning and memory in male offspring. Sexual behavior was also touched [51]. Perinatal BPA exposure also perturbs the basal and stress-induced activity of hypothalamic-pituitary axis(HPA) in a sexually dimorphic manner at adolescence [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 disordesr (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 transformationin 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, and epigenetically inherited tothe progeny generations [64,65].

Transmaternal BPA exposure in utero andduring 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. The selection is arbitrary and can be absolutely concluded, that all systems and organs of the human organism are included. 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 hormones and receptors are influenced principally[67]. 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 effectand 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, 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 notor not at all. 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 tothe 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. However, it is not sure, that presently known disruptors will be found as responsible, because of the appearence of new endocrine disruptors sometimes having non-steroid structures.

As faulty hormonal imprinting is an epigenetic process, its hereditary transmission tothe 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. However, positive process is also imaginable[68,69]. Namely, in earlier ages there were not tools and intentions to measure the effects of natural endocrine disruptors (aromatic hydrocarbons, as benzpyrene or dioxin, phytoestrogens, mycoestrogens etc[70]onthe alteration of endocrine system and its infuences, consequently it is not known what were the effects of them tothe formation of the at present known endocrine system[68,69]. So, this could be a driving force in the shaping of the present endocrine system. Considering this, as a forming factor, it can be imagined that the present dayendocrine disruptors are and will be the driving force to develop that 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 could be only some salvation for the medical soul.

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, asimpossible to avoid them. Considering this pessimistic prognostication, the importance of the understanding of faulty hormonal imprinting seems to be growing and this is manifested in the intensifying interest to DOHaD[71] and other theories. The Thalidomid catastrophe[72] in the sixties of the last century learned the medicine-oriented mankind to test the possible morphological teratogens and the DES-catastrophe[73] did the same in case of functional teratogens. 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) substances threaten 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 usecan 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[74]. Some of these products or materials for producing the tools (e.g. bisphenol A in plastic industry or vinclozoline and atrazine in agrotechnics), are 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 manmust be tolerated. This has to be considered, and the medical mentality has to be adapted to it.

It seems to be likely, that more diseases can be deduced to the effects of endocrine disruptors than have been 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. [77]These are first of all diseases of the nervous system (e.g.autism spectrum disorders, ADHD)[75,76], the intestine (e.g.irritable bowel disease) and the immune system (e.g.autoimmune disorders), however, other systems are also not exceptions [77]. In a lot of these cases the endocrine disruptor is not the cause of the disease, butit is the provocator[78], 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 at present the direct effects (tothe 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 isvalid 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. The recognition of functional teratogenesis[79-82] demands more attention, than the morphological one, which is easily observable at birth.

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 imprinting is open. This are the weaning, the adolescence and in case of continuously differentiating (dividing) cells (e.g. in the bone marrow, or any stem-cells), the whole life. This means that faulty hormonal imprinting can be provoked later in the life, and the effects are also durable. However, the main (decising) 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) [83,84], in the mentioned periods.

There are enormous amount of chemicals in use and about 1000 were identified as endocrine disruptor [84]. A lot of them harms male and female fertility, causing personal and demographical (social) problems [85,86]. These problemes are present already now, and in all probability will be more serious in the future.

Special attention have to be dedicated to the epigenetic heredity of imprinting, as the recognition of interrelations between the provokator and manifestation is more difficult. In the case of the diethylstilbestrol disaster already the third generation can be studied, and neonatal mortality is eight times higher among DES grandchildren and there is more frequent the hypospadias in grandsons. The interrelation is easily observed in these cases [87]. However,though DES offspring are in the front of interest, there are not observations onthe solely functional alterations up to now. Neverteheless, animal (rat) experiments point tothe interrelations in case of lipid soluble vitamins (A and D)[88].

REFERENCES

[1]. Finnell, R.H.: Teratology: General considerations and principles. J Allergy Clin Immunol 1999, 103, S337-S342.

[2]. Csaba, G.: Phylogeny and ontogeny of hormone receptors: the selection theory of receptor formation and hormonal imprinting. Biol Rev Camb Philos Soc 1980, 55, 47-63.

[3]. Csaba, G.: The present state in the phylogeny and ontogeny of hormone receptors. Horm Metab Res 1984, 16, 329-335.

[4]. Csaba, G.: Hormonal imprinting: its role during the evolution and development of hormones and receptors. Cell Biol Int 2000, 24, 407-414.

