Clinical Obstetrics, Gynecology and Reproductive Medicine

Research Article ISSN: 2059-4828

Dangerous faulty perinatal imprinting by medication: Review and hypothesis

György Csaba*

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

Abstract

Likewise to the perinatal exposure of endocrine disruptors, some drugs (e.g. painkillers, antibiotics, lipid-soluble vitamins, medicinally used marihuana, vaccine preservative thimerosal, digoxin) are causing faulty imprinting perinatally which could provoke late manifested alterations or diseases. In contrast to the similar perinatal faulty hormonal imprinting, the mechanism of the effect is unknown. The molecules (drugs) which are useful in the perinatal acute situation are originators of late (adult) diseases, which require further medical interventions. These drugs are functional teratogens, and only a selection of a mass of medicaments, which have not been studied from this aspect. As the fetus and infant in the perinatal period are rather sensitive to epigenetically active molecules, it seems important to attend the late sequels of this type of perinatal interventions as well, as oxytocin. Especially important the avoidance and monitoring of lipid-soluble vitamins, which are bound -regardless of their structure- by hormone receptors. The human observations point to the possibility of similar effects by perinatal exposures of any chemical interventions with similar consequences. There is also a possibility of inclination -by imprinting- to diseases, activated by certain effects in adult age. As windows for developmental imprinting are open at puberty, some similar phenomena can be observed also at this period.

Introduction

After fertilization human development is started with the embryonal period (first three months) which is very sensitive to morphological (structural) maldevelopments-causing teratogens, and the results can be observed already at birth. After that, in the fetal, prenatal and early postnatal period the provocation of morphological malformations becames scarcer and these periods are dominated by the functional teratogenicity [1], which are manifested later, in adults, or any time postnatally. Faulty hormonal imprinting seems to be responsible for these latter alterations.

Hormonal imprinting is a physiological phenomenon which is taking place during the development of the receptor-hormone complex. It is needed for the normal function of the endocrine system and its duration is lifelong [2-4] . Without imprinting of the developing receptor there is not satisfactory hormone binding and reaction to it [5]. However, in the critical period of the imprinting's development, when the window for the process is open, not only the physiological hormones, but related molecules (members of the same hormone family, structural analogues, as natural or man-made endocrine disruptors, can be bound by the receptors, causing faulty hormonal imprinting with lifelong consequences, provoking the process of DOHaD (developmental origin of health and disease) [6,7]. The faulty imprinting is inherited to the members of the cell line as well as transgenerationally, to the progenies of the imprinted individuum [3,8]. Among the consequences are mild or strong alterations of one or more functions of the cells and their descendants, as well, as known and likely up to now unknown diseases. In animal experiments the impact of faulty hormonal imprinting was justified in case of many organs and organ systems, however systematic investigations in man were not done, at most only observations support the interrelation between the perinatal effect and adult manifestation.

Physiological and faulty hormonal imprinting is an epigenetic process, in which without the change of base-sequence of the DNA, gene expression durably changes. In the process the DNA transmethylase enzymes are participating (changing the methylation pattern of genes (DNA)) as well, as histone acetylases and small non-coding RNAs.

Presently known endocrine disruptors entering into the maternal organism (during gestation) or directly into the infant (early postnatally, by breastmik or any other route) can provoke faulty hormonal imprinting with lifelong consequences.

In the present aspect endocrine disruptors are steroids or steroid-like molecules, which can be bound by the members of nuclear hormone receptor family disturbing the normal (physiological) endocrine activity [9]. This is done by giving -through the receptor- false message which will be executed by the accepting cells, or by inhibiting the binding of the physiological -target- hormone, excluding the transmission and execution of the normal message.

Endocrine disruptors have been and will be present at all times in the human evolutionary environment, in the air, as products of volcanic eruptions, and result of burning (as sequel of waste gases or forest fires as well, as tobacco smoking) in drinking water, as unfiltered components, in the food (as phytostrogens of soy or mycoestrogens), in man-made and used objects (e.g. bisphenol in plastics, herbicides and pesticides etc in agriculture) and at last, as natural or man-made drugs, in the service of human health . This latter is the subject of this paper, in which such molecules are listed and investigated, which have

Correspondence to: György Csaba, Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary, E-mail: csaba.gyorgy@med.semmelweis-univ.hu

Key words: *teratogen, embryo, fetus, perinatal, postnatal, hormonal imprinting, DOHaD, paracetamol, vitamins, oxytocin*

Received: August 10, 2019; **Accepted:** August 26, 2019; **Published:** August 28, 2019

endocrine disruptor-like effects, without having steroid structures, that is inappropriate to the endocrine disruptor definition however, congruent from other aspects.

