Austin Journal of Lung Cancer Research

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Austin Publishing Group

Special Article - Sertoli Cells

Role of Endocrine Disruptors on Testicular Sertoli Cells

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Received: October 16, 2018; **Accepted:** November 22, 2018; **Published:** November 29, 2018

Short Communication

Endocrine disruptors are of various types which include pesticides, fungicides, insecticides, herbicides and plastics. Polychlorinated biphenyls are used in transformers and capacitors as dielectric properties in the formulation of lubricating and cutting oils, additive paints, copying paper, adhesive, sealents and plastics. DEHP (di (2-Ethyl Hexyl Phthalate) is widely used plasticizer found at high concentrations in plastic products including medical devices.

Presence of these compounds in umbilical cord blood, breast milk and amniotic fluid has been studied recently and have been linked to reduce semen quality and fertility [1]. DEHP exposure showed incidence of anomalies such as cryptorchidism and shortened Ano-Genital Distance (AGD) on new born males suggesting testicular function is disrupted [2].

Endocrine disruptors was associated with increased risk of myocardial infarction in men, defects in the learning and motor co-ordination. A series of studies from our laboratory reported that exposure to PCB (Poly Chlorinated Biphenyls) alters testicular function by affecting Sertoli, Leydig cells and male accessory sex organs such as prostate, epididymis and thus leads to infertility in adult rats [3-8].

In men, the reproductive system is composed of a pair of testis and a reproductive tract. The gonads have two major functions such as endocrine (to produce hormones) and exocrine (to produce gamate) function. The gametogenic function of testis and physiology of the reproductive tract are critically dependent on the hormone function of the testis. The presence of seminiferous tubules in the lobules of the testis creates two compartments within each lobule:

An intra-tubular compartment which is composed of the seminiferous epithelium of the seminiferous tubule and a peri-tubular compartment which is composed of neurovascular elements, connective tissue cells, immune cells and the interstitial cells of Leydig whose main function is to produce testosterone.

The intratubular compartment of seminiferous tubules contains Sertoli cells and developing sperm. Nursing cells have been invented by Enrico Sertoli; therefore they named Sertoli, have a nursing function providing micro-environment for sperm development. Sertoli cells have an important exocrine function producing fluid and androgen binding protein. They have endocrine function producing mullerian inhibiting substance called anti-mullerian hormone and inhibin. They express the androgen receptor and FSH receptor.

Spermatogenesis involves mitosis and meiosis. The final product is haploid spermatozoa. Sertoli cell provided androgen regulation. Dysfunction in Sertoli cells has adverse effects on spermatogenesis. Endocrine contaminants impair the viability and function of Sertoli cells and have a negative impact on the normal growth of germ cell. The testicular toxicity of PCBs and DEHP in adult male rats has been extensively studied in our laboratory. The PCB or DEHP transfer could occur from mother to offspring and information concerning the effects of neonatal PCB/DEHP exposure *via* milk on the reproductive function of F1 male offspring has been recently studied in our lab [9,10].

The rapid increase in male reproductive problems and geographical variations indicate that environmental exposure is the important contributor and they disturb the development of reproductive organs during fetal life. Since 2008, our studies proved that PCB/DEHP induced adverse effects on both Leydig and Sertoli cellular function in both adult and F1 progeny. We have estimated serum PCB on both lactating dams and male pups. Ano-genital distance, serum testosterone and estradiol were decreased after PCB/DEHP exposure. The critical genes expression such as ER, 5 alpha reductase, aromatase, androgen receptors on Leydig cells, FSH receptor, inhibin on Sertoli cells have been decreased after PCB exposure [3-10].

In human population, studies are available assessing the association between phthalate exposure and male reproductive developmental endpoints such as decreased ano-genital distance, hypospadias, cryptorchididsm and gynaecomastia [11]. Our studies demonstrated that lactational exposure of DEHP caused dose dependent changes in testicular Sertoli cellular function of male offspring through ROS induced apoptosis and perturbation of the eight junctional proteins such as occludin, claudin, junctional adhesion molecules, zona occludens protein 1, zona occludens protein 2 and afadin 6 [12]. Early post-natal exposure of DEHP disrupts histoarchitecture of testis and Sertoli cellular function in puberal Wistar rats [10].

The exposure to endocrine disruptors plays a key role in the epigenome shaping, thereby altering the endocrine function [13]. The endocrine disruptors can affect the different levels of epigenetic control. DNA methylation is the addition of methyl group at fifth position of cytosine residue within cpg dinucleotide motifs on both strands of DNA [14]. Unmethylated cpg islands are targets of transcription factors to start transcription. In contrast, the cpg sequences in inactive genes are usually methylated to suppress their expression [15].

