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Impact of fluoxetine on testosterone levels and spermatogenic cell production of male albino mice

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ABSTRACT

Fluoxetine is a widely used antidepressant that acts as a selective serotonin reuptake inhibitor. This study investigated the effects of fluoxetine hydrochloride on the hypothalamic-pituitary-testicular axis and spermatogenesis in male albino mice. Fifty mice were divided into five distinct groups, comprising a control group, an observation group and three separate experimental cohorts receiving oral fluoxetine at doses of 50, 100, and 150 mg kg^{-1} for 28 days. Testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels were measured by radioimmunoassay. Testicular tissue was analyzed for changes in seminiferous tubule sperm count and spermatogenic cell populations. The high-dose fluoxetine group showed decreased testosterone, increased LH and FSH, reduced seminiferous tubule sperm density, as well as fewer spermatogonia and primary spermatocytes versus controls. Histology revealed reduced germinal epithelium layers and increased vacuolization in the fluoxetine-treated mice. These findings demonstrate that chronic high-dose fluoxetine administration inhibits steroidogenesis and spermatogenesis in male mice, likely by increasing serotonin levels which suppress testosterone synthesis. Further research on fluoxetine's effects on male fertility are warranted given its widespread clinical use. This study affirms the need for judicious fluoxetine prescribing in patients with reproductive concerns.

Keywords: Fluoxetine, Male albino mice, Spermatogenesis, Reproductive physiology.
Article type: Research Article.

INTRODUCTION

Mood disorders, prominently exemplified by major depression, have witnessed a significant upsurge in global prevalence, affecting an expansive cohort of over 280 million individuals (Ortega *et al.* 2022; Bahrami *et al.* 2023). The ramifications of this escalation extend beyond societal and economic impacts, significantly straining healthcare systems and standing as a primary contributor to chronic disability (Cao *et al.* 2022). The early onset of these disorders not only depletes productive life-years but also engenders a decline in educational attainment (Seabury *et al.* 2019). While several theories have been proposed, the precise pathogenesis underlying depression remains elusive. The prevailing hypothesis centers around dysregulation of key neurotransmitters like dopamine, serotonin, and norepinephrine in the brain. Aligning with this notion, medications rectifying neurotransmitter

