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The effect of Clomipramine versus Sertraline on the structure of Rat Submandibular Salivary Gland

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ABSTRACT

Objectives: The objective of this study is to evaluate the effect of clomipramine and sertraline on the histological structure of the rat submandibular salivary gland. *Methods:* Thirty-six adult male albino rats were divided into three equal groups, each comprising 12 rats. Group I served as the control group. Group II received a daily oral dose of clomipramine that was equivalent to the therapeutic dose (equivalent to 25 mg/kg) for eight weeks. Group III received sertraline (equivalent to 30 mg/kg). Three rats from each group were sacrificed, and their submandibular salivary glands were dissected, prepared, and stained with hematoxylin and eosin. The stained samples were examined under a light microscope. *Results:* The administration of either drug induced degenerative and atrophic changes in the submandibular salivary gland. These changes were more evident in the samples from rats that received clomipramine than in those that received sertraline. The degenerative and atrophic changes in the submandibular salivary glands of

the rats that received clomipramine were pronounced and progressive while in the sertraline group, they were mild and ceased after four weeks. *Conclusion:* Sertraline proved to be preferable over clomipramine because it has less deleterious effects on the submandibular salivary gland.

Keywords: Antidepressants; Clomipramine; Salivary glands; Sertraline; Submandibular gland

1. INTRODUCTION

Saliva serves a wide range of physiologic needs, and it is essential to maintain oral health and promote normal functions of oral integuments and dentition (Dawes, 1987; Mandel and Wotman, 1976; Schubert and Izutsu, 1987). Additionally, saliva acts as a buffer to organic acids produced by dental plaque; it also preserves dentition by maintaining a re-mineralizing environment in the oral cavity (Atkinson and Wu, 1994). Thus, a decrease in salivary flow rates is probably associated with an increased risk of dental caries (Hopcraft and Tan, 2010).

Several reasons may cause a decrease in the secretion of saliva (Atkinson et al., 2005; Guggenheimer and Moore, 2003). However, the most frequent cause is drugs (Schubert and Izutsu, 1987; Sreebny and Valdini, 1988). These include diuretics, anticonvulsants, neuroleptics, antihistaminics, anticholinergics, antihypertensives, antipsychotics, and antidepressants (Hunter and Wilson, 1995; Marton et al., 2004; Schubert and Izutsu, 1987; Wolff et al., 2008). These drugs have been associated with salivary gland hypofunction, an alteration of the threshold for the perception of dry mouth, or both (Thomson, 2015). Previously, it was reported that the risk of experiencing drug-induced dry mouth might be greater in older patients (Patel et al., 2001). Furthermore, the degree of salivary gland hypofunction is greater in older patients than in younger adults (Patel et al., 2001).

Antidepressants are widely used in the treatment of depressive illness induced by sleep disorders, nervous tension, and mental stress (Buscemi et al., 2007; Hunter and Wilson, 1995; Schubert and Izutsu, 1987; Wade, 2006). It has been reported that these drugs can inhibit saliva secretion. Therefore, patients receiving chronic treatment with antidepressants may have an increased risk of developing oral diseases (Dawes, 1987; McIntyre, 2001; Schubert and Izutsu, 1987) resulting from xerostomia and dry mouth, which appear to be the main complaint of these patients (Nelson et al., 1984; Sreebny et al., 1989).

It is well known that saliva secretion is mediated by both the parasympathetic and sympathetic nervous supply to each salivary gland (Garrett, 1987). These reflexes appear to be mediated through M3-muscarinic and B2-adrenergic receptors for the parasympathetic and sympathetic autonomous systems, respectively. Alpha-adrenoreceptors, substance P, and vasoactive intestinal polypeptide may also be involved to a lesser extent (Baum, 1987). All inputs are thought to be secretomotor. The epithelial parenchymal cells of the salivary glands are stimulated by the parasympathetic autonomous system, which acts as the main stimulus for saliva volume and fluid formation by these cells. On the other hand, the sympathetic nerves tend to affect the composition of saliva (Garrett, 1987; Looms et al., 1998).

The mechanism of reduced salivation induced by antidepressants appears to be a muscarinic blockade, which has been shown to affect saliva secretion peripherally and probably centrally (Schubert and Izutsu, 1987). This mechanism occurs mainly in cases of chronic treatment with tricyclic antidepressants (TCAs) (Clemmesen, 1998, 1988). To limit the treatment-related adverse events of TCAs, their structure has been modified extensively to yield a new generation of antidepressants known as selective serotonin reuptake inhibitors (SSRI) (Wade, 2006).