DNA methylation is catalyzed by DNA methyltransferases enzymes such as Dnmt1, Dnmt3ab and DNA methyl transferase 3 like (Dnmt 31) which transfer the methyl groups to the cytosine ring. Dnmt1 is involved in the maintenance of methylation status during

Citation: Arunakaran J. Role of Endocrine Disruptors on Testicular Sertoli Cells. Austin J Lung Cancer Res. 2018; 3(1): 1015.

replication. Dnmt 3s (de nova DNA methyltransferases including Dnmt 3ab and the regulatory subunit Dnmt 31) are responsible for the establishment of genomic DNA methylation patterns [16,17]. The Dnmt 31 is genetically proven to be a necessary factor for DNA methylation of maternally imprinted genes and spermatogenesis [18].

Histones are core proteins of nucleosomes and acetylation of nuclear histones is regulated by histone acetyltransferase and Histone Deacetylase (HDAC). Histone acetyl transferase leads to the acetylation of core histone and it enhances nucleosomal relaxation and subsequently induces transcription. The HDAC1 stabilizes nucleosomal structure and represses transcription [19].

Endocrine disrupting chemicals cross the placenta freely because of their lipophilicity and affect the developing fetus. Their exposure can reduce the ratio of male to female births and also caused intelligence quotient deficits in the baby [20]. PCB may alter the transcriptomic profile particularly during development and it also disrupts epigenetic mechanism [13]. The pregnant rats exposed to PCB during gestation decreased the expression and the activities of Dnmts in the liver of the offspring [21].

Our earlier studies demonstrated that PCB exposure affected the expression of LHR and steroidgenic regulating enzymes thereby it disrupts the steroidogenic pathway in adult male rats [22] Krishnamoorthy et al, [23] in our team have shown that PCB exposure decreased the FSHR, AR, connexin 43 expression in Sertoli cells of adult rats. In 2016, Sugnatha Priya et al, of our team [24] studied that lactational exposure of PCBs affects the testicular architecture, testosterone, ABP and estradiol levels in both serum and testicular fluid. It also decreased the expression levels of FSHR, AR and transferrin in Sertoli cells of both F1 prepuberal and puberal offspring. In continuation of this we focused to determine the molecular mechanism behind decreased level of FSHR, AR and transferrin level in Sertoli cells by determining the level of transcription factors involved in it and DNA methylation pattern in the promoter region.

Steroidogenic Factor 1 (SF1) activates FSHR expression by directly binding to the E box response element in FSHR promoter region. The USF 1 and USF 2 are DNA binding proteins which act as a co regulator of SF1 in FSHR transcription. Griswold and Kim (2001) [25] have found that methylation of a cpg sequence within a consensus E box element decreased the binding affinity of USF 1 and USF 2 transcription factors for this element. Our early studies Priya et al, [26] demonstrated that lactational exposure of PCBs resulted DNA methylation in the E box element of FSHR promoter so this may affect the binding affinity of USF 1 and USF 2.

They also studied the decreased expression levels of c-fos, c-jun and methylation in the promoter of AR which may be the reason for the decreased level of AR gene expression in Sertoli cells of F1 offspring. Dnmt1, Dnmt 3ab and Dnmt 3l levels were increased in all the PCBs treated groups in Sertoli cells of F1 offspring. The increased levels of DNA methyltransferases is responsible for the methylation observed in the promoter of FSHR, AR and SF 1. Thus these studies proved that PCBs affect Sertoli cellular functional regulators through epigenetic mediated mechanism.

Alpha tocopherol is an anti-oxidant, fat soluble and biologically active form of vitamin E protects the cells, tissues from oxidative damage. Several researchers proved that alpha tocopherol plays an important role in maintaining the physiological integrity of testis, epididymis and accessory sex organs. Our earlier studies also Murugesan et al, [6] proved that alpha tocopherol scavenges the ROS which is generated by PCBs thereby it protects the Leydig cell function and prevents infertility. Literature is also available on supplementation of alpha tocopherol which prevents oxidative DNA damage in testis and sperm [27,28]. Very recently our team demonstated [29] that the lactational exposure of PCBs affects the FSHR, AR, estrogen receptor alpha and beta, inhibin beta, androgen binding protein, transferrin, transcription factors regulating FSHR, AR and junctional proteins such as connexin 43, claudin 11, occludin and E cadherin protein level in Sertoli cells and this effect was restored by the simultaneous administration of alpha tocopherol in Sertoli cells of F1 progeny.

These results suggested that alpha tocopherol has ameliorative role against endocrine contaminant induced testicular Sertoli cell dysfunction in F1 progeny. Thus endocrine disruptors particularly PCB or DEHP was associated with increased risk of myocardial infarction in men, defects in the learning and motor co-ordination. Our laboratory studies are also available on the same [30].

In conclusion, the present review demonstrated that endocrine disruptors affect Sertoli functional regulators through epigenetic mediated mechanism. Alpha tocopherol has ameliorative role against the same. Further studies are warranted on human population.

Acknowledgement

University of Madras, University grants commission and Department of Science and Technology (Govt. of India) are acknowledged for the financial assistance.

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Austin J Lung Cancer Res - Volume 3 Issue 1 - 2018
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Citation: Arunakaran J. Role of Endocrine Disruptors on Testicular Sertoli Cells. Austin J Lung Cancer Res. 2018; 3(1): 1015.