Abstract

The genes of the human genome contain the information for the building of organism and for the possibilities for execution of the program described in it. However, the genes are identical in each cell of an organism and the epigenomic machinery selects from the gene pool the sorts, which are working in one certain cell and provokes its action as well, as inhibits it (first of all) by methylation of DNA. The methylation pattern of DNA determines the program of a cell, organ or system and the subsequent activation and inhibition of the pattern is responsible for the running of the program, either in case of a polypeptide folding, or in the initiation of puberty. Endocrine disruptors, acting in the critical periods of development (e.g. perinatally or at adolescence) as steroid hormone-like molecules provokes faulty hormonalim printing and can disturb the program by it, with lifelong harmful effects, which is manifested in alteration of functions regulated by the program or in late appearing diseases. The Developmental Origin of Health and Disease (DOHaD) theory as well, as the new notion of functional teratogenesis can be deduced and explained by faulty hormonalim printing. As the variants and volume of endocrine disruptors are growing, the increase of developmentally established diseases and functional teratogenicity in all probability also will be enhanced.

Keywords: DNA-methylation; Developmental program; Perinatal epigenetics; Pubertal epigenetics; hormones; Steroids; Transgenerational effects

Introduction

The 46 chromosomes of the human genome contain the whole program of development as well, asthe program for the later function of cells and organs. Although each cell of an organism contains the same genes or inments, the different cell types and different or gans are executing different functions according to the need of the organism and the acute claims. This means that there must be a distribution of the functioning genes in different organs and occasions and for this a further regulation is necessary. This further (higher) regulation is named epigenetic, what determines the function of the given cell (organ). There are more components of this regulation, as methylation of cytosins (CpGislets) in the DNA or methylation and acetylation of histones as well, as activity of some small ribonucleic acids. The pattern of methylation seems to be the main regulator, hindering the expression of methylated genes for life or temporarily, for the period of provoked acute function [1]. Genes could be methylated, hypo- or hypermethylated, demethylated or remethylated by the contribution of the enzymes, DNA methyltransferases [2].

Ontogeny and Programming

The fertilized egg, the zygote is totipotent, what means that it is able to create all of the organs during the ontogenetic development, while its totipotency is narrowed to pluripotency (when more direction for development is possible, but not all) and at last to unipotency, when the cells exist and are able to divide, creating new similar cells, or –having determined function there is not cell division at all. In the earliest, embryonic phase of development the organism is very sensitive to strange materials which are able to completely destroy it, later multiple (systemic) effects is observed. This means that in man the first three months of development are the most sensitive to teratogens which is resulted in morphological destructions and it can be observed directly at birth. In the fetal period, the teratogenic effects touche single organs. However, in the fetal period harmful materials are causing functional teratogenesis (troubles of epigenetic regulation), which is not manifested at the time of birth, but later, mostly in adulthood, as different diseases. The epigenetic mechanism, named developmental programming starts to work in the late phase of intruterine development and early postnatally and in these phases the hormonal imprinting is taking place, during the first encounter between the developing hormone receptors and their target hormones. This encounter determines the normal (physiological) function of the receptor-hormone complex for life, as the bindig capacity of receptors is inherited from cell to cell in the given cell line. Very small amounts of hormones (down to \(10^{-21}\) M) can provoke imprinting, and the amount of hormones participating in the process is as important, as the time of its presence. The process of potency-shrinking runs parallel to the methylation [6]. For example, DNA methyltransferase, which is responsible for the methylation of DNA has the highest level in the testis of rat between the 7 to 21 days of age and decreased by 45% by day 28, which shows that no matter when the imprinter impacts [7]. Hormonal imprinting is a part of the developmental programming and it could be executed only in the critical periods, when the developmental window for it is open. Considering teratogenesis, this functional form is prolonged to the early postnatal period. Part of the programming is the hormonal imprinting, when the developing hormone receptor, in the plasma membrane or intracellularly (nuclear receptors) and its target hormone meet each-other in the first occasion and the binding capacity or receptors is adjusted by it [8].