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imbalances prove efficacious as antidepressant therapy (Wu *et al.* 2021; Meltzer-Brody 2022). Sexual dysfunction is a prevalent concern in individuals suffering from depression, affecting approximately 50% to 70% of this demographic (Al–Hadidy & Mostafa 2022; Aziz Mahdi Al-badry 2022). Notably, the occurrence of sexual dysfunction can, in certain instances, precipitate the onset of depression. Predominantly, depression manifests as diminished sexual desire, with disorders related to arousal, orgasm, or ejaculation being less frequent. It is worth emphasizing that effective treatment of depression may yield improvements in sexual functioning, particularly with regard to libido, among select patients (Atmaca 2020; Goncalves *et al.* 2023). Fluoxetine (Prozac), a widely prescribed antidepressant, is commonly categorized as a selective inhibitor of 5-Hydroxytryptamine (5-HT or serotonin) reuptake (Chen 2023). However, mounting evidence suggests an additional capacity to inhibit norepinephrine reuptake within the brain, with no significant impact on follicle-stimulating hormone (FSH) levels (Barry 2019; Zhang, Wang, *et al.* 2020; Salahinejad *et al.* 2022). It is crucial to acknowledge that pharmacological agents targeting 5-HT reuptake have been associated with sexual side effects in both male and female individuals (Jamu & Okamoto 2022). While certain reports suggest potential improvements in sexual behavior following fluoxetine administration (Power-Smith 1994), intriguingly, counteracting evidence also points towards a plausible connection between the administration of fluoxetine and the manifestation of sexual dysfunction (Shen & Hsu 1995; Olivier & Olivier 2019; Singh *et al.* 2022; Winter *et al.* 2022). Furthermore, fluoxetine induces modifications in sexual conduct in rodents, exemplified by an augmented frequency of mount bouts per ejaculation, elevated instances of mounts per mount bout, prolonged ejaculation latency, extended grooming periods, increased time-outs, and heightened intermount-bout intervals (Yells *et al.* 1995; Bataineh & Daradka 2007). Daily use of fluoxetine in the dosage range of 20 to 60 mg kg^{-1} proves to be an efficacious treatment strategy for sleep disorders (Holder & Narula 2022). This drug's unique ability to breach the blood-brain barrier enhances its utility as an antihistamine for allergic individuals, owing to its antagonistic properties against the H_1 receptor (Isik *et al.* 2010). Furthermore, it plays a vital role in the reduction of mucosal pain experienced by patients with cancer (Zhang *et al.* 2020). This medication exhibits the capacity to alleviate erythema and alleviate skin itching by acting as an antagonist for both H_1 and H_2 receptors (Li *et al.* 2016). In the treatment of anorexia nervosa, fluoxetine serves as an H_1 receptor antagonist within the amygdala and hippocampus, presenting a viable therapeutic approach (Frank & Shott 2016). Comprehensive scientific investigations have provided insights into the adverse effects of antidepressant medications on sexual function, including the development of erectile dysfunction. It is plausible that fluoxetine may exert analogous effects, potentially leading to ejaculation disorders and sexual impairment (Rosen *et al.* 1999; Rosen & Marin 2003). Additionally, research has elucidated that imipramine, a pharmaceutical agent belonging to the same drug class, exhibits inhibitory properties on sperm motility and diminishes sperm survival when subjected to controlled laboratory conditions (Alipour-Kivi *et al.* 2023; Moses & Javanbakht 2023). Antidepressant drugs have emerged as a potential etiological factor in male infertility, mainly attributed to their propensity to induce chromatin/DNA damage in spermatozoa (Bezerra *et al.* 2019). As the incidence of depression rises within communities, the utilization of antidepressants, such as fluoxetine, has become increasingly prevalent. This study aims to elucidate fluoxetine's effects on the hypothalamic-pituitary-gonadal (HPG) axis and testicular tissue. Findings will provide valuable insights on fluoxetine's clinical applications, guiding safe regulation, advancement or limitations. Understanding fluoxetine's impact on reproductive hormones and testicular function holds critical importance given rising utilization in the context of growing depression prevalence worldwide.

MATERIALS AND METHODS

This study adhered to the authorization granted by the animal care committee, affirming the observance of established ethical guidelines for animal research. Adult male albino mice, with an approximate weight of 25-30 g, were bred within the Animal House Unit at the University of Baghdad, maintaining a controlled environment with a temperature of 28 ± 2 °C and a light/dark cycle of 12:12 hours. These mice were provided with unrestricted access to both food and water. In this research, the animals were randomly distributed into five groups, each comprising ten mice. These groups were characterized as control, observation, and three distinct experimental treatments. The control group remained untreated, devoid of any drug or non-drug interventions. Meanwhile, the observation group was subjected to daily oral administration of the drug solvent, which consisted of 3 mL distilled water. In contrast, the experimental groups received daily doses of fluoxetine, with quantities set at 50, 100, and 150 mg kg^{-1}, over a period of 28 days. Following a 28-day period, the animals were anesthetized through the

