Lifelong impact of breastmilk-transmitted hormones and endocrine disruptors.

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Abstract

BACKGROUND: Endocrine disruptors are hormone-like -usually lipid-soluble- natural or man-made molecules, which can be bound by human hormone receptors, simulating, stimulating or inhibiting the action of physiological hormones. They are harmful in adults however, more harmful perinatally, when faulty hormonal imprinting is provoked by them, with lifelong consequences (functional teratogenicity). By this effect alterations in hormone binding, hormone synthesis, sexual behavior, immune response, bone development, inclination to, or manifestation of diseases, etc in adult age, occur.

REVIEW: Breastmilk is the main transporter of endocrine disruptors to the infant, as the mentioned molecules are concentrated in it. The perinatal faulty hormonal imprinting is epigenetically inherited to the progeny generations however, it is not known in man how many generations will be touched (experiments on unicellulars show at least 1000 generations, in rats two generations).

CONCLUSION: Acknowledging the advances of breastfeeding in general, its disruptor-transmissing faulty imprinting-effect must be known in our chemically „infected" environment, in the light of developmental origin of health and disease (DOHaD).

Keywords: Hormones, hormonal imprinting, endocrine disruptors, perinatal, mother-milk.

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Introduction

During pregnancy the hormones of the mother's endocrine system influence different functions of the fetus, targeting the hormone receptors on the surface of the cells, or inside, in the cytoplasm however, approaching the birth and after birth the receptors meet the fetal and infant hormones and develops the hormonal imprinting. It is a physiological process, which is needed for the normal funtion of the receptor-hormone complex and its effect is maintained lifelong [1-3]. Nevertheless, in this critical period -perinatally- when the developmental window for imprinting is open, molecules similar to the physiological (target) hormone, as other members of the hormone family or natural or synthetic hormone-like molecules (endocrine disruptors) are also bind to the receptor causing faulty hormonal imprinting, with lifelong consequences. The faulty perinatal hormonal imprinting is a functional teratogen [4,5], which alters the receptor's binding capacity, consequently disturbing the normal function of the target cell. This could be manifested in the disturbances of hormone binding [6,7] and hormone production [8] of the given cells, in the sexual behavior [9-11], in diseases of bones [12] etc. at any period of life, giving the basis of metabolic and immunological imprinting [13,14] as well, as the developmental origin of health and disease (DOHaD) [15,16].

The perinatal period includes the prenatal period, the birth and the postnatal period, when (in the case of the latter) environmental factors are able to touch the infant directly (e.g. by inhalation or with the transmission of skin) however, the most important and intimate contact in the transport of materals is the breastfeeding, when the lactating mother transports materials, which are present in her blood circulation to the infant, whose cells have the open window for faulty imprinting. This means that functional teratogenicity is working also postnatally, first of all by the transmission of mother-milk. In our modern age numerous strange molecules, named endocrine disruptors are transferred from the mother to the infant by breastmilk. These endocrine disruptors are natural or mostly human-made and human-used molecules, similar to (first of all steroid) hormones, which can bind to steroid hormone (nuclear) receptors stimulating the cell for function or inhibiting the binding and effect of physiological target-hormone.

Selected Facts

Numerous substances are concentrated in breastmilk and can be passed to the infant. Some of them are hormones or endocrine disruptors, influencing the physiology of the infant or provoke faulty hormonal imprinting with lifelong consequences.

Experiments and observations on animals

Estrogenic compounds (endocrine disruptors, eg. diethylstilbestrol=DES) which are injected to the mother are passed by breastfeeding into the neonates as it was justified by induction of CaBP-9k gene expression [16,17]. programmed hypertension in adult male offspring. Stabilizing T-reg cell differentiation, breastmilk can protect against atopic and autoimmune diesases [18]. Maternal melatonin or agomelatonine treatment during lactation prevented the light-programmed hypertension in the progenies [19,20]. Flaxseed supplementation of lactating maternal diet provoked hormonal imprinting in rats and caused increased risk for later development of diabetes mellitus [21]. Leptin treatment of rat