Clomipramine, a TCA, was first discovered in 1964, and it has been widely and effectively used worldwide for several decades. This agent is a unique antidepressant due to its strong serotonergic effects, which was first described about five decades ago (Fernández Córdoba and López-Ibor Aliño, 1967). Clomipramine is more effective in the treatment of OCD than other TCAs, and it is the only non-SSRI recommended by the National Institute for Health and Care Excellence (2005) for the treatment of OCD. However, clomipramine is not usually recommended as an initial treatment option in OCD and is used as a second-line treatment in OCD.

Sertraline, a new generation SSRI, is usually recommended as an alternative to TCAs and is widely used in clinical practice. It is very effective in the treatment of OCD in adults and children and is better tolerated than clomipramine (Pittenger and Bloch, 2014). Additionally, sertraline has been shown to be as effective as TCAs in the treatment of depression, and it has a better safety profile (Anderson, 2000).

Although the antimuscarinic potency of SSRIs is much less than that of the tricyclic drugs (Rudorfer and Potter, 1989), dry mouth continues to be a problem associated with their administration (Lehne, 2007; Marton et al., 2004; Tacke, 1989; Thomas et al., 1987; Thomson, 2015; Wolff et al., 2008). Dry mouth may arise from several factors, including structural changes in the salivary glands and

the inhibition of salivary flow triggered by these agents (Alsakran Altamimi, 2014). Thus, it is worth studying the effects of these drugs, including how they affect the structure of the rat submandibular glands.

This study aims to investigate and compare the effect of an older drug and a newer one from two different groups of antidepressants—clomipramine (a TCA) and sertraline (SSRIs)—on the histological structure of the rat submandibular salivary glands.

2. METHODS

This experiment was conducted on 36 healthy adult male albino rats that were about three months old and weighing 200–250 grams. The rats were each placed in separate stainless-steel cages. They were fed a standardized, balanced laboratory diet and given water *ad libitum*.

The animals were divided into three equal groups, each consisting of 12 rats. Group I served as controls and received water. Group II received clomipramine for eight weeks, which was delivered orally at a dose equivalent to the therapeutic dose (25 mg/kg) (Frank, 1977) using an oro-pharyngeal metallic curved tube. Group III received sertraline, which was administered in a dose equal to the therapeutic one (30 mg/kg) (Mahmood et al., 2010). The sertraline was also administered for eight weeks using an oro-pharyngeal metallic curved tube.

Three rats from each group were sacrificed one, two, four, and eight weeks after the beginning of the experiment. The submandibular salivary glands were carefully dissected and prepared for histopathological examination.

Tissue Processing for Light Microscopy

The dissected gland was fixed in 10% calciformol, dehydrated in ascending grades of alcohol, cleared in xylol, and embedded in paraffin wax. Sections of about six microns thick were deparaffinized and stained with hematoxylin and eosin for examination under a light microscope.

3. RESULTS

Light Microscopic Examination

Group I (control group)

