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Smoking, as epigenetically active endocrine disruptor: Perinatal impact

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Abstract

Different types of cells of the human organism have receptors belonging to the steroid (nuclear) receptor superfamily which bind polycyclic aromatic hydrocarbon (PAH) molecules. As these molecules are present in the human environment and enter into man, disturb the physiological function of endocrine system, inhibiting the transmission of physiological stimuli or by giving false signal. These hormone-like molecules are massively present in the human environment as products or byproducts of the industrial activity (as plasticizers), as agrotechnical tools (insecticides, herbicides, pesticides) or medicaments etc and named endocrine disruptors. As their direct function is useful, rather difficult to avoid them. Similar PAH molecules (dioxine and benzpyrene) are present in the cigarette smoke enjoyed since the ancient times, causing voluntarily, similar destructive effect. These disruptors are rather harmful for adults however they are more harmful for fetus or newborn (perinatal exposure), causing faulty hormonal imprinting with lifelong consequences (diseases, inclination to diseases, or alterations of cellular functions in later (adult) age. Faulty perinatal hormonal imprinting can explain the developmental origin of health and disease (DOHaD). However, although imprinting is the most decisive (and dangerous) perinatally it is not restricted to this period of life, it can be provoked at weaning and outstandingly at adolescence causing also lifelong problems.

Introduction

At present the mankind is living in an environment, which is filled with natural or man-made endocrine disruptors, hormone-like molecules which are entering into the human organism, bound by hormone -(first of all steroid hormone)- receptors disturbing the physiological regulation of and the effect by, the endocrine system. The endocrine disruptors are transported to the human organism by air, water, food, medicaments, cosmetics etc. Some of them can be avoided but others not and there are such routes, which could be avoided, however others are willfully used as bad habits of men, for example smoking. In the tobacco smoke hundreds of aromatic hydrocarbons are present, which can be bound by aromatic hydrocarbon (PAH) or steroid hormone receptors. Many mothers during gravidity are smoking, provoking lifelong consequences

The physiological and faulty hormonal imprinting: In the structure of the endocrine system hormones and their receptors are the two most important components. Hormones are produced by cells of the endocrine glands, while receptors are present on or in any cells of the organism (endocrine cells included). The two components are developing independently however, under the direction of the genetic program, and meet each other in a certain point of fetal development, taking place the hormonal imprinting which determines the binding capacity of receptors for life. This is an important point of the development of receptor-hormone complex without which there is not normal (physiological) function [1]. However, in this critical developmental period, when the window for imprinting is open, other-related- molecules (e.g. members of the hormone family or endocrine disruptors) also can bind to the developing receptor, causing faulty hormonal imprinting also with lifelong consequences [2]. This latters [3] could be some diseases, or inclination to diseases (which request further impulses for manifestation) or only mild or strong functional alterations. Although the main imprinting is taking place perinatally, the manifestation of its effect happens in adult age or at any time during life (late onset diseases) of the person touched (functional teratogenicity [4,5]. It is difficult to recognize the interrelation between the exposure of faulty imprinting and its manifestation, because of the long time between them, however animal experiments justify it [4-7]. There are a lot of endocrine disruptors in the tobacco smoke however, there are two, which were studied thoroughly and are in closed correlation with disruptor activity: dioxin and benzpyrene.

Early (imprinting) effects and late pathological manifestations

Selected facts:

Effect of smoking, as a whole: In cigarette smoke approximately 4.000 constituents can be found [8] in which about 500 different polycyclic aromatic hydrocarbons (PAHs) [9,10]. Estrogene synthesis is influenced by the cytochrome P 450 family and members of the family are involved in the hydroxylation of estradiol. These processes are influenced by cigarette smoke.This means that, first of all CYP1A1 and 2 are influencing estradiol synthesis . These effects can influence fertility and fetal programming causing serious pathological problems in later life [11-13]

Thyroid functions are attacked by smoking [14,15]. Male cigarette smokers have higher thyroxine levels and lower TSH levels than never-smokers and former-smokers. Manifestation of diabetes and obesity are influenced by it [16]. Pregnancy rate decreases, spontaneus abortions are increased [17]. All stages of reproductive functions are touched in males and females [18,19]. PAHs in urban environment adversely affect children cognitive development [20-23]. Prenatal tobacco smoke

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exposure is associated with DNA-methylation [24] and consequently with epigenetic disturbances. In females lower concentrations of dioxin were measured [25], which points to gender dependency. Smokers have a higher frequency of goiter and increased thyroglobulin levels, especially in iodine deficient areas [26-28]. It could be responsible for male infertility [29-31].