[5]. Csaba, G.: The biological basis and clinical significance of hormonal imprinting, an epigenetic process. Clin Epigenetics 2011, 2, 187-196.

[6]. Csaba, G.: The faulty perinatal hormonal imprinting as functional teratogen. Curr Pediatr Rev 2016, 12, 222-229.

[7]. Csaba, G.: Aromatic hydrocarbon receptors in the immune system: Review and hypotheses. Acta Microbiol Immunol Hung 2019, doi. 10.1556/030.66.2019.003.

[8]. Csaba, G.: Immunoendocrinology: faulty hormonal imprinting in the immune system. Acta Microbiol Immunol Hung 2014, 61, 89-106.

[9]. Csaba, G., Tekes, K.: Is the brain hormonally imprintable? Brain Dev 2005, 27, 465-471.

[10]. Tekes, K., Gyenge, M., Hantos, M., Csaba, G.: Effect of beta-endorphin imprinting during late pregnancy on the brain serotonin and plasma nocistatin levels of adult male rats. Horm Metab Res 2007, 39, 479-481.

[11]. Tekes, K., Hantos, M., Csaba, G.: Single neonatal treatment with beta-endorphin (hormonal imprinting) extremely enhances nocistatin level of cerebrospinal fluid in adult rats. Life Sci 2004, 74, 1993-1997.

[12]. Csaba, G.: Bone manifestation of faulty perinatal hormonal imprinting: a review. Curr Pediatr Rev 2018, doi. 10.2174/1573396315666181126110110.

[13]. Csaba, G.: The present and future of human sexuality: Impact of faulty perinatal hormonal imprinting. Sex Med Rev 2017, 5, 163-169.

[14]. Csaba, G., Knippel, B., Karabélyos, C., Inczefi-Gonda, Á., Hantos, M., Tóthfalusi, L., Tekes, K.: Effect of neonatal beta-endorphin imprinting on sexual behavior and brain serotonin level in adult rats. Life Sci, 3003, 73, 103-114.

[15]. Csaba, G., Inczefi-Gonda, Á.: Transgenerational effect of a single neonatal benzpyrene treatment on the glucocorticoid receptor of the rat thymus. Hum Exp Toxicol 1988, 17, 88-92.

[16]. Csaba, G.: Transgenerational effects of perinatal hormonal imprinting. In: Transgenerational epigenetics, Ed. T. Tollefsbol, pp. 255-267. Elsevier, New York

[17]. Csaba, G.: Impact of endocrine disruptors on sexuality. Glob Med Ther 2018, doi. 10.1576/GMT.10000110

[18]. Csaba, G.:Endocrine disruptors-caused faulty hormonal imprinting: Focus on women. ARCH Women Health Care 2018, 1, 1-6.

[19]. Csaba, G.: Effects of early endocrine disruptor exposures (faulty hormonal imprinting) on immunity. Austin Immunol 2018, 3, 1-7.

[20]. Csaba, G.: Lifelong impact of breastmilk-transmitted hormones and endocrine disruptors. J Clin Endocrinol Res 2018, 1, 29-34.

[21]. Csaba, G.: The role of endocrine disruptors in the present and future human endocrine evolution: The ED-exohormone system. J Transl Sci 2019, doi.10.15761/JTS.1000312.

[22]. Miller, R.K.: Perinatal toxicology: its recognition and fundamentals. Ann J Ind Med 4, 205-244, 1883.

[23]. Foster, P.M., McIntyre, B.S.: Endocrine active agents: implications of adverse and non-adverse changes. Toxicol Pathol 2002, 30, 59-65.

[24]. Gaspari, L., Sampaio, D.R., Paris, F., Audran, F., Orsini, M., Neto, J.B., Sultan, C.: High prevalence of micropenis in 2710 male newborns from an intensive-use pesticide area of Northeastern Brazil. Int J Androl 2012, 35, 253-264.

[25]. El Kholy, M., Hamza, R.T., Saleh, M., Elsedfy, H.: Penile length and genital anomalies in Egyptian male newborns: eidemiology and influence of endocrine disruptors. J Pediatr Endocrinol Metab 2013, 26, 509-513.

[26]. Garcia, J., Ventura, M.I., Requena, M., Hernandez, A.F., Parrón, T., Alarcon, R.: Association of reproductive disorders and male congenital anomalies with environmental exposure to endocrine active pesticides. Reprod Toxicol 2017, 71, 95-100.

