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Original Article

Anatomy Section

Dose and Duration Dependent Effect of Fluoxetine on Dorsolateral Lobe of Prostate of Albino Rats- An Experimental Study

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ABSTRACT

Introduction: Fluoxetine is a prototype drug of the Selective Serotonin Reuptake Inhibitors (SSRIs) group of antidepressants. SSRIs help prostatic disease patients by improving quality of life in terms of decreased requirement of anti-inflammatory and antibiotic medication, decreasing the pain in the genital area, pain, and difficulty during urination, and improving urinary flow.

Aim: To investigate histological changes in the prostate (dorsolateral lobe) produced by different doses (10, 20 and 40 mg/kg/day) of fluoxetine given for different duration (Phases) in adult male albino rats.

Materials and Methods: An experimental study was done in the Anatomy Department, Himalayan Institute Medical Sciences (HIMS), Swami Rama Himalayan University, Jolly Grant, Dehradun, Uttarakhand, India. The duration of the study was twelve months from May 2009-April 2010. Present study was done on 36 adult male albino rats divided into Control (Group 1) and Experimental (Group 2, 3 and 4). Rats received 10 mg/kg/day, 20 mg/kg/day, and 40 mg/kg/day of fluoxetine intraperitoneally (I/P) for phases of 2 weeks, 4 weeks, and 12 weeks. Prostate (dorsolateral lobe) tissue was collected, processed, and examined in a light microscope after Haematoxylin and Eosin (H&E) staining. Morphometric and statistical analysis (mean, standard deviation and student's t-test) was done.

Results: Group 2 rats received fluoxetine for 12 weeks, Group 3 rats received fluoxetine for 4 weeks and 12 weeks, and Group 4 rats received fluoxetine for 7-10 days showed histological changes in the dorsolateral lobe of the prostate gland and stroma in the form of Smooth Muscle (SM) hypertrophy, epithelial cell changes (become cuboidal to flatten), epithelial cell degeneration, decreased diameter of the prostate acinus, and decrease in epithelial infoldings.

Conclusion: Fluoxetine (SSRI) alters the histology (both glandular acini as well as stroma) of the dorsolateral lobe of the prostate if used in low doses for a long duration, moderate doses for a few weeks and also for a long duration, and high dose for one week. This changed histology might be helpful in relieving the symptoms, pain, and discomfort felt by prostatic disease patients.

Keywords: Benign prostatic hyperplasia, Prostatic carcinoma, Prostatic disease, Selective serotonin reuptake inhibitors, Testosterone

INTRODUCTION

The Selective Serotonin Reuptake Inhibitors (SSRIs) are the most widely prescribed, relatively safe antidepressants used for many psychiatric illnesses [1,2]. Various clinical and animal studies showed that SSRIs not only influence sexual behaviour but also change genital organ histology [2-4]. Fluoxetine; the prototype drug of SSRIs significantly decreases Testosterone (T) levels [5]. Clinical studies showed that fluoxetine improves the quality of life of men suffering from refractory chronic prostatitis by decreasing chronic genital pain, difficulty in micturition, and increasing urine flow [6]. Fluoxetine also relieves symptoms of chronic pelvic pain syndrome. In elderly depressed patients with Benign Prostatic Hyperplasia (BPH), SSRIs improve quality of life by decreasing symptoms associated with BPH [7].

The prostate is the largest, highly specialised male accessory reproductive gland. It is a fibro-muscular-glandular organ surrounding the male urethra just beneath the urinary bladder [8]. The prostatic fluid is rich in citric acid, zinc, proteins, protein-splitting enzymes, lipids, metal ions, calcium, sodium, potassium, and amines [9]. McNeal divided the human prostate based on morphology and appearance into Peripheral Zone (PZ)-70%, Central Zone (CZ)-25%, and Transition Zone (TZ)-05% [10]. The PZ is most prone to prostatic carcinoma (PCa) and TZ is most prone to BPH. The TZ lies near the prostatic urethra so any enlargement in this zone produces urinary symptoms [11].