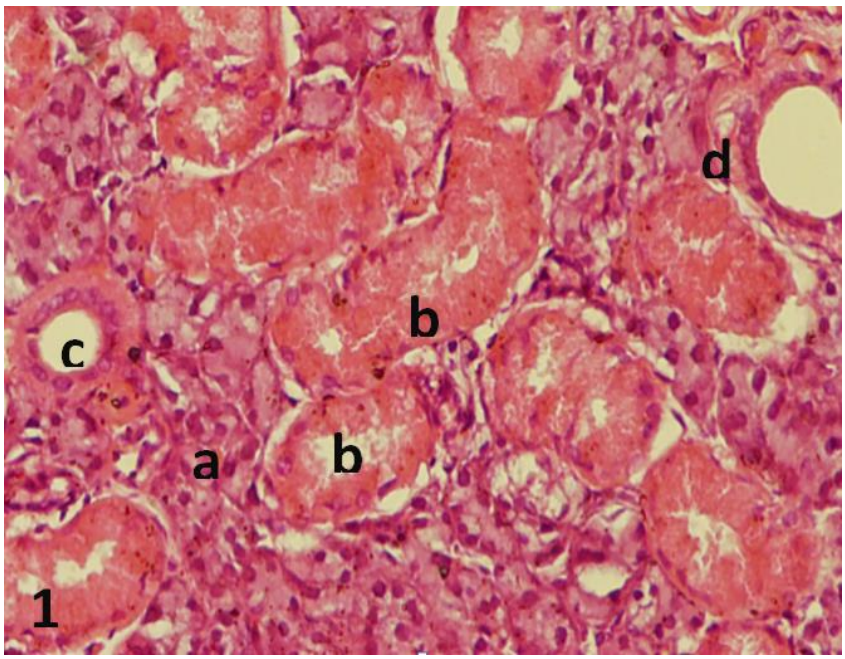

Figure 1 Control group showing serous acini (a), granular tubules (b), striated duct (c), and excretory duct (d).

The submandibular salivary gland consisted of serous acini, some mucous portions, several types of duct systems, and connective tissue stroma. The serous acini appeared small in size, lined with a single layer of pyramidal cells with basally situated rounded nuclei and apical secretory granules, basophilic cytoplasm and surrounding a narrow lumen. The striated ducts were lined with a single layer of columnar cells with eosinophilic cytoplasm and centrally placed nuclei and appeared with their characteristic basal striations.

The granular convoluted tubules were lined with columnar cells with darkly stained and basally placed nuclei. They were extensively packed with eosinophilic granules. The excretory ducts were found between the lobes of the glands surrounded by connective tissue stroma and lined with pseudostratified columnar epithelium with goblet cells (Figure 1). The mucous portions appeared large in size and were lined by a layer of high cuboidal cells surrounding a wide lumen with basally situated flattened nuclei and low refractive index (Figure 2).

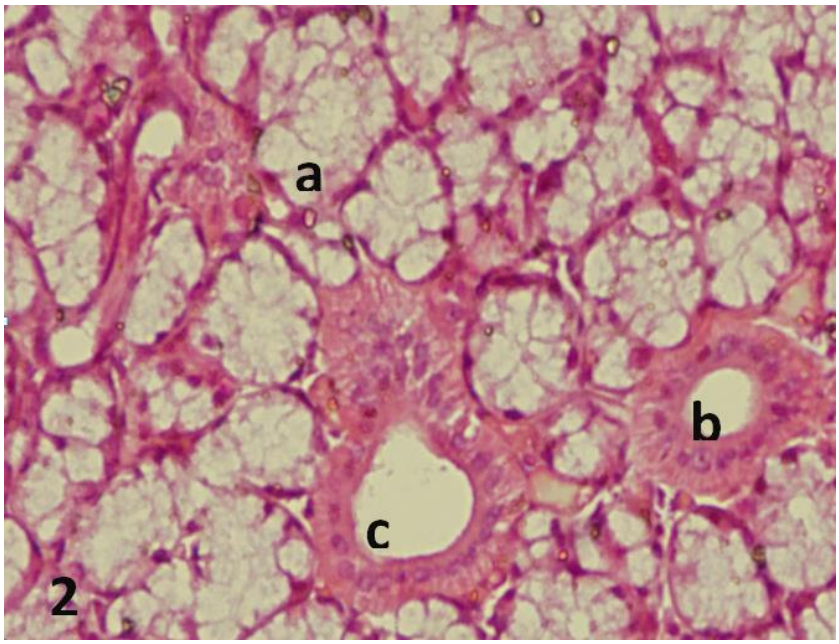

Figure 2 Control group showing mucous portions (a), striated duct (b), and excretory duct (c).

