

Impact of Endocrine Disruptors on the Aging Process: Biological and Medical Aspects

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Abstract

The aging process is rather complicated, and it could be regulated at first by the brain and likely executed by the pineal-thymic axis and immune system. Its complexity is accounted for the attack by endocrine disruptors from the perinatal period to the old age. The impact seems to be most dangerous perinatally by late manifested faulty hormonal imprinting however, the disruptors can harmfully influence aging during the whole life, by disturbing the physiological function of the endocrine and immune systems. The aging-influencing impact is inherited to the progenies as troubles of epigenetic programming and reprogramming. The recognition of interrelations between the action of disruptor and manifestation of the sequel is warm for the observers (doctors) in man, because of the long distance between the action (endocrine disruption by faulty hormonal imprinting) and manifestation of the sequel (appreciable symptoms) as well, as the variability of symptoms. The amount and variations of endocrine disruptors are extremely growing, similar to the human lifespan, what means that must be increasingly calculate with known and new endocrine disruptor provoked aging diseases in the near future, which requests the transformation of medical curriculum.

Keywords: Faulty hormonal imprinting; Steroid hormones; Programming; Critical developmental window; Bisphenol A

Introduction

The multitudinous appearance of a special precancerous and clear-cell adenocarcinoma of young girls born for gestationally diethylstilbestrol (DES) treated mothers called attention to the endocrine disrupting chemicals [1] which later have been discovered also in the human environment, in air, water and food. as well, as in the industry and agriculture, and not ultimately as medicaments (e.g. as anti-concipients). Most of them are man-made materials, which are present in the plastic bottles and metal food cans, in toys and cosmetics etc., however they can be consumed in foods (phytoestrogens of soy), or products of volcanic eruptions as well, as components of waste gases (dioxin and benzopyrene) in short, as unavoidable components of our modern life: the endocrine disruptors (EDs). They are steroid hormone-like materials and can be recognized and bound by nuclear hormone receptors, which transmit the endocrine disruptor bearing message to the receptor-bearing cell, which receives and executes the command [2]. However, there is another possibility: the endocrine disruptor occupies the binding site of the physiological hormone, which are not able to be bound. In both situation the ED disturbs -in addition to the direct target organs- the complete normal endocrine regulation, causing problems of different systems of the (human) organism, as steroid (nuclear) receptors are in many (not directly target) cells and there are many overlapping's [3]. Nevertheless, the impact of endocrine disruptors depends on the time (period) of their action. Adult (mature) cells (organs) are less sensitive, while fetal or perinatal exposure (faulty hormonal imprinting) causes lifelong effects [4,5], with sequelae in adult age, which also can be manifested in elderlies. This could mean that manifestation of diseases in elderly is a specific area of DOHAD (developmental origin of health and disease [6], which could deserve accentuated discussion in another forum.

The gestational (fetal) and early postnatal effects seem to be the most dangerous partly because of the higher sensitivity of developing cells and systems, partly by the length of manifestation-period, when the alterations caused by the faulty hormonal imprinting [7] can be appeared. However, in addition to this decisive period, there are other periods when the critical window for (faulty) imprinting is open and this are at weaning and at puberty

(adolescence). In this latter the perinatal programming could be reprogrammed, and the reprogrammed variation will be predominant in the further period of life, obviously in the old age [8,9]. As hormonal imprinting is an epigenetic process [10], (which means that although the heritable change does not request the change of base-sequence of DNA, only the methylation pattern of DNA is changing) consequently its effect is inherited to the progenies in which changes in the aging process is also expected [11].

Aging is a rather complex process [12], which is influenced in a lot of factors and organs and is manifested in signs belonging to different systems. It is started in an early period of life, when its signs not yet be observed and become observable and smarted, when these signs accumulated. It is difficult to study and boldly assert that a symptom provoked by endocrine disruptors does belong to aging, as the observation and recognition of the endocrine disruptor effects are too fresh, however, there are signs which can be already observed. There are human observations among them however, most of them were observed in animal experiments.

Facts

Animal experiments

Bisphenol A (a plasticizer, which is used for softening plastics and is present from nursing bottles to containers of food and beverages) exposure accelerated the aging process (with shortened lifespan, mediated by induction of oxidative stress) in the nematode model organism, *Caenorhabditis elegans* [13].

Mixtures of EDs (13 anti-androgenic and estrogenic chemicals) between 7-22 days of gestation in rats caused earlier female reproductive senescence [14] as well as reduced sperm counts of offspring, measured when were 19-month-old [15]. It caused also proliferative lesions in rat prostate at old age [16]. Increased incidence of prostatic lesions (inflammatory infiltration, intraepithelial prostatic neoplasia) were observed after developmental heterogenization by bisphenol A. [17]. Bisphenol A treatment from gestational day 11 till birth caused reduced fertility with age of female mice [18]. Enhanced cellular senescence were observed in aging vascular endothelial cell lines after bisphenol A treatment [19].

Estrogenic endocrine disruptors (as diethylstilbestrol -DES, alpha-zeranol, genistein-phytoestrogens) modulated the immune system of aged (74-week-old) mice [20]. Vinclozolin, an antiandrogenic molecule, used in geotechnics as fungicide, trans generationally induced adult or aged onset diseases in rats [21]. Chronic exposure to DDT and TCDD accelerated the development of albuminuria (sign of disease activity) in murine systemic lupus erythematosus [22]. Accumulation of organochlorine pesticides in man was observed in the adipose tissue parallel with aging and Parkinson disease [23]. In long-living mice hormonal signals by EDs can reprogram aging [24]. Premature reproductive aging (early senescence) is caused because of reprogramming the hypothalamus by EDs in rats after exposure perinatally with methoxychlor [25]. In aged mice, pubertally exposed to bisphenol A, cognitive deficits

(spatial memory impairment) were observed [26]. Prenatal or early postnatal exposure to stress changes the successful aging trans generationally [27]).

