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Prenatal imprinting by environmental toxicants: really an important issue?

Prenatalne naznaczenie genetyczne (*imprinting*) wywołane przez toksyny środowiskowe – czy rzeczywiście ważna sprawa?

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SUMMARY

Prenatal imprinting of sexual behaviour and of other traits by environmental toxicants has been one important topic in the ongoing discussions in environmental medicine. This review of the literature shows that, so far, concrete data are sparse and, in part, contradictory.

Key words: endocrine disruptors, phthalates, PCDD/F, PCB, bisphenol A, prenatal imprinting of sexual behaviour

STRESZCZENIE

Prenatalne naznaczenie, czyli *imprinting* zachowania seksualnego i innych cech wywołane toksynami środowiskowymi było ważnym tematem w toczących się dyskusjach w medycynie środowiskowej. Przegląd dotychczasowego piśmiennictwa wykazuje, że udokumentowane dane są skąpe i w części sprzeczne.

Słowa kluczowe: Dysruptory endokrynne, ftalany, PCDD/F, bisfenol A, prenatalne naznaczenie genetyczne zachowania seksualnego

INTRODUCTION

Endocrine disruption (ED) is one of the dominant topics of the last decade's environmental discussions. The pertaining literature is voluminous and contradictory. This is due to several factors: the fact that a greater number of chemical and natural hormonally active substances are to be evaluated; the co-existence of possible synergic and antagonistic mechanisms of action and the fact that many results are based on epidemiological evaluations of subtle modifications which might become visible only after decades.

There are well known EDs that modify puberal development: ethinylestradiol as medication to induce earlier puberty in tall girls, androgens in girls with untreated congenital adrenal hyperplasia (CAH, adrenogenital syndrome) and during pregnancy, inducing masculinisation. But what about environmental toxicants, "chemicals", what about long term effects of low doses, of "toxic cocktails"?

The World Health Organisation (WHO) and the United Nations Environmental Program (UNEP) published, in 2013, a disturbing review: State of Science of Endocrine Disrupting Chemicals 2012 [1]; disturbing because in itself contradictory. In the

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Summary for Decision Makers, early puberty is said to belong to "diseases induced by exposure to EDCs during development in animal models and human studies", whereas the review itself states that: "demonstrated epidemiological associations are absent and warrant further investigations". Which of the two statements might be correct, or: is the summary politically biased? The WHO review has been, in the meantime, harshly criticized as not thorough enough to claim to have written a "State of the Science" [2].

We will focus here on a few selected aspects of endocrine disruption.

TESTICULAR CANCER

Germ cell malignancies are known to occur more frequently in some regions. Thus, the annual incidence rate is 12.7 per 100,000 in Norway, 13.4 in Denmark, 12.7 in Switzerland [3], and the incidence in these countries has been increasing during recent decades, whereas in Germany the incidence has remained stable during the last 15 years, at a rate of 9.5 per 100,000 [4]. In Denmark, immigrants have incidences only half as important as compared to indigenous men, but in the second generation incidences are equal [5]. Such findings indicate clearly that environmental factors play an important role; but, finally, we do not know what can be the reason: sexual practices, narrow pants, cycling, nutrition, or endocrine disrupting chemical substances?

HYPOSPADIAS

Hypospadias, a morphologic result of endocrine disruption, are only in a minority of cases the result of inherited, syndromatic disturbances of hormone synthesis or receptor affinities; most of them occur sporadically. Frequently, the occurrence of hypospadias is taken as a sign of environmental endocrine disruption. However, European malformation registries show that the incidence of hypospadias has not increased during the last decades.

POSSIBLE PRENATAL IMPRINTING AND CONDITIONING BY PCDD/F (POLYCHLORINATED DIBENZODIOXINES AND -FURANES) AND PCB (POLYCHLORINATED BIPHENYLS)

In girls, increased androgen exposure (in CAH) during pregnancy results not only in masculinisation of external genitalia, but also in psycho-intellectual alterations leading to boyish play and social behavior. Those are effects of relatively high dose exposures. On the other hand, antiandrogens, given to rodents during pregnancy, later suppress masculine sex-specific comportment in adult offsprings. Such sexually dimorph alterations of behavior can be explained with some plausibilty with the findings on the prenatal structural formation of the fetal brain.

But what about the effects of low dose endocrine disruptors that are active over long periods?

Vreughdenhil et al. investigated a cohort of 207 children in early school age, 50% of each gender, and they compared breast fed and non breast fed children. PCDD/F and PCB had been measured in cord blood, mother's blood and milk. Higher prenatal loads went along with less boyish, masculine play habitudes in boys. Girls had increased boyish play behavior (the latter statistically not significant) [6].

