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Review

Puberty dysregulation and increased risk of disease in adult life: Possible modes of action

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ABSTRACT

Puberty is the developmental window when the final maturation of body systems is orchestrated by hormones; lifelong sex-related differences and capacity to interact with the environment are defined during this life stage. Increased incidence in a number of chronic, multifactorial diseases could be related to environmental exposures during puberty: however, insight on the susceptibility of the peripubertal period is still limited. The estrogen/androgen balance is a crucial axis in harmonizing the whole pubertal development, pointing out the significance of exposures to endocrine disruptors. Besides the reproductive system, endocrine-related perturbations may affect the maturation of **s**keleton, adipose tissues, brain, immune system, as well as cancer predisposition. Thus, risk assessment of environmental stressors should duly consider specific aspects of the pubertal window. Besides endocrine-related mechanisms, suggested research priorities include signaling molecules (e.g., kisspeptins, dopamine) as xenobiotic targets and disturbances of specific pubertal methylation processes potentially involved in neurobehavioral disorders and cancer risk in adulthood.

Contents

1. Introduction: puberty and environmental exposures

Life is made up of a constant synchronization of processes in the organism. The chemico-physical interactions of molecules build complex pathways which change with time, thus causing development and aging. Life stages are sequential physiological entities with their own specific characteristics. Accordingly, human medicine as well as toxicology has abandoned the concept of the child as being equivalent to a small adult. Environmentally-caused perturbations during development may be more severe and persistent, and may occur at dose levels lower than in adult organisms; thus, up-to-date toxicological risk assessments provide specific attention toward mechanisms and effects affecting the dynamics of life stages [1]. The impact of the environment on intrauterine development, a period of unique susceptibility, attracted much attention during the last decade [2,3]. Moreover, it was shown that early childhood (the first two years of a person's life) is somewhat of a transitional life stage, highly susceptible to hazards affecting the ongoing development of the nervous, immune, metabolic and excretory systems [4].

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Growth until adulthood is marked not only by an increase in mass and maturation but also by intense endocrine changes influencing body form and composition, as well as metabolism and behavior during the critical periods of pre-puberty and puberty. These changes make up the final programming of the organism for sexual maturity, adulthood and fine tuning with one's living environment. Puberty, therefore, features as a potentially susceptible window; to which, until now, toxicologists have devoted little attention [5,6]. Toxicological studies investigating the effects of endocrine disruptors (ED) on puberty onset have recently been reviewed and discussed [7]. However, an appraisal of the xenobiotic effects on the multi-faceted events of puberty has not yet been attempted; indeed, the diverse environmental effects on the parameters of puberty (growth, behavior, sexual maturity, etc.) might lead to increased health risks such as cardiovascular diseases or cancer in young adulthood. The estrogen-regulated pathways are examples of complex hormonal pathways playing major roles in puberty, as estrogen signaling has many endocrine (maturation of reproductive organs, skeleton, etc.) as well as paracrine (neuromodulator and neurotransmitter) activities [8]. Tissue-specific estrogen levels, puberty- and sex-related expressions of nuclear and cytoplasmic estrogen receptors (ERs), including genetic polymorphisms, the cross-talks both between ERs and of ERs with other receptors, are all crucial regulating factors during peripubertal maturation [9–11]. Nuclear receptors (NR) are recognized ED targets, as are the enzymes regulating hormone synthesis (e.g. aromatase); whereas significant progress has been made, and is being made, concerning ED-NR interactions during fetal programming and their consequences [12,13], the impact throughout postnatal developmental windows has yet to be thoroughly investigated.

Puberty is the life stage when sex differences are stressed and determined for the oncoming adulthood. Thus, any appraisal of a toxicant's effects during puberty must devote due attention to sex differences and their potential outcomes later in life. For instance, most cancers show sex-specific ER changes, which levels are used in decisions on antineoplastic therapies and for predicting sex-related survival rates [14,15].

Exposure to chemical agents and radiation during puberty may change cancer incidence in adulthood [16]. Interestingly, a study on time trends (1972–2003) in cancer incidence among 0–24 year-old residents of Province of Trieste, Italy, showed the highest incidence increase in the 15–24 age group; although this data should not be over-interpreted, it may hint toward a peripubertal susceptibility to environmental factors within the general population [17].

