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Effect of sertraline and fluoxetine on the reproductive abilities of male rats *Rattus norvegicus*

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Abstract:-

The present study was designed to know the effect of sertraline and fluoxetine on the reproductive abilities of male rats. The experiment consisted of five groups (each group contains of 5 males), the first (control) group was injected (I.P) with 0.25ml of normal saline, the second group was injected with sertraline (10 mg / kg), the third group was injected with sertraline (20 mg / kg), the fourth group was injected with fluoxetine (5 mg / kg) and the fifth group was injected with fluoxetine (10 mg / kg). .The results showed a significant decrease ($P \leq 0.05$) in the number of sperms and in the level of testosterone hormone and a significant increase ($P \leq 0.05$) in the percentage of sperm deformities in all treated groups when compared with control group. The histologically examination showed that there was changes in the testis including the dissociation of the connective tissue in second and fifth groups, decrease in the number of spermatgonia, and Leydig cells, bloody congestion in third and fifth groups, hemorrhage and necrosis in forth group.
Key words:- Fluoxetine, Sertraline, Sperms, Testis, Rats.

Introduction:-

The depression has increasing significantly among communities (Sadock and Sadock, 2000). Selective Serotonin reuptake inhibitors (SSRI) are one of antidepressants that are used to treat this disorder in the long and short term, as it is the first line drugs to treat this disorder (Bystritsky *et al.*,2013) . Selective Serotonin reuptake inhibitors (SSRI) increase serotonin concentration in synaptic cleft by inhibiting its reabsorption (Porter and Brums,2000).fluoxetine and sertraline are selective Serotonin reuptake inhibitors that are used to treat depression and anxiety (Davies *et al.*,2016; Sanchez *et al.*,2014; Lu S *et al.*,2009). Treatment with SSRIs causes many hormonal and neurochemical changes associated with the central and peripheral nervous system, which are responsible for harmful effects on the reproductive system (Attia and Bakheet, 2013). SSRIs are known to cause harmful sexual effects such as erectile dysfunction and decreased libido (Csoka and Shipko, 2006).

Infertility is defined as inability to reproduce after 12 months of normal sexual life without using any contraindications for both sexes (Jungwirth *et al* ., 2013). Drugs play a potential role in the causes of male infertility. Recently, it has been found that SSRIs drugs may affect the signs of infertility (number of sperms, motility and morphology) (Brambilla *et al* ., 2005) .The present study aimed to investigate the effect of sertraline and fluoxetine on the reproductive abilities of male rats.

Material and method:-

Experimental Animals:-

Twenty five healthy male rats(*Rattus norvegicus*) 10-12 week old and weighting 190-210g were obtained from Department of Biology, Collage of Science, Thi-Qar university. The rats were housed in controlled temperature room (23-25) under a 12h- dark /12 h – light cycle .The animals given pellet diet and tap water *ad libitum*. The rats were divided into five groups (each group contain five males):

1- The first (control) group: injected with normal saline for 4 weeks.
2- The second group: injected with 10 mg /g of sertraline for 4 weeks.
3-The third group: injected with 20mg /g of sertraline for 4 weeks.

4- The fourth group : injected with 5mg /g of fluoxetine for 4 weeks.
5-The fifth group : injected with 10mg /g of fluoxetine for 4 weeks.
The rats were injected by intraperitoneal membrane.

Calculation of numbers of sperms in male rats:-

To investigate the effect of sertraline and fluoxetine on numbers of sperms, Scoto's method (1983) was used.

Calculation of deformities of sperms in male rats:-

To investigate effect of sertraline and fluoxetine on deformities of sperm, Wyrobek and Bruce' s method (1975) was used.

Estimation of testosterone hormone concentration:-

To investigate effect of sertraline and fluoxetine on testosterone hormone, Kicklighter and Norman's method (1989) was used.

Histological section:-

To prepare tissue sections (testis), Bancroft and Gamble's method (2008) was used.

Statistical analysis:

Statically analysis were performed by using SPSS. The results were expressed as mean ±standard error, $p \leq 0.05$ was considered as significant in this study.

Results:-

Effect of sertraline and fluoxetine on numbers and deformities of sperms in male rat:-

The results showed a significant decrease ($p \leq 0.05$) in the numbers of sperms in all treated groups compared with the control group. Also, the results showed a significant decrease in the third group comparison with the second, and the fifth group comparison with the fourth group as shown in table (1).

