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Effects of Early Endocrine Disruptor Exposures (Faulty Hormonal Imprinting) on Immunity

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Abstract

Endocrine disruptors are (mainly steroid-) hormone-like molecules, which binding to the hormone receptors disturb the endocrine functions, causing troubles (diseases) in human adults. Perinatally (in fetal, neonatal, and early postnatal period), the developing immune system is touched by them, causing faulty hormonal imprinting, consequently late and life-long failures of immunity. In addition to the perinatal period there are other critical periods, as weaning and adolescence, in which faulty immune-imprinting can be provoked and this are also taking place in continously dividing and differentiating cells during the whole life however, the perinatal period has the determining role. The physiological hormonal imprinting is specific however, the faulty imprinting can be overlapping to not related hormones. Stressors can execute faulty imprinting-like effects by mobilizing stress hormones. The broad spectrum of faulty imprinting causing factors (endocrine disruptors) makes unavoidable the meeting with them. The alterations, caused by the endocrine disruptors are epigenetically inherited, so it can be supposed that the present state of human immunity had been formed by earlyer (natural) endocrine disruptors as e.g phytoestrogens, aromatic hydrocarbons, metals etc. “Endocrine disruptors” are a new category, but endocrine disruption has been present and influenced the development of the immune system since millions of years. However, the disruptors’ number and amount enormously increasing, so the future changes in the immune system caused by man-made endocrine disruptors must be attended. At present these changes seem to be harmful however, the chance for positive changes (transformation of human endocrine system) could be -after long time- possible. It is also worth to study the faulty hormonal imprinting effect of endocrine disruptors, as they seem responsible for numerous immune alterations (consequently diseases) manifested in adult age.

Keywords: Immune system; Endocrine system; Perinatal exposure; Development; Functional errors; Ah-receptors

Introduction

The Endocrine Disuptors (EDs) are such molecules of our environment, which are similar to hormones (first of all steroid hormones) or can influence the effect of these hormones, by binding to the hormone-specific receptors or disturbing the transmission process betwen the receptor-hormone complex and the response by the cell. EDs can act to the endocrine system at any time of life however, the consequences are different, depending on the developmental period. From this point of view, the early stages of development seem to be rather critical, as in this periods (late prenatal, early postnatal, named perinatal) the further fate of the endocrine system (consequently the organs and systems regulated by it) is determined by hormonal imprinting.

The perinatal hormonal imprinting

In the womb the fetus is in a very closed connection with the mother, whose endocrine system mainly regulates the functions of it. However, before birth the mother’s regulation must be conveyed to the to be newborn and this process is continued after birth. During the perinatal period the developing receptors must recognize the structure of the target hormones produced by its own glands, and react according to the messages contained by them. This is the process of hormonal imprinting, which is needed for the later normal function of receptor-hormone complex, which is the basis of the normal (physiological) endocrine regulation [1-3]. During the period of hormonal imprinting (perinatally) the developmental window for hormones (imprinters) is open and this gives the possibility for the action of other (non-physiological) hormone-like molecules to disturb the genetically determined physiological imprinting, causing faulty imprinting with life-long consequences. These consequences are the alteration of hormone binding capacity of the receptors, as well, as the hormone production of the given cell, changes in sexual behavior (310), differences in neurotransmitter production and pain sensitivity [4-6] etc.

Development of the immune system

The immune system of mammals develops in two steps: at first the innate immune system, after that the adaptive one. About 1600 genes are responsible for the the functions and production of components of the human immune response [7,8], which shows that the immune system can be offended in numerous points. However, the cells of both immune systems are developing from pluripotential hemopoietic stem cells [9] in the thymus and bone

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marrow which are providing microenvironment and factors needed for the development of functionally immunocompetent cells. In this period the developing immune system is very sensitive to internal effects [10] and is touched by the microbiota [11,12], which modify the immune system. However, in this period the immune system is not immunologically naive [13]. It is perinatally imprinted by the physiological hormones and can be imprinted by related strange molecules (faulty imprinting) [3,14,15]. It is not known whether the imprinting takes place in the thymus or bone marrow or other places to where the cells are migrating (lymph nodes, spleen, mucosa). Both types (physiological and faulty) of imprinting is valid for life and their effects are transmitted to the progeny generations of the imprinted cells as well, as to progenies of the imprinted individuum. The change provoked by the imprinting is epigenetic and it is also epigenetically inherited [16].

