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Histological Influence of Fluoxetine Treatment on Parotid Gland in Rats

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Abstract

This study attempted to assess the impact of fluoxetine on the submandibular salivary gland of Albino rats. Thirty rats weighing 160–230 gm was randomly divided into 3 groups, 7 rats each; group I (control group), group II (20mg/kg single dose fluoxetine-treated group included 10 rats that received 20mg/kg fluoxetine as a single intraperitoneal dose, while the group III were treated with (60mg /kg body weight) of fluoxetine. Blood samples were collected for measuring malondialdehyde (MDA) superoxide dismutase (SOD), hydrogen peroxide H_2O_2 and histopathological examination for both salivary and parotid gland tissue. According to the histological study's findings, the second group (G2) experienced histopathological changes that included. The study upheld that reiterated by oral intake of fluoxetine induced significant toxic impacts on blood parameters, increased serum MDA and H_2O_2 levels while downregulated SOD and GSH-Px level and histopathological changes in parotid gland. The current study decided that fluoxetine has many toxic effects on blood parameters, induces oxidative stress and histopathological alteration in the parotid gland.

Keywords: *Fluoxetine, Oxidative Stress, Selective Serotonin-Reuptake Inhibitor.*

Introduction

Saliva carries important functions for oral hygiene due to the presence of high contents of salivary proteins, which play an important functional role in digestion, microbial killing, maintenance of teeth health, and protection of oral mucosa [1-3]. The salivary glands are made up of three pairs allocated around the mouth wall; the sublingual glands under the tongue, the submandibular glands under the floor of the mouth, and the parotid glands in the posterior aspect of the mouth at the retromandibular fossae [4, 5]. The parotid gland is fundamentally made up of serous acinar cells, the submandibular gland is primarily made up of an admixture of serous and mucinous cells, and the sublingual gland is completely made up of mucinous cells and considered a minor salivary gland [6].

The salivary glands (SG) are a collection of highly differentiated tissues that release saliva from these three glands and their structure. Saliva is a clear watery material essential for different healthy physiological functions, such as, the protection of the teeth and surrounding soft tissues by neutralizing acidic components in food, the lubrication of the oral cavity via protein components in the saliva, speech support via lubrication provided by salivary components, and the perception of taste in foods via lubrication and dissoving food components [7]. Moreover, the salivary glands play an essential part in innate and adaptive immunity and protection via protein components of the saliva. Various immune cells, such as B cells, T cells, macrophages, and dendritic cells, as well as immunoglobulins (IgA and IgG), have been found in salivary glands [8].

Fluoxetine, {N-methyl-3-phenyl-3-[4-(trifluoromethyl) phenoxy] propan-1-amine}, is the most commonly prescribed drug for

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depression and other neuro-psychotic disorders. It is a classic antidepressant belonging to the selective serotonin-reuptake inhibitor (SSRI) class, which was used for the pharmacological validation of new therapies and drugs. It plays an antidepressant role through enhancing the level of 5-hydroxytryptamine (5-HT) in the synaptic cleft by selectively inhibiting the absorption of 5-HT by the presynaptic membrane. However, the varied symptoms are not relieved by fluoxetine due to the complicated mechanism of depression, in addition to the slowed therapeutic effect or intolerable side effects [9, 10].

Fluoxetine and its active metabolite, norfluoxetine, both work on 5-HT. Fluoxetine and norfluoxetine differ in pharmacokinetic properties, with a longer half-life (4–16 days) of norfluoxetine versus 4–6 days for fluoxetine, making the dose of 20 mg–80 mg/day an acceptable [11]. This study was therefore designed to examine the effect of two doses of fluoxetine: 20 and 60 mg/kg body weight on the submandibular salivary gland of Albino rats. Some oxidative stress and some antioxidant defence system in rats.

Materials and Methods

A total of 30 adult rats (age 8-12 weeks, weight 160–230 g) were employed for this research. The rats were acclimatized under proper healthy conditions (12:12 h, light: dark cycle; moisture, 65%–70%; temperature, 22±1ºC; feed with the proper food and water ad libitum). After 7 days of adaptation, rats were unsystematically subdivided into 3 groups (10 rats each with 5 rats per cage). These groups were as follows:

1. Group I, which is also called the control group, the rats in this group were given 0.9% of normal saline as a single intraperitoneal dose.
2. Group II, which is also called the fluoxetine group, the rats in this group were given a single intraperitoneal dose of fluoxetine 20mg/kg.
3. Group III, which is also called the fluoxetine group, the rats in this group were given a single intraperitoneal dose of fluoxetine 60mg/kg.