The mother's smoking changes DNA methylation of detoxification genes in the fetus, increasing the risk of manifestation of diseases later [32]. Thyroid and adrenal disfunctions were observed in adults which had been exposed to maternal smoking during pregnancy or breastfeeding [33]. Prenatal exposure to PAHs alters DNA methylation and increases the manifestation of asthma in childhood [34]. Other diseases are also provoked because of the epigenetic dysregulation.

A special problem is the difference in timing of puberty. In sons, months earlier can be observed pubic hair development and voice break, in girls breast development, pubic hair development and menarche [35]. Environmental smoking was partly responsible for the symptoms, and cognitive deficit was also observed [36-38].

An other special problem is the transgenerational effect of smoking which is manifested in the instability of genome [39] as well as the inheritance of imprinting (see benzpyrene).

Effects of dioxin

Animal experiments: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a highly toxic chemical compound, which is present in the human environment. It is one of the most toxic substances known to humans. It is produced naturally by volcanoes, erupting into the air, by the (plastics, paper and herbicide, etc) industry and (by personal decision) in the tobacco smoke [40], however this latter touches also other persons, especially in the closer environment. It is estimated that smoking 20 cigarettes/day leads to a dioxin intake almost equivalent to that from food (1-3 pg TEQ/kg bw/day), the major source of human exposure. It is mostly present in fatty meats, diary products and fish. There is a high level of TCDD in cigarette smoke [41]. It is accumulating in human fat and remains there to a very long time [42], with the half-life of 7-12 years. It is excreted by feces and breast-milk .

In animal (rat) experiments single TCDD treatment of gestational day 15 decreased the androgen receptor level, also the weight of urogenital complex and ventral prostate were observed as well as the glans penis length, the testicular and epididymal weigth and anogenital distance were also reduced, measured at the peripubertal period [43]. When TCDD was chronically added during gestation serum thyroxine and triiodothyronine levels was decreased and TSH levels were increased up to the 30th day after birth. TCDD exposure at gestational day 15 suppressed sexual maturation of rat offspring after growing up [44]. There was an induction of transgenerational inheritance of adult onset diseases (kidney diseases in males, ovarian primordial follicle loss and polycystic ovary disease in females) up to the 3rd generation [45]. Disturbed ovarian function and spermatogenic capacity was also observed [46]. TCDD caused an elongation of the period for sensitivity to cancerogenes. In a spermatogenesis related factor gene-clonal experiment the expression of genes was decreased in TCDD treated animals [47]. Altered fecundity, endometriosis and some cancers were observed in monkeys [48]. TCDD exposure influences porcin reproductive hormonal activity as ovulatory disruptor and abortificiens [49]. Early postnatal TCDD exposure decreased neurogenesis and gene expression in the brain with consequent behavioral effects . Perinatal TCDD exposure caused adult onset autoimmune disease.

Human observations: Perinatal dioxin exposure influenced neurodevelopmental alterations already in the first three years of life, in boys (decrease of motor and expressive communication scores, while there was no effect in girls [50] however, increased infant growth and increased body mass index (BMI) was observed in school -age girls. Triiodothyronine (T3) level was associated with serum dioxine levels in Vietnam [51]. TCDD causes mitochondrial dysfunction and apoptosis in human trophoblast-like cell cultures [52].

Effects of benzpyrene

Animal experiments: Benzpyrene treatment during gestation makes susceptible male and female rats to mutagenic effects and this is manifested in adult age to higher sister chromatid exchange [53]. Benzpyrene exposure of newborn rats caused an increase of glucocorticorticoid receptor's binding capacity in adult males, while a decrease in females [54]. These effects appeared after a period of lability. Not only perinatal benzpyrene exposure is causing receptor-modifying effect, but also pubertal [55] and also in uterine estrogen receptors [56]. Single neonatal or repeated benzpyrene exposure of rats influenced serotonin content of adults' immune cells [57].

