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ALTERATIONS IN THE HISTOLOGY OF THE PROSTATE OF SPRAGUE-DAWLEY RATS TREATED WITH OXYTOCIN

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ABSTRACT

Background: The role of oxytocin in female reproductive system has been well studied. Very little is known about the long-term administration of oxytocin in prostatic tissues. This study aimed to assess the histological effects of prolonged administration of exogenous oxytocin on prostate in the male Sprague-Dawley rats. **Methods:** Twenty adult male Sprague-Dawley rats weighing between 180-250g were randomly distributed into four groups A, B, C and D of five rats each. Group A served as the control while groups B to D were the treated groups. Oxytocin was administered intramuscularly two days per week at the doses of 1, 2 and 3 IU/kg/b.w. to groups B, C and D respectively while 0.5ml of physiologic saline was administered to the control. The treatment was carried out over a period of 8 weeks (one spermatogenic cycle). At the end of study, blood was collected for testosterone assay and the prostate was also harvested for histological procedure. **Result:** Result showed significant decrease in the prostatic weight of all the treated groups. However, testosterone significantly increased in group D and the histology revealed moderate to severe stroma fibrosis, high vascularization with vascular congestion which was due to severe infiltration of inflammatory cells in a dose dependent manner. **Conclusion:** Prolonged administration of exogenous oxytocin could led to a decrease in prostatic weight. Hence, clinician prescribing oxytocin for the treatment of oligozoospermia should be conscious of the risk of exogenous oxytocin in inducing prostatic disorders.

Key words: Prostate, Oxytocin, Histology, Fibrosis, Testosterone

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INTRODUCTION

Oxytocin (OT) is a neurohypophysial hormone produced by the hypothalamic magnocellular neurons and stored in the posterior pituitary gland until their release into the blood stream (Thackare et al., 2006; Nicholson and Whittington, 2007). Oxytocin influences the autonomic nervous system and the immune system (Kingsbury and Bilbo, 2019; Carter et al., 2020). Oxytocin has numerous peripheral actions such as lactation, smooth muscle contraction, wound healing, natriuresis, sexual behaviour and mostly known as social behaviour hormone which increases trust and reduces fear, monogamous pair and maternal bonding (Veening et al., 2015; Jurek and Neumann, 2018).

Oxytocin stimulates steroidogenesis in several organs by modulating activity of 3-hydroxysteroid dehydrogenases and steroid 5α-reductases (5AR) in both the androgen-dependent LNCaP and androgen-independent PC-3 human prostate cancer cell lines (Assinder et al., 2015). It is also known to modulate sperm production, contractility of the male tract to regulate sperm transport and maturation (Thackare et al., 2006). Oxytocin is known to increase basal testicular testosterone production and the activity of 5α-reductase (Nicholson and Jenkin, 1995; Frayne and Nicholson, 1995; Stadler et al., 2020). It is also involved in regulating the conversion from testosterone to dihydrotestosterone (DHT) by differential regulation of 5AR I/II (Assinder et al., 2004; Stadler et al., 2020). The enzyme, 5α-reductases (5AR) is expressed as well as active in the hyperplastic prostate where its activity is elevated (Nicholson and Jenkin, 1995; Habib et al., 1998). Furthermore, the intensity of orgasm in both men and women are found to correlate with plasma OT levels (Carmichael et al., 1994).

In the prostate tissue, OT participates in the proliferative process both in epithelia cells as well as stromal cells (Xu et al., 2017). Oxytocin have been reported to have an autocrine or paracrine regulator in the prostate and is a major controller of the prostate contractions (Nicholson, 1996; Li et al., 2018; Lee et al., 2021). This implies that OT could be involved in supporting prostatic tone and co-ordinating contractions of the prostate during ejaculation (Frayne et al., 1996; Thackare et al., 2006). However, OT increases prostatic growth in rats as well as increase in prostate cancer growth (Jenkin and Nicholson, 1999; Assinder and Nicholson, 2004; Xu et al., 2017). Higher level of OT have been detected in the prostate hyperplasia and prostatic intraepithelial neoplasia (Whittington et al., 2004). Thus, OT contributes considerably to the prostatic disease development.

In support of physiological roles of oxytocin in the prostate, a specific oxytocin receptor mRNA have been identified in the marmoset prostate; and peptide have also been detected in the macaque and human prostate (Einspanier and Ivell, 1997; Frayne and Nicholson, 1998).