The flouxetine was reconstituted in 0.9% normal saline, freshly prepared at a concentration of 100mg/ml to be administered to rats on need and based on the required concentration according to the specified group.

At the end of the study, the serum samples were collected from individual animals by cervical dislocation and the animals were sacrificed for tissue histological study. The required tissue samples were collected and initially washed by suspending in cold 0.9% normal saline for 3 minutes, then washed with normal saline twice. In the next step, the tissues were suspended in 10% formalin for fixation. The fixed tissues were further processed into paraffin wax to be dehydrated by sequential steps of alcohol/xylene. Followed by paraffin infiltration, to be then sectioned into slices by rotatory microtome and then stained with the standard dye hematoxylin and eosin. In the subsequent step, the slides were microscopically eamined and pictures were taken [12-14]. The study was approved by the ethical committee for animal experimentation of the College of Veterinary Medicine/Tikrit University, where the work was done.

The isolated serum samples were used to quantify the oxidant/pro-oxidant markers, including malondialdehyde (MDA), hydrogen peroxide (H_2O_2), glutathione peroxidase (GPx), and superoxide dismutase (SOD) using kits supplied by LabScience (France) as per manufacturer instructions supplied in the leaflet of the kits.

Malondialdehyde (MDA) Measurement: The serum samples were mixed with thiobarbituric acid (TBA) and an acidic buffer (provided in the kit) and left in a water bath for 15 minutes to allow the reaction to complete, forming a pink-colored complex. The absorbance was measured at 532nm using a

spectrophotometer. The MDA were quantified in the serum based on the standard curve.

Hydrogen peroxide measurement: The serum samples separated from blood were mixed with a reagent containing peroxidase and tetramethylbenzidine (chromogenic substrate). Hydrogen peroxide in the sample reacts with the substrate in the presence of peroxidase, producing a colored product to be quantified at an optical density of 450 nm using a spectrophotometer. The hydrogen peroxide was quantified in the serum based on the standard curve.

Glutathione peroxidase (GSH-Px) measurement: GSH-Px activity is measured based on its ability to catalyze the reduction of H_2O_2 or organic hydroperoxides, coupled with the oxidation of reduced glutathione (GSH). The serum was mixed with a reaction mixture containing GSH, NADPH, glutathione reductase, and a peroxide substrate (provided in the kit). GPx catalyzes the reduction of the peroxide, oxidizing GSH to GSSG (oxidized glutathione). Glutathione reductase then reduces GSSG back to GSH, consuming NADPH. We monitored the decrease in NADPH absorbance at 340 nm over time using a spectrophotometer. The rate of NADPH consumption is proportional to GSH-Px activity. GSH-Px calculated activity in units per milliliter (U/mL) or per milligram of protein, based on the rate of NADPH oxidation.

Superoxide Dismutase (SOD) Measurement: SOD activity is quantified by its ability to inhibit the reduction of a tetrazolium dye (e.g., nitroblue tetrazolium, NBT) by superoxide radicals. The serum was mixed with a reaction mixture containing xanthine, xanthine oxidase (to generate superoxide radicals), and NBT. SOD in the sample inhibits the reduction of NBT by superoxide radicals. The rate of blockage of NBT reduction is reciprocal to the SOD activity. The absorbance was measured at 560 nm using a spectrophotometer. SOD activity calculated in units per milliliter (U/mL) or per milligram of protein, based on the inhibition curve.

Results

The structure of the parenchyma of the lining tissue of the salivary gland was formed by acini, each acinus was coated by pyramidal epithelial cells whose nuclei were made up of spherical basophilic nuclei with grayish cytoplasm releasing serous media. Each acinus was fenced by fragile connective tissue, and trabeculae or setae confronted a group of acini, intra and inter lobular ducts reinforced by plain cuboidal cells, which were allocated inside these tissues (Figure 1).