administration of ether after being weighed, and cardiac blood samples were procured. Each mouse contributed approximately 4-5 mL blood, which was then placed in sterilized test tubes devoid of anticoagulants. The collected blood samples were subsequently subjected to centrifugation at a speed of 2500 rpm for a duration of 20 min to facilitate the separation of serum from the clot. Thereafter, the specimens were stored at -18 °C for the measurement of serum concentrations of FSH, luteinizing hormone (LH), and testosterone, employing the radioimmunoassay (RIA) technique. In this research, the hormonal diagnostic kits applied featured standard solutions containing radioactive iodine, antibodies, and a wash buffer. Following the abdominal incision of the samples, both testes were excised from all experimental groups. Subsequently, tissue specimens were processed, stained with hematoxylin and eosin (H & E), and assessed for alterations in sperm concentration within the seminiferous tubules using graticule. Histological investigations were conducted to assess variations in the count of interstitial Sertoli cells and the progression of spermatogenesis between the experimental and control groups. Following immersion in a 12% formalin solution, the testicular specimens underwent a sequential dehydration process utilizing ascending concentrations of ethyl alcohol, followed by clearance in xylene, and ultimately, embedding within paraffin wax. Subsequently, sections measuring 5-6 µm in thickness were prepared and subjected to staining procedures involving H & E, along with Mallory's trichrome stain. These stained slides served as the basis for histopathological and morphometric assessments, with visual documentation facilitated through optical microscopy. To perform a rigorous statistical assessment of the findings across the experimental and control sets, we applied ANOVA and Duncan tests. A significance threshold of 0.05 was set to ascertain the presence of statistically meaningful distinctions between the experimental and control groups.

RESULTS

The results revealed a significant decrease in serum testosterone concentration by the conclusion of the 28-day treatment period, specifically within the group subjected to a drug dosage of 150 mg kg^{-1}, compared to the control group. Additionally, at the culmination of the 28-day interval, there was a pronounced rise in serum FSH and LH levels within the group exposed to a drug dosage of 150 mg kg^{-1}, as compared to the control group. Following the administration of fluoxetine, mice experienced a noteworthy reduction ($p < 0.05$) in their body mass. Notably, the body weight of individuals in both the control and observation cohorts exhibited a statistically significant elevation. Nonetheless, no statistically significant deviation was discerned between the observation and control groups (Table 1).

Table 1. Mean (± standard deviation) serum testosterone hormone, LH and FSH levels upon completion of the 28-day period.

Groups	Control	Observation	Fluoxetine (50 mg kg^{-1})	Fluoxetine (100 mg kg^{-1})	Fluoxetine (150 mg kg^{-1})
Body weight (g)	28 ± 1.31	29 ± 3.71	25 ± 2.63*	24 ± 4.52*	21 ± 3.46*
Testosterone (ng mL^{-1})	6.1 ± 0.75	5.9 ± 1.25	5.8 ± 0.43	5.1 ± 0.27	4.3 ± 0.1.25*
LH (mIU mL^{-1})	4.4 ± 0.19	4.5 ± 0.46	4.6 ± 0.84	5.1 ± 0.79	5.2 ± 0.26*
FSH (mIU mL^{-1})	7.9 ± 0.31	7.8 ± 0.42	7.9 ± 0.36	8.0 ± 0.38	8.3 ± 0.53*

Note: * $p < 0.05$; ng: nanogram; mIU: milli-international units

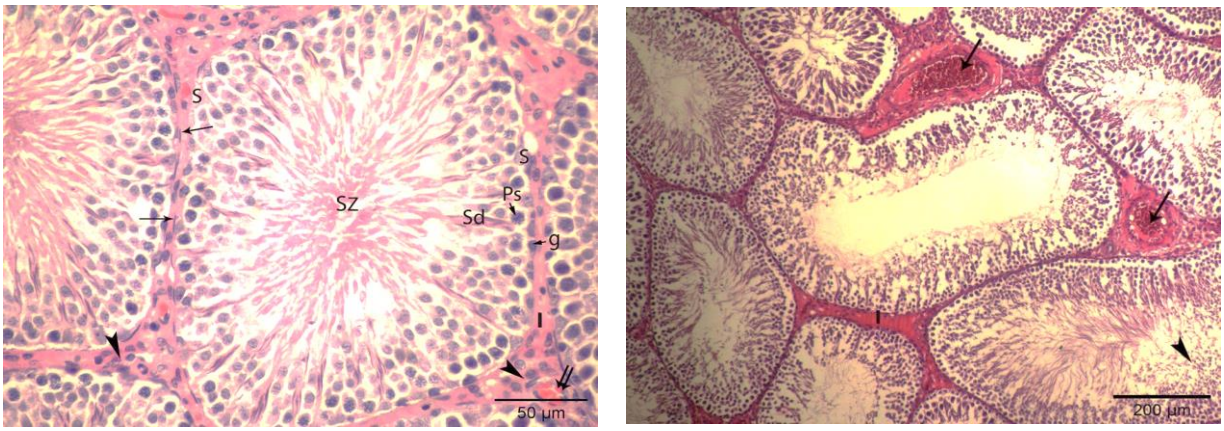
In the group subjected to a drug dosage of 150 mg kg^{-1}, a concomitant reduction in serum testosterone levels was associated with a decrease in both sperm density within the seminiferous tubules and the counts of spermatogonial cells and primary spermatocytes. Conversely, the numbers of Sertoli and Leydig cells within the experimental cohorts showed no statistically significant disparities in comparison with the control groups after the 28-day study period (Table 2).