[27]. Kalfa, N., Paris, F., Soyer-Gobillard, M.O., Daures, J.P., Sultan, C.: Prevalence of hypospadias in grandsons of women exposed to diethylstilbestrol during pregnancy: a multigenerational national cohort study. Fertil Steril 2011, 95, 2574- 2577.

[28]. Virtanen, H.E., Adamsson, A.: Cryptorchidism and endocrine disrupting chemicals. Mol Cell Endocrinol 2012, 355, 208-220.

[29]. Botta, S., Cunha, G.R., Baskin, L.S.: Do endocrine disruptors cause hypospadias? Transl Androl Urol 2014, 3, 330-339.

[30]. Hayes, T.B., Anderson, L.L., Beasley, V.R. et al. Demasculinization and feminization of male gonads by atrazine: consistent effects across vertebrate classes. J Steroid Biochem Mol Biol 2011, 127, 64-73.

[31]. Maffini, M.V., Rubin, B.S., Sonnenschein, C., Soto, A.M.: Endocrine disruptors and reproductive health: the case of bisphenol A. Mol Cell Endocrinol 2006, 25, 179-186.

[32]. Mileva, G., Baker, S.L., Konkle, A.T., Bielajew, C.: Bisphenol-A: epigenetic reprogramming and effects on reproduction and behavior. Int J Environ Res Public Health 2014, 11, 7537-7561.

[33]. Jones, B.A., Shimell, JJ, Watson, N.V.: Pre-and postnatal bisphenol A treatment results in persistent deficits in sexual behavior of male rats, but not female rats, in adulthood. Horm Behav 2011, 59, 246-251.

[34]. deBarros, A.L., Rosa, J.L., Cvariani, M.M., et al.: In utero and lactational exposure to fipronil in female rats: Pregnancy outcomes and sexual development. J Toxicol Environ Health A. 2016, 79, 266-273.

[35]. Steinberg, R.M., Walker, D.M., Juenger, T.E., Woller, M.J., Gore, A.C.: Effects of perinatal polychlorinated biphenyls on adult female rat reproduction: development, reproductive physiology, and second generational effects. Biol Reprod 2008, 1091-1100.

[36]. Salian, S., Doshi, T., Vanage, G.: Perinatal exposure of rats to Bisphenol A affects the fertility of male offspring. Life Sci 2009, 85, 742-752.

[37]. Gore, A.C., Walker, D.M., Zama, A.M., Armenti, A.E., Uzumcu, M.: Early life exposure to endocrine-disrupting chemicals causes lifelong molecular reprogramming of the hypothalamus and premature reproductive aging. Mol Endocrinol 2011, 25, 2157-2168.

[38]. Newbold, R.R.., Padilla-Banks, E., Jefferson, W.E., Heindel, J.J.: Effects on endocrine disruptors on obesity. Int J Androl 2008, 31, 201-208.

[39]. Marques-Pinto, A., Carvalho, D.: Human infertility: are endocrine disruptors to blame? Endocrine Connections 2013, 2, 815-829.

[40]. Manikkam, M., Tracey, R., Guerrero-Bosagna, C., Skinner, M.K.: Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations. PLoS One 2012, 7, e46249.

[41]. Chang, H.S., Anway, M.D., Rekow, S.S., Skinner, M.K.: Transgenerational epigenetic imprinting of the male germline by endocrine disruptor exposure during gonadal sex determination. Endocrinology 2006, 147, 5524-5541.

[42]. Oliveira, I.M., Romano, R.M., de Campos, P., Cavalin, M.D., Oliveira, C.M., Romano, M.A:. Delayed onset of puberty in male offspring from bisphenol-A treated dams is followed by the modulation of gene expression in the hypothalamic-pituitary-testis axis in adulthood. Reprod Fertil Dev. 2017, 29, 2496-2505.

[43]. Barrett, E.S., Sollewski, M.: Polycystic ovary syndrome: do endocrine-disrupting chemicals play a role? Semin Reprod Med 2014, 32, 166-176.

[44]. Yu, C., Tai, F., Song, Z., Wu, R., Zhang, X., He, F.: Pubertal exposure to bisphenol A disrupts behavior in adult C57BL/6J mice. Environ Toxicol Pharmacol. 2011, 31, 88-99.

[45]. Schoeters, G., Den Hond, E., Dhooge, W., van Larebeke, N., Leijs, M.: Endocrine disruptors and abnormalities of pubertal development. Basic Clin Pharmacol Toxicol 2008, 102, 168-175.