In the rat, a feedback mechanism to regulate local oxytocin concentration have been proposed (Jenkin and Nicholson, 1999). Increase concentrations of testosterone and DHT reduce prostatic oxytocin and expression of its receptor, which in turn reduces the activity of 5α-reductase, thus reducing local DHT concentrations and preventing prostatic overgrowth. Indeed, when exposed to elevated levels of oxytocin for periods longer than 3 days, 5α-reductase activity in the rat prostate decreases as reported by (Nicholson and Jenkin, 1995).

Many researchers have reported the activity of short term administration of oxytocin injection on the prostate. However, there is need to elucidate the effects of prolonged administration of exogenous oxytocin on the histology of the prostate of Sprague-Dawley rats.

MATERIALS AND METHODS

Experimental Animals

Twenty adult male Sprague-Dawley rats weighing between 180-250g was purchased from a commercial farm in Ogbomoso, Oyo State, Nigeria. The animals were housed in well-ventilated plastic cages under standard room temperature in the Animal house of the Department of Anatomy, College of Medicine of the University of Lagos. The rats were fed with standard rat chow and water was provided ad libitum. The rats were acclimatized for two weeks before the commencement of the experiment. Ethical approval from Department of Anatomy Ethics Committee was obtained.

Experimental Drug

Oxytocin (Hubei Tianyao Pharmaceutical, China, marketed by Pemason Pharmaceutical, Agege Road, Alakara, Lagos, Nigeria). Testosterone ELISA Kit Catalog No: E-EL-R003 supplied by Wuhan Elabscience Biotechnology Co., Ltd. China.

Animal ethics

All techniques involving animals in this research was adapted from the Guiding Principles in the Care and Use of Animals (2011).

Grouping of the Animals

Rats were randomly assigned to four groups of five rats, group A (control) was administered with physiologic saline of 0.5 ml. while groups B, C and D were administered with oxytocin intramuscularly at 1, 2 and 3 IU/Kg/body weight twice a week for three days interval respectively. The administration was done over a period of 8 weeks (one spermatogenic cycle). Using a top loading digital scale (Mettler, Electronic Balance, Model HS-502N Switzerland) the initial weight of each rat prior to the commencement; and weekly, during the experiment was done. At the end of eight weeks, animals were sacrificed by cervical subluxation. Laparotomy was done and the prostate was harvested and weighed; the prostate was prepared for histological assessment.

Hormonal assay

Prior to the sacrifice, blood samples were taken from the left ventricle, centrifuged at 3000 rpm, 25°C for 10 min in an angle head centrifuge. Blood sera collected were separated and immediately assayed using the enzyme linked immunosorbent assay (ELISA) method for testosterone assays.

Histology

The prostate was fixed in formaldehyde for histopathological processing using haematoxylin and eosin staining techniques (Lillie and Fullmer, 1976). Photomicrographs were taken with a JVC

mounted on an Olympus light microscope (Olympus UK Ltd, Essex, UK).

Statistical Analysis

Statistical evaluation was done by randomized complete block analysis of variance (ANOVA) using graphpad prism version 6.0. Significant difference was acknowledged if $P < 0.05$.

RESULTS

Effect of oxytocin on the weight of the prostate

Groups B, C and D showed a significant decrease in prostatic weight ($P < 0.05$) when compared to the control (Table 1).

Table 1: Effect of exogenous oxytocin on prostatic weight (g) at 8 weeks

Groups	Doses	Weight of prostrate at 8 weeks
A	0.5ml 0.9% N/S (control)	0.69±0.02
B	1 IU/Kg b.w. Oxytocin	0.44±0.04*
C	2 IU/Kg b.w. Oxytocin	0.42±0.01*
D	3 IU/Kg b.w. Oxytocin	0.41±0.01*

Values are expressed as mean ± SD, * indicates significance at $P < 0.05$.

Effect of oxytocin on testosterone

There was a non-significant increase in testosterone levels in groups B and C when compared to the control. However, a significant ($P < 0.05$) increase in serum testosterone was observed in group D when compared to the control (Group A) (Table 2).