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**The Hormonal Imprinting**

Hormonal imprinting is very sensitive to related molecules, which are or could also be present in the organism incritical periods of the open developmental windows and can be recognized and bound by the receptor. These molecules could be members of the same hormone family, physiologically present in the human organism, related man-made artificial molecules, as medicaments (e.g. synthetic hormones, lipid soluble vitamins), environmental pollutants (products of volcanic eruptions, communal pollution originating e.g. from cars or cigarettes), industrial pollutants, agrotechnical materials, which are collectively named endocrine disruptors. These molecules can be recognized and bound by the hormone receptors in anytime of life of an organism, however, there are serious differences in their effects depending on the period of life. In adults they can provoke an acute hormone-like effect, or inhibit the binding of the physiological hormone however, in theperiod of perinatal development they cause faulty hormonal imprinting with later, life long consequences [8]. This means that there are not easily observable alterations in the time of faulty imprinting and the impact (e.g. in theform of a disease) can be observed only years or decades after the intervention [9]. This makes difficult to notice the connection between the faulty imprinting and its consequences and only animal experiments help to clear it. These experiments unanimously show that perinatal faulty imprinting causes differences in the binding capacity of receptors, in the hormone production of cells, in the sexual behavior of male and female animals, in the immunity, in the construction of bones, in the neurotransmitter content of the brain etc. There are not exceptions in the reactions of the organs, all of them, which had been studied at all, demonstrated alterations in the cellular responses mentioned before. This means that the faulty hormonal imprinting is able to disturb the whole program and this is prolonged for life [10,11]. In addition, it is sneaking, as the consequences are hidden for a very long time.

The main programming is taking place in the fetal period of development and early postnatally however, there is also a possibility for reprogramming or adjusting the original program in different later periods of life [12]. It seems likely that later reprogramming periods are at weaning and adolescence in general however, with special late opening the developmental window for the different organs, as their aging course is also different. In the case of continuously dividing (differentiating) cells there is a continuous possibility of reprogramming endogenously or by faulty imprinters (endogene disruptors) and this can be best observed in the case of bone marrow cells, which is manifested in the immune system, when reprogramming could cause autoimmunity or allergic diseases [13].

Hormonal (physiological or faulty) imprinting is an epigenetic process.

It is believed that endocrine disruptor effect to the developmental program is a new phenomenon, as man-made endocrine disruptors appeared in the last time, but this is not right. Endocrine disruptors always were present in the human environment, as products of volcanic eruptions, and rather as components of human nourishment, phytosteroenzymes, mycoestrogens etc. What is an important difference between the past and present: the amount and variations of endocrine disruptors by human activity and human claims for more pleasant life, by medical treatments and by the increase of population, which requests more food, and urban life-style. This results in the common and combined effects of endocrine disruptors, which was not present earlier. Men was always living together with endocrine disruptors, which were not called by this name, and were stable and homogeneous. This coexistence formed our organism which had similar outer appearance millennia ago however, inner indexes changed seriously (rivista). Now, these changes accelerated and led to them is belief on novelty of endocrine disruptors and their effects [14].

The epigenetic alteration without changing the base sequence (not causing mutation) is inherited not only inside the cell line, but inherited to the progeny generations, and the new endocrine disruptors affect this altered (reprogrammed) genome. The series of impulses change the basic character of the genome, which is manifested in the altered functions and responsibility to external attacks. This could be registered as a new type of evolution however, it is quite independent from the conventional evolution by selection [15,16].

It is believed in the case of numerous diseases that the flood of endocrine disruptors are responsible for the proliferation of them. This is possible indeed however, this is a self-exciting process. At first, as steroid hormone-like materials are mostly the present-day disruptors, steroid receptor bearing cells (organs) are mis-influenced by them. These organs or organ systems could be direct targets of endocrine disruptors, as the organs of sexual sphere or the immune system however, numerous such cells have steroid receptors which are present in other systems. In addition there is a connection between steroid receptors and other receptors (e.g. polypeptide hormone receptors), somass-raction and chain-reaction can be provoked, which are more likely, if the receptors are present in (on) brain cells. Considering the epigenetic inheritance, the growth of disruptor-caused diseases can happen without the enhancement of variation or amount of disruptors, simply by the increment of disruptor-influenced progeny generations. Nevertheless this is not the problem of the present time, but that of the future.

As endocrine disruptors are steroid hormone-like molecules, at first such diseases are provoked which are connected with steroid hormones [17]. However, it is worth to mention diabetes as a consequence of endocrine disruptor imprinting, while diabetes is connected with insulin, a polypeptide hormone. Nevertheless, presence of food contaminants (such as bisphenol A) in the mother's organism, during the development of pancreas causes disturbances in metabolic programming, which could be manifested in type 2 diabetes in adult age and is inherited to the progenies [18-20]. In this case have to be considered the stress-effect of endocrine disruptors which will be discussed later.