[46]. Crews, D., Gore, A.C., Hau, T.S., Dangleben, N.L., Spinetta, M., Schallert, T., Anway, M.D., Skinner, M.K.: Transgenerational epigenetic imprints on mate preference. Proc Natl Acad Sci U.S.A. 2007, 104, 5942-5246.

[47]. Rubin, B.S., Soto, A.M.: Bispheenol A: Perinatal exposure and body weight. Mol Cell Endocrinol 2009, 304, 55-62.

[48]. Bansal, A., Rashid, C., Xin, F., Li, C. et al. Sex and dose-specific effects of maternal bisphenol A exposure on pancreatic islets of first and second-generation adult mice offspring. Environ Health Perspect 2017, 125, 097022.

[49]. Ball, E.R., Caniglia, M.K, Wilcox, J.L. et al. Effects of genistein in the maternal diet on reproductive development and spatial learning in male rats. Horm Behav 2010, 57, 313-322,

[50]. Kuwahara, R., Kawaguchi, S., Kohara, Y., Cui, H., Yamashita, K.: Perinatal exposure to low-dose bisphenol A impairs spatial learning and memory in male rats. J Pharmacol Sci 2013, 123, 132-139.

[51]. Takahama, K., Shirasaki, T.: Endocrine disruptors and brain estrogen receptors: the current state of behavioral, neurochemical, and moleular biological studies. Nihon Shinkai Seishin Yakurigaku Zasshi 2001, 21. 103-111.

[52]. Panagiotidou E., Zerva, S., Mitsiou, D.J., Alexis, M.N.. Kitraki, E.:Perinatal exposure to low-dose bisphenol A affects the neuroendocrine stress response in rats. J Endocrinol 2014, 220, 207-218.

[53]. Ezequiel, P., Miguel, G., Gustavo, H.M., Nora, M.: Toxicology of organochlorines: Implications of presence in breast milk. J Appl Life Sci Int 2015, 006.

[54]. Sarrouilhe, D., Dejean, C.: Autism spectrum disorders and bisphenol A: Is serotonin the lacking link in the chain? Encephale 2017, 43,402-404.

[55]. Sharf-El-Deen O., Bakry, S., Abo Shaeir, W, Mohamed F.E., Adel, M.: Teratogenicity of bisphenol-A (BPA). Am-Euras J Toxicol Sci 2015, 7, 229-238.

[56]. Walker, D.M., Gore, A.C.: Epigenetic impacts of endocrine disruptors in the brain. Front Neuroendocrinol 2017, 44, 1-26.

[57]. Malaisé, Y.,Ménard, S., Cartier, C., Lencina, C. et al.: Consequences of biphenol A perinatal exposure on immune responses and gut barrier function in mice. Arch Toxicol 2018, 92, 347-358.

[58]. Csaba, G.: Effect of endocine disruptor phytoestrogens on the immune system: present and future. Acta Micr Immunol Hung 2018, 65, 1-14.

[59]. Csaba, G.: Bone manifestation of faulty peinatal hormonal imprinting: A review. Curr Pediatr Rev 2019, 15, 4-9.

[60]. Weinhouse, C., Anderson, O.S, Gyekis, J-P., Dingman, M.A., Yang, J., Dolinoy, J.C.: Dose-dependent incidence of hepatic tumors in adult mice following perinatal exposure to bisphenol A. Environ Health Perspect 2014, 122, 485-491.

[61]. McGrath, J.: Does „imprinting" with low prenatal vitamin D contribute to the risk of various adult disorders? Med Hypotheses 2001, 56, 367-371.

[62]. Prins, G.S., Birch, L., Tang, W,Y., Ho, S.M.: Developmental estrogen exposures predispose to carcinogenesis with aging. Reprod Toxicol 2007, 23, 374-382.

[63]. Prins, G.S., Tang, W.Y., Belmonte, J., Ho, S.M.: Perinatal exposure to oestradiol and bisphenol A alters the prostate epigenom and increases susceptibility to carcinogenesis. Basic Clin Pharmacol Toxicol 2008, 102, 134-138.

[64]. Csaba, G.: Faulty perinatal hormonal imprinting caused by exogeneous vitamin D – dangers and problems. Austin J Nutr Food Sci 2016, 4, 1075-1080.

[65]. Csaba, G.: Vitamin.caused faulty perinatal hormonal imprinting and its consequences in adult age. Physiol Int 2017, 104, 217-225.