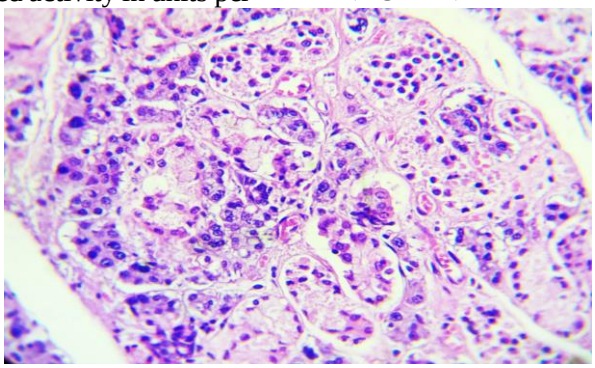

Figure 1. Normal Histological Architecture in the Sub Maxillary Gland in the Control Group Showing Acini of the Gland and Clear Parenchymal Lining.

The interlobular trabeculae had interlobular ducts and blood vessels within a few fibroblasts and lymphocyte (Figure 2).

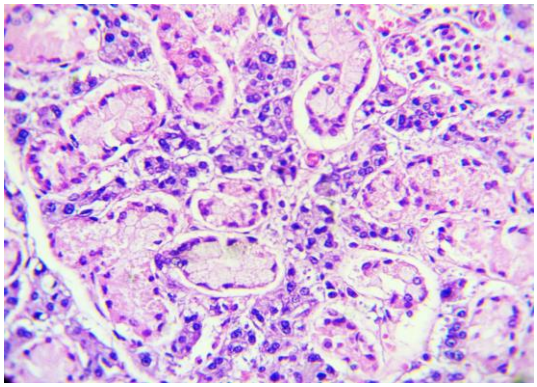

Figure 2. Normal Histological Architecture in the Sub Maxillary Gland in the Control Group Showing Inter Lobular Trabeculae.

The acini of the gland had ill-defined epithelial cells with pycnotic nuclei; certain cells had a vacuolar zone around their nuclei. The interlobular blood vessels were congested with blood, and the interlobular ducts were surrounded by inflammatory WBCS (Figure 3).

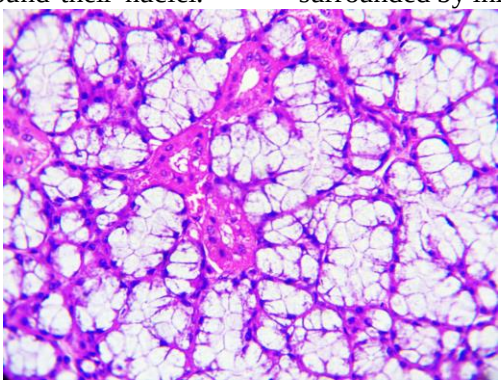

Figure 3. Fluoxetine 20mg/kg/day Induced Histopathological Changes in the Submaxillary Gland, Showing Vacuolar zones around its Nuclei.

The acini of the gland contained degenerated epithelial cells, and the cytoplasm of most cells had peri-nuclear vacuoles and Most nuclei were pycnotic peritubular blood vessels were present around the intralobular ducts (Figure 4).

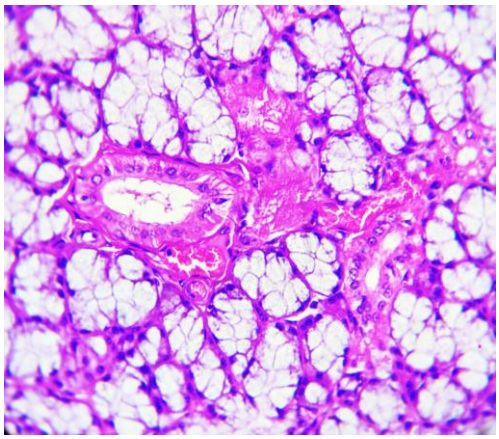

Figure 4. Fluoxetine 20mg/kg/day Induced Histopathological Changes in the Submaxillary Gland, Showing Hemorrhage.

The serous acini had degenerated epithelial cells associated with pycnotic nuclei. Most of the intra-lobular ducts were intact, lined by simple cuboidal cells (Figure 5).

