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Endocrine disrupting chemicals on female reproduction

Introduction

Endocrine disrupting chemicals comprise natural substances like phytoestrogens, pesticides and fungicides, substances used in production of plastics or as plasticizers (bisphenol and phthalates), industrial chemicals (polychlorinated biphenyls) and metals. These chemicals are available in the environment and affect internal hormonal milieu. The potential adverse effects of occupational and environmental exposures to endocrine disrupting chemicals are increasing concern in recent years. It affects mammalian fetus in which the intrauterine environment may alter endocrine and homeostatic processes, Thus, the environment needs to be redefined to include not only environmental factors or ask the people to take so much of plant derived anti-oxidants.

Epidemiological studies are available for environmental endocrine disruption in humans. For the past two decades, our laboratory worked on the effect of polychlorinated biphenyls (PCBs) / Bis (2-ethylhexyl) phthalate (DEHP) on male reproduction as well on selected brain regions on albino rats only. Zala & Penn[1] studied on populations of wildlife and they are impacted by endocrine disruption.

Apart from toxicity, the embryonic period is particularly important in this regard, as it is a developmental window when DNA becomes modified through methylation, demethylation and or remethylation, a process that is thought to play a key role in cellular differentiation. Studies available on the high urinary concentrations of phthalate monoesters, the primary metabolites of phthalates and the incidence of anomalies such as cryptorchidism and shortened Anogenital distances (AGD) on new born males suggesting that the Leydig cell function is disrupted. Our recent study demonstrated that *in utero* exposure to phthalates downregulates critical genes in testicular Leydig cells of F1 male progeny.[2]

Lactational exposure of PCBs downregulates critical genes in Leydig cells of F1 male progeny (Post natal day 21).[3] It impairs Leydig cellular steroidogenesis in F1 progeny (post natal day 60).[4] Phthalate causes long term disruption in testicular Sertoli cells of F1 generation of pubertal rats.[5] PCBs affect rat Sertoli cell markers and functional regulators in F1 offspring.[6] Lactational exposure of PCBs affects FSHR, ERα , ERβ, inhibin β, ABP, transferrin, transcription factors regulating FSHR, AR and the Sertoli cellular junctional proteins of F1 progeny.[7] Previous studies also proved in adult animals.[8–10]

Endocrine disruptors induced epigenetic changes in specific genes that are involved in the regulation of endocrine pancreas,[11] thyroid, testicular,[2,5] ovarian and uterian function[12] appear to play a significant role. Studies on sperm parameters are lacking.

DEHP reduced the serum insulin, testosterone and increased blood glucose, T_3 and T_4 in rats. Rajesh et al.[11] studied that DEHP impairs insulin receptor and glucose transporter 4 gene expression in L6 myotubes. Apart from this, studies on female animals are also lacking. Literature proved that endocrine disruptor reduces serum testosterone and estradiol. DEHP/PCBs effects on expression of genes involved in steroidogenic machinery, translation, transcription regulation on male gametes have been studied.

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Seegal et al.[13] studied that PCBs suppresses dopamine concentrations in the rat brain, non-human primates, selected brain regions[14,15] and hypothalamus.[16] Lactational exposure to DEHP induces oxidative stress and causes neurodegeneration in hippocampus of offspring female albino rats.[17] Bavithra et al.[14,15] demonstrated the role of melatonin on PCB induced neurotoxicity on selected brain regions of albino rats. PCB elicits a spectrum of biochemical and neurotoxic responses in human and laboratory animals. Glutamate and BDNF play critical roles in the physiology of the central nervous system as it can control many functions such as memory, learning, cognitive, emotional, endocrine and other visceral functions.

The excess activation of glutamate induces excitotoxicity. Glutamate excitotoxicity induces various neurodegernative diseases such as cerebral ischemia, epilepsy, Alzheimer's, Parkinson's diseases and multiple Sclerosis. PCB impairs learning and motor co-ordination which may be related to cerebral dysfunction. PCBs exposure decreases spontaneous motor activity. PCB induces oxidative stress which may cause excess glutamatergic neurotransmission and may eventually lead to neurodegenerative diseases by disrupting the neurotropins (BDNF signaling) and activating the apoptotic signaling. In our laboratory Bavithra et al.[18] studied that PCBs impaired glutamate/BDNF signaling, neuronal apoptosis and neurodegeneration on the cerebral cortex of adult rats. Selvakumar et al.[19] proved that PCBs impair blood-brain barrier integrity via disruption of tight junctional proteins in cerebellum, cerebrum and hippocampus of female rats.

PCBs also decreased dopaminergic receptors and caused neurodegeneration in cerebellum via Production of ROS[14] and cerebral cortex.[20] PCBs induced oxidative stress mediated neurodegenaration in hippocampus has also been studied in our laboratory.[19] Protective role of melatonin on PCBs induced oxidative stress in rat cerebellum, cerebral cortex and hippocampus were also studied.[21]

There is a molecular link between endocrine disruptors and infertility. In female population, endocrine disruptors have been associated with increased abnormalities in menstrual cycles, endometriosis, hormonal changes, altered onset of puberty, premature menopause, reduced fecundity, pre-term labor and low birth weight baby.[22] Animal studies have provided support for many of these associations and have elucidated mechanisms of toxicity. However,

further well designed research studies on human population are necessary to clarify these associations. The study on various endocrine disruptors and the impact of biomonitoring in public health are necessary. The understanding of their toxicokinetics in different populations and with different doses with emphasize on fetal and neo natal exposure is needed urgently.

Therefore, it is tempting to think that a programme to protect health from endocrine disruptors. They disrupt neurotransmitter system, thyroid function, glucose, calcium, and sodium and potassium homeostasis. They have effects on both male and female system as well decreasing the motor and cognitive functions. To eradicate this, the studies on ameliorative role of quercetin, lycopene, vitamin C/E and the free radical induced damage to maintain pro- oxidant and anti- oxidant system on endocrine disruptors induced situations are necessary. Our pilot studies on the ameliorative role of quercetin, lycopene, vitamin C/E also are available in the literature.[8,16,19,23–28] Therefore, studies on the female reproductive health and endocrine disruptors are necessary to improve Chemicals Regulations Policy in global population.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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