Although there are some other periods during life in which imprinting can be provoked by outer and perhaps inner imprinters, the perinatal period is outstandingly important. In this period children and especially newborns are more sensitive to environmental factors than adults and more sensitive than at weaning or adolescence [17,18], in which periods imprinting can be also provoked. However, the imprintig in the mentioned periods can modify the effect of early (perinatal) imprinting [19]. The broad possibility of imprinting can be clearly demonstrated in the immune system, as its cells are continuously dividing and maturing during the long periods of life [16].

As it was mentioned, faulty imprinting can cause different alterations in different systems (immune system included) and initiates diseases later, in adult age or helps the manifestation of them. May be this suggested the DOHaD (Developmental Origin of Health and Diseases) hypothesis [20,21] which supposes the close correlation betwen the adulthood diseases and perinatal exposures [22]. This hypothesis uses the elements of hormonal imprinting (which was described earlier, in which the epigenetic factors are playing the main role, as it does happen in both cases. The epigenetic programming of the immune system is disturbed by faulty hormonal imprinting as well, as in case of DOHaD, and the changed epigenom is inherited to the cell lines of the individual as well, as to the progeny generations. The transformation of the epigenetic program (maladaptive alterations of organs and cells) transforms also the response ability of the immune system, causing weaker effectiveness in the struggle against infectious diseases as well, as stronger effectiveness of faulty response manifested in allergic or autoimmune diseases [7,23-26].

Hormesis seems to be very important in the program alterations of the immune system [27-29]. Such molecules, which negatively influence immune defense in adult age (given in a higher dose) can affect the immune program in a minimal dose, perinatally. This could be right also in case of phytoestrogens [30,31] which are present in the infant formulas, consumed by infants or in early childhood.

In the case of the immune system it is not known that the developmental (critical) window is open for hormonal imprinting (the setting of the immune system to the effects of neurohormonal system) or for the setting to the microbiota, which is also very important for the future of the immune program [32-34]. However it seems to be sure, that endocrine disruptors favorize this period of life, causing late manifesting diseases.

Due to the development of the immune system in the perinatal period it is not sure, that certain immune cells are directly targeted by some imprinter (hormones or endocrine disruptors) however stem cells are present and can be influenced [35], the effect of which will be manifested later, in adult age, together (after) provocation by inner or first of all outer factors or without them. It is also possible that the effect is not specific, however it provokes a general reaction (9), by which another function (hormone) will be touched. It seems to be likely, that there is a hormonal network inside the immune system, which is working in adult age [36-38] and this is already present in the more sensitive perinatal period [39]. This could be manifested in case of early-gestational alcohol consumption, demonstrated by the reduced insulin binding by peritoneal, blood and thymic lymphocytes and monocytes [40], and in the immune suppressive effect of early exposure to arsenic [41] and other toxic metals [39]. This general effect is similar to the basic observations of Selye (68[]) named stress by him [42,43]. In the case of faulty imprinting a non-specific change of developmental program can be imagined, caused by the alteration of methylation pattern of DNA and the epigenetic transformation is observed in later periods of life. This is characteristic to the very early (perinatal) period of life [44], which is exceptional, however – as it was mentioned- almost repeated in some later periods (weaning [45], adolescence [19] and during the whole life in continuously differentiating and dividing cells.