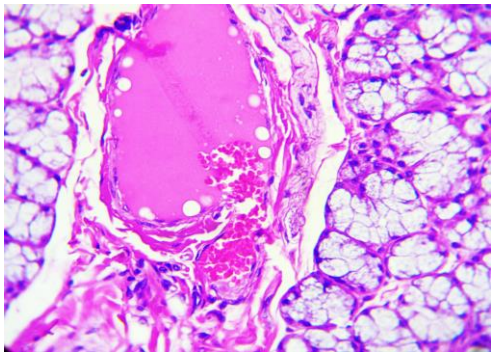

Figure 5. Fluoxetine 20mg/kg/day Induced Histopathological Changes in the Submaxillary Gland, Showing Degenerated Epithelial Cells.

The parenchyma of the gland was engorged with serous acini and packed together; certain acinar cells were degenerated with pyknotic nuclei. The intralobular blood vessels were filled with hemolyzed blood around the intralobular ducts. The ducts were intact (Figure 6).

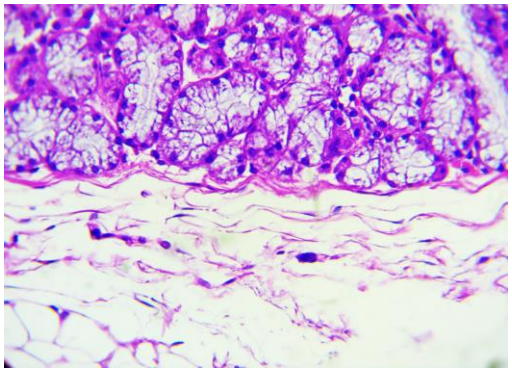

Figure 6. Fluoxetine 60mg/kg/day Induced Histopathological Changes in the Submaxillary Gland, showing that Acinar Cells were Degenerated with Pyknotic Nuclei.

The intralobular ducts of the parotid gland were lined by simple columnar cells; certain epithelial cells of those ducts were desquamated. The lumen of the ducts had glandular enzymatic secretion. The intralobular blood vessels were hyperemic. The connective tissue of setae had fibroblast with few WBCS infiltration and macrophage (Figure 7).

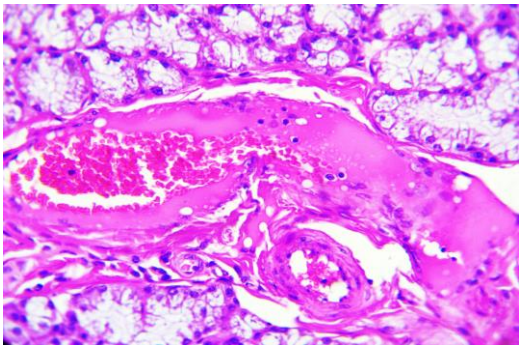

Figure 7. Fluoxetine 60mg/kg/day Induced Histopathological Changes in the Submaxillary Gland, Showing Intralobular Blood Vessels were Hyperemic with Fibroblast and WBCS Infiltration.

The glandular acini of lobules contained degenerated acinar serous cells with pyknotic nuclei. The intralobular septate had striated ducts which were surrounded by macrophages and congested blood vessels (Figure 8).

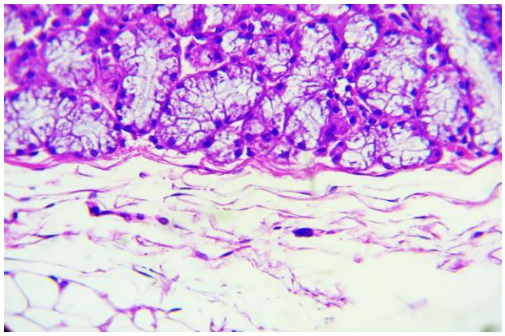

Figure 8. Fluoxetine 60mg/kg/day Induced Histopathological Changes in the Submaxillary Gland, Showing Degenerated Acinar Serous Cells with Pyknotic Nuclei.

Degenerated acinar serous cells were detected with pyknotic nuclei of those cells. The intralobular ducts were intact, with few WBCS around them. The capsule of the gland was detached from the parenchyma of the gland with delicate collagen fibres encountered within the capsule (Figure 9).