dams during the first 10 days of lactation caused hypothyroidism in the offspring, which could be observed already at the 30th day of age and was continued by a higher thyroid function in the adulthood by leptin treatment on the neonatal period [22]. Dioxin (TCDD) exposure during lactation of rats influenced hepatic metabolism and sexual differentiation of microsomal enzyme activities [23]. Breastmilk exposure to bisphenol (BP) AF impairs reproductive functions of male offspring [24] and ovarian dysfunctions had been demonstrated in adult females [25]. Lactationally transmitted dibutyl phtalate adversely affected reproductive capacity of female rats [26]. Nonylphenol exposure by breastmilk caused neurodevelopmental and behavioral destruction of offspring [27]. Strongly protein restricted diet (8%) during lactation deeply influenced thyroid regulation in adult rats, showing a higher thyroid function in the restricted group [28]. Maternal soybean diet during lactation (in rats) reprogrammed the lipid profile for adult males causing lowered metabolic risk by decreasing serum triglicerides and low density lipoprotein cholesterol (LDL) and also protects glucose metabolism [29]. Prolonged benzpyrene exposure during lactation of rat reduced glucocorticoid receptor's number for adult age, without alteration of receptor affinity [30]. Single (at the 3rd day of life) or prolonged (for 21 days) alcohol exposure of rat dams, enhanced nocistatin level of blood plasma and cerebrospinal fluid measured in adult offspring [31]. Retinoid (vitamin A or retinoic acid) imprinting through breastmilk has been transmitted to progenies, disturbing binding capacity of glucocorticoid and estrogen receptors [32]. High concentration of insulin and leptin of offspring of malnutritioned rat dams in adult age was observed [33]. N-butylparaben caused rat reproductive disorders [34]. Lactationally transferred BP A adversely influenced fertility of adult mice, inducing decreased sperm quality, antioxidant capacity and changes in testicular tissue [35]. Lactational transfer of phytoestrogens provoked hypertrophy of adult male mammary glands [36]. Lactationally transmitted bisphenol AF increased testosterone level in rats measured when adults [37]. Hepatic tumors develop in mice whose mother was fed perinatally with BP A containing diet [38]. Type 1 diabetes developed in mice, whose mother was treated with BP A perinatally [39]. Lactational exposure of mice perinatally to BP A slightly modulate innate immunity (to influenza A virus) in adults, but does not impair adaptive immune response [40].

Observations on humans

LH-RH enters into the human breast-milk in higher concentrations than it is present in the blood, by passive diffusion or by concentrating mechanism [41]. Prolonged breast-feeding is associated with increased LDL-cholesterol and consequently higher death rate from ischemic heart disease in adult age. This is explained by the presence of thyroid hormones in breast-milk and hormonal imprinting by it [42]. Breastfeeding protects against chilhood obesity by metabolic imprinting [43]. At the same time, maternal undernutrition, obesity and diabetes during lactation could provoke obesity in offspring [44]. Maternal undernutrition, overnurition and diabetes could provoke obesity of offspring by metabolic reprogramming (metabolic imprinting) transmitted and breastmilk [45]. Childhood obesity can be deduced to low maternal vitamin D status and short duration of breast-feeding [46].

Endocrine disruptors (EDs) originating from the industrially contaminated environment are present in breastmilk [47,48]. However their effects could be combined with phytoestrogens present in human nourishments, first of all in soy. Consumption of canned coffee drink causes the presence of BP A in breast milk, if the container is coated with vinyl chloride resin [49]. Though only a minute amount of these substances are present in the breast milk, this is enough for reprogramming the development [50], and the amount in the milk is higher than that of the blood serum [49]. Polybrominated diphenyl esters (PBDEs) can be demonstrated in breast milk (having estrogen and anti-androgen activity in a relatively high amount, which seems to be the highest in North America [51] and it is rapidly increasing. Colostrum contains BP A in a higher amount, than it is present in the blood [52]. BP A, a substance which is absolutely needed for plastic industry (plasticizer) in a Korean study was found in 79.5–100% of human maternal breast milk [53]. Environmental estrogen disruptors having estrogen and antiandrogen activity can act in low doses by transmission of breastmilk [54]. Persistent and non-persistent pesticides are also present in breast-milk, causing disturbances in metabolic, neurologic and immune systems [55]. A positive correlation between DDT contents of human milk and later backward school children was observed [56]. Grapes' procyanidin consumption during lactation increased atherogenic risk indexes in adult offspring by impairing reverse cholesterol transport [57].

Diseases

Breastfeeding strengthens the immune system, protecting against infections and inner disturbances [58]. It promotes gastrointestinal mucosa maturation, alter gut microflora, and modulate the development of diseases by growth factors, cytokines and hormone [59]. The occurrence of diseases is less frequent in breast-fed persons, e.g. rheumatoid arthritis is inversely related to breast-feeding for more than 12 months [60]. However, polychlorinated byphenils, as PCB138 was significantly associated with breast cancer, acting through breastmilk [61]. Bisphenol A stimuli are correlated with obesity, diabetes, cardiovascular diseases, polycystic ovarian syndrome and low sperm count [62]. Bisphenol A seems to be responsible to more frequent incidence of breast and prostate cancer [63]. Lactational transfer of endocrine disruptors are also responsible for glucose homeostasis in adults [64]. Lactational smoking also can affect infertility, spontaneous abortion, placenta insufficiency, clubfoot, childhood respiratory diseases, attention deficit disorder and some childhood cancers [65,66]. Cryptorchidism in many cases are related to higher endocrine disruptor levels in maternal breastmilk [67].