Human observations

Some diseases characteristic to elderlies, as Parkinson, Alzheimer, chronic obstructive pulmonary disease (COPD), chronic fatigue syndrome etc. are promoted by chronic exposure to pesticides [28]. Higher urinary bisphenol A concentrations were found associated with abnormal liver functions in elderly [29]. The viability of central neurons of aged people are contested by polychlorinated biphenyl's [30]).

Discussion

There are enough data for viewpoint formation on the effect of different endocrine disruptors in animal experiments, at the same time there are hardly observations in human relation. This shows, that researchers comprehended the importance of the mass-attack by endocrine disruptors, while doctors are expecting more data, before suiting the hunting of endocrine disruptors in the anamnesis, into the random program of patients' inspection. The present-day human endocrine system is suited perfectly, accommodated to the local (inside organismic) and environmental factors. Although the data on exposures to endocrine disruptors are scarce, unanimously show negative tendency evaluated by a geriatric aspect: in animal experiments and human observations alike, in each index and in each subject (from the nematode model to mammals) as well as in human observations they provoke pathological processes and shortens life prospects. Outstandingly scarce are the human data however, this is understandable as consideration of possible effects of endocrine disruptors in case of human diseases is sparse and long time is needed for the systematic searching and appreciation in case of different diseases. Nevertheless, it is important to know that in case of the imprinting effect of EDs there is not downmost limit [31,32], nanomolar concentrations can provoke prolonged (lifelong) effects [33,34], whilst the concentrations of different disruptors are disastrously growing. Brain is the main regulator of life processes, including aging. Earlier it was believed that brain cells are not able to reproduce themselves in aged conditions however in the last time it was justified that hippocampal structures are able to do this; even similar processes were observed in the cerebral cortex [35]. This help the preservation of cognitive function in elderlies, and this is strongly impaired by the effect of endocrine disruptors [36].

As brain regulates the secretion of sexual hormones (which are also needed for the preservation of cognitive functions) the decrease of them under the effect of endocrine disruptors also deteriorates cognition. In this harmful process the perinatal events of hormonal mis-imprinting-causing lifelong impact on the endocrine system-reprograms the genetic structure of the brain regulator center, hypothalamus, which causes advanced reproductive senescence [25]. This observation by animal experiments is supported by human observations on capacitor-workers, having increased incidence of Parkinson's disease [30]. In addition to the hypothalamus-pituitary system of the brain, there is another regulatory system in it, and

this is working in the pineal gland, which regulates the thymus and the immune system. The prominent role of thymus in the immune system was discovered, when Miller thymectomies young rats and wasting disease was the result of the operation [37].

However, pinealectomy of young rats also provoked wasting disease, with the breakdown of the immune system [38]. As the immune system is incriminated with the regulation of lifespan, this could mean, that a continuous abrasion of the cell-pool has a role in aging, and the brain-pineal-thymus system could be responsible for the aging and lifespan [39]. Considering these possibilities, the harmful effect of endocrine disruptors to the immune system as a whole and outstandingly to the thymus [40,41] can influence the process of aging. At puberty, the critical developmental window for imprinting is also open and faulty imprinting by endocrine disruptors can be executed [42]. The effect of them can be observed later, in elderlies. At present the amount of known endocrine disruptors is extremely high and quickly growing, supplemented by new variations, while the longevity of man is also growing, what means that the number of aged people (and their ED-free health) will be one of the most important problems of the future (the number of 60+ people, who are elderly by the present rating is expected to 2030, as 1.4 billion and 80+ (senile) people is forecasted to be 125 million in 2050 [43].

This requests the thorough study and exploration of possible ED-effects in geriatric diseases as well, as the more intense inserting of animal experiments and human observations on possible ED-effects. This is a difficult duty for the present and near-future doctors and researchers, however unavoidable. The change of human environment by artificial interventions requests the change of doctors' approach. It is important in each medical case however, more important in case of geriatrics, considering the complexity of events causing aging. In addition, as far is the sequel from the provoking action, as problematic the verification of their interrelations. This is especially right, when perinatal action (faulty imprinting) is considered as a cause of reactions by elderly). In other words, long time will be passed before the recognition and acceptance of urgent importance in case of interrelations between endocrine disruptors and aging. This paper wanted to promote this course of events.

Conclusion

There are not materials (medicaments) which could be able to neutralize the harmful effects of EDs (although antioxidants as e.g. vitamin C and E are contributing in this process [44]. However, the discovery of panacea could not be expected. The growing mass of mankind demands the use of endocrine disruptors irrespective of their negative health effect (e.g. pesticides, herbicides, plasticizers, anti-concipients [45-49] and some medicaments) and this will grow further in the future (although already at present EDs can be found also in the Arctic [46]). This means that the doctors of the future (regardless of their qualification), will be forced to calculate with diseases, which are provoked by faulty imprinting perinatally or by direct effects of EDs in the whole life. As the manifestation

of non-infective diseases is more frequent in aged people; outstandingly because of the transformation of the immune system (autoimmunity included) the consideration of endocrine disruptor effects will also touch the structure of the present and rather the future hospitals as well, as the health insurance and not ultimately the focusing of medical training.

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