Single neonatal benzpyrene treatment reduced the thymic glucocorticoid receptors' density in adult offspings up to the third (F2) generation [58-60].

Human observations: See at effects of smoking as a whole.

Discussion

The destructive effects of smoking to human health were demonstrated already earlier in many cases however, there was not a trial from the aspect of hormonal imprinting . The data selected clearly show that cigarette smoking as well as their polycyclic aromatic hydrocarbon components are strong imprinters and are able to cause serious alterations in the mammalian and human organisms. In contrast to this old knowledge (not considering faulty hormonal imprinting) only a minority of smokers inclined to give up smoking, when pregnant. As an example, in Scotland, an economically and socially developed country more than 25% of the women is smoking whilst pregnant and this percent grows to over 60% in the most deprived social categories. These mothers expose their children to different diseases manifested in later life however, only about 4% of them stop smoking during pregnancy. Similar data are known worldwide. Considering the data listed in the Facts, more reason would be for abandoning smoking during gravidity.

There are enormous amount of different endocrine disruptors in the human environment. These dangerous molecules are produced by the industry, agrotechnics or medicine, which are -as used to be told wrightfully, or without it- as unavoidable, because of the progress of mankind. These are derivatives of useful products for which the mankind feels worth to suffer, although their expected prolonged consequences are not known, only guessed. Smoking does not belong among them. This is a bed habit, the prolonged personal consequences are known in case of adults (eg. cancer) however, the effect of maternal smoking begins to be known only now, in the light of faulty hormonal imprinting [61,62] and developmental origin of health and disease (DOHaD) [63]. The speciality of this harm is a.) the voluntaryness (by the mother), b.) the antisociality (by the local environment: smoking people: passive smoking), c.) the timing of impact, d) the long distance between the exposure and manifestation of the effect, e.) the epigenetic transgenerational inheritance. f.) the prolongation of the endangered period in the early life (late prenatal and early postnatal period), g.) consequently the functional teratogenicity.

As long as women were working in the houshold maternal smoking was scarce and dependent on the direct environment, as the habits of the husband or other members of the family. However, after the emancipation and mainly, with the entering of women into the industry, pregnant women begin to massively smoke, as this was one of the signs of equality (with man) and similar to present-day teenagers in the way of becoming adult, they also tried to demonstrate this with smoking. In that time nothing believed that this could be dangerous for the fetus when the women is pregnant, the knowledge of the medical science was too less, for dealing with it. Consequently, women's smoking has been a tradition, neglecting the interest of the fetus developing in the womb, and when the science pointed to this mistake, it was very difficult to consider it. At present there are more than 200 million women smoker worldvide and it expected to grow for triple up to 2025.

Problems of puberty

Faulty hormonal imprinting is not time-dependent, but dependent on the developmental state of the cells (organs), so it is executed at weaning, puberty and at any time, when the cells are continuosly dividing (differentiating). It seems to be the most important period the puberty, which is in general the time of instability and when smoking used to be started. The National Institute on Drug Abuse of the USA reported that at 2017 9.7 percent of 12th graders, 5.0% of 10th graders and 1.9% of 8th graders used cigarettes in the past month. According to the American Lung Association „every day almost 2500 children under 18 years of age try their first cigarette and more than 400 of them will become new regular daily smokers". In 2015 9.3% of high school students reported smoking cigarettes in the last 30 days however, this amount was 36.4% in 1997 (this is – fortunately- a decreasing tendency, nevertheless it is still too much). Adolescent smoking causes various acute health problems (upper respiratory infections, immature lung development, lung cancer) and become a gateway for all kinds of substance abuse. However, it seems to be likely that pubertal faulty imprinting causes more problem, than the treatible acut diseases, considering its long and inheriting nature. Puberty is the time, when the nervous system and the systems regulated by it are overwrited in the program and if this happens in the crude presence of such imprinters, as dioxin and benzpyrene make deep traces in such systems, as e.g. reproduction , immunity and behavior. Some signs of these already can be observed, without knowing that faulty pubertal imprinting is the cause of them. In addition -what is a more serious problem- we do not know, what will be shown in the next generations. Up to the 3rd generation the inheritance of imprinting is justified in mammals however because of the long changes of generations this was not studied further, or had not been studied in man. Nevertheless in a unicellular model system (Tetrahymena) the effect was observed up to the 1000th generations [64,65]. And there is not known -at present- the way for undoing.