Discussion

Exposure by different materials through the mother's transmission can be happen: by the way of blood circulation or by the transport of breastmilk. In the embryonal or early fetal period the maternal blood circulation is involved in the transport and this have a role in morphological malformations. However, later, perinatally (before and after birth) functional teratogenicity [3-5,10,68] can be observed, as an aftermath of faulty hormonal imprinting. In this latter the transmission by

breastmilk have a serious role. Breastfeeding was believed the best and most recommended for the newborn and infant up to now however, this became dubious considering the increased concentrations of endocrine disrupting chemicals in the mother-milk. Nevertheless, these harmful substances are also concentrated in cow-milk [69], which means, that theoretically only different infant formulas can substitute the breastmilk, without harmful consequences. The problem is, that the most frequent soy-based infant formules contain phytoestrogens, as genistein and daidzein, which are themselves endocrine disruptors and their amount in the infant formulas so high, as if one tablet of anticoncipient/day would be given for the infant. This means that this trap can not be avoided and in this case, the adventageous properties of breastmilk can override the use of other nourishments. The traditional belief (on the best-being of breast-feeding) remains, but doctors must know that today's mothermilk is not the same as was hundred years before and it can cause problems (some of them mentioned among facts), which have to be calculated when diagnosis is composed considering the patient's occupation, domicile, hobby etc [70]. Also important to know, that perinatal hormonal imprinting influences not only later hormonal effects, but also hepatic drug metabolizing microsomal enzymatic activities [71,72] and other related factors which will be cleared in the future. It seems to be also a later duty the study of hormetic effect of breastmilk-transported endocrine disruptors, which could have a positive impact [73].

Most of the endocrine disruptors are lipid-soluble molecules. After the entrance into the body they are settled in the adipose tissue, and forms a stock, from which gradually liberated into the blood circulation. The best way of elimination is the passage into the lipid-rich breastmilk however, this route does not lead back to the environment, but into the infant. Corticosteroids, sex hormones, major tranquillizers, tricyclic antidepressants, antihypertensives have this route as well, as pesticides, herbicides, insecticides and other lipid soluble environmental contaminants [74]. The amount of drugs is not more, than 1-2% of maternal dose [75] however this is copiously enough for provoking lifelong faulty imprinting. At the same time, the highly lipid-soluble insecticides are passed more easily, reaching a concentration, higher than the allowable daily intake, according to the WHO [76].

The increase of endocrine disruptors' amount in the environment is independent on medical interactions, in general. However, in some cases medical intervention causes the problems. This is manifested in the case of pervasive developmental diseases (autism spectrum disorders), when hormonal imprinting by oxytocin disturbed the biogenic amine level of the brain, provoking perinatal faulty imprinting for lifelong consequences. Though in our experiments [77] single neonatal oxytocin treatment caused alteration in the brain biogenic amine level, this can happen also by (prolonged) breast-milk transmission [78].

Although endocrine disruptors are dangerous at adult age, their effects seem to be more dangerous in the perinatal period. In adults there is a direct effect, provoking acute or chronic diseases or inclination to diseases (by weakening the immune system), the perinatal exposure to endocrine disruptors disturbs (reprogram) fuctions for life. This means that its effect is longer and deeper lasting, than in adult age. Breastfeeding is the main transmitter of our modern age endocrine disruptors.

Perinatal faulty hormonal imprinting is an epigenetic process [68]. This means that related hormones or endocrine disruptors do not affect directly genes, causing mutations, but their effect is manifested in the epigenetic regulation, which influences the expression of genes, namely determining what genes be functioning or inhibited [79]. This is done mainly by the methylation of cytosin bases in DNA, which hinders the function of the touched genes. By this there is a reprogramming of the genetic machinery [80]. The modified (reprogrammed) methylation pattern is usually erased in the next generations however, this is not complete and the remaining change ot methylation pattern is suitable to transmit the information to the next generation [81]. This means that the change is inherited to the cell line and also to the progeny generations of the individuum, namely imprintings in the new generations are settled on, considering the alterations. This causes the continuous accumulation of errors, which could be manifested in the growing number of certain diseases. As the diseases in connection with faulty perinatal imprinting are not completely mapped, the growing number of them can be expected. Already in the last time attention was called to the relation between endocrine disruptors and autism spectrum disorder (ASD) as well, as attention deficit hyperactivity disorders (ADHD) [82,83], as also on differences in the case of the immune system [84,85]. It seems likely that tumor development will be the next, the relation of which will be demonstrated [86] and accepted. As it was mentioned, breastmilk transmitted perinatal faulty hormonal imprinting is unavoidable and its effect is manifested later, in adult age, and in the progeny generations. In mammalian experiments its inheritance also was justified. However it is not known how much human generations will show this effect. In unicellular protozoans the effect of hormonal impring at least lasts up to the 1000th generation [87], however this can not be studied in human beings. By all means, it is worthwhile to observe and consider as a factor which could influence the setting and outcome of a disease.

Conclusion

Studying the references and considering the discussion, the conclusion can be drawn: breastmilk transmission of endocrine disruptors into the infant is a very important effect on the developing endocrine system and its target organs. This transmission can contribute to the manifestation of different diseases in adult age(DOHaD) [88,89] by provoking faulty hormonal imprinting, which seems to be the most plausible explanation for DOHaD [1-3,6]. Knowing the enormous proliferation of new and further endocrine disruptors in the environment, the danger of alterations by faulty hormonal imprinting is imminent.

Conflict of Interest: There is not conflict of intrest.

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