It seems to be dangerous, that continuously differentiating (dividing) cells could be faulty-imprinted during the whole life. In these cells there programming by endocrine disruptors could lead to malignancies in any period of life, from they oungerage, to senescence. Reprogramming basically alters the physiological program of the genom in the touched cells, consequently these cells behave independently of the whole organism (tumor formation and tumor behavior).

Methylation of a gene reduced the possibility of its expression. About 80% of cytosins (CpGdinucleotide) is methylated normally. Hypermethylation means that the gene is strongly suppressed, its expression is not likely. In case of hypomethylation the gene is easily expressed. However hypo- and hyper-methylation could be occured together in the same cells, when there is a global hypomethylation...
and regional hypermethylation. Both process is done by the enzyme, DNA-methyl-transferase. There are genes in the genomic, the activation of which promotes malignant tumor formation, while others have tumor suppressor activity (p53gene). The induction and further fate of tumor is dependent of the function of these genes and on factors, which are influencing these genes, mainly the special activity of DNA methyltransferase. The methylation pattern can be modified. Xenoestrogens, as endocrine disruptors can deregulate the methylation pattern of DNA as well as the histone, which disturbs the development of progenitor cells, leading them to a tumorous direction. If tumor suppressor genes are hypermethylated malignancies are manifested as well, as when tumor forming genes are hypomethylated. This seems to be right in general, however individual susceptibility by different other factors influence the genes’ effect. This susceptibility is determined at the perinatal period by faulty hormonal imprinting of endocrine disruptors. It is suspected that the increased incidence of breast cancer in European and American human populations over the last 50 years can be assigned to the enormous amount of endocrine disruptors. Though inheritance is an important factor in the manifestation of breast tumors (which is the most-common non-skin cancer) over 70% of breast cancer-bearing women have sporadic, non-inherited cancers and perinatal influence of endocrine disruptors are suspected as causal factors. In case of hematopoetic neoplasms (leukemia) it also has a role in the dysregulation of the program.

Perinatal Stress, As General Imprinter

Maternal stress has a deleterious effect to the normal programming of the fetus. The stress harmfully influences the hypothalamo-pituitary-adrenal axis. This stress can be caused by psychological factors, as anxiety as well, as by some endocrine disruptors in the time of openness of developmental windows for imprinting. This could lead to neuroendocrine or behavioral distortions as well, as gonadal problems in adult age. As it was mentioned, maternal nutrition has also a keyrole in metabolic programming and this can be disturbed during pregnancy by different components, which can lead to type 2 diabetes in the adult offspring. Food contamination with endocrine disruptors (e.g., bisphenol A) leads to later metabolic disorders (obesity, diabetes), depending on the time of exposures, from maternal and fetal genotypes and almost independently from exposure levels [21-25].

Early-life stress impacts the hypothalomo-pituitary adrenal axis and could promote the manifestation of psychiatric disorders in the offspring in adult age [26]. Problematic psychological development is caused by the disruption of program, by prenatal stress with increased susceptibility to environmental effects, while the enhancement of postnatal plasticity in adults increases.

Early-life stress during the critical period of imprinting could lead to enduring neuroendocrine alterations (hyper or hypo-activation of the stress-system) modulating the long-term risk of disease vulnerability in adulthood, and modifying epigenetic regulation of gene expression for life [27,28].

When Hans Selye recognized the uniform response (GAS=General Adaptation Syndrome) to different interventions, he named it „stress” and the uniformity of reaction was the new and most important [29]. In the present case stress effects caused faulty hormonal imprinting. This provokes the question: how specific is the effect of endocrine disruptors? There is a possibility that endocrine disruptors are not only specific faulty imprinters (as this is justified) but general stressors, or this latter is also measured when the imprinter’s effect is studied? If there is a non-specific stress effect of the endocrine disruptors, this can explain why so many different cells respond to a certain faulty imprinter, which was believed earlier to the presence of steroid receptors in different cell types.