Table 2: Effect of exogenous oxytocin on serum testosterone at 8 weeks

Groups	Treatment	Testosterone at 8 weeks
A	0.5ml 0.9% N/S(control)	0.23±0.15
B	1 IU/Kg b.w. Oxytocin	0.43±0.12
C	2 IU/Kg b.w. Oxytocin	0.45±0.09
D	3 IU/Kg b.w. Oxytocin	2.23±0.96*

Values are expressed as mean ± SD, * indicates significance from control at $P < 0.05$

Effect of oxytocin on histology of the prostate

Histology of the control group showed normal prostatic glands containing secretions and corpora amylacea. The glands are lined by normal tall columnar secretory cells and normal stroma smooth mucles fibers (Fig. 1A). The prostatic stroma showed moderate fibrosis and vascularization with severe infiltration of inflammatory cells in group B treated with 1 IU/kg bw of OT (Fig. 1B). While, severe fibrosis, stroma cells degeneration with moderate vascular congestion was seen in group C that received 2 IU/kg bw of OT (Fig. 1C). Group D (3 IU/kg bw of OT) showed severe fibrosis and infiltrated with severe inflammatory cells aggregate as shown in (Fig. 1D).

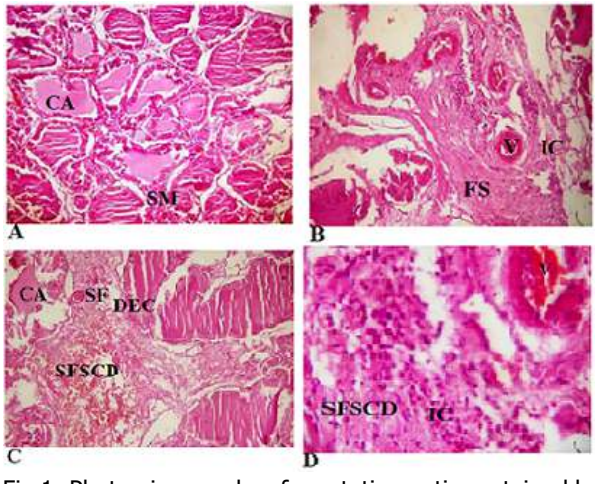

Fig 1: Photomicrographs of prostatic sections stained by haematoxylin and eosin at x400.CA: corporal amylacea; SM: stroma smooth muscle; FS:fibro stroma cells; DEC: degenerated epithelial cells; IC:inflammatory cells; SCD:stroma cell degeneration; SF:severe fibrosis; SFSCD:severe fibrosis and stroma cell degeneration; V/VC: vascularisation

DISCUSSION

This study showed that administration of oxytocin for 8 weeks significantly reduced the weight of the prostate, and there was severe fibrosis of the prostatic stroma when compared to the control. This decrease in the prostatic weight could be due to oxytocin having been shown to stimulate the conversion of testosterone to DHT in prostate; by stimulating the activity of the 5α reductase enzyme (Stadler et al., 2020). More so, it has been postulated that oxytocin regulate prostatic growth and is also involved in pathogenesis of prostate disorders (Nicholson, 1996).

Serum testosterone of group D (3 IU) was significantly increased at 8 weeks. These results agrees with similar study that showed a significant increase of testicular and plasma testosterone levels throughout the 4 and 8 weeks study period of administration of oxytocin to adult rat testis (Yama et al., 2018). Early report by (Tahri-Joutei and Pointis, 1988) demonstrated that treatment with oxytocin might have a stimulatory effect on testicular androgen synthesis. Also, (Frayne and Nicholson, 1998) have re-evaluated the effects of oxytocin on testicular steroidogenesis and

demonstrated that oxytocin significantly increased the basal testosterone production.

The severe stroma fibrosis, high vascularization with vascular congestion which was due to severe infiltration of inflammatory cells as seen in the histology of the groups that received 2 and 3 IU/Kg b.w of OT, could be as a result of high serum testosterone. These findings are in support of research work by (Tahri-Joutei and Pointis, 1988) who postulated that high serum testosterone through a feedback mechanism inhibits further production of testosterone, thus leading to fibrosis within the prostatic stroma despite continuous administration of oxytocin.

CONCLUSION

Chronic administration of oxytocin increases the testosterone level. However, there was a decease on the prostate weight and severe stroma fibrosis on the prostate. It is therefore suggested that clinicians should take precaution measure when administering of oxytocin to men with oligospermia and asthernozospermia.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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