Women, during pregnancy (and postnatally) can determine the further fate of their offsprings by smoking or not smoking. However, pregnant women are adults, whose responsibility for their children can not be questioned, although in most of cases the liability of environment seems to be also responsible. The behavior of human environment forces (?) the women for passively smoking and even more the teenagers, who bears also to record the adulthood by it. However, the teenager (in general) does not bear with the accountability of adults for itself and others, at the same time it can faultily imprint its own systems for the further life and for their progenies.

Exposure in adulthood

As the differentiating capacity, as well, as the period of differentiation are different, there are many kind of cells which are sensitive to faulty hormonal imprintig in adults. This are mainly the cells of the immune system and the stem cells. Nothing is known on the imprinting sensitivity of stem cells however, there are data on immune cells. This latters show, that faulty imprinting of adult immune cells influences the reactivity of the immune system, although the exact signs or direction are not detected [66].

The future and the transgenerational faulty imprinting

As hormonal imprinting is an epigenetic process, it is inherited to the progenies of the touched cells (cell-line). This seems to be natural and understandable: imprinting touches directly the receptor bearing cell, which in an adult person is independent on the germ cells which are participating in the process of fertilization. However, the experimental results show, that the signs of faulty impring appear even in the 1000th generation in unicellulars. This could be explained in this case, that the transmission of hereditary information of cells here happens by the division of the treated cells however, in the case of mammals by special (germinal) cells, which are independent entities of the same organism. Nevertheless, inheritance was observed until the third generation.This means that faulty imprinting influences the receptors of the whole organism, or ovogonia and spermatogonia has similar nuclear receptors for PAHs, as the direct target cells and the epigenetic -reprogramming- effect is also manifested in these cells. There is not data on the span of heredity, that is: how many generations will be touched in human beings. Nevertheless, the faulty imprinting in the further generations will be manifested in an altered epigenetic milieu, and can be accumulated. This means that in the future must lay on the accounts with faulty hormonal imprinting. As faulty hormonal imprinting is not a new non-physiological process, which never had been before, only its incidence is enormously growing, it is not known how much had been its role in the formation of the present day endocrine system, so there is not possibility to forecast of the impact of massive present-day endocine disruptor influences. Nevertheless, the preseent-day disruptor influences are so strong, that adverse impacts are expected.

Conclusion

The (epigenetic) process of hormonal imprinting had been recognized by us 40 years ago and later the possibility of faulty imprinting also have been justified in animal (unicellular and mammalian) experiments. The physiological and faulty hormonal imprinting theory, as well,as the functional teratogenicity was based on these observations [2,3,5,61,62,64-70]. However, its human importance have been confirmed in the last time by Barker's DOHaD (developmental origin of health and disease) theorys [67,68] and its evidences. The growing presence of endocrine disruptors in the human environment and the provocation of later onset and inherited diseases by them calls attention to the magnitude of danger [69,70]. This requests the increased attention on the problem.

References

1. Csaba G, Nagy SU (1985) Influence of neonatal suppression of TSH production (neonatal hyperthyroidism) on response to TSH in adulthood**.** *J Endocrinol Invest* 8: 557-559.

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

3. Csaba G (2008) Hormonal imprinting: phylogeny, ontogeny, diseases and possible role in present-day human evolution. *Cell Biochem Funct* 26: 1-10.

4. Csaba G (2015) Revaluation of the concept of developmental abnormality: the importance of faulty perinatal hormonal imprinting. *Orv Hetil* 156: 1120-1127.

5. Csaba G (2016) The faulty perinatal hormonal imprinting as functional teratogen. *Curr Ped Rev* 12: 222-229.

6. Tchernitchin AN, Tchernitchin NN, Mena MA, Undo C, Soto J, et al. (1999) Imprinting: perinatal exposures cause the development of diseases during the adult age. *Acta Biol Hung* 50: 425-440.

7. Goudochnikov (2015) VI. Role of hormones in perinatal and early postnatal development: Possible contribution to programming/imprinting phenomena. *Ontogenez* 46: 285-294.