Within the prostate 5-alpha-reductase (5-AR) metabolise T to more potent androgen Dihydrotestosterone (DHT). T and DHT are essential for the development, differentiation, proliferation, and survival of prostatic cells and play an important role in prostatic diseases [12]. Prostate size and secretory functions depend on the T level. Prostatic involution/atrophy occurs rapidly on T withdrawal (bilateral orchidectomy/castration) and rapid reactivation of tissue growth occurs upon androgen replacement [13]. In the healthy human male, up to 95% of T is derived from testicular Leydig cells. T levels fluctuate diurnally but remain highest in the morning. In most males after 50 years of age, a slow but highly variable decline in T levels is observed [14].

Middle aged males were found to suffer from prostate pathologies such as BPH and PCa which contribute to male morbidity and mortality. A study published in European Urology reported that men with unusually low amounts of T in their blood are 23% less likely to develop PCa. Scientists conducted a study on blood samples of 19,000 men aged 34-76 years collected between 1959 and 2004. They divided them into ten groups according to the lowest amount of blood T to those with the highest amount and compared their PCa risk. Of these men, 6900 went on to develop PCa. Men with the lowest levels of T were significantly less likely to develop PCa compared to all other men. In the metastatic stage of carcinoma prostate (PCa), androgen deprivation therapy has been used to inhibit androgen-dependent PCa and for symptom

amelioration [15]. Tamim HM et al., studied 7767 PCa patients diagnosed between 1981 and 2000 and found a positive significant association between the risk of PCa and Tricycle Antidepressants (TCA) but not found any positive association between PCa and SSRIs [16]. Because of above mentioned clinical reports of relief in various painful symptoms of prostatic diseases after the use of SSRI [6,7] and there are no previous studies which evaluate the effect of fluoxetine on the histology of the prostate of albino rats. The present study was done to determine the histological effect of different doses for different duration of fluoxetine on the dorsolateral lobe of the rat prostate.

MATERIALS AND METHODS

The present study was an experimental animal study. This study was done in the Anatomy Department, Himalayan Institute Medical Sciences (HIMS), Swami Rama Himalayan University (SRHU), Jolly Grant, Dehradun, Uttarakhand, India. The duration of the study was twelve months from May 2009-April 2010. Approval from the Institutional Animal Ethical Committee (IAEC-(Registration No.589/02/a/CPCSEA) was obtained.

Study Procedure

The present study was done on 36 adult male albino rats; about 120-160 gm weight of Rattus norwegicus strain. These rats were obtained from the institutional central animal house. All the rats were housed in separate cages according to their groups. All the rats were healthy and disease/disability-free. Throughout the experiment, rats were fed on a standard balanced laboratory diet and water ad libitum with a 12-hour: 12-hour light-dark cycle; the water was changed and the cages were cleaned weekly.

The experimental drug was-Fluoxetine Hydrochloride-20 mg capsule (cap. Flunil-20 mg-INTAS Pharmaceuticals). The drug was injected once a day I/P according to the rat weight. 20 mg drug was dissolved in 2 mL of Normal Saline (NS) to obtain a concentration of 10 mg/mL. The drug was injected for 3 phases: 2 weeks, 4 weeks, and 12 weeks duration. Each phase consists of 12 animals which were further randomly subdivided into 4 groups of 3 albino rats each. Group 1 (Control)-received vehicle-NS, Group 2, Group 3, and Group 4 rats received I/P fluoxetine 10 mg/kg, 20 mg/kg, and 40 mg/kg of body weight/day, respectively [17]. For the calculation of drug dose and growth monitoring, all the rats were weighed on alternate days. At the end of each phase, the rats were sacrificed after giving ether anaesthesia. Abdominal dissection was done immediately. Rats were infused with NS to wash out the blood. Prostatic tissues (dorsolateral lobe) were procured. Prostate tissue was fixed in 10% formalin. A 3-5 mm thick prostate tissue slices were taken and processed. A 4-5 µ thickness sections were obtained via microtome cutting. Cut sections were stained with Harris Haematoxylin & Eosin (H&E) stain. Histological examination and morphometric analysis of the dorsolateral lobe of the prostate were done under a light microscope with 20X magnification. Ten randomly selected fields were examined. Various features such as epithelial cell changes (cell number, cell height), degenerative changes, stromal changes, and SM changes were noted.