[66]. Bodin, J., Belling, A.K., Becher, R., Kuper, F., Levik, M., Nygaard, U.C.: Transmaternal bisphenol A exposure accelerates diabetes type 1 development in NOD mice. Toxicol Sci 2014, 137, 311-323.

[67]. Mauduit, C., Siddaek, B., Benahmed, M.: Developmental and environmental origin of male infertility. Med Sci (Paris) 2016, 32, 45-50.

[68]. Csaba, G.: The role of endocrine disruptors in the present and future human endocrine evolution. The ED-exohormone system. J Transl Sci 2019, 5, 1-3.

[69]. Csaba, G.: Hormonal imprinting: its role during the evolution and development of hormones and receptors. Cell Biol Int 2000, 24, 407-414.

[70]. Beszterda, M., Franski, R.: Endocrine disruptor compounds in environment: As a danger for children health. Pediatr Endocrinol Diabetes Metab 2018, 24, 88-95.

[71]. Hoffman, D.J., Reynolds, R.M., Hardy, D.B.: Developmental origins of health and disease: current knowledge and potential mechanisms. Pediatr Rev 2017, 75, 951-970.

[72]. Wilson, J.G.: The evolution of teratological testing, Teratology 1979, 20, 205-211.

[73]. Tournaire, M., Devouche, E., Espié, M. et al. Cancer risk in women exposed to diethylstilbestrol in utero. Therapie 2015,70,433-441.

[74]. Csaba, G.: Thoughts on the cultural evolution of man. Developmental imprinting and transgeneretional effect. Riv Biol 2007, 100, 461-474.

[75]. de Cock, M., Maas, Y.G., van de Bor, M.: Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. Acta Paediatr, 2012, 10, 811-818.

[76]. Hashemi, F., Tekes, K., Laufer R., Szegi, P., Tóthfalusi, L., Csaba, G.: Effect of a single neonatal oxytocin treatment (hormonal imprinting) on the biogenic amine level of the adult rat brain: could oxytocin induced labor cause pervasive developmental diseases?.: Reprod Sci 2013, 20, 1255-1263.

[77]. Martinez-Arguelles, D.B., McIntosh, M., Rohlicek, C.V. et al: Maternal in utero exposure to the endocrine disruptor di-(2-ethylhexyl) phtalate affects the blood pressure of adult male offspring. Toxicol Appl Pharmacol 2013, 266, 95-100.

[78]. Plagemann, A.: Perinatal programming and functional teratogenesis: impact on body weight regulation and obesity. Physiol Behav 2005,86, 661-668.

[79]. Csaba, G,: The faulty perinatal hormonal imprinting as functional teratogen. Curr PediatrRev 2016, 12, 222-229.

[80]. Wells, P.G., Lee, C.J., McCallum, G.P., Perstin, J., Harper, P.A.: Receptor- and reactive intermediate.mediated mechanisms of teratogenesis. HandbExp Pharmacol 2010, 196, 131-162.

[81]. Plagemann, A.: „Fetal programming" and „functional teratogenesis": on epigenetic mechanisms and prevention of perinatally acquired lasting health risks. J Perinat Med 2004, 32, 297-305.

[82]. Seaver,L.H., Hoyme, H.E.:,Teratology in pediatric practice. Pediatr Clin North Am 1992, 39, 111-134.

[83]. Mirzahosseini, S., Karabélyos, C., Dobozy, O., Csaba, G.: Changes in sexual behavior of adult male and female rats neonatally treated with vitamin D3. Hum Exp Toxicol. 1996, 15, 573-576.

[84]. Palanza, P., Nagel, S.C., Parmigiani, S., Vom Saal, F.S.: Perinatal exposure to endocrine disruptors: sex, timing and behavioral endpoints. Curr Opin Behav Sci 2016, 7, 69-75.

[86]. Fenichel, P., Brucker-Davis, F., Chevalier, N.: Endocrine disruptors, reproduction and hormone-dependent cancers. Presse Med 2016, 45, 63-72.

[87]. No authors. Diethylstilbestrol (DES9: also harms the third generation. Prescrire 2016, 25, 294-298.

[88]. Tekes, K., Gyenge, M., Hantos, M., Csaba, G.: Transgenerational hormonal imprinting caused by vitamin A and vitamin D treatment of newborn rats. Alterations in the biogenic amine contents of the adult. Brain Dev 2009, 31, 666-670.

INTERNATIONAL JOURNAL OF PLANT, ANIMAL AND ENVIRONMENTAL SCIENCES

ISSN 2231-4490

International Journal of Plant, Animal and Environmental Sciences