The role of aromatic hydrocarbons

It is generally believed that bisphenol A is the most dangerous endocrine disruptor considering its produced amount and broad spectrum of utility in plastic industry. It influences the methylation status of DNA and by it alters the gene expression from the touched individual to its progenies, epigenetically inherited to them [46]. Its effect is broadly manifested in the organism in different systems, immune system included. Bisphenol A has been detected in about 90% of analyzed human urine samples [47]. However, it seems to be likely that aromatic hydrocarbons and especially Benzpyrene and Dioxin (TCDD) are similarly important environmental pollutants [48,49], which cause faulty perinatal imprinting of steroid hormone receptors. These endocrine disruptors are present in the air, resulted by volcanic eruptions as well, as by the results of urban traffic and cigarette smoking, and by agrotechnical use, they are present in food packaging, combustion products, plant health treatments, detergents and in production of the chemical industry in general (medicaments included) [50]. They are harmful for human health introduced into the organism in adult age however, they are dangerous causing faulty imprinting of steroid hormone receptors perinatally and by this, chronic diseases later in life [51-53]. Immune cells have steroid hormone receptors however, these substances are also bound by the Aryl Hydrocarbon Receptors (AhR) which are ligand activated transcription factors. They are also present in the immune cells and important modulators of the development and function of the innate and adaptive immune system [54-59]. There is a cross-talk between nuclear (steroid) receptors and Ah receptors (xenosensors) and this enhances endocrine disruption [60-62].

Thymic Glucocorticoid Receptors' number is decreased at 6 weeks of age after benzpyrene exposure at the 19th day of pregnancy

(in rats) [63] with some differences dependent on gender. Benzpyrene exposure during lactation also caused similar effects, without touching receptor affinity in both cases [64]. In contrast to these results neonatal combined treatment with benzpyrene, allylestrenol, vitamin A and vitamin D3 increased the later studied receptor number [65]. However, not only steroid receptors' number was influenced by neonatal benzpyrene imprinting, but certain hormone productions by the immune cells, as serotonin content of blood lymphocytes, monocytes, granulocytes, peritoneal fluid lymphocytes, mast cells and granulocytes, thymic lymphocytes [66]. Similarly, endorphin content of blood cells and peritoneal immune cells were influenced (elevated in this case) two months after single benzpyrene treatment however, while in the blood cells of females the elevation was typical, in males the hormone production decreased [67]. Neonatal faulty imprinting with dioxin (TCDD) decreased the number of thymic glucocorticoid receptors in both genders [68]. Neonatal benzpyrene imprinting decreased dexamethasone binding capacity (receptor number) in Walker ascitic tumor bearing rats [69]. If neonatal allylestrenol treatment was executed before benzpyrene treatment in adult animals, the increase of glucocorticoid receptor number in rats was observed in contrast to neonatally not treated animals (20). The benzpyrene imprinting influenced the later benzpyrene input by other model cells [70].

Stress, endocrine disruptors and perinatally established immune influence

There are correlations between the neuroendocrine and immune system [71]. The Hypothalamic Pituitary Adrenal (HPA) system has a deep impact on the development and function of the immune system, consequently stress effects can influence the activity of it [71,72]. These effects are stronger during the development of the immune system causing not only immediate changes but prolonged alterations which are manifested later, in adult age [73]. The state of methylation of DNA cytosins (CpGs) determines the functionality of certain brain structures and social as well, as chemical stressors, e.g. bisphenol A offend DNA methyl transferase [74]. In addition to the HPA axis, microglia which are innate immune effector, also has a role [75]). Hippocampus has a high expression level of glucocorticoid receptors [76] and this means that highly sensitive to endocrine disruptors and these, as stressors indirectly influence the later activity of the immune system. This can explain why childhood maltreatment -as psychological stressor- is associated with chronic inflammatory state in adults [77]. The high sensitivity of neuro-immune system in early life to stressors can cause the nutrition-provoked immune disorders [78,79], considering that nutriments could contain endocrine disruptors. At the same time, vitamin A, which has receptors in the nuclear receptor superfamily and really it is an endocrine disruptor, increases the number of immune cells as a consequence of early life exposures. Meanwhile, perinatal strong stress negatively influences immunity [80], moderate stress can do this positively [81], possibly by hormetic effects. Inflammation as stressor also can influence the program. Endocrine disruptors can touch the fetus passing across the placenta, or the infant, presenting in mother's milk. The stress-effect on the neuro-immune system is dependent on the stage of pregnancy and also on the gender of the fetus or infant [82,83]. The late stages of ontogenetic early development are more vulnerable [17,84] however faulty imprinting in later critical periods, or on cells which are continuosly dividing (as e.g. immune cells) in the whole life [85] are also sensitive.

