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Manifestation of false Developmental Reprogramming in adult age: Faulty Hormonal Imprinting and DOHaD.

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The paper calls attention to the similarities between hormonal imprinting (published in 1980 by Biological Reviews of Cambridge Philosophical Society as well as in Horm Metab Res, 1984; and DOHaD (Developmental Origin of Health and Disease), published in 1986 by Lancet. Both theories point to a relationship between an event (reprogramming) during ontogenetic development and the manifestation of an alteration (disease) in adult age. Hormonal imprinting and its faulty variants had been justified in animal experiments, while DOHaD were verified using epidemiological-statistical analyses. The two theories supplement and support each other. For faulty imprinting only the encounter between the developing hormone receptor and the target hormone (imprinter) is needed at critical periods of development (perinatally, during adolescence or during differentiation of adult cells) , whilst DOHaD (in the present standpoint) requests the pathological state perinatally, as provocator. In addition to the original -perinatal- observations especially important the observation and registration of the non-perinatal (pubertal and adult) provocations. The precognition of both theories by doctors seems to be necessary at present and even more in the future, as the amount and variants of man-made synthetic molecules (e.g endocrine disruptors) are extremely growing in the human environment and their presence in the critical developmental periods of man can explain the proliferation of non-communicable diseases.

The functions of genes are regulated by epigenetic factors. Each cell of a living organism contain identical gene pool however, non-functional genes are inhibited by methylation, while functional genes are non-methylated and stimulated by transcription factors. The methyl groups can be changed by demethylase enzymes and the genes can be reprogrammed by the fitting of new methyl groups by methyltransferases during the whole life however, there are critical periods of development when the reprogramming not only a possibility, but a request. This is the perinatal (fetal = late gestational; early postnatal period) as well, as the adolescence, or in the occasion of differentation of the cells in any periods of life. These are the periods when hormonal imprinting can be established [1-3], which is needed for the physiological function of the receptor hormone system for life. After reprogramming the transformed program is valid for life. However, in the critical periods the developmental window is open, which establishes the possibility for strange (related) molecules for provoking faulty imprinting, which is also valid for life.

The hormonal imprinting and its pathological form (faulty imprinting) was published at 1980 (in Biological Reviews of Cambridge Philosophical Society) [1], proving that an interaction during the critical periods of development (e.g. perinatally) can provoke a response with adult age manifestation, without causing disease in the time of provocation (faulty imprinting). This was demonstrated in targeted animal experiments however, its validity was not proven in human beings, and the confirmation of this seemed to be difficult.

In 1986 Barker and Osmond published a paper in the Lancet, in which -using epidemiological-statistical methods- they compared the weight of newborns and perinatal mortality with the occurrence of cardiovascular diseases and hearth mortality in adults and found close interrelations [4-6]. They draw the conclusion that the

state of fetus or infant can determine the health or disease of the adult, and this led to the theory of DOHaD (developmental origin of health and disease) which had been rather successful, establishing local and international scientific societies, a journal, congresses etc. and provoking the publication of many papers in the subject. Barker and his co-workers could likely consider the results of hormonal imprinting theory which were gained in animal experiments, as they had a good grip of the subject [7,8], although the approach was different: animal experiments in case of hormonal imprinting and epidemiological-statistical methods in case of DOHaD. However, the principle of both theories is the manifestation of an early faulty developmental reprogramming in adult age [9]. What was demonstrated in animal experiments pointing to the endocrine (receptor-hormone) system in case of hormonal imprinting had been generalized, pointing to human diseases in case of DOHaD. The (faulty) hormonal imprinting and DOHaD concepts support each other and explain the reason of many diseases, the origin of which were misterious before.

The DOHaD theory is targeted to the perinatal period and alterations of this time provokes the diseases in adults. However, it seems to be likely that the time (for provocation) is not fundamental: the essential is the state of the cells (organs, systems) touched, and this is the state of differentation. This could be taken place at any period of life (however, most frequent perinatally, indeed). In case of hormonal imprinting this is proved in animal experiments and this makes possible the provocation of lifelong faulty hormonal imprinting during puberty [10-12]. The explanation by the DOHaD theory is also presumable in man during adolescence however, it was studied infrequently up to now.