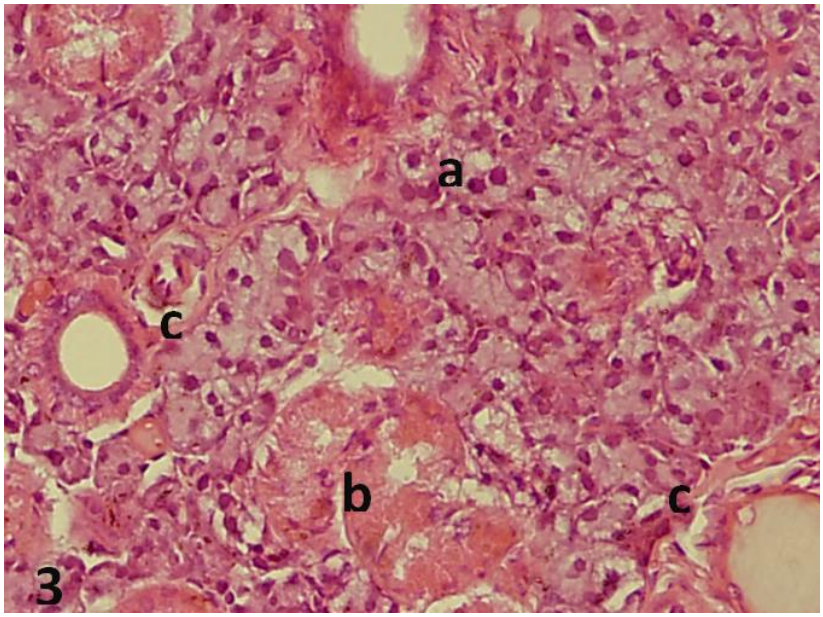

Figure 3 Clomipramine group in the second week showing a decrease in the secretory granules of both serous portions (a) and granular tubules (b) and normal blood vessels (c).

Group II (clomipramine group)

One week after starting the drug administration, the glandular architecture was nearly similar to that of the control. However, in the second week, a moderate decrease in the secretory granules of both serous portions and granular tubules was noticed (Figure 3). In the fourth week, the serous acini revealed extensive intracytoplasmic vacuolization and both serous portions and granular tubules

became smaller in size and showed a marked reduction in their granules. The striated duct appeared distended with ill-defined basal striations (Figure 4). In the eighth week, the glandular tissue revealed noticeable, small-sized serous acini with ill-defined cell outlines and few secretory granules, as well as widened interacinar spaces. The granular tubules appeared smaller in size with cellular degeneration and an apparent reduction in their acidophilic granules while the striated duct showed ill-defined basal striations (Figure 5).

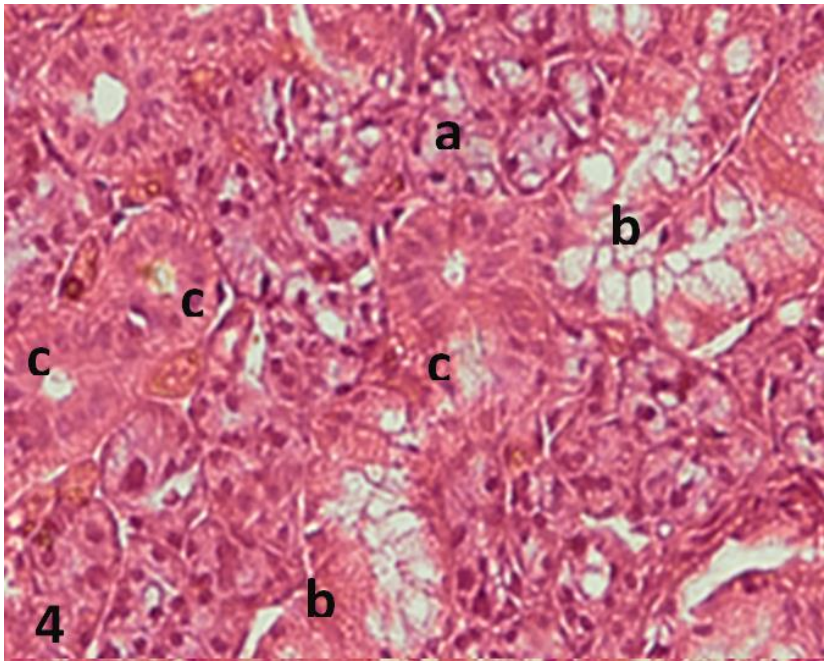

Figure 4 Clomipramine group in the fourth week showing extensive intracytoplasmic vacuolization and marked reduction in the secretory granules of both serous portions (a) and granular tubules (b) and ill-defined basal striation of the striated duct (c).