Last but not least, puberty is characterized by significant changes in behavior. Together with an increased level of awareness of and interest for the surrounding world, changes often entrain an increase of risk-taking behaviors which concern all aspects of daily life: diet (e.g., intake of fast food, canned beverages, energy drinks), peer-pressure-related behaviors (tasting alcohol, cigarettes, marijuana, etc.), increased use and changes in types of cosmetic and personal care products, use of contraceptives and increased cell phone usage. These behavioral changes are considerably fast and often dramatic. This way, new types of exposures and new modulating co-factors are rapidly introduced into the living environment.

Our paper will review the evidence on effects and modes of actions for two major groups of agents that may affect pubertal development: i) ED as regards non-reproductive targets, such as body growth and composition and neuroendocrine and immune tuning; ii) genotoxic and tumor-promoting agents, including radiation, as regards impact of pubertal exposures on cancer risk. Possible developments relevant to toxicological testing and risk assessment will also be discussed.

2. Endocrine disruptors and non-reproductive targets in puberty

2.1. Puberty-specific hormonal changes and xenobiotic metabolism

Susceptibility to ED is modulated by the life stage-dependent hormone balance. As dramatic physiological changes occur throughout puberty, the peripubertal organism has different and changing susceptibility as compared to both childhood and adulthood. The most important mechanism for normal development and sexual maturation is the interaction between growth, thyroid and steroid hormones [18]. The age-related changes of the pituitary-testicular function in human males have been described in a seminal paper [19]. Serum luteinizing hormone and follicle-stimulating hormone levels are low before puberty, but increase during puberty to levels somewhat above those of adults. Steroid globulin binding capacity is high in pre-pubertal boys but decreases in adult men. As for estradiol, sex-related differences are already evident in the pre-pubertal phase, with mean levels in girls being four times higher than in boys [20]. The circadian variation of estradiol levels in peripubertal humans is also sex-related, with the trough occurring 08.00–20.00 h in girls, and 12.00–20.00 h in boys [20]. A study conducted on pigs indicated that peripubertal females have a reduced clearance of estradiol-17β as compared to pre-pubertal ones [21]. In humans, estradiol levels follow growth hormone levels during puberty [22]. During pre-puberty and puberty, a decrease of sex-steroid-binding plasma protein is reported, which is the consequence of an increase in testosterone, estradiol and dehydroepiandrosterone levels [23].

Xenoestrogens may disturb pubertal processes by binding the sex-hormone binding globulin to human plasma (hSHBG), thus being transported through the plasma and/or displacing endogenous sex steroid hormones from hSHBG binding sites [24]. That way, any factor increasing estradiol production during puberty would lead to more sustained and possibly altered feed-back mechanisms, which might result in an altered androgen-to-estrogen balance. Such factors need not necessarily be xenobiotics: cows' milk, produced under current conditions of intensive husbandry, may lead to a considerable intake of estrogen (and progesterone), since animals are milked during the later half of pregnancy [25].

Different age-related toxicokinetics of ED can also occur: In pre-pubertal children the elimination rate of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is much higher than in adults [26]. However, environmental exposure to TCDD reduces levels of estrogen in pre-pubertal and pubertal boys, but not in adults, probably by aromatase inhibition. Consequently, increased TCDD internal levels affect sperm concentrations in peripubertal subjects but not in adults [27], suggesting a higher, age-related biological susceptibility during puberty in spite of higher clearance. Pubertal males are likely to be susceptible to ED: exposure to low doses of polychlorobiphenyls (PCB) and dichlorodiphenyldichloroethylene (DDE) is related to disturbances of aromatase index, testosterone and estradiol levels [28].

Puberty is also an age of increasing, as well as conflicting, attitudes toward one's physical appearance. A major age-related issue is skin changes, including the appearance of acne. Therefore, puberty sees a varied, often increasing, use of personal care products and cosmetics, which may contain parabens, phthalates and endocrine-active plant products. However, the potential transcutaneous exposure, if any, to ED from cosmetics cannot yet be ascertained with certainty [29]. Products against acne often contain the antibacterial compound triclocarban, which increases the expression levels of several NRs (ER alpha, Constitutive Androstane Receptor) in vitro, thus featuring as a potential ED [30,31]. Triclocarban also altered brain-specific expression of aromatase in early

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