The methylation pattern of the genes can be modified and this is taking place physiologically during the ontogenetic development, by the physiological imprinting and in the non-perinatal critical periods of development, e.g. in case of puberty [30]. However, in the critical periods endocrine disruptors are also able to make modifications, which are sometimes brutal and meaningless and these modifications also lifelong disturb the function of cells (organs) and can cause malignant tumor as well, as insufficient functions (diseases). Endocrine disruptors can provoke oxidative stress at cellular level as well as organismic stress through the hypothalamo-hypophysel-adrenal route and this is valid in case of the openness of the critical window perinatally [31-36]. The combination of chemical and non-chemical (e.g. psychical) stress is also possible with a more expressed effect [34,37]. The non-specific reprogramming caused by endocrine disruptors increases the specific effects and cannot be differentially recognized, so it is attributed to the specific effect and it might contribute to the increased susceptibility to endocrine disruptor-related specific effects (disorders) in later life [36,38-40]. Although there are such studies which denies the harmful effects of endocrine disruptors [.,despite, of 20 years of research of human health risk from exposure to low concentrations of exogenous chemical substances with weak hormone-like activities remains an unproven and unlikely hypothesis" - 41), the animal experiments on faulty hormonal imprinting and human observations unanimously demonstrate their intervention to the developmental programming and the consequences manifested in the cell's response as well, as in diseases [41,42].

Faulty Imprinting and Faulty Programming

Genes of an individuum contains the whole inventar of possibilities with which the person possess, packed in humans into 46 chromosomes, and the epigenetic mechanism selects the actual genes which is needed to give information. However, the epigenetic mechanism is also individual, determined by the genome. This means that the genomic basis is the most important nevertheless, the epigenetic can to chip on the execution. The epigenetic mechanism is the executor of gene-selection, by the work of methyltransferase enzymes, while the direction of the work, consequently the result depend on the genome. It is not known, whether the genome or the epigenome is directly influenced by the endocrine disrupter chemicals, however, the epigenome is easier influenceable. In contrast to this property, the alterations which happened in the program are inherited inside the given cell line, and between the parents and progeny. This revaluate the epigenetic alterations.

The effect of endocrine disruptors causing later diseases after early exposures does not mean that the manifestation of the disease must happen in adult age: it is relevant only in the distance between the exposure and the manifestation, which could also be in the childhood. A characteristic example of this is the childhood obesity, which touches about 17% of children in the United States and similar data are found in many developed countries.

The program is prepared for life. However, there are not real observations on its durability, and it is not restricted to the endocrine system [43,44]. The name „endocrine disruptor” was given, as they have hormone (steroid)-like structures, and their effects were
discovered in this region. Not the „endocrine” attribute seems to be the most important, but the „disruptor” (which disturbs the methylation pattern of DNA), which can appear in different forms of chemicals, flooding the environment. This means that by the proliferation of new chemicals in the environment could touch other organs, which does not belong to the endocrine system [45]. In aged people a lot of life-functions weaken, which shows that the program is not so exact, as it was earlier. This can be observed in the case of hearing, which is generally deteriorates during aging. Otoxicants, a new class of chemicals tressors can be responsible for this deterioration, in addition to the earlier known factors. In the near future other program-dependent negative alterations are expected in the case of rigorous observations [46].

Although perinatal faulty hormonal imprinting by endocrine disruptors influences later events for life, the adolescent fault imprinting also is not negligible. In animal experiments it disrupts later behavior, aslo comotion, exploitation, anxiety, and sociability, masculinizing female social and emotional behavior, influences the immune system [47,48].

Considering hormones is it is likely that perinatal hormonal imprinting played a role in the evolution of neuroendocrine regulation as well as in the defense against the genetic deterioration during evolution. The single meeting between the developing receptor and mini-doses of endocrine disruptors, which are suitable for provoking faulty imprinting could be rather frequent during the evolution, and this could form the whole system, while protected it against the crude effect of large doses. The psychogenic stressors (the presence and strength of predators’ threat) could influence the later effect, manifested in behavioral differences, caused by the alteration of originally built-in developmental program [40].

Biological Micro- and Macprograms

All of the events in the human life are programmed by the methylation pattern of genes and initiated after triggered by some material oraction, or seemingly spontaneous. The majority of these programs are short (microprograms) in this reading e.g. preparation of a polypeptide chain from aminoacids or its folding to a protein. However, there are also macprograms, in this reading long programs, or a series of programs successively switching one-another, which apparently spontaneous (this means that the reason is unknown) and self-activating. These macro-programs belong to the process of life and manifested in different points of life, as e.g. dentition, puberty and aging (senescence). This are necessary, the default of which has serious consequences and are also influenced by endocrine disruptors.

From this point of view, the least studied macro program is the dentition (permanent teeth eruption) however, it must be influenced by the endocrine disruptors, as it is dependent on endogeneous hormones. Although there are not targeted studies, delayed permanent teeth eruption was observed in case of hypothyroidism, hypopituitarism and hypoparathyroidism [49] and accelerated dentition in increased secretion of thyroidhormones [50]. This means that the cells have receptors of the nuclear receptor super family, which must be sensitive to different steroid-like endocrine disruptors.