Facts

Animal experiments

Vitamins: Lipid-soluble vitamins (A,D,E,K) after perinatal employment causes lifelong effect on sexuality, brain function, immunity, bone development and the effect is transgenerationally inherited [10].

Neonatal vitamin D3 treatment of rats changed sexual behavior in adulthood. Single low-dose treatment (2,5 ug/newborn) completely inhibited the ejaculation of adult males, without touching sexual desire (libido), while high dose treatment (250 ug/newborn) abolished sexual desire and completely inhibited ejaculation in adults [11].

Single neonatal treatment with vitamin A (retinol) dramatically reduced the sexual activity of adult male rats [12]. Retinol treatment decreased serum testosterone and progesterone levels measured in adult age in male and female animals respectively, however retinoic acid reduced only progesterone level [13].

Single neonatal vitamin A treatment increased the apoptosis of peripheral lymphocytes when adult [14]

The retinoids (vitamin A or retinoic acid) are effecting through breastmilk on the tymic glucocorticoid and uterine estrogen receptors of the adult rat offspring [15].

Neonatal estrogen imprinting causes persistent proliferation and cornification of the mouse vagina, which can be blocked by concurrent retinol acetate treatment [16].

Single neonatal vitamin E treatment of rats increases receptor's affinity and density of thymic glucocorticoid receptors in six week old rats, and decreased affinity in twelwe weeks old animals. Thousandfold tocopherol could not compete, with labeled dexamethasone [17].

Single neonatal vitamin K1 treatment increased the density of thymic glucocorticoid receptors of adolescent rats and uterine estrogen receptor's of adult females [18].

Single neonatal treatment were done with vitamin E or K1 and sexual activity was lowered in adults in both sexes [19]. The effect of vitamin E was stronger.

Endorphin. Single low dose (3 ug) beta endorphin treatment of newborn rats caused decreased sexual activity and more protest against mounting in females as well, as increased aggressivity and cerebrospinal nocistatin level in adult males, where also the brain serotonin level was lower [20].

Single neonatal exposure of newborn rats with beta endorphin decreased the brain serotonin content and extremely increased nocistatin level of cerebrospinal fluid when adults [21]. Endorphin treatment at weaning enhanced sexual activity, uterine estrogen receptors' binding capacity, and brain serotonin level in adult female rats [22].

Treatment at weaning with serotonin antagonist (and antidepressant, as a medicament) mianserin seriously influenced the nocistatin level of cerebrospinal fluid in adult female rats [23].

Neonatal triiodothyronine treatment influenced sexual behavior of male rats, increasing mounting and decreasing intromissions of male adult mice [24].

Digoxin exposure at 15th, 17th and 19th days of pregnancy (9 ug altogether) caused changes in sexual behavior of rats. Number of active males were higher and ejaculation as well as multiple ejaculation occured only in the treated groups. Females became more receptable [25].

Postnatal doxycycline exposure of mice disrupted Leydig cells mitochondrial function and decreased quality of sperm as well as caused gut microbiota differences, studied at adult age [26].

Treatment at adolescence

Chronic metamphetamine exposure during adolescence of rats altered late behavior and amount of corticostriatal mono-amines in social isolation-reared rats [27].

Retinol treatment of adolescent rats diminished testosterone level in adult male rats, without influencing progesterone level of females [28].

Human observations

Acetaminophen (paracetamol), which is thought the safest analgesic and antipyretic for pregnants can cause lower IQ, ADHD, autism and other childhood behavioral problems [29], given prenatally. This observation is supported by the study of one and a half thousand mothers and children in Denmark [30].

Impaired neurodevelopmental state was observed in case of maternal or fetal exposure of medicinal use of marihuana [31].

Thimerosal (a mercury based preservative used in vaccines) after perinatal exposure in case of vaccination povokes premature puberty [32].