8. Dai JB, Wang ZX, Qiao ZD (2009) The effects of tobacco on male fertility. *Asian J Androl* 17: 954-960.

9. Rodgman A, Cook LC (2009) The composition of cigarette smoke. An historical perspective of several polycyclic aromatic hydrocarbons. *Contributions to Tobacco Research* 23: 384-386.

10. Lofroth G, Rannug A (1988) Ah receptor ligands in tobacco smoke. *Tox Lett* 42: 131-136.

11. Duskova M, Hruskovicova H, Simunkova K, Starka L, Parizek A, et al. (2014) The effects of smoking on steroid metabolism and fetal programming. *Steroid Biochem Mol Biol* 138-143.

12. Kapoor D, Jones TH (2005) Smoking and hormones in health and endocrine disorders. *Eur J Endocrinol* 152: 491-499.

13. Reynolds LM, Magid HS, Chi GC, Lohman K, Graham Barr R, et al. (2017) Secondhand tobacco smoke exposure associations with DNA methylation of the aryl hydrocarbon receptor repressor. *Nicotine Tob Res* 19: 442-451.

14. Kelishadi R, Sobhani P, Poursafa P, Amin MM, Ebrahimpour K, et al. (2018) Is there any association between urinary metabolites of polycyclic aromatic hydrocarbons and thyroid hormone levels in children and adolescents? *Environ Sci Pollut Res Int* 25: 1962-1968.

15. Fisher CL, Manning DM, Herman WH, Frumkin H (1997) Cigarette smoking and thyroid hormone levels in males. *In J Epidemiol* 26: 972-977.

16. Tweed JO, Hsia SH, Friedman TC (2012) The endocrine effects of nicotine and cigarette smoke. *Trends Endocrine Metab* 23: 334-342.

17. Sepaniak S, Forges T, Monnier-Barbarino P (2006) Cigarette smoking and fertility in women and men. *Gynecol Obstet Fertil* 34: 945-949.

18. Dechanet C, Anahory T, Mathieu Daude JC, Quantin X, Reyftman L, et al. (2011) Effects of cigarette smoking on reproduction. *Human Reprod Update* 17: 76-95.

19. Harley A, Agarwal A, Gunes SO, Shelly A (2015) Smoking and male infertility: an evidence- based review. *World J Mens Health* 33: 143-160.

20. Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D, et al. (2006) Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the 3 years of life among inner-city children. *Environ Health Perspect* 114: 1287-1292.

21. Perera FP, Whyatt R, Hoepner L, Wang S, Camann D, et al. (2009) Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. *Pediatrics* 124: 195-202.

22. Rauh VA, Whyatt RM, Garfinkel R, Andrews H (2004) Developmental effects of exposure to environmental tobacco smoke and material hardship among inner-city children. *Neurotox Teratol* 26: 373-385.

23. Hutz RJ, Carvan MJ, Baldridge MG, Conley LK (2006) Environmental toxicants and effects on female reproductive functions. *Tren Reprod Bio* 2: 1-11.

24. Flerens S, Eppe G, De Pauw E, Bernard A (2005) Gender dependent accumulation of dioxins in smokers. *Occup Environ Med* 62: 61-62.

25. Bertelsen JB, Hegedus L (1994) Cigarette smoking and the thyroid. *Thyroid* 4: 327-331.

26. Gunes S, Metin Mehmetoglu A, Arslan MA, Henkel R (2018) Smoking induced genetic and epigenetic alterations in infertile men. *Andrologia* 50.

27. Bundhun PK, Janoo G, Bhurtu A, Teeluck, AR, Soogund MZS, et al. (2009) Tobacco smoking and semen quality in infertile males: a systematic review and meta-analysis. *BMC Public Health.*

28. Fragou D, Pakkidi E, Aschner M, Samanidou V, Kovatsi L (2019) Smoking and DNA methylaton: Correlation of methylation with diseases and fetus development following prenatal exposure. *Food Chem Toxicol* 129: 312-327.

29. Yang F, Li L, Yuan W, Chen JP, Liu XQ, et al. (2017) Couple's infertility in relation to male smoking in a Chinese rural area. *Asian J Androl* 19: 311-315.