The case of pubertal timing is more complicated and a lot of studies were done to clear it. A consistent decline in the onset of puberty was observed at first in the United States, at the mid–1990s and lateral so in Europe [51] in girls. From this time-point endocrine disruptors was believed as responsible factors. The development of breast initiated one year earlier, which was followed by the change of initiating time of menarche. In boys the signs were also observed however, these were more uncertain. In boys nondioxin-like polychlorinated by phynyls accelerated puberty, where as insecticides and dioxine-like compounds help edetodelay it [52]. Some Manifestations of puberty had been observed (e.g. breast development) and others had been unvisible or least visible (e.g. menarche, pubic hair development [53]). The time of the initiation of puberty was also changed in boys [54]. Although there are some contrasting data, showing delay of puberty [55], the majority of data point to the increasingly younger age of it [56], as the disruptors increase the endogeneous sex hormone levels [57]. Although a lot of endocrine disruptors act the timing of puberty, the most important are the agricultural ones [58]. It is important to know, that the epigenetic effect is acting at a genomic base and the effect could be different depending on the different genomic (e.g. ethnic) base [59].

Aging is a special case of programming. It is partly coded by the genom however, many-non-genomic and non-epigenomic factors play a role in it so curence [60–62]. If the role of pineal gland and thymus in the regulation of aging is accepted, the programming seems to be clear, as both organs are involuting, executing an endogeneous (built-in) program [63,64]. Nevertheless a lot of other factors have roles in the process which are exogenous and endogenous alike, and only 20% is estimated clearly genetic (genomic) one. The programmed senescence had been described at first by Weissman and was criticized and supplemented later [65]. It is connected to the endogeneous alterations of reproductive ability as well, as by the brain [66,67] and is executed by the abrasive effects of free radicals, directed by the brain-pineal-thymusaxis and theimmune system in human beings. However, it can be imagined that aging is not more, than the accumulation of deleterious materials, strongly influenced by exogeneous factors (infections, smoking, high cholesterol consumption, endocrine disruptors etc) however, in this case the balance between tolerance and intolerance must be considered, and this is epigenetically influenced.

Non-Perinatal Program-Alterations

The behavior of a developing person is dramatically changed during and after puberty [68]. This means that there is a remodeling of different key brain areas [69–71], which is also manifested in the changes of estrogen receptor bearing cells and number of receptors, in there actions to estrogen and progesterone and these changes are lifelong-lasting. The changes show epigenetic character and estrogenes as well as anti androgen can scan partly causes the disturbance of the process as well, as during and after puberty there action to these substances will be different than it was before [72,73]. As Endocrine Disruptors Are Estrogens Or Anti-androgenes, they are partly causative factors, partly act otherwise than before puberty [74]. As it was mentioned earlier, faulty imprinting can be developed, when the developmental window is open and this happens perinatally. However, the window is opening during puberty and this permits the intervention of exogeneous steroid-like molecules, causing faulty imprinting with life-long effects [69,75,76]. These reprogramming effects can be manifested not only in changes of behavior, but mental defects [77] as well, as cellularmal development (cancers) in sensitive tissues as breast [78] or prostate [79].

Afterwords

The studies of (and publications on) hormonal imprinting started at the 70s of the last century, when epigenetics was not yet accepted. The term “epigenetics” was given by C.H. Waddington at
1942, when some genetic phenomena were not explainable without it [80]. However, it was not officially accepted. From the mid-seventies the state of understanding started changing [80,81]. The phenomenon seemed to be suitable to explain why acquired traits sometimes inherited and this was exploited by some researchers of the Soviet-Union (T.D.Lysenko and his followers), to resuscite lamarckian thoughts on the heredity of acquired traits and to eradicate mendelian heredity (lysenkoism, [82]). Hormonal imprinting, which inherited -after perinatal exposure- to the given cell-line and inter-individually could not be listed as epigenetic process in that ime, so it was named to receptor memory and later (after demonstrating the role of methylation and heredity in a unicellular model system [83] was recognised as an epigenetic process. However, it was the first cellular evidence foruni- and multicellular repigenetic heredity (in animal experiments), and it issthe experimental evidence and explanation for the developmental origin of health and disease (DOHaD) in man. At present the amount and variability of endocrine disruptors are growing and seems to be unavoidable, which -by faulty perinatal programming and reprogramming the epigenetic system -could cause the increase of presently known diseases and appearance of hit harto known pathological changes [84]. Some signs of these alterations in man a real ready observed.

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