STATISTICAL ANALYSIS

The histological measurements were done with the help of an eyepiece micrometre. Mean, standard deviations (SD), and student's t-test was calculated after data collection.

RESULTS

The initial mean age of rats was 13.2±5.66 weeks and the mean weight was 14.56±6.56 grams. The mean number of epithelial cells per 10 µm length and epithelial cell height per 10 µm length of the prostatic follicle/acinus epithelium was studied in the Group-1, Group-2, 3, and 4 albino rats of all three phases (2 weeks, 4 weeks and 12 weeks). The mean number of epithelial cells at the end of phases 1, 2, and 3 in Group-1 rats were 8.00±0.40, and 7.7±0.46 respectively; in Group-2 rats was 8.20±0.42, 7.90±0.30, and 8.00±0.00 (p=0.04) respectively; in Group-3 rats was 7.7±0.48 (p=0.04), 8.00±0.00, 8.00±0.00 (p=0.04) respectively; and in survived rats of Group-4 of phase 1 rats was 7.70±0.48 (p=0.04) [Table/Fig-1].

Groups	2 weeks (Mean±SD)	4 weeks (Mean±SD)	12 weeks (Mean±SD)
Group-1 (Control)	8.00±0.00	8.2±0.40	7.7±0.46
Group-2 (10 mg/kg/day)	8.20±0.42 p=0.084	7.90±0.30 p=0.097	8.00 ±0.00 p=0.04
Group-3 (20 mg/kg/day)	7.7±0.48 p=0.0406	8.00±0.00 p=0.083	8.00±0.00 p=0.4
Group-4 (40 mg/kg/day)	7.70±0.48 p=0.041	No rat survived	No rat survived

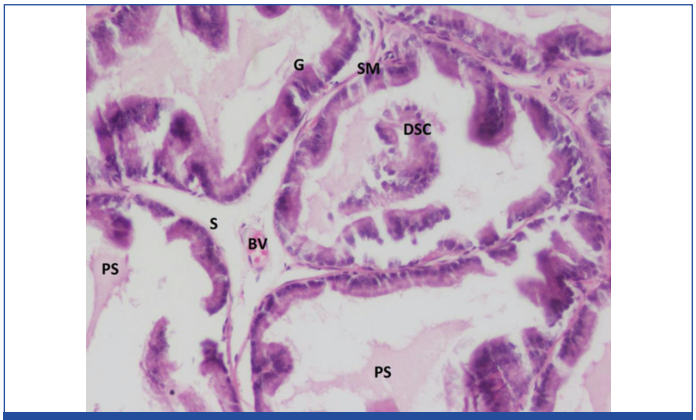
[Table/Fig-1]: Changes in mean number of cells/10 µm length of prostatic acinus epithelium.
(p<0.01-Highly significant, p<0.05-Significant, p>0.05-Non significant)

The mean cell height at the end of 2 weeks, 4 weeks, and 12 weeks in Group-1 rats was found 2.54±0.00 µm, 2.5±0.30 µm, and 2.3±0.40 µm, respectively; in Group-2 rats was 2.50±0.53 µm, 2.40±0.49 µm and 1.90±0.30 µm respectively; in Group-3 rats was 2.20±0.42 µm, 1.40±0.49 µm and 1.60±0.49 µm respectively; and survived rats of Group-4 of phase 1 was 1.20±0.42 µm (p=0.01) [Table/Fig-2], Group-3 rats prostate showed a decrease in cell height as the duration of drug exposure increased. Phase 2 and Phase 3 values were highly significant (p<0.01). The decrease in the cellular height may be due to degenerative changes in the cell

Groups	2 weeks (Mean±SD)	4 weeks (Mean±SD)	12 weeks (Mean±SD)
Group-1 (Control)	2.54±0.00	2.5±0.30	2.3±0.40
Group-2 (10 mg/kg/day)	2.50±0.53 p=0.22	2.40±0.49 p=0.097	1.90±0.30 p=0.04
Group-3 (20 mg/kg/day)	2.2±0.42 p=0.29	1.40±0.49 p=0.00000005	1.60±0.49 p=0.025
Group-4 (40 mg/kg/day)	1.20±0.42 p=0.001	No rat survived	No rat survived

