Dangerous faulty perinatal imprinting by medication: Review and hypothesis

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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 becomes 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 disrupters entering into the maternal organism (during gestation) or directly into the infant (early postnatally, by breastmilk or any other route) can provoke faulty hormonal imprinting with lifelong consequences.

In the present aspect endocrine disrupters 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 disrupters 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 phystostrogens of soy or mycoestrogens), in man-made and used objects (e.g. bishenol 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

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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].


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 thymic 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 twelve 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 recepitable [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 pregnancies 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 marhuana [31].

Thimerosal (a mercury based preservative used in vaccines) after perinatal exposure in case of vaccination provokes 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 inventory 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 important, 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 recognized 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 medications used perinatally) which must be considered at medical interventions. 4.) while structural teratogenicy 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 imprinting 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 spontaneous 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 autism, 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 imprints 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 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 eighties of the last century and its importance continuously 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.

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