The comparison between the effects of sertraline and fluoxetine, the results showed a significant decrease ($p \leq 0.05$) in the fourth group compared with the second and the fifth group compared with the third group.

The results showed a significant increase in the percentage of malformation of sperms in all treated groups compared with the control group. Also, the results showed non-significant increase in the percentage of malformation of sperms in the third group when compared with the second group and a significant increase in the fifth group compared with the fourth group as shown in table (1) and pictures (1-4).

The comparison between the effects of sertraline and fluoxetine, the results showed a significant increase in the second group compared with the fourth group and in the third group compared to the fifth group.

Table(1): Effect of sertraline and fluoxetine on numbers and deformities of sperms of male rats (mean ±standard error)

Groups	Numbers of sperms ($\times 10^4$)	Percentage of deformities of sperms (%)
First group (control)	535.80 ± 8.75 a	9.20 ± 3.19 a
Second group	419.80 ± 8.34 b	84.40 ± 2.30 b
Third group	381.40 ± 5.41 c	88.00 ± 3.67 b
Fourth group	377.00 ± 5.00 d	74.60 ±2.96 d
Fifth group	361.20 ± 4.91 e	83.80 ±3.56 e
L.S.D	7.82	3.83

Different letters refer to a significant differences at ($P \leq 0.05$)

Effect of sertraline and fluoxetine on concentration of testosterone hormone in male rats:-

The results showed a significant decrease ($p \leq 0.05$) in the concentration of testosterone in all treated groups compared with the control group. There was a significant decrease in the third group when compared with the second group and in the fifth group when compared with the fourth group as shown in table (2).

The comparison between the effects of sertraline and fluoxetine, the results showed a significant decrease in the second group compared with the fourth group and in the third group compared with the fifth group.

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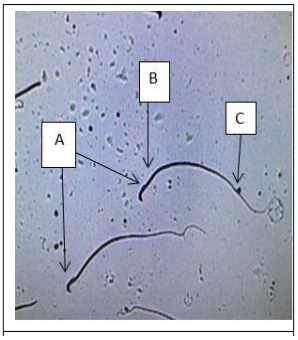
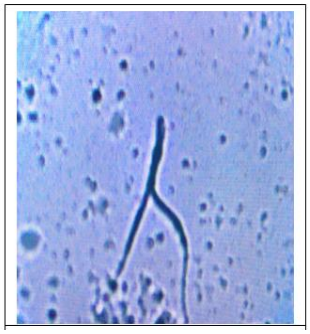
Table (2): Effect of sertraline and fluoxetine on concentration of testosterone hormone of male rats (mean ±standard error)

Groups	Concentration of testosterone (ng/mL)
First group (control)	2.02 ± 0.12 a
Second group	1.18 ± 0.11 b
Third group	0.51 ± 0.05 c
Fourth group	1.35 ± 0.09 d
Fifth group	1.01 ± 0 .13 e
L.S.D	0.13

Different letters refer to a significant differences at (P≤0.05)



Picture (1) normal sperms from control group shows A-head ,B –mid piece , C-tail(100XH&E)



Picture (2) abnormal sperm(split tail) from treated group

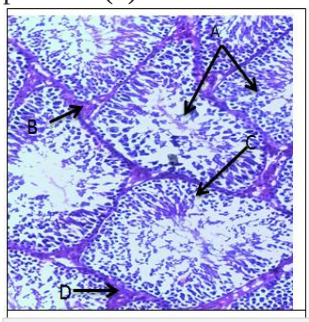
Picture (3) abnormal sperm(hook less) from treated group(100XH&E)

Picture (4) abnormal sperms(headless sperms) from treated group(100XH&E)

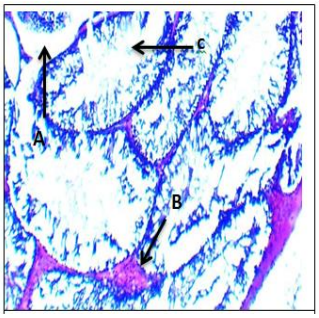
Effect of sertraline and fluoxetine on testis tissue damage in male rats:-

The results of the histological study of the animals of the control group showed its basic structure, which is composed of many seminiferous tubules, which contain all the stages of the spermatogenesis , seminiferous tubules dissociates from each other by the connective tissue as shown in picture (1).