Winneke et al., investigated 110 children (50% boys and girls) at the age of 6 to 7, in whose mother's blood and milk PCDD/F and PCB had been measured by the time of birth. They state that (translation by the authors) "our study shows that even relatively low prenatal exposure of dioxines and PCBs can change sexual behavior in school children". The higher the loads, the more girlish was the comportment in boys. Girls, however, showed, after higher exposure, less female behavioural traits [7].

Swan et al. measured phthalate metabolites in the urine of women at mid-pregnancy. In 145 preschool children, high concentrations were significantly associated with less boyish behavior in boys, however not in girls [8].

The results of these three studies are partly contradictory. The cohorts are small, results rely on (validated) questionnaires answered by the parents. Therefore, authors are only cautiously giving their interpretations, generating hypotheses, not conclusive results.

BISPHENOL A

There exist many chemical products and substances – all of them measurably present in breast milk – that have effects on hormone production or receptor affinities [9]. One of them is the recently very frequently focused Bisphenol A (BPA) which is important for the production of polycarbonates, an important substances necessary for the production of many daily life articles [10]. Originally, BPA was

developed as a synthetic estrogen. However, its estrogenic activity is lower by four orders of magnitude, as compared to estradiol. In man BPA is quickly glucuronised and sulfatised, and these metabolites have no estrogenic effects [11].

Braun et al. have measured BPA in urine samples in 244 mother-child-pairs, twice in pregnancy and at birth, and in the children at age 1, 2 and 3 years. BPA was present in more than 97% of all samples. Parents answered questionnaires when the children were 3 years old. High BPA concentrations were "positively associated" with angst, hyperactivity, and depression in girls. In boys, however, higher loads lead to less hyperactivity. These effects were seen after higher loads during pregnancy and at birth. No correlations were seen between BPA concentrations at age 1 to 3 years and behavioral traits. The authors admit that the cohort was not very big and that, since very many correlations have been calculated, they had no done any statistical evaluations [12].

Recently, the European Food Safety Agency (EFSA) has lowered the tolerable daily intake (TDI) limit for BPA to 4 µg/kg/day, considering this level to be safe for all, including infants, children, and prenatal exposure. Actually, the estimated exposure is lower than the TDI limit by a factor of 3 to 5 [13]. The German Children's Environmental Survey (KUS) has shown that the average urine concentration (median) is 2.66 µg/l, and the 95 centile 14 µg/l. The German human biomonitoring value (HBM I, below which concentrations are considered to be safe) is given as 150 µg/l, hence higher by more than one order of magnitude. However, some authors consider BPA's epigenetic effects (at very low dose exposure) to be harmful [14]. A detailed compilation and analysis of present regulations is given by Vandenberg [15], but this paper has been harshly criticized by other competent authors; and discussion is ongoing.

BPA meanwhile is an ubiquitous chemical product, measurable in practically every human sample. In high doses, it produces estrogenic effects. Present loads, however, are lower by several orders of magnitude than those which are effective in laboratory animals.

Additionally, there exist a plenitude of further publications with regard to several other chemical compounds on prenatal imprinting, concerning diverse behavioral aspects, motor and cognitive abilities, and intelligence, both in laboratory animals and in man. Usually, much higher toxicant loads are used in animals, as compared to environmental concentrations [16–31].

CAVEATS AND FINAL REMARKS

1) Mankind, and fauna, are exposed not only to BPA, PCDD/F and PCB, but also to other endocrinologically active substances with possible synergies (but also antagonistic effects). The evaluation of single substances is necessary, but may be not sufficient [32].
2) Some effects can be seen only later in life or decades after exposure. Diethylstilbestrol is known to have produced vaginal carcinomas in adult daughters of women who have been treated with this substance during pregnancy, probably via epigenetic effects.
3) In some cases, apparently very small amounts of toxicants can produce deleterious epigenetic effects; e.g. isotretinoid: dermal application for acne treatment and resulting absorptions of possibly minimal amounts of the substance during pregnancy can induce severe malformations in the offspring.

There exist numerous observations pointing to endocrine disruption by environmental toxicants. Both chemical products, and phytoestrogens must be considered. Single substances and synergism of similarly acting substances, potentiation and antagonistic actions, and long latencies before the manifestation of subtle effects must be taken into account. There are, as cited above, a few serious findings showing that environmental toxicants can prenatally influence sex-specific comportment; insofar as they come from animal experiments, dosage has been higher mostly by several orders of magnitude [33].

For many chemical products it holds true that it is practically impossible to eliminate or forbid them. Many of them are important constituents of modern daily life. We must be aware, however, of that some classes of chemical compounds are persistent and will stay in our human as well as in fauna's and flora's environment for decades and possibly centuries. Some of them are globally detectable, e.g. both in ice bears and in penguins.

Therefore, Rachel Carson's Silent Spring [34] still is an important parable, and the lesson must be that minimization and substitution of harmful and persistent substances by less harmful products remains mandatory.

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