The effect of stressors is transmitted to the progeny generations [86], similar to the case of faulty hormonal imprinting, by chemical factors.

Impact of perinatal hormonal effects on the hormone production of immune cells

The cells of the immune system can produce hormones, characteristic to the endocrine system [87,88]. The presence of hormones which had been justified are the POMC-hormones, endorphin and ACTH, the thyroid system hormones, TRH, TSH, T3, the growth hormone, prolactin, melatonin, histamine, serotonin, catecholamines, GnRH, LHRH, hCG, renin, VIP, ANG II, which shows that immune cells are producing and containing all of the homones, which had been searched at all [89]. This hormones can be transported by the immune cells to different sites of the body, where their effects are needed [90]. This is demonstrated by the packed transport theory [90,91]. This hormone production is seriously influenced by perinatal hormone treatments and endocrine disruptor exposures [90,91]. Total deprivation of food and water for 48h just before or after delivery caused ACTH level elevation in adult males and less, but significant elevation in female rats [92]. After vitamin A neonatal treatment, T3 content in immune cells was decreased in adult age, while vitamin D treatment did not cause change in hormone levels [93]. Treatment at weaning with endorphin decreased the endorphin and serotonin levels of immune cells when adults [94]. Single treatment at weaning with benzpyrene and chlorpheniramine (a H1 receptor blocker antihistamine) strongly influenced the hormone contents of immune cells, measured after 3 weeks [95]. In a similar situation deprenyl, and its derivative without MAO-B inhibitory activity strongly however, differently influenced the serotonin content of peritoneal immune cells [96]. The effect of different treatments (imprinting) was transgenerational, the alteration was observed up to the F2 generation [97-100]

Not only the hormone production is touched by the perinatal hormonal effects, but similarly, the hormone binding. The combined phytoestrogen genistein+ benzpyrene imprinting neonatally significantly and strongly decreased the binding capacity of glucocorticoid receptors of the thymus in adult age. In this model a nutritional factor (genistein) and an environmental (air) pollutant has been combined, which can happen in any time [101].

Perinatally the human milk contains such components, as microbes, hormones etc which challenges the developing immune system and by this, forms its reactivity for later life [102,103]. This seems to be absolutly needed for the normal development of the immune system. It is possible, that among the components EDs are also listed in our modern world, and these components could be useful by this interaction. The meeting with new bacteria could cause stress effect as well, as a meeting with an endocrine disruptor, which can be bound by natural hormone receptors however, they are strange.

In the faulty hormonal imprinting of the immune system some hormones can overlap with another without closed chemical relations. In adult mice, in *in vitro* experiments insulin strongly

influenced the ACTH, triiodothyronine, histamine and serotonin production, which has been reduced by treatment of female animals, but does not touched males [104]. The overlap is not immune system specific, it can be observed also in other cases [105-108].

Conclusion

In the last 50 years about 5 million man-made chemicals appeared in the environment [109], and about 1000 of them had been reported with endocrine disruptor effects at 2013 [110]. However their number is enormously and continuously growing.

There are many data on the -mainly harmful- effects of endocrine disruptors on adult human organism, and a lot of these effects are manifested in the immune system, as EDs influences cytokine and immunoglobulin productions and activation as well, as survival of immune cells [111]. Nevertheless, very modest is the inventar of observations on the perinatal effects. However, on the basis of animal experiments and human observations it can be concluded that there is a thorough difference between the effects in these two life periods [112]. Perinatally the immune system is undifferentiated and its structure as well, as its functionality is developing, which means that while in adult age a functioning complete immune system is offended by the endocrine disruptors, causing acute or chonical diseases, in the developmental period, when the setting of the immune system is taking place in physiological conditions, the consequences are such alterations, which change the program [17]. The impact of alterations are manifested later, in any period of life, adolescent, adult or senescent periods included.