Treatments in puberty

Successful chemotherapy of pubertal Hodgkin's lymphoma provoked breast cancer and cardiotoxicity, decades past treatment [33]

Discussion

The paper does not want to give an inventar of drugs which are avoidable in the perinatal period, only points to the possibility of endocrine disruptor effect otherwise, than it was accepted before and to call attention that faulty imprinting also have to be considered as explanation of the peculiar effect of any medicaments. So, the list is not complete however, it shows that not only arteficial (or natural) steroid-like structures are able to provoke late-acting impacts, causing late manifested diseases, similar to endocrine disruptors. In the case of steroid-like endocrine disruptors this can be explained very easily by the faulty hormonal imprinting [1-4] however, in the case of a painkiller, as for example paracetamol, the structural similarity (consequently the „cheated" developing receptor) can not be estimated. This is not the only situation, when the mechanism remain unexplained, in many cases of developmental origin of health and disease (DOHaD)[6] is a similar state. DOHaD is a very important and theoretically well-grounded theory, nevertheless its mechanism is unknown, except the cases of faulty hormonal imprinting [7], however it can not explain e.g. the interrelations between a possible perinatal intervention and the appearence of a cardial insufficiency in adult age or the relationship between the paracetamol treatment perinatally and the manifestation of ADHD, or autism. At the same time, these human manifestations are extraordinarily importants, considering that their number are extremely growing, in all probability by perinatal faulty imprinting and DOHaD.

Teratogens were believed molecules, which are causing structural (morphological) alterations which can be reecognized already at birth. These alterations are provoked by effects which influences the development in the early phase of ontogeny (first of all in the embryonal period (with a decreasing effect after that), and later as well, as after birth these molecules seem to be harmless from this point of view, as the developing fetus (infant) reaches such a grade of development, when structural changes are not expected. However, functional alterations can be emerged. This is the functional teratogenicity [1], which basically changes the aspects on maldevelopment. This means that 1.) functional maldevelopment can be more serious, than structural one (compare the absence of the little finger with diabetes or autism), 2.) birth is not a borderline of teratogenic effect, as functional teratogens are working also after weeks of delivery (perinatally, which includes also the early postnatal period), 3.) a lot of new molecules appear among teratogenes (e.g endocrine disruptors or medicaments used perinatally) which must be considered at medical interventions. 4.) while structural teratogenicity has not an inheriting character, this can be observed in the case of functional teratogenicity. 5.)Functional teratogenicity can be manifested also in oversensitivity (inclination) to certain interventions, which are needed for the representation of the disease.

Hormonal imprinting can be provoked not only in the perinatal critical period of life, but the window for imprintig is open in further critical periods, as puberty, to which a general lability is characteristic, or in certain systems (e.g. immune system, because of the continuous differentiation of cells) in the whole life. This makes plausible that non-hormone materials are also able to execute imprinting after the end of the most sensitive perinatal period. Although the experiments in this direction are scarce, some of them point to this possibility [27,28].

A special problem is the already mentioned inheritance of faulty perinatal hormonal imprinting . Hormonal imprinting is an epigenetic process, in which the methylation of DNA have the main role. This is altered by the imprinter and the DNA with the new methylation pattern are transmitted to the touched cell line and to the progenies of the imprinted individuum. If we suppose that the imprinting of non-steroidal materials has a mechanism similar to that of endocrine disruptors, this means that they are causing deeper alterations than it was believed before, and in the long run influence further evolution of men.

Oxytocin is a pituitary hormone which is expansively used for initiating or during delivery in developed states. For example in France at 2010 sixty-four percent of laboring women and 58 percent of women with a sponteneous onset of labor received oxytocin treatment [34]. In animal experiments perinatal oxytocin treatment alters brain neurotransmitter levels and -theoretically- could influence the manifestation of pervasive diseases, as auitism, ADHD, etc [35].

Conclusions

Certain molecules (medicaments) used perinatally for treatment of diseases or. symptoms could cause late-manifested diseases, which can appear in any periods of life, similar to the perinatal impact of endocrine disruptors. In contrast to the perinatal effect of endocrine disruptors, in this case the mechanism of effect is not clear and very difficult to explain. However, considering the amount of treatments and the danger of effects, it seems to be worth to avoid the treatments perinatally or have to be cautious if the treatment is inevitable. If the treatment by them was done, a continuous attention and the publication of their results are recommended. It is possible that the process is more general, than it could be believed on the basis of the introduced facts and more imprinters are among the medicaments used perinatally. Especially important the attention and cogitation of treatments with lipid-soluble vitamins in this period of life, as the intervention of them into the endocrine system is justified. and they are obtainable without prescription. Their intake -regardless of the the life periods- at present is medicinally propagated. The other prominently important duty would be the observation of oxytocin treatment, as it is extremely widespread and growing, at the same time, its imprinter effect is justified.