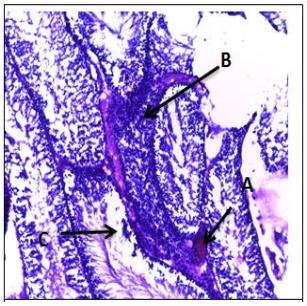
The results of the histological study of animals treated with sertraline and fluoxetine showed histological changes including the dissociation of the interstitial tissue (connective tissue) between seminiferous tubules as shown in pictures(6,8 and 9), the decrease in the number of (spematogonia , sperm, leydige cells) as shown in pictures (6,7,8,and 8) , congestion of the blood vessels as shown in pictures (7and 9) necrosis and bloody hemorrhage as shown in pictures (8).



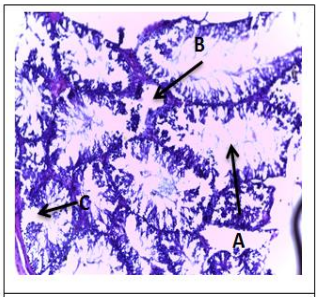
Picture(5) Cross section of testis from control group shows A-seminiferous tubules ,B-connective tissue ,C-spermatogonia ,D-leydig



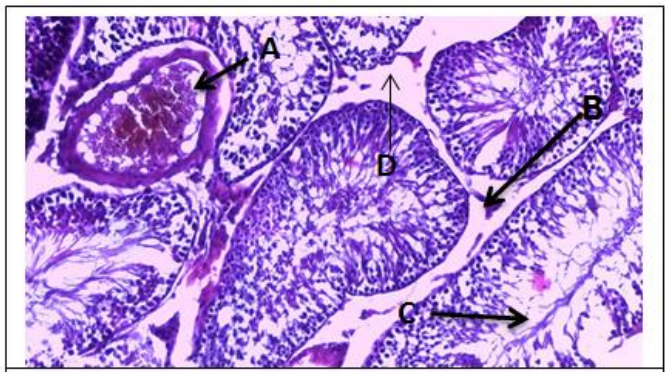
Picture (6) Cross section of testis from second group shows A-dissociation of connective tissue, B-bloody hemorrhage ,C- decrease of number of spermatogonium , (400XH&E)



Picture (7) Cross section of testis from third group shows A- bloody congestion ,B –infiltration of inflammatory cells ,C-decrease of sperms (400XH&E)



Picture 8) Cross section of testis from fourth group shows A- decrease of spermatogonia,B- ,B-dissociation of connective tissue, C-Necrosis (400XH&E)



Picture(9) Cross section of testis from fifth group shows A- bloody congestion ,B- dissociation of connective tissue ,C-decrease of spermatocytes D- decrease of leydig cells (400XH&E)

Discussion:-

The results of the current study showed a significant decrease in the number of sperms and increase in percentage of its deformities in the groups treated with sertraline and fluoxetine comparison with the control group.

The process of spermatogenesis in the testis depends on the axis of hormones hypothalamus - pituitary - testicular (Babu *et al.*, 2004 ; Ramaswamy and Weinbaur, 2014), the release of GnRH hormones from hypothalamus that stimulate the release of FSH and LH, FSH mediates in the process of spermatogenesis by the association with special receptors, LH stimulates the release of the testosterone by affecting on the cells of the Leydig by binding to its receptors found in the cells of Ledig (Babu *et al.*, 2004; Ramaswamy and Weinbaur, 2014; Ahmed *et al.*, 2014), Therefore, the decrease in the number of sperms is either due to a low concentration of testosterone and confirmed by this study ,or as a result of the effect on the hormones of FSH and LH , Erdemir *et al.* (2014) has shown a reduction in the concentration of FSH and LH hormones when taking antidepressants (escitalopram sertraline, fluoxetine, paroxetine**).**

