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Bisphenol A Triggers Abnormal Production of Testosterone and Androstenedione Causing Imbalance in the Hormonal Functions in Female Albino Wistar Rats

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Abstract:
BPA is a white solid crystals or flakes with a mild phenolic odour at room temperature. It is a monomer used in the production of polycarbonate and epoxy resin used in a wide range of consumer products. Due to its properties, bisphenol A can be easily released from the polymer products. Accumulating evidence from animal studies suggests that BPA potentially cause a wide range of reproductive and sexual abnormalities. It is well known for its estrogen-mimicking properties, and its role in sex hormone metabolism. This study investigates the possibility of testosterone and androstenedione perturbations at prevailing low exposure rates in female albino Wistar rats, following exposure for the period of three (3) month. To eleven experimental groups each containing ten (10) non-pregnant female rats were administered 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1 mg of BPA/kgbw/day. To the twelveth (12^{th}) control group was given water. Blood was collected from animals at the end of every week of the study and serum sample specimens analyzed by routine diagnostic procedures for testosterone and androstenedione using Autochemical Analyzer. Significantly increased concentrations of serum testosterone and androstenedione were observed at all concentrations of BPA exposure suggesting that bisphenol A upsets testosterone and androstenedione level and causes fluntuation of internal hormonal homeostasis.

Key words: *BPA, testosterone, androstenedione, exposure, sex hormone.*

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I. Introduction

BisphenolA (BPA) is a monomer used primarily in the production of polycarbonate (PC) resins and epoxy resin widely used in consumer products [1], with other uses that include the synthesis of flame retardant, unsaturated polyester resin, polysulfone (PS) resin and polyetherimides (PEI) [2]. BisphenolA (BPA) is a known endocrine disruptor. BPA enters the body by the ingestion of contaminated food or beverages. It leaks from polycarbonate plastics. Further minor ways of penetrating into the body are through the skin e.g. contact with thermal receipts [2,3]or inhalation e.g. cigarette smoke or dust [4,5]. Several studies have reported that absorption of BPA has cause extensive damage to the liver and kidney [6,7], formation of multinucleated giant cells in liver hepatocytes, DNA this chemical compound is been linked to adipose tissue dysfunction, metabolic/endocrine dysfunctions, cancer and fertility problems [8,9], impaired plasma glucose [10], involved in insulin resistance [11], causes permanent chromosomal damage linked to recurrent miscarriage and birth defects [12], spur both the formation and growth of fat cells, [4].These disturbing facts raise questions about the extent to which current, widespread exposures to BPA are contributing to the burden of infertility and reproductive health challenges. The aim of this study is to monitor the possible effects of Bisphenol A on androstenedione and testosterone in female wistar albino rats for three (3) month.

II. Materials And Methods

One hundred and ten (110) non-pregnant female rats of age 5 weeks were acclimatized in the laboratory for seven days and randomly divided into eleven (11) groups experimental of 10 rats each and respectively administered 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1 mg of BPA/kgbw/day. The first group which served as control did not receive any treatment but distilled water instead. The graded doses of

BPA were dissolved in distilled water and administered by oral gavage using intubation canular. Blood were obtained from the tail of the various groups by capillary action weekly, after BPA administration for thirteen (13) weeks. Blood samples were processed for clinical assay.

Animals were housed in aluminum wire-mesh cages in a well-ventilated animal house with a 12 h dark/light cycle and at room temperature and were provided commercial rat pellets (Vital feed from Vital group of Company, Nigeria) and water ad libitum.

At the end of the experiments serum androstenedione and testosterone were assayed using Chemwell 2910 Auotanalyser. All reagents were commercially obtained as already prepared kits. The kits for androstenedione and testosterone were purchased from Diagnostic automation/Cortez diagnostics inc, CA. and Enzolife sciences inc, NY respectively. Individual tests were carried out according to the kit specifications

Statistical analysis of obtained values were carried out by one-way analysis of variance (ANOVA) using SPSS software version 20.0 followed by the Tukey-Kramer multiple comparison test. A $P \leq 0.05$ was taken as a criterion for a statistically significant difference.

