ROLE OF DEVELOPMENTAL EXPOSURE TO ENDOCRINE DISRUPTORS IN CANCER

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Introduction

Development is a highly integrated process, involving rapid proliferation and differentiation. Thus, the developing child represents a particularly susceptible population to environmental insult. Developing organisms have increased susceptibility to cancer if exposed to environmental toxicants during periods of rapid growth and differentiation. Human studies have demonstrated clear increases in cancer following prenatal exposure to ionizing radiation, and there is suggestive evidence for brain tumors and leukemia in association with parental exposure to chemicals[1]. The clear association between fetal exposure to diethylstilbestrol (DES) and vaginal adenocarcinoma in young women[2] has led to the suggestion that developmental exposure to endocrine active substances could also be associated with delayed cancer.

Early Life Stage Carcinogens in Animal Models

There is convincing data from experimental animal studies relating developmental exposures and adult cancers. Early life-stage exposures to radiation, enthyl-nitrosourea, urethane, and N-nitrosodiethylamine all cause tumors in rodent offspring[3], but the effects are very dependant upon the chemical, dose, and timing of exposure. Exposure to various chemicals has led to tumors in multiple tissues in mice, rats, hamsters, opossums, rabbits, monkeys[1]. Perinatal exposure to polybrominated biphenyls (PBBs) was hepatocarcinogenic in rats and mice and enhanced the response if combined with adult exposure as well [4].

Endocrine Disruptors During Development and Rodent Tumors

While DES, a synthetic estrogen, is clearly carcinogenic following in utero exposure, there is little epidemiological data for other prenatally hormonally mediated cancers in people. However, there is a growing amount of data in laboratory animals for the role of endocrine disrupting chemicals (EDCs) in prenatal induction of tumors. Neonatal exposure to DES causes reproductive tract tumors in mice [5]. Prenatal exposure of rats to genistein, a natural phytoestrogen, leads to an increase in carcinogen-induced mammary tumors in the pups [6], while neonatal exposure to mice leads to an increase in uterine tumors [7]. Tamoxifen, both an estrogen agonist and agonist, depending upon the tissue and age, also resulted in enhanced sensitivity of the pup to mammary carcinogens when given during gestation to the dam [8]. PBBs, which cause liver tumors following perinatal exposures [4], are representative polyhalogenated aromatic hydrocarbons (PHAHs) which are also endocrine disruptors [9].

Prenatal Endocrine Disruption and Mammary Tumors

TCDD, the prototypical PHAH acting through the Ah receptor, is carcinogenic in humans as well as in multiple animal species, at multiple sites, and in both sexes [10] . Brown and coworkers [11]

demonstrated that prenatal exposure of rats to TCDD led to an increase in DMBA-induced breast tumors in the adult offspring. This was associated with an increased number of terminal end buds in the mammary gland at sexual maturity, the time of carcinogen treatment. In addition, our laboratory [12] has demonstrated that *in utero* exposure to TCDD results in fewer primary ducts, stunted epithelial progression in to the fat pad, fewer terminal buds, decreased lateral branching, delayed lobule formation and retention of terminal end buds at a time when they are gone in control glands . These developmental delays in the gland could be detected as early as postnatal day 4, and persisted throughout adulthood. In fact, the glands never fully recovered. The critical window was also shown to be at the end of organogenesis [12]. The alterations in mammary gland structure are associated with functional changes, with the exposed offspring producing less milk than controls for their own pups [13] . Thus, prenatal TCDD alters the proliferation and differentiation of the mammary gland, prolonging the window of sensitivity to carcinogenesis. Recently, postnatal exposure to TCDD, as well as to PCBs, has also been shown to increase the incidence of MNU-induced tumors [14] .

Atrazine, a chlorotriazine herbicide, is one of the most commonly used herbicides., and has been shown to cause mammary cancer in adult rats. This appears due to premature reproductive senescence and is unlikely to be applicable to humans [15]. However, exposure of pregnant rats to atrazine during late gestation delayed the normal epithelial progression into the fat pad, and led to enhanced sensitivity to DMBA tumorigenesis at sexual maturity [16] . These effects are reminiscent of what has been seen following *in utero* TCDD exposure. It is important to note that both alter the endocrine status of the dam.

Recently, Markey and coworkers [17] have demonstrated that prenatal exposure of mice to bisphenol A also alters mammary gland development. Whether these changes are actually associated with an enhanced carcinogen sensitivity remains to be determined. Of interest are the preliminary reports suggesting that arsenic may be an endocrine disruptor. Gestational exposure of mice results in multiple tissues developing tumors in the offspring held for over a year [18] . The pattern of tumors resemble those seen following developmental exposure to estrogens, and may be associated with the arsenic-induced up-regulation of the estrogen receptor noted in mouse liver following chronic exposure [19].

Human Impact?

It is clear that early life stage exposure to endocrine disruptors can alter the sensitivity of offspring, both animal and human, to cancer. This raises the question: are we trying to correlate exposure and effects at the wrong time? If developmental exposure is leading to altered sensitivity of the adult to carcinogenesis, why are we measuring such exposures in the adult when the critical window of sensitivity was in the fetus or neonate? Overall, epidemiological studies looking at exposure to environmental chemicals, including organochlorines and atrazine, and breast cancer have been inconclusive, at best [20] . Maybe we've been looking at the wrong time!

Acknowledgments

This abstract does not necessarily reflect EPA policy.

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