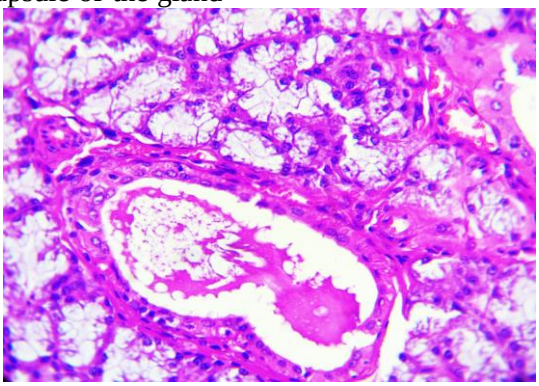

Figure 9. Fluoxetine 60mg/kg/day Induced Histopathological Changes in the Submaxillary Gland, Showing Degenerated Acinar Serous Cells with Pyknotic Nuclei.

Fluoxetine treated rats in Group II and Group III had a significantly increased in serum MDA and H2O2 when compared with the control group (17.15±1.05 and 20.14±2.11 vs 11.1±0.86 nM/mg tissue) and (20.21±1.25 and 21.5±1.25 vs 17.77±1.04nM/g tissue), respectively. The SOD and GSH-Px level was significantly lowered in the serum of rats administered with 20mg/kg/day and 40mg/kg/day of fluoxetine when compared with the control rats (78.11±1.26 and 65.2±5.1vs 107±3.32 µ/mg tissue: $p < 0.05$), (190.07±2.081 and 167±2.4 vs 227.5±9.31 U/g protein: $p<0.05$), respectively (Table 1).

Table 1. Effects of Fluoxetine on the Serum Biochemical Parameters in Rats

Groups	**SOD (µ/mg tissue)**	**MDA (nM/mg tissue)**	**H2O2 (nM/g tissue)**	**GSH-Px (U/g protein)**
Group I	107±3.32	11.1±0.86	17.77±1.04	227.5±9.31
Group II	78.11±1.26	17.15±1.05	20.21±1.25	190.07±2.081
Group III	65.2±5.1	20.14±2.11	21.5±1.25	167±2.4

Discussion

Histological examination of the liver and kidneys of treated rats indicated changes that corroborated our biochemical findings. Our results revealed a significant increase in serum MDA in rats treated with fluoxetine. Similar results were obtained in our previous study [15].

MDA is a byproduct of lipid peroxidation, which could be potentiated by xenobiotic, such as drugs like fluoxetine [16, 17]. Drugs or xenobiotic, including herbal remedies have been participated in the increased lipid peroxidation leading to elevation of MDA, mediated by ROS, which is a significant contributor to fluoxetine -mediated tissue damage [18, 19]. The fluoxetine treatment has been associated with an increase in MDA levels, reduced antioxidant enzymes; this finding has been associated with the findings of another study conducted by Qin et al. (2022) [20].

The levels of GSH-Px were down-regulated by fluoxetine, and the reduction is dependent on the dose used, with higher dose associated with more reduction [21, 22]. This finding harmonized with the research conducted by Safhi et al., who have also reported that fluoxetine is associated with a reduction in GSH-Px due to fluoxetine use [23]. The fluoxetine induced GSH-Px reduction could potentially be inked to its conjugation with fluoxetine to form fluoxetine-glutathione complex or adduct and/or its fast catabolism by the glutathione-dependent enzymes or its extraconsumption by the cell, possibly to combat ROS generation in the treated rats.

Our results revealed that fluoxetine down-regulated the activity of SOD and upregulated the activity of GSH-Px-treated groups. SOD is a imperative enzyme of the antioxidant defense system in contradiction of free radicals. SOD catalyzes the dismutation of super oxide anion into hydrogen peroxide which is a less harmful compounds, and then the hydrogen peroxide was eliminated by catalase and glutathione, subsididized to the control of oxido-reductive homeostasis and mitigation of oxidative attacks on cells. It has inhibitory effects on cellular apoptosis, which are initiated by oxidative damage [24, 25]. The current study demonstrated that the exposure to fluoxetine resulted in elevated serum levels of SOD levels when compared with control group, consistent with the study of Jayakumar et al 2017 [26].

Fluoxetine was found to induce inflammation of the parotid gland. SSRIs were also reported to increase the production of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β in a tissue [27]. Thus, long-term intake of fluoxetine caused damage to the parotid gland due to increased production of ROS during its biotransformation in the parotid gland, leading to cellular disintegration and necrosis of cells [28-30].

Conclusion

It has been found that repeated oral administration of fluoxetine leads to significant increase in MDA and H2O2 whereas decrease in SOD and GSH-Px levels induces oxidative stress and histopathological changes of submaxillary gland.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

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