III. Results

EFFECT OF BPA ON TESTOSTERONE

There is a significant increase in the testosterone level of treated rats when compared with the control at $p \leq 0.05$. This increase which is across board is most pronounced in groups exposed to 0.4mg/kg, 0.7mg/kg, 0.8mg/kg, 0.9mg/kg and 1mg/kg of BPA (fig.1). the group that was administered with 0.05mg/kg BPA, showed no statistical difference when compared with the control (fig.1). Testosterone level in the BPA treated groups were observed to show a slight and steady increase with time. A characteristic increase that is time dependent was observed in the group exposed to 0.8mg/kg BPA. Except for groups of animal administered 0.8mg/kg (800µg/kg.bw) and group 0.2mg/kg and 1mg/kg, increased effect of BPA on testosterone does not show sensitivity to duration of dministration.

Fig.1 showed a dose dependent effect which initially peaks at dose 0.4mg/kg, then decline in 0.5mg/kg, again rise to peak at dose 0.7mg/kg, dropped at dose 0.8mg/kg and finally rise through 0.9mg/kg to 1mg/kg (fig.1). Over time the value obtained for each dose group remained within the same range, except for dose 0.2mg/kg and 0.8mg/kg that showed weekly effect, while 0.2mg/kg weekly effect was mild, 0.8mg/kg weekly effect was very pronounced, with week-13 showing the maximum effect (fig.1).

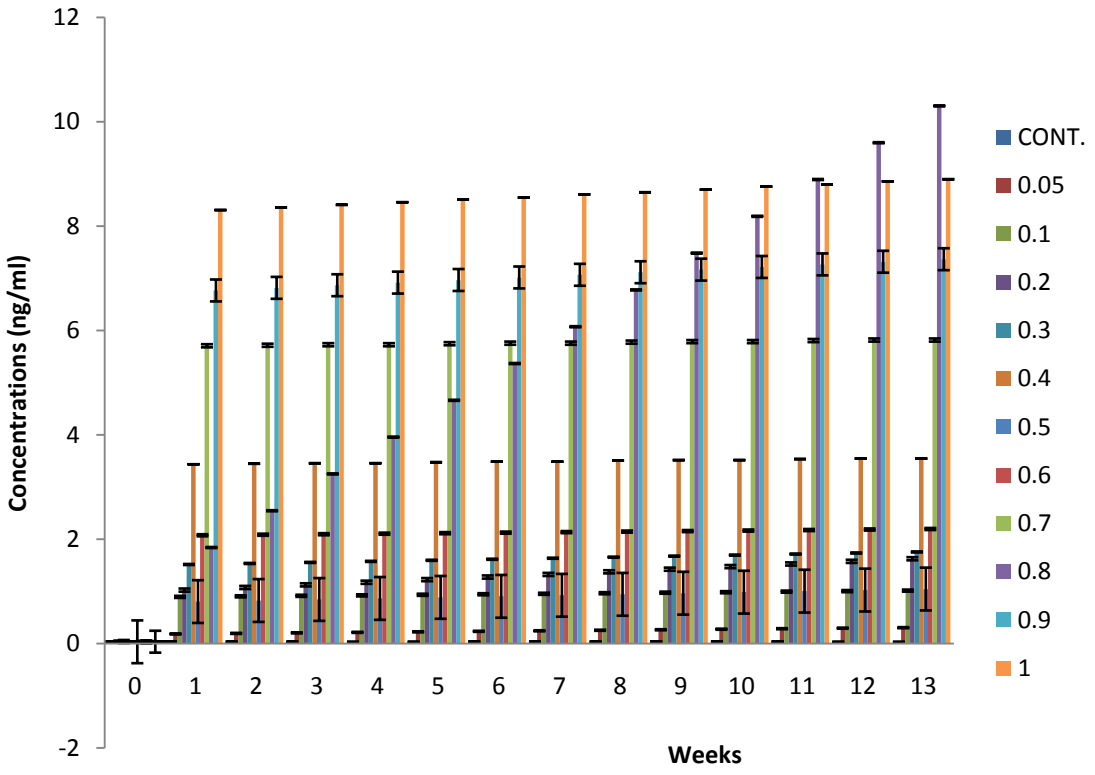

Fig. 1; Chart of concentration against weeks (durations) for serum testosterone concentration.