Table 2. Mean (± standard deviation) count of sperm precursor cells, Sertoli and Leydig cells within a seminiferous tubule following the oral intake of fluoxetine

Groups	Control	Observation	Fluoxetine (50 mg kg^{-1})	Fluoxetine (100 mg kg^{-1})	Fluoxetine (150 mg kg^{-1})
Spermatogonia	43 ± 1.1	44 ± 0.9	40 ± 1.7	3 ± 1.3	2 ± 1.8
Spermatocytes	78 ± 0.8	79 ± 2.8	77 ± 1.3	75 ± 1.6	65 ± 1.2
Spermatids	147 ± 1.7	146 ± 0.9	142 ± 1.8	129 ± 1.3	125 ± 2.1
Sertoli	19 ± 0.3	18 ± 0.1	19 ± 0.2	18 ± 0.2	17 ± 0.3

Leydig	68 ± 0.9	66 ± 0.5	69 ± 0.6	68 ± 0.6	67 ± 0.3

According to examination of the testicular tissue specimens subjected to H & E staining, the control cohort displayed a histological configuration conforming to the norm. The seminiferous tubules exhibited an elliptical morphology characterized by a uniform perimeter, and their epithelial lining contained spermatogenic cells representing diverse stages of development. In fluoxetine treated mice, there was a noticeable reduction in the layers of the germinal epithelium, accompanied by the presence of vacuoles between spermatogenic cells (Fig. 1).



(a) (b)

Fig. 1. Histological analysis of testicular tissue in adult male albino mice: **(a)** A microphotograph depicting a cross-section of the testicular tissue in a control mouse showcases elliptical seminiferous tubules housing aggregations of spermatozoa within their luminal spaces (SZ). These tubules are lined with a variety of spermatogenic cell types, encompassing Sertoli cells (S), spermatids (Sd), primary spermatocytes (Ps), and spermatogonia (g). Within the restricted interstitial space denoted as (I), one can readily discern the presence of delicate vascular structures characterized by slender walls (double arrows), as well as accumulations of Leydig cells (arrowhead). Furthermore, a solitary layer of myoid cells (arrow) envelops the tubules; **(b)** A microphotograph capturing a cross-sectional perspective of the testicular tissue in mice exposed to fluoxetine treatment, distinct uniform deposition of acidophilic substance is observed within the interstitial region (I), along with observable thickening of the walls in congested blood vessels (thin arrow). Additionally, the tubular lumen contains exfoliated germ cells (arrowhead).