Hormonal imprinting was observed at first in the seventies of the last century by us, and has been supported by other observations and experiments [e.g. 36-38] and its name was introduced at 1980 [2]. Faulty imprinting was published at first in the eigthies of the last century and its importance continously complete itself (in animal experiments) since then. It is strongly supported by the theory and human observations of DOHaD [39]. The collection of the listed cases in this paper suggests the broader significance of the process.

References

1. Csaba G (2016) The faulty perinatal hormonal imprinting as functional teratogen. *Curr Ped Rev* 12: 222-229. [Crossref]
2. 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. [Crossref]
3. Csaba G (2008) Hormonal imprinting: phylogeny, ontogeny, diseases and possible role in present-day human evolution. *Cell Biochem Funct* 26: 1-10. [Crossref]
4. Csaba G (2011) The biological basis and clinical significance of hormonal imprinting, an epigenetic process. *Clin Epigenetics* 2: 187-196. [Crossref]
5. 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. [Crossref]
6. Sata F (2016) Developmental origins of health and disease (DOHaD) and epidemiology. *Nihon Eiseigaku Zasshi* 71: 41-46. [Crossref]
7. Phillips DI, Barker DJ, Osmond C (1993) Infant feeding, fetal growth and adult thyroid function. *Acta Endocrinol (Copenh)* 129: 134-138. [Crossref]
8. Csaba G (2014) Transgenerational effects of perinatal hormonal imprinting. In: Transgenerational epigenetics. Ed.: Tollefsbol T. Elsevier, New York. 255-267.
9. Rubin BS (2011) Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *Steroid Biochem Mol Biol* 127: 27-34. [Crossref]
10. Csaba G (2017) Vitamin-caused faulty perinatal hormonal imprinting and its consequences in adult age. *Physiol Int* 104: 217-225. [Crossref]
11. Csaba G (2016) Faulty perinatal hormonal imprinting caused by exogeneous vitamin D – dangers and problems. *Austin J Nutr Food Sci* 4: 1075-1078.
12. Csaba G, Gaál A (1997) Effect of perinatal vitamin A or retinoic acid treatment (hormonal imprinting) on the sexual behavior of adult rats. *Hum Exp Toxicol* 16: 193-197. [Crossref]
13. Gaál A, Csaba G (1998) Testosterone and progesterone level alterations in the adult rat after retinoid (retinol or retinoic acid) treatment (imprinting) in neonatal or adolescent age. *Horm Metab Res* 30: 487-489. [Crossref]
14. Gaál A, Bocsi J, Falus A, Szende B, Csaba G (1997) Increased apoptosis of adult rat lymphocytes after single neonatal vitamin A tratment (hormonal imprinting). A flow cytometric analysis. *Life Sci* 61: 339-342. [Crossref]
15. Gaál A, Csaba G (1998) Effect of retinoid (vitamin A or retinoic acid) treatment (hormonal imprinting) through breastmilk on the glucocorticoid receptor and estrogen receptor binding capacity of the adult rat offspring. *Hum Exp Toxicol* 17: 560-563. [Crossref]
16. Masui F, Matsuda M, Akazome Y,Imaoka T, Mori T (2001) Prevention of neonatal estrogen imprinting by vitamin A as indicated by estrogen receptor expression in the mouse vagina. *Cell Tissue Res* 306: 441-447. [Crossref]
17. Csaba G, Inczefi-Gonda Á (1998) Neonatal vitamin E treatment induces long term glucocorticoid receptor changes: an unusual hormonal imprinting effect. *Life Sci* 63: 101-105. [Crossref]

18. Csaba G, Inczefi-Gonda Á (1999) Effect of a single neonatal vitamin K1 treatment (imprinting) on the binding capacity of thymic glucocorticoid and uterine estrogen receptors of adolescent and adult rats. *Life Sci* 65: PL 1-5. [Crossref]

19. Csaba G, Karabélyos CS (2000) Influence of a single treatment with vitamin E or K (hormonal imprinting) of neonatal rats on the sexual behavior of adults. *Acta Physiol Hung* 87: 25-30. [Crossref]

20. Csaba G, Knippel B, Inczefi-Gonda Á, Hantos M, Tóthfalusi L, et al. (2003) Effect of neonatal beta-endorphin imprinting on sexual behavior and brain serotonin level in adult rats. *Life Sci* 23: 103-114.