In case of DOHaD, in the present standpoint the perinatal disease or pathological alteration is needed for the manifestation of adult disease. In case of faulty imprinting only the encounter of the developing hormone receptor with the target-hormone related molecule is enough for the provocation or manifestation of an alteration in adult age. This is understandable, as in the case of DOHaD the consequences were drawn by comparison of statistical data (for which the manifestation of early disease or alteration had been needed), while in the case of hormonal imprinting from results of experiments were done on living animals. Considering the similarity of the two theories and their conditions it seems to be likely that in the case of DOHaD also sufficient the presence of perinatal provocator for the development of the later disease, however it is very difficult its study in man by statistical methods.

In our modern age the amount of infectious diseases are decreasing due to the better hygiene and antibiotics, whilst the number of chronic non-communicable diseases is increasing, due to the prolongation of human lifespan as well, as the amount and variations of hormone-like chemicals around us [13,14]. The plastic industry is using bisphenol A, the agrotechnic is using herbicides, fungicides and insecticides, the human nutrition is using more and more soy with genistein and daidzein and the traffic emits enormous quantity of gases, containing benzpyrene and dioxin. All of them are steroid hormone like molecules, which are disturbing the function of endocrine system (endocrine disruptors) in any period of human life however, the differentiating cells are extremely sensitive at the critical periods of development, when the developmental window is open (perinatally, during weaning and puberty) and in some continuously differentating organ systems, as the immune system, causing late manifested diseases. This means that although similar molecules could be present in any earlier time of human evolution, only now appeared such amount and variations of these materials, which can provoke evolutionary changes. The earlier sporadic effect of endocrine disruptors incidentally also could touch (even positively) the human evolution, nevertheless it is not sure that the sudden mass of disruptor invasion is or will be tolerable.

Hormonal imprinting and faulty imprinting are inherited inside the cell line and transgenerationally [15]. At present in animal (rat) experiments heredity is observed up to the 3rd generation, as it was not studied further [16-18], considering the relatively scarce change of generations however, in the unicellular model cell, Tetrahymena it was observed up to the 1000th generation [19]. This means that reprogramming during differentiation of cells (organs, organisms) could be an important factor of the animals' (human) evolution. At the same time it participates in the sustenance of diseases and inclination to diseases across generations. In the last time it was observed that certain non-hormonal drugs can provoke faulty hormonal imprinting-like effects with dangerous consequences which can be explained by contact with similar molecules in critical periods of life in previous generations, however at present there are not factual evidences [20]. However, hormonal imprinting and DOHaD concepts are in developing state with concrete theories and less-factual evidences. Nevertheless the inserting of new data (observations) into the concepts is in progress and develops day after day. Because of this it seems to be needed to call attention on the dangers of hormonal imprinting and consequently on DOHaD, which will be growing in the near and far future.

Barker studied the connections between perinatal pathological events with diseases of the adult age, as statistical data were at his disposal in this direction and this led to the DOHaD theory. However, differentiation of cells continue in many organs or systems during the whole life. An outstanding case is the immune system. and really, faulty hormonal imprinting of the immune system can be executed in animal experiments during the whole life, nevertheless the evaluation of the results is rather difficult, as problematic to determine the differences between the direct effect of imprinter and its distant (disease-provoking) impact. However, the pubertal (adolescent) effect of faulty hormonal imprinting is proved and it seems to be likely, that epidemiological-statistical analysis could confirm it, similar to the original (perinatal – adult) comparison.

Although the hormonal imprinting was recognized and published earlier than DOHaD, the latter became more known and more popular in medical territories, thanks to its human disease-orientation, more understandable name and its abbreviation and last but not least thanks to the professional potency of Lancet. However, the hormonal imprinting concept also had followers and upgraders, but in significantly less amount, than DOHaD [e.g. 21-26].

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