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Faulty hormonal imprinting and its importance in the clinical medicine

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Abstract

Hormonal imprinting is a physiological process, taking place perinatally at the first encounter between the developing receptor and its target hormone. It is needed for the normal function of the receptor-hormone complex and it is valid for life. Faulty imprinting can be provoked by related molecules (e.g. medication, communal or industrial endocrine disruptors) which lifelong disturb the normal hormonal effects, provoking late-manifested diseases.

Introduction

Parallel with the development and differentiation of cells during the ontogenetic development, they make hormone receptors (in the plasma membrane or inside the cells) and hormones which can be bound by these receptors, regulating the cells' functions by a humoral way, under the control of the nervous system. However, these two components must be adjusted to each-other. This purpose is solved by the hormonal imprinting, when the two components are tuned up, in an early period of life. Hormonal imprinting is needed for the normal endocrine regulation, which could not be normal without this [1].

Physiological and faulty hormonal imprinting

Hormonal imprinting takes place perinatally at the first encounter between the developing hormone receptors and the hormones of fetus or infant. This process lifelong influences the recognition of hormones by receptors, consequently the normal (physiological) function of receptor-hormone complex [2-6]. However, during the perinatal period, when the developmental window for imprinting is open, related (similar) molecules, present in the environment (blood circulation) also can be bound by the receptors, causing altered effects of the system for life [3,6] These related molecules can be other members of tha same hormone family, synthetic hormone analogues, administered as therapeutic factors as well, as endocrine disruptors (hormone-like molecules). The related molecules can disturb the normal receptor-hormone contact and action by binding to the receptors giving false information or displacing the physiological hormone, not permitting the transmission of the normal message. The receptors are rather sensitive to imprinting, as well as to faulty imprinting, when the critical developmental window for imprinting is open [7]; femtomolar concentrations [8] of physiological imprinters as well, as faulty imprinters are suitable for provoking it. Creditable and multitudinous animal experiments justify that the effect of the perinatal faulty imprinting is manifested later [e.g. ref. 9,10] in adult age, when -in men- the connection between the faulty imprinting and the disease is difficult to determine.

Hormonal imprinting does not cause alteration in the DNA sequences (code), however provokes epigenetic changes (expression of genes) which are inherited from cells to cells in the same individuum. This causes the late manifestation of diseases, caused by the faulty imprinting and this could be the basis of developmental origin of health and disease (DOHaD) [11,12] as well as, the metabolic imprinting [13,14] and immunological imprinting [15,16]. As an epigenetic process, it is inherited to the progeny generations, which was observed in mammalian (rat) experiments [17-23] up to the third generation [24], however in case of unicellulars up to the 1000th generation [8]. Of course, there are no data on inheritance in human relation, however this is presumable.

Functional teratogenesis

Faulty hormonal imprinting is a functional teratogen [25]. In contrast to the morphological teratogens the faulty hormonal imprinting effect is not observable at birth, however it is manifested in later phases of life. This justified in animal experiments in many systemes of the mammalian organism, as the immune system [15], skeletal system [26,27], neuroendocrine system [28-33], sexuality [34-36], where the faulty imprinters' effect can be studied. These studies show that the faulty imprinting causes heavy and light pathological changes alike, depending on the importance of the given system in the organism and the effect of imprinter. Functional teratogenicity is as important as morphological one. Obesity or diabetes could be more dangerous than the absence of the little finger [37]. In addition: functional teratogenicity prolong the period when cautiousness is needed: „perinatal" includes „early postnatal" and this surpass the period of gravidity, consequently the period after birth as important from the aspect of functional teratogenesis, as the embryonic one in morphological ones.

Although the perinatal period is the most sensitive for faulty imprinting, there are other periods of life, when faulty imprinting can be provoked. These are the time of weaning, outstandingly the period

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of adolescence and in continuously muliplicating cells (e.g. in the bone marrow), the whole life [38-40]. However, the perinatal imprinting the most determining, imprintings of the other periods are also important but not so decisive, while as it is supposed, they can modify the maladjustment by the perinatal faulty imprinting.

Faulty imprinters, endocrine disruptors

Faulty hormonal imprinting could develop spontaneously and endogeneously, without external intervention, as in case of overproduction of the target hormone or overproduction of related hormone from the same hormone family, however these cases seem to be rare. Its development by medical intervention (therapy) by materials (medicaments) are more frequent. There are vitamins, as vitamin A and D, which are really hormones having receptors in the steroid receptor superfamily and giving them in the period of openness of the developmental window for steroid receptors could provoke faulty imprinting in animal experiments [41]. However, in our modern age, the faulty imprinting by environmental endocrine disruptors seem to be the most frequent. Our environment is filled with endocrine disruptors from aromatic hydrocarbons (in cigarette smoke and exhaust fume) to our food [42] where soy flavonoids (genistein, daidzein) represent them (also in baby formulas) [43]. The endocrine disruptors are enriched in breastmilk and are transported from the mother to the infant by the most recommended nourishing form, in the most sensitive imprinting-period of life [44-48]. However there is not a possibility to avoid the contamination by endocrine disruptors: they are present in the surface of sprayed fruits, in the feeding bottle of infants and flasks of mineral water, etc. There is a possibility to forbid the known disruptors however immediately a mass of new molecules appear instead of them. At the same time it is not known what will be the consequence of the chronic bombardment by the endocrine disruptors, as this could be a positive effect by transforming the endocrine system consequently better adaptation of regulation by the human organism in a long run, but could be catastrophal, considering the present tendencies [49]. Hormonal imprinting has been described about 40 years ago [2] and since this time it must be considered in pathological processes however, in the present time, when the chemization is extremely growing by the use of classical disruptors (as e.g. bisphenol A, in plastic industry, vinclozolin in agrotechnics, etc-) and production of a mass of new types of molecules which are produced every day, seems to be more important.

Faulty imprinting and late diseases

The clinician wants to know the origin of the diagnosed disease, and in many cases only the consideration of faulty hormonal imprinting helps to do this. At the same time this knowledge helps to avoid the manifestation of the disease which would be caused by medical intervention. The weight of faulty imprinting depends on the organ system or organ in wich it is provoked. A faulty imprinting which touches the steroid receptor hormone family causes a heavy -system level -alteration, as mass of different cells have steroid receptors, and peroxisome proliferator receptors as well, as aromatic hydrocarbon receptors are also included [50,51]. Present day endocrine disruptors mainly have steroid character and this badly influences human sexuality from the shifting of sex-proportion at birth [52] to the sexual aberrations and homosexuality [53,54]. Faulty imprinting which touches the nervous system also causes heavy -mostly behavioural-problems as well, as the faulty imprinting of the immune system, which could disturb the complete series of defense reactions, from infections to carcinogenesis and lifespan [55-56]. `As faulty hormonal imprinting and its consequences (e.g. DOHaD) are newcomers in clinical medicine, most of its effects are not completely mapped however -considering the extremely growing variants and enormous amount of endocrine disruptors as well, as perinatal medications- must be counted, preparing diagnosis.

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