DISCUSSION

By observing the reduction in testosterone hormone levels within the group administered 150 mg kg^{-1} of the drug, it appears that fluoxetine elevates this neurotransmitter's concentration through the inhibition of serotonin reuptake. Elevated serotonin levels subsequently impede the action of enzymes engaged in testicular tissue steroid synthesis, ultimately resulting in testosterone decline (Winter *et al.* 2022; Chen 2023). The administration of fluoxetine results in heightened melatonin levels (Bataineh & Daradka 2007), which in turn, suppress the synthesis of Steroidogenic Acute Regulatory (STAR) Protein. STAR protein plays a crucial role in the transport of cholesterol into the mitochondria of cells in the testes and adrenal glands, where it is converted into pregnenolone, a precursor of various steroid hormones. This inhibition of STAR protein production interferes with the conversion of cholesterol into pregnenolone and disrupts the normal functioning of enzymes within the steroid production pathway. Research has unequivocally demonstrated that fluoxetine diminishes ACTH (Adrenocorticotropic Hormone) levels by mitigating histamine production (Inder *et al.* 2001). Consequently, the reduced ACTH levels lead to diminished cellular activity within the adrenal cortical region responsible for steroid synthesis. Notably, a critical aspect of ACTH-driven steroid regulation involves the weakening of protein kinase A (PKA) enzyme activation necessary for cholesterol-to-pregnenolone conversion, a key step in the synthesis of steroid hormones. This testosterone-mediated decline initiates a negative feedback loop, fostering increased secretion of GnRH (Gonadotropin-Releasing Hormone) from the hypothalamus and subsequently amplified release of LH and FSH from the anterior pituitary (Igoumenou 2020). Previous research has unveiled the existence of a neural pathway connecting the brain and the testicles. Activation of this pathway by corticotropin-releasing factor (CRF) exerts an influence on Leydig cell function (Olivier & Olivier 2019; Singh *et al.* 2022). Testosterone, in turn, acts as an inhibitor of the monoamine oxidase enzyme, responsible for dopamine catabolism. A decrease in this enzyme's activity potentially leads to elevated dopamine levels (Alipour-Kivi *et al.* 2023). Consequently, the reduction in testosterone may diminish its inhibitory effect on this enzyme, resulting in a lowered concentration of dopamine.

Dopamine, as a regulator, hampers the production of gonadotropin hormones by affecting the arcuate nucleus. A decrease in dopamine levels consequently gives rise to an increase in gonadotropin secretion (Jamu & Okamoto 2022). The findings of the present investigation demonstrate an increase in LH and FSH, alongside a decrease in testosterone, in the experimental group receiving 150 mg kg^{-1} of the drug at the conclusion of the 28-day study period, in contrast to the control group. Additionally, the study results indicated a reduction in sperm concentration within the spermatogenic tubules of the experimental group subjected to the 150 mg kg^{-1} drug dosage compared to the control group. Prior research has established that testosterone exerts a direct influence on Sertoli cells, which are essential in nurturing dividing germ cells through the secretion of tubular fluid (Corpuz-Hilsabeck & Culty 2023). It also generates an array of proteins, including growth factors and transferrin, each possessing distinct functions in the division of germ cells and, subsequently, sperm production. Notably, testosterone assumes an additional role by directly influencing the division of germ cells. Given the pivotal role of testosterone in spermatogenesis, it becomes apparent that a decrease in its secretion leads to a reduction in sperm density, though this area warrants further investigation through additional research. The histological analysis revealed noticeable alterations in testicular structure of fluoxetine-treated mice compared to controls. Specifically, there was a reduction in layers of germinal epithelium and elevated presence of vacuoles between spermatogenic cells in the seminiferous tubules of treated mice. This corroborates the findings of reduced sperm counts and provides further evidence of impaired spermatogenesis (Camara *et al.* 2019).

CONCLUSION

In conclusion, this study demonstrates that chronic high-dose administration of fluoxetine has adverse effects on the hypothalamic-pituitary-gonadal axis and testicular function in male albino mice. The decline in testosterone levels, increase in FSH and LH secretion, reduced sperm counts, and histological changes observed with 150 mg kg^{-1} fluoxetine treatment confirm the drug's inhibitory effects on steroidogenesis and spermatogenesis. The presence of vacuoles and exfoliated germ cells indicates disruption of Sertoli cell support for germ cell development. Although fluoxetine is widely prescribed for depression, caution should be exercised with long-term use, especially at high doses, due to the potential for negative impacts on fertility and testicular morphology. Further studies are warranted to determine if these effects are reversible and to elucidate the precise mechanisms through which fluoxetine alters hormonal regulation and spermatogenesis. Nonetheless, these findings affirm the need for judicious use of fluoxetine in patients with reproductive concerns.

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