i) EFFECT ON ANDROSTENEDIONE

There is a significant time- dependent increase in the androstenedine level when compared with the control at $p \leq 0.05$. The dose concentrations that induce increases significant in androstenedione level are 50 µg/kg(gp1), 100 µg/kg(gp2), 600 µg/kg(gp7), 700 µg/kg(gp8), 800 µg/kg(gp9), 900 µg/kg(gp10) and 1000 µg/kg(gp11). Other doses (200 µg/kg to 500 µg/kg (gp 3-6) triggered a no- significant decrease in androstenedione concentrations at weeks-1 to 5, and a non-significant increase at weeks-6 to 8 (fig 2). Group 0.2mg/kg – 0.5mg/kg showed a relatively constant level of adrostenedione. It was observed that, they were not only constant but also decrease below the control for the first 5 weeks of exposure (fig.2), after which the weeks concentration of androstenedione were above the control level, although, the other weeks that showed higher values were not significant when compared with the control at $p \leq 0.05$ except week-9 to 13.

The established pattern of response was observed in week-1 to 7 such that dose group 0.05mg/kg and 0.1mg/kg showed increase in serum androstenedione level which was steady throughout the experiment with concentration of androstenedione exhibited by dose group 0.05mg/kgaways higher than those of 0.1mg/kg. The dose group 0.2mg/kg to 0.5mg/kg showed a dose dependent increase, which were lower than those of the control at week-1 to 4, but gradually increases above the control in weeks-5 to 13 (fig.2). The dose group 0.2mg/kg to 0.7mg/kg showed a dose dependent increase that peaked at dose 0.7mg/kg for weeks-1 to 7, the observed increased were consistent and steady throughout the experiment, but at weeks-8 to 13 the concentration of androstenedione dropped below its 0.6mg/kg counterpart, making dose 0.6mg/kg the peak at these weeks (fig.2). Again, it was observed that the dose group 0.8mg/kg showed a decline below relative to its 0.6mg/kg and 0.7mg/kg dose group counterparts, there was a rise in the concentration by 0.9mg/kg dose groups, with 1mg/kg dose group showing a decline in serum level of androstenedione relative to 0.9mg/kg dose groups, although the decline was not below those of the control (fig.2). Throughout the study the entire dosage group showed consistent increase in androstenedione over time, the dose group 0.9mg/kg showed the highest level of androstenedione throughout the study (fig.2). The peak was observed at week-13(318.90±0.003) and (320.67±0.006) for 0.6mg/kg and 0.9mg/kg respectively.

Fig.2 showed a clear time dependent effect with week-1 showing the lowest level for the entire dose groups, as the duration of the study increases the level of serum androstenedione increases with week-13 showing the maximum effect for all the dose groups.