The perinatal effect of endocrine disruptors, which are hormone-like molecules, provokes faulty hormonal imprinting, with life-long consequences. The physiological hormonal imprinting is needed for the normal setting of receptor-hormone recognition, which is a basic requirement of normal endocrine regulation. For ensuring this aim, the developmental window for imprinting is open perinatally and not only the specific physiological hormones can be bound by the developing receptors, but related physiological hormones as well as arteficial synthetic molecules entering into the organism. This makes possible the faulty hormonal imprinting with consequences for life. As the developing immune cells have hormone receptors (as estrogen receptors, thyroid hormone receptors, aryl hydrocarbon receptors etc) which can transmit important messages into the cells, the faulty imprinting is taking place by them. Although there are other (later) critical periods of life (weaning, adolescence and in continuously dividing and differentiating cells in the whole life), when faulty imprinting can be provoked, the basic period is the perinatal, which determines the function of receptors for life. So, the response ability of immune cells is determined perinatally.

In general, it is believed that that endocrine disruptors are always new synthetic molecules however, a lot of them is natural, Even they are incorporated in the human organism. Phytoestrogens are also endocrine disruptors [31], and they are used in old and modern kitchens, and likely they participated in the formation of human immunity. Vitamins A and D are also endocrine disruptors and they are inavoidable components of our physiology [113]. Endocrine disruptors could be physiological hormones in case of overdosage or arriving to the developing receptors in inadequate time or associated with another hormone-like material. Endocrine disruption also can be provoked by non-hormone materials, as e.g. gestational alcohol consumption [114] which can disturb the endocrine system in this very sensitive and vulnerable critical period. Though "endocrine disruptor" is a new notion of our moden age, endocrine disruption was always present, perinatally influencing the hormone reception of different cell types and from this aspect, immune system was not an exception. It can be supposed that the present state of human immunity had been deeply formed by natural endocrine disruptors (e.g. phytoestrogens, aromatic hydrocarbons, metals) [115], which acted and acts continuously.

Gender seems to be a basic determining factor in case of perinatal faulty imprinting [116,117]. However, the gender differences can be observed also in other cases, the enhanced immune activity of females compared to males is known [118]) and perinatally the males' inclination to diseases is more expressed. It can be supposed that the reason of it can be deduced to the double X-chromosomes, however the immune activity promoting influence of estrogen hormones also can be responsible [119]. The gender difference is obvious also in case of adolescent imprinting [120]. It is very important to know, that, the impact of endocrine disruptors is transgenerational [121-124] and this is manifested also in the case of immune system. This is an epigenetic (not mutational) inheritance, caused by the changes of the methylation pattern of DNA. Although there are not data enough on the number of generations to which the epigenetic inheritance is valid, considering the enormously growing number of endocrine disruptors and their quantity, the future seems to be worrying. It is not known at present that the changes in the different systems will be positive or negative as a consequence of endocrine disruptors, it seems likely that the functionality of immune (and other) systems will be other, than it is presently. The other important problem is the possibility of mixed imprinting, when e.g. a chemical and psychical (stress) imprinting are present at the same time perinatally and together influence the developing immune system.

Afterwords

In the earliest (embryonic) period of development noxious substances used to be teratogenic, which means that morphological alterations are dominating. The immune system is less suitable for studying them, so it is not surprising that there are no data on this type of effect caused by endocrine disruptors. Though in the fetal period also there is a possibility for teratogenesis (as cryptorchidism, hypospadias, micropenis) this period is dominating by lifelong lasting functional alterations [125-130], which are manifested in any later period of life from adolescence to senescence. The immune system is very sensitive, as its basic development is executed in the fetal period and this is prolonged to the perinatal, neonatal and early juvenile periods. Considering the early origin and late manifestation of alterations, the impact of outer factors are basically different from the adult age, when acute effects are executed with mainly acute consequences, as immune suppression (paralysis), autoimmunity and allergy. This means that the perinatal ED effects must be handled separately with outstanding attention, as some diseases of the immune system can be deduced to perinatal exposure (faulty hormonal imprinting).

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