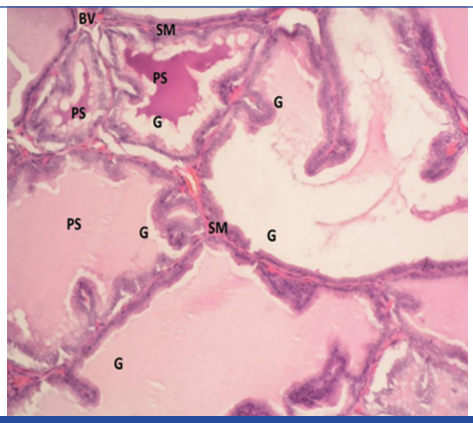
[Table/Fig-2]: Changes in the mean height of prostatic epithelial cells.
(p<0.01-Highly significant, p<0.05-Significant, p>0.05-Non significant)

In the present study, the Group-1 (Control) rats dorsolateral lobe prostatic tissue showed characteristic architecture; glandular acini are lined with secretory simple columnar epithelial cells with few epithelial infoldings. Detached epithelial cells present in the lumen within eosinophilic PS. Basal cells with stem cell characteristics (low nucleus-to-cytoplasmic ratio) have been identified in between secretory cells. A thin layer of circular SM surrounds the epithelium of glandular acini. In between the acini, there was a thin layer of fibromuscular stroma with blood vessels [Table/Fig-3].

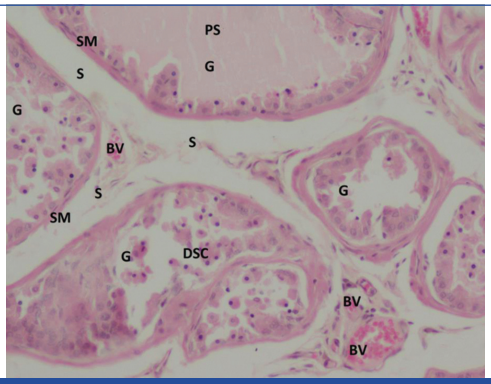


[Table/Fig-3]: Photomicrograph of the dorsolateral prostate of Group-1 (Control) albino rats showing glandular prostatic acini (G) lined by secretory (simple columnar cell) epithelium with epithelial infolding). Acini are surrounded by a thin Smooth Muscle (SM) layer and separated by fibromuscular stroma (S). The acinus lumen (L) contains Prostatic Secretions (PS). Desquamated Epithelial Cells (DSC) is also seen in the lumen of acini (H&E stain 200 X).

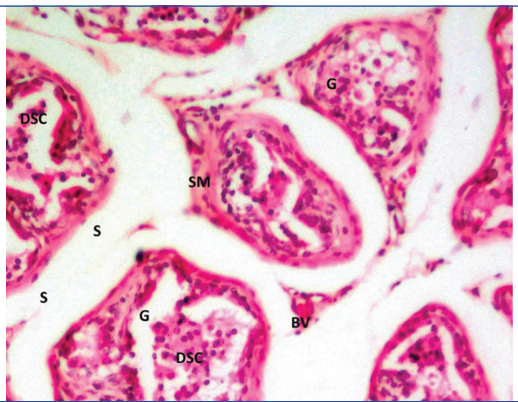
The histopathology of the dorsolateral lobe of prostate of Group-2 phase 1, 2 and 3 are descriped in [Table/Fig-4-6]. Group-2 (10 mg/kg/day) Phase 3 (12 weeks) rats dorsolateral lobe showing smaller prostatic acini with a decrease in epithelial cell height and a decrease in the secretory activity of epithelial cells. The epithelium showed proliferative changes in the form of hyperplasia, stratification, and the epithelial folds in the prostatic acini lumen. The SM layer surrounding these acini appeared thicker as compared with the SM layer surrounding the prostatic acini of Group-1 and Group-2 (Phase 1 and Phase 2). The prostatic non muscle Stroma (S) has a large volume in comparision to control and Group-2 phase 1 and phase 2. In the stroma, small caliber blood vessels were found.