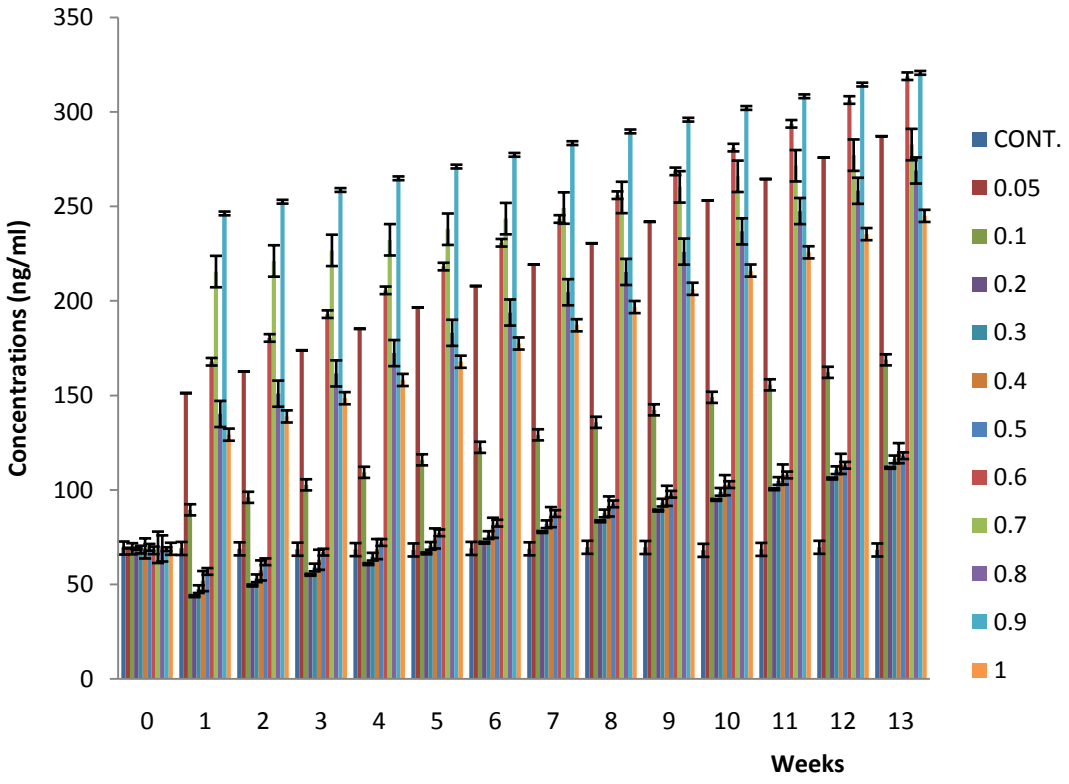

Fig. 2; Chart of concentration against weeks (durations) for androstenedione concentration

IV. Discussion

The findings of these results showed an increase in androstenedione and testosterone, after BPA exposure.Androstenedione, is an endogenousandrogensteroid hormone and intermediate in the biosynthesis of testosterone and of estrone. Androstenedione is a precursor of testosterone and other androgens, as well as of estrogens like estrone, in the body. Androstenedione has androgenic activity and estrogenic activity in its own right. In concordance with these results, Increase testosterone synthesis was reported by[13]Zhou*et al.,* 2008.[14] Zhou *et al.,* (2013) observed that the serum AD concentration in BPA exposed male workers was lower than that in unexposed workers, and the serum BPA concentration was inversely associated with the serum AD level. [15]Kandaraki*et al.,* (2011) reported an association between serum BPA levels and increased testosterone and androstenedione levels in women. Another study reported an association between serum BPA levels and increased testosterone and androstenedione levels [15]. Further, low dose BPA increased testosterone levels [16, 17]. [18]Galloway *et al.,* (2010) found that higher daily BPA excretion was associated with a higher total testosterone concentration. In rodents, low dose BPA exposure lead to increased testosterone production [16]. [19]Takeuchi and Tsutsumi 2002 also found significant positive correlations between serum BPA concentrations and total testosterone and free testosterone (FT) levels. [14]Zhou *et al.,* (2013) study observed inverse associations between serum BPA concentration and serum AD and FT levels. The serum BPA concentration was positively associated with the serum SHBG level.It has been shown that elevated androstanedione levels have negative effects onthe reproductive system [20].BPA act as an androgen antagonist that interrupts normal androgen receptor binding activity and thereby alters the interaction between androgen receptor and androgen [21].Hyperandrostenedionemiacan adversely affect the normal negative feedbackeffects of sex hormone [20], and in turn reduce fertility.Although epidemiological studies on BPA suggests that both low and high doses of BPA increase plasma testosterone levels due to an increase in mRNA expression of corticotrophin releasing hormone and activation of protein kinase C [17]. The mechanism underpinnings the ability of BPA to exert these effects may be found in the fact that BPA alters the expression of steroidogenic enzymes [22, 23](and alters follicle-stimulating hormone levels, which are required to stimulate steroidogenesis[24]. The observed increase in serumandrostanedione and testosteronecan be caused by BPA exposure[25]. It could also be as result of testosterone catabolism inhibition[26]. In addition, the female system tends to be a target for BPA action as it alters the conversion of androstenedione to testosterone and prevent androgen receptor activity, resulting in decreased bound androgen levelsand enhancing the synthesis of moreandrostenedione and testosterone[27]as suggested byLee *et al.,* 2003.

V. Conclusion

This study demonstrated that dose of BPA not only increases the androstenedione and testosterone concentrations but also alters hormonal balance in the system, this will provid an insight into the link between exposure to BPA and the hormonal system.

Authors contributions: the study conception and design was done by Ezeonu Francis Chukwuemeka. Material preparation, data collection and analysis were performed by OguazuChinenye E. The first draft of the manuscript was written by OguazuChinenye E. And both authors commented on the previous versions of the manuscript. Both authors read and approved the final manuscript.

Conflict of Interest: the authors declare that they have no conflict of interest.

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