30. No authors. Smoking and infertility. Fertil Steril 2008, 90, Suppl. S254-259.

31. Practice Committee of American Society for Reproductive Medicine (2018) Smoking and infertility: a committee opinion. *Fertil Steril* 110: 611-618.

32. Breton CV, Byun HM, Wenten M, Pan F, Yang A, et al. (2009) Prenatal tobacco smoke exposure affects global and gene specific DNA methylation. *Am J Respir Crit Care Med* 180: 462-467.

33. Lisboa PC, de Moura EG (2012) Obesity and endocrine dysfunction programmed by maternal smoking in pregnancy and lactation. *Front Physiol*.

34. Perera F, Tang WY, Herbstman J, Tang D, Levin L, et al. (2009) Relation of DNA methylation of 5'CpG islands of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. *PLoS One* 4: e4488.

35. Perera F, Herbstman J (2011) Environmental exposures, epigenetics, and disease. *Repr Toxicol* 31: 363-373.

36. Brix N, Ernst A, Lauridsen LLB, Parner ET, Olsen J, et al. (2019) Maternal smoking during pregnancy and timing of puberty in sons and daughters: a population-based cohort study *Am J Epidemiol* 188: 47-56.

37. Gollenberg, AE, Addo OY, Zhang Z, Hediger ML, Himes JH, et al. (2015) In utero exposure to cigarette smoking, environmental tobacco smoke and reproductive hormones in US girls approaching puberty. *Horm Res Paediatr* 83: 36-44.

38. Ferris JS, Flom JD, Tehranifar P, Myne ST, Terry MB, et al. (2010) Prenatal and childhod environmental tobacco smoke exposure and age at menarche. *Pediatr Perinat Epidemiol* 24: 515-523.

39. Laubenthal J, Zlobinskaya O, Poterlowicz K, Baumgartnein, Gdula MR, et al. (2012) Cigarette smoke-induced transgenerational alterations in genome stability in cord blood of human F1 offspring. *FASEB J* 26: 3946-3956.

40. Fierens S, Eppe G, de Pauw E, Bernard A (2004) Contribution of tobacco smoking to dioxin accumulation: opposite effects according to gender. *Halogen Compounds* 66: 2518

41. Kasai A, Hiramatsu N, Yao J, Maeda S, Kitamura M, et al. (2006) High levels of dioxin-like potential in cigarette smoke evidenced by in vitro and in vivo biosensing. *Cancer Res* 66: 7143-7150.

42. Unuvar T, Buyukgebiz A (2012) Fetal and neonatal endocrine disruptors. *J Clin Res Pediatr Endocrinol* 4: 51-60.

43. Ohsako S, Miyabara Y, Sakaue M, Ishimura R, Kakeyama M, et al. (2002) Developmental stage-specific effects of perinatal 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure on reproductive organs of male rat offspring. *Toxicol Sci* 66: 283-292.

44. Takeda T (2017) Molecular mechanism whereby maternal exposure to dioxin suppresses sexual maturation after growing up. *Yakugashu Zasshi* 137: 1373-1379.

45. Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK (2012) Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations. PLoS One.

46. Maguerres-Battistoni B, Odet F, Guigon C, Verot A, Guyot R, et al. (2006) Evidence for sex-specific effects of TCDD on male and female progeny exposed in utero. *Epidemiology* 17: S93

47. Yamano Y, Ohyama K, Ohta M, Sano T, Ritani A, Shimada J, et al. (2005) A novel spermatogenesis related factor-2 (SRF-2) gene expression affected by TCD treatment. *Endocr J* 52: 75-81.

48. Hutz RJ (1999) Reproductive endocrine disruption by environmental xenobiotics that modulate the estrogen signaling pathway, particularly tetrachlorodibenzo-p-dioxin (TCDD). *J Reprod Dev* 45: 1-12.

49. Gregoraszczuk EI (2002) Dioxin exposure and porcin reproductive hormonal activity. *Cad Saude Publica* 18: 1678.

50. Tai PT, Nishijo M, Nghi TN, Nakagawa H, Van Luong H, et al. (2016) Effects of perinatal dioxin exposure on development of children during the first 3 years of life. *J Pediatr* 175: 159-166.