[Table/Fig-4]: Photomicrograph of dorsolateral lobe of prostate of Group-2 (10 mg/kg/day) Phase-1 (2 weeks) Experimental rats showing prostatic acini (G) lined by secretory simple columnar epithelium with Prostatic Secretions (PS) and epithelial infoldings in their lumen. A thin layer of Smooth Muscle (SM) surrounds the acini. Acini are separated by minimal fibromuscular stroma (S) (H&E Stain 200 X).

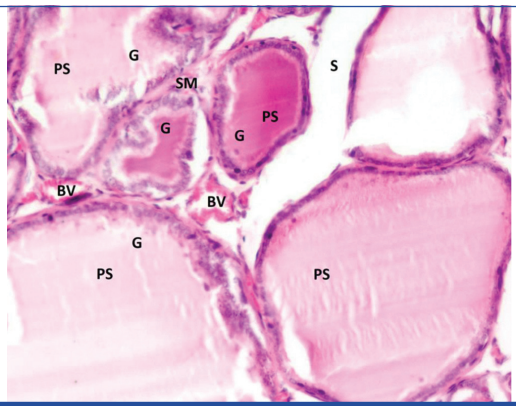


[Table/Fig-5]: Photomicrograph of dorsolateral lobe of prostate of Group-2 (10 mg/kg/day) Phase-2 (4 weeks) Experimental rats showing prostatic acini (G) with decreased epithelial cell height. Desquamated Cells (DSC) present in lumen. Acini are surrounded by thin layer of Smooth Muscle (SM). Acini are separated by fibromuscular stroma (S). (H&E stain 200 X).

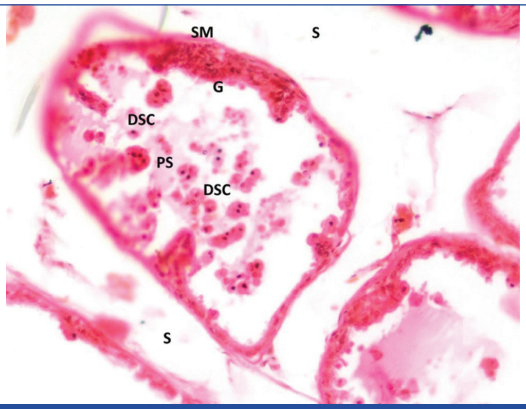


[Table/Fig-6]: Photomicrograph of the dorsolateral prostate of Group 2 (10 mg/kg/day) Phase-3 (12 weeks) Experimental albino rats showing widely separated glandular acini (G) by Interacinar fibromuscular stroma (S). Acini are smaller in size in comparison to the control and there is cellular stratification. At a few places, acini are lined by simple cuboidal epithelium while at a few places by simple squamous epithelium with epithelial infoldings. Acini are surrounded by a thick layer of Smooth Muscle (SM). Desquamated Epithelial Cells (DSC) lie in the acini lumen within Prostatic Secretion (PS). (H&E stain 200X).

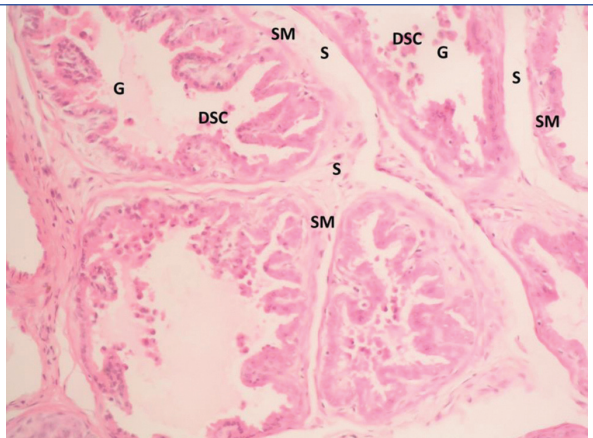
The histopathology of the dorsolateral lobe of prostate of Group-2 phase 1, 2 and 3 are described in [Table/Fig-7-9]. Group-3 (20 mg/kg/day) Phase 2 (4 weeks) rats dorsolateral lobe showed a highly significant decrease in epithelial cell height of glandular acini. DSC present in the lumen within eosinophilic PS. Glandular acini are surrounded by a very thin layer of Smooth Muscle (SM) fibres and widely separated by connective tissue stroma [Table/Fig-8]. Group-3 (20 mg/kg/day) Phase 3 (12 weeks) rats dorsolateral lobe showed stratification of epithelium, decrease in epithelial cell height (significant), epithelial infolding in glandular acini [Table/Fig-9].