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

22. Csaba G, Knippel B, Karabélyos C, Inczefi-Gonda Á, Hantos M, et al. (2004) Endorphin excess at weaning durably influences sexual activity, uterine estrogen receptor's binding capacity and brain serotonin level of female rats. *Horm Metab Res* 36: 39-43. [Crossref]

23. Csaba G, Knippel B, Karabélyos C, Inczefi-Gonda Á, Hantos M, et al. (2004) Effect of treatment at weaning with the serotonin antagonist mianserin on the brain serotonin and cerebrospinal fluid nocistatin level of adult female rats: a case of late imprinting. *Life Sci* 75: 939-946. [Crossref]

24. Karabélyos C, Csaba G (1997-1998) Effect of neonatal triiodothyronine (T3) treatment (hormonal imprinting) ont the sexual behavior of adult rats. *Acta Physiol Hung* 85: 11-15. [Crossref]

25. Karabélyos C, Csaba G (1998) Effect of fetal digoxin exposure (imprinting) on the sexual behavior of adult rats. *Gen Pharmacol* 31: 367-369. [Crossref]

26. Hou X, Zhu L, Zhang X, Bao H, Tang M, et al. (2019) Testosterone disruptor effect and gut microbiome perturbation in mice: early life exposure to doxycycline. *Chemosphere* 222: 722-731. [Crossref]

27. Strauss L, Brink CB, Möller M, Stein DJ, Harvey BH (2014) Late life effects of chronic metamphetamine exposure during puberty on behavior and corticostriatal monoamines in isolation-reared rats. *Dev Neurobiol* 36: 18-28. [Crossref]

28. Gaál A, Csaba G (1998) Testosterone and progesterone level alterations in the adult rat after retinoid (retinol or retinoic acid) treatment (imprinting) in neonatal or adolescent age. *Horm Metab Res* 30: 487-489. [Crossref]

29. Toda K (2017) Acetaminophen treatment. Safe in pregnancy? *Scand J Pain* 17: 445-446.

30. Liew Z, Bach CC, Asamow RF, Ritz B, Olsen J (2018) Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. *Int J Epidemiol* 45: 2009-20017. [Crossref]

31. Thompson R, De Jong K, LO J (2019) Marihuana use in pregnancy: a review. *Obstet Gynecol Surv* 74: 415-428. [Crossref]

32. Geier DA, Young HA, Geier MR (2010) Thimerosal exposure & increasing trends of premature puberty in the vaccine safety datalink. *Indian J Med Res* 131: 500-507. [Crossref]

33. Candela JL (2016) Cardiotoxicity and breast cancer as late effects of pediatric and adolescent Hodgkin lymphoma. *Am J Nurs* 116: 32-42. [Crossref]

34. Belghiti J, Coulm B, Kayem G, Blondel B, Deneux-Tharaux C (2013) Oxytocin administration during labor. Results from 2010 French National Perinatal Survey. *Gynecol Obstet Biol Reprod (Paris)* 42: 662-670. [Crossref]

35. Hashemi F, Tekes K, Laufer R, Szegi P, Tóthfalusi L, et al. (2013) 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 disease? *Reprod Sci* 20: 1255-1263. [Crossref]

36. Tchernitchin AN, Tchernitchin NN, Mena MA, Linda C, Soto J (1999) Imprinting: perinatal exposures cause the development of diseases during the adult age. *Acta Biol Hung* 50: 425-440. [Crossref]

37. Goudochnikov V (2015) Role of hormones in perinatal and early postnatal development: possible contribution to programming/imprinting phenomena. *Ontogenez* 46: 285-294. [Crossref]

38. McGrath J (2001) Does 'imprinting' with low prenatal vitamin D contribute to the risk of various adult disorders? *Med Hypotheses* 56: 367-371. [Crossref]

39. Barker DJ (2007) The origins of the developmental origins theory. *J Intern Med* 261: 412-417. [Crossref]