51. Khoa TV, Truong DT, Bac ND, Tai PT, Quang LB, et al. (2015) Effects of dioxin exposure on thyroid hormones of populations living in hot spots of dioxin contamination in Vietnam. *Aging Sci*.

52. Chen S-C, Liao T-L, Wei Y-H, Tzeng C-R, Kao S-H, et al. (2010) Endocrine disruptor, dioxin (TCDD)-induced mitochondrial dysfunction and apoptosis in human trophoblast-like JAR cells. *MHR-BSRM* 16: 361-372.

53. Igaz P, Toth S, Csaba G (1995) Long-lasting persistence of elevated sister-chromatid exchange frequencies induced by perinatal benzo(a)pyrene treatment in rat bone-marrow cells. *Experientia* 51: 612-615.

54. Csaba G, Inczefi-Gonda A (2001) Binding capacity of rat liver glucocorticoid receptor in different periods after single neonatal benzpyrene treatment (imprinting). *Acta Physiol Hung* 88: 125-129.

55. Csaba, G, Karabelyos C (1995) Pubertal benzpyrene exposition decreases durably the sexual activity of the adult male and female rats. *Horm Metab Res* 27: 279-282.

56. Csaba G, Inczefi-Gonda A (1997) Effect of combined neonatal imprinting by vitamin A, vitamin D3, benzpyrene and allylestrenol on adult rat thymus glucocorticoid and uterine estrogen receptors. *Gen Pharmacol* 29: 779-781.

57. Csaba G, Pallinger E (2004) Effect of single neonatal or repeated benzpyrene exposure on the serotonin content of immune cells in young male rats. *Acta Physiol Hung* 91: 205-210.

58. Csaba, G, Inczefi- Gonda A (1998) Transgenerational effect of a single neonatal benzpyrene treatment on the glucocorticoid receptor of the rat thymus. *Hum Exp Toxicol* 17: 88-92.

59. Inczefi-Gonda A (1999) The environmental pollutant aromatic hydrocarbon, benzpyrene has deleterious effect on hormone receptor development. *Acta Biol Hung* 50: 355-361.

60. Csaba G, Inczefi-Gonda A (1999) Direct and transgenerational effect of benzpyrene treatment at adolescent age on the uterine estrogen receptor and thymic glucocorticoid receptor of the adult rat. *Acta Physiol Hung* 86: 29-36.

61. Csaba G (1980) Phylogeny and ontogeny of hormone receptors: the selection theory of receptor formation and hormonal imprinting. *Biol Rev Camb Philos Soc* 55: 47-63.

62. Csaba G (2018) Environmental pollution and non-perinatal hormonal imprinting. A critical review. *Int Ped Chi Care* 1: 54-62.

63. Charles MA, Delpierre C, Breant B (2016) Developmental origin of health and adult diseases (DOHaD): evolution of a concept over three decades. *Med Sci* (Paris) 32: 15-20.

64. Csaba G (2014) Transgenerational epignetics in the unicellular Tetrahymena. In: Transgenrational epigenetics. Ed. T. Tollefsbol. 163-172, 2014, Academic Press, New York.

65. Kohidai L, Lajko E, Pallinger E, Csaba G (2012) Verification of epigenetic inheritance in a unicellular model system: multigenerational effects of hormonal imprinting. *Cell Biol Int* 36: 951-959.

66. Csaba G (2014) Immunoendocrinology: faulty hormonal imprinting in the immune sytem. *Acta Microbiol Immunol Hung* 61: 89-106.

67. Suzuki K (2018) The developing world of DOHaD. *Dev Orig Health Dis* 9: 266-269.

68. Phillips D, Barker DJ, Osmond C (2018) Infant feeding, fetal growth and adult thyroid function. *Acta Endocrinol* (Copenh) 129: 134-138.

69. Csaba G (1984) The present state in the phylogeny and ontogeny of hormone receptors. *Horm Metab Res* 16: 329-335.

70. Csaba G (2007) Thoughts on the cultural evolution of man. Developmental imprinting and transgenerational effect. *Riv Biol* 100: 461-464.

71. Csaba G (2019) The role of endocrine disruptors in the present and future human endocrine evolution. *J Transl Sci* 5: 1-3.