[Table/Fig-7]: Photomicrograph of dorsolateral lobe of prostate of Group-3 (20 mg/kg/day) Phase-1 (2 weeks) experimental albino rats showing glandular acini (G) separated by fibromuscular stroma (S). In a few places, acini are lined by simple low columnar epithelium. In a few places, acini are lined by simple squamous epithelium. Acini have Prostatic Secretions (PS) with few epithelial infoldings in the lumen. Acini are lined by very thin layer of Smooth Muscle (SM). (H&E Stain 200 X).

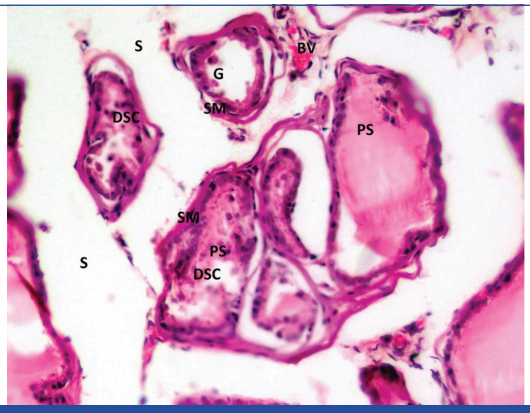


[Table/Fig-8]: Photomicrograph of dorsolateral lobe of prostate of Group-3 (20 mg/kg/day) Phase-2 (4 weeks) experimental albino rats showing widely separated glandular acini (G) by fibromuscular stroma (S). At a few places, acini are lined by simple cuboidal epithelium with pyknotic nuclei while at a few places by simple squamous epithelium. Acini are surrounded by a thin layer of Smooth Muscle (SM). Acini also contain Epithelial infoldings. DSC with hyperchromatic nuclei lie in the lumen within scanty Prostatic Secretion (PS). (H&E stain 200 X).



[Table/Fig-9]: Photomicrograph of dorsolateral lobe of prostate of Group-3 (20 mg/kg/day) Phase-3 (12 weeks) experimental albino rats showing glandular acini (G). Acini are lined by low columnar epithelium and separated by fibromuscular stroma (S) and surrounded by thin layer of Smooth Muscle (SM). Acini contain multiple epithelial infoldings and in the lumen there is presence of DSC. (H&E stain 200 X).

Very scanty prostate tissue was procured in survived rats of Group-4. Group-4 Phase-1 survived rats dorsolateral lobe showed an increased volume of fibromuscular stroma in between the prostatic glandular acini (G). Acini are smaller in size with few epithelial infoldings and surrounded by a thin layer of SM. In most places, acini are lined by simple squamous epithelial cells while in a few places acini are lined by simple cuboidal cells. DSC lies in the lumen within Prostatic Secretion (PS) [Table/Fig-10].



[Table/Fig-10]: Photomicrograph of dorsolateral prostate of Group 4 (40 mg/kg/day) (7 days) experimental albino rats showing widely separated glandular acini (G) by fibromuscular stroma (S). Acini are smaller in size in comparison to the control. In some places, acini are lined by simple cuboidal epithelium whereas in some places acini are lined by simple squamous epithelium with pyknotic nuclei. Acini are surrounded by a thin layer of Smooth Muscle (SM). Acini also contain a few epithelial infoldings. DSC with pyknotic nuclei lie in the lumen within Prostatic Secretion (PS). (H&E stain 200X).