Oxidative stress is associated with an increase in the rate of cellular damage caused by oxygen and oxygen derived -oxidants known as ROS (Tinkel *et al*., 2012), which is an important factor in infertility causes (Aitken and Roman, 2008; Aktan *et al*., 2013), The main targets of ROS are plasma membranes fats in a process called lipid peroxidation, it is recognized that testicular tissue and sperms are very sensitive to ROS attack due to the high content of unsaturated fatty acids in the sperms membranes (Aitken and Roman ,2008 ; Aktan *et al* ., 2013 ; Erdemir *et al* ., 2014 ; Sharma *et al* ., 2014) and here it is possible to correlate the decrease number of sperms and increase its deformities caused by ROS induced by antidepressants ,Erdemir *et al* .(2014) has shown that sertraline and fluoxetine caused a high concentration of MDA ,which a sign of oxidative stress , many studies have indicated that ROS caused a decrease in the number of sperms and increased its deformities (Agarwal *et al.*, 2006; Tremellen, 2008).

The decrease in the number of sperms may be due to the effect of oxidative stress on the Sertoli cells, which play an important role in the process of spermatogenesis Lector, (1996) suggests that oxidative stress directly affects Sertoli cells, which play an important role in spermatogenesis . The decrease in the number of sperms and increase its deformities can be attributed to the effect of free radicals on leydig cells and inhibition of testosterone secretion, which plays an important role in the spermatogenesis (Nishimura *et al.*, 2001).

Kumar *et al.* (2006) suggests that the spermicidal action by antidepressants is due to influencing ATP production by inhibition of oxidative phosphorylation in mitochondria of sperm, or by interacting with phosphate lipids in the mitochondrial membrane and interfering with the sulfhydrl group present in the sperm membrane. Sanocka and Kurpisz, (2004) suggest that free radicals cause decrease number of sperms and increased its deformities because they inhibit DNA synthesis and alteration of the structure of the sperms. Trividi *et al.* (2010) suggested that DNA damage leads to abnormalities in the head of the sperm.

The process of spermatogenesis depends on the safety of the testis tissue, which is the main site for the safe production, the results of the current study have shown clear tissue changes that may have a significant impact on the production of sperm. Moreover, the absence of serotonin receptors in the epididymis, testis, Leydig cells, Sertoli cells, and sperms encourages the hypothesis that SSRIs are likely to worsen semen standards and affect fertility (Erdemir *et al*., 2014). The results of the present study showed a significant decrease in the level of testosterone in male rats treated with sertraline and fluoxetine.

This decrease in testosterone may be due to a defect in the process of its production from leydig cells that operate under the stimulation of LH hormone secreted from the pituitary gland, so any factor

affecting the secretion of this hormone or affect the its receptors have a negative impact on the production of testosterone and therefore low its concentration in the blood ,Dobashi *et al*. (2001) has shown that selective serotonin reuptake inhibitors increase the production of cortisol, which negatively affects LH receptors in leydig cells, thus causing dysfunction in the production of testosterone and low its concentration, Cortisol also inhibits certain enzymes involved in the production of steroid (Hartters *et al.*, 2000).

Or it may be because serotonin reuptake inhibitors increase the concentration of serotonin and increase serotonin will inhibit the activity of the enzymes involved in the production of steroid in testicular tissue and this process will lead to the reduction of testosterone (Hajak *et al.*, 1996). The results of the reading of the histological section of the treated rats testis showed clear effects, including bloody congestion, necrosis and hemorrhagic, this may be due to changes in the mitochondrial membranes of the sperm cells, which result in a change in ATP production and thus reduce the amount of blood reaching to the cells and this leads to necrosis and death, Galal *et al*. (2015) has shown increased of programmed cell death in the testicular tissue after taking antidepressant fluvoxamine.

The histological sections of the testis showed the dissociation of the connective tissue between the seminiferous tubules, may be due to an increase in the LH hormone, which causes germ cells degradation (Sarkrar *et al*., 2000; Fattahi *et al.*, 2009).

Presumably, exposure to drugs generates ROS in the body of the mammalia, which neutralizes the endogenous antioxidants (Abdel-Diam *et al*., 2014), The imbalance between the production of ROS and antioxidants defence stimulates oxidative stress, which leads to fat, protein and DNA damage, consequently leading to Programmed cell death and necrosis (Mohmed *et al*., 2015).

Csaba *et al*. (1998) showed that serotonin injections in adult rats cause atrophy of the testis, impotent in the process of spermatogenesis and inhibition in the production of steroids.

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