DISCUSSION

Present study, focused only on the dorsolateral lobe of the prostate for histologic changes produced by fluoxetine. Price D studied the normal development of the prostate and seminal vesicle of the male albino rats at the University of Chicago and described different lobes (anterior lobe or coagulation gland, ventral lobe, paired lateral and dorsal lobe) of the prostate in rats [18]. Hayashi N et al., studied morphogenesis and adult ductal branching patterns in the Sprague-Dawley rats prostate by microdissection method at the University of California, San Francisco, California, and found that each lobe has a unique ductal and acinar pattern although the epithelium of dorsal and lateral prostatic lobes more closely resembles each other; the so-considered dorsolateral lobe [19]. Many investigators focused on one or two lobes of the rat prostate for their studies. The ventral lobe of the rat prostate has been preferred to see androgen action on the prostate [20]. The dorsal and lateral lobes of the prostate have been preferred to see age-dependent prostatic hyperplasia [21].

Hayashi N et al., studied morphogenesis and adult ductal branching pattern in the Sprague-Dawley rats prostate by microdissection method at the University of California, San Francisco, California, and found that the dorsolateral lobe of the rat prostate has a ductal-acinar glandular structure with 5-7 pairs of main ducts. The dorsolateral lobe acinus has moderate to few epithelial infoldings and detached epithelial cells present in the eosinophilic secretion of the acinus lumen [19]. In the present study, the control (Group-1) rats the dorsolateral lobe prostatic tissue showed the same acinar architecture.

In the present study, the dorsolateral lobe of the prostate showed changes on injecting low-dose fluoxetine for long period as well as high-dose fluoxetine for a few days in the form of shrinkage of the prostatic acini with epithelial changes (cells become cuboidal and flattened), atrophic changes in the prostatic acini epithelium (epithelial cells showed shrunken nuclei with condensed chromatin), and an increased stroma/gland ratio compared with controls. Moderate doses induce changes in the form of epithelial changes (cells become cuboidal) and atrophic changes of acini epithelial cells (pyknotic nucleus) with detached epithelial cells in the lumen. Stroma increased without shrinkage of acini. Liu RF et al., studied the androgen effect on 40 healthy castrated Sprague-Dawley rat prostate histology and found that androgen administration inhibits apoptosis and induces prostate hyperplasia in the form of compacted glandular acini with thickened glandular epithelium with increased stromal cells [22].

Prostate epithelium and fibromuscular stroma depend upon androgenic hormones for their functional and structural integrity [13]. Oliviera SM et al., (Brasil) studied 20 male adults (90-day-old) in Wistar rats, the effect of T on rat prostate tissue and found an increase in epithelial height with an increase in the secretory activity of epithelial cells in the form of increased eosinophilic secretion in the lumen. The epithelium showed proliferative characteristics, such as stratification and the presence of numerous epithelial folds in the prostatic lumen. Prostate acini were large and the muscular layer surrounding these acini appeared thinner as compared with the control. The prostatic stromal compartment was of large volume [23].

In the present study, as the dose of fluoxetine increased the glandular epithelium become flattened with pyknotic nuclei and increased stromal thickness. Low-dose fluoxetine administered for long period also showed attenuation of dorsolateral acini epithelium. These findings of the present study showed that the effect of fluoxetine was the opposite of the effect of androgen.

In the inhibition of pituitary hormones and gonadal steroids, prostatic atrophy occurs. A 5-AR enzyme (involved in the intraprostatic conversion of testosterone to its biologically active form dihydrotestosterone) inhibitors (finasteride and episteride) and antiandrogen substances (hydroxyflutamide) are known to induce prostate atrophy. Prostate atrophy grossly appears as glandular shrinkage and is microscopically seen as a reduction in the size of acini, attenuation (flattening) of lining epithelial cells, scanty secretory material in acini lumen, and increased stroma. Atrophy involves all lobes of the prostate [24]. In the present study, scanty prostate tissue was procured from Group-4 survived rats and the same microscopic features were found.

Limitation(s)

The limitation of the present study was the lack of proper skill of dissection to procure the whole tissue of the prostate of the albino rat.

CONCLUSION(S)

Present study showed that fluoxetine in mild doses for a long duration, moderate doses within a few weeks, and high doses within a few days alters prostate histology. The present study findings provide a rationale for further investigations on microdissected prostate to see the fluoxetine-induced histological and morphometric changes in the prostate. These studies may establish fluoxetine's effect on prostate pathologies such as PCa and BPH.

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