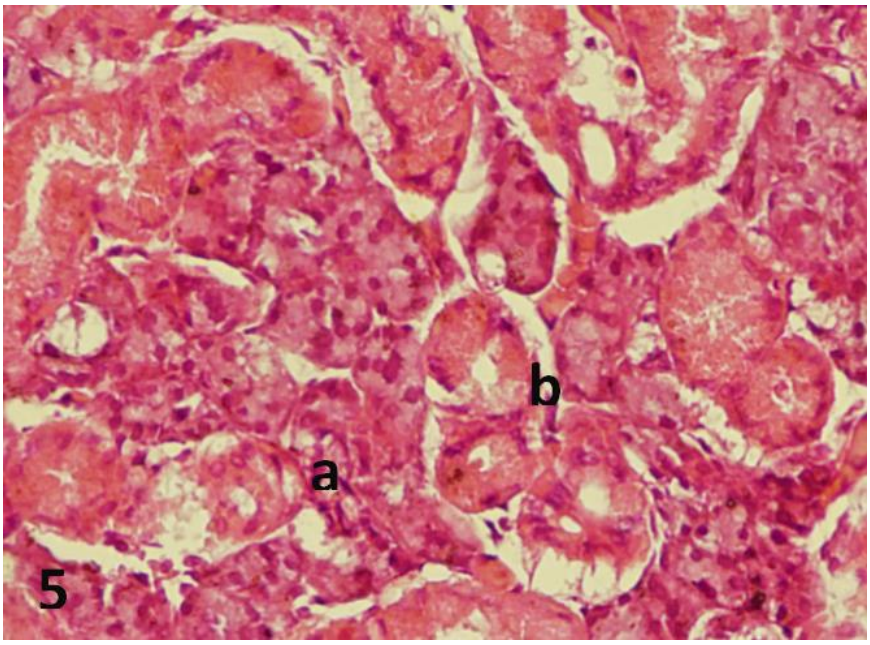

Figure 5 Clomipramine group in the eighth week showing small-sized serous portions with intracytoplasmic vacuolization and widened interacinar spaces (a) and a marked reduction in the granules of the small sized and degenerated granular tubules (b).

Throughout the experiment, the mucous portions, as well as the excretory ducts, presented noticeable distension with secretory material. Thickened fibrous connective tissue septa with dilated and congested blood vessels could be seen at the eighth week.

Group III (sertraline group)

One week after administering sertraline, the glandular features showed no apparent change from those of the control group. In the second week, similar findings were observed except for a mild reduction in the secretory granules of some serous portions (Figure 6). In the fourth week, both serous portions and granular tubules revealed faintly stained cytoplasm accompanied by a moderate reduction in their granular contents with intracellular vacuolization (Figure 7). In the eighth week, the glandular configuration remained unchanged and was nearly similar to that seen in the fourth week.

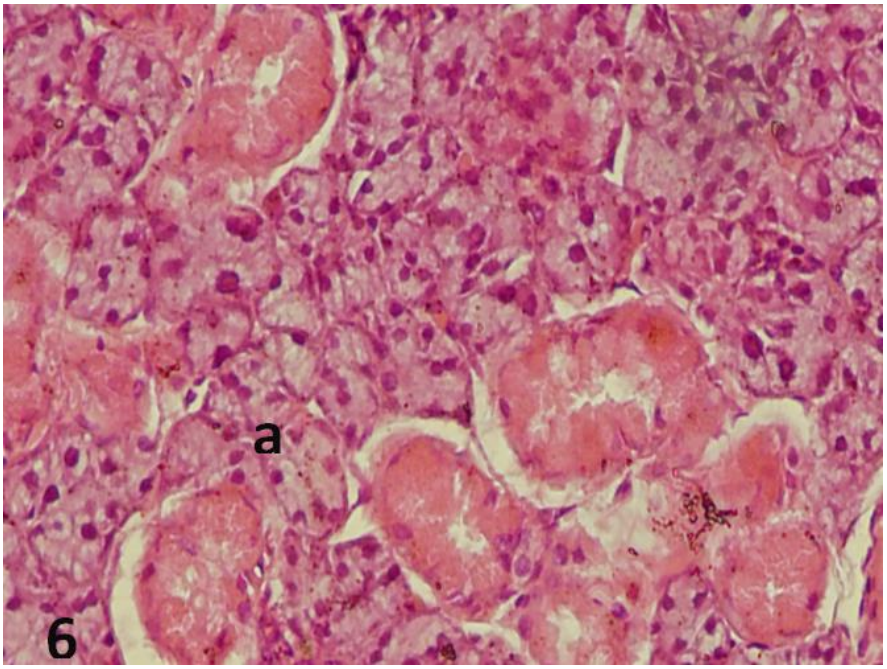

Figure 6 Sertraline group in the second week showing a mild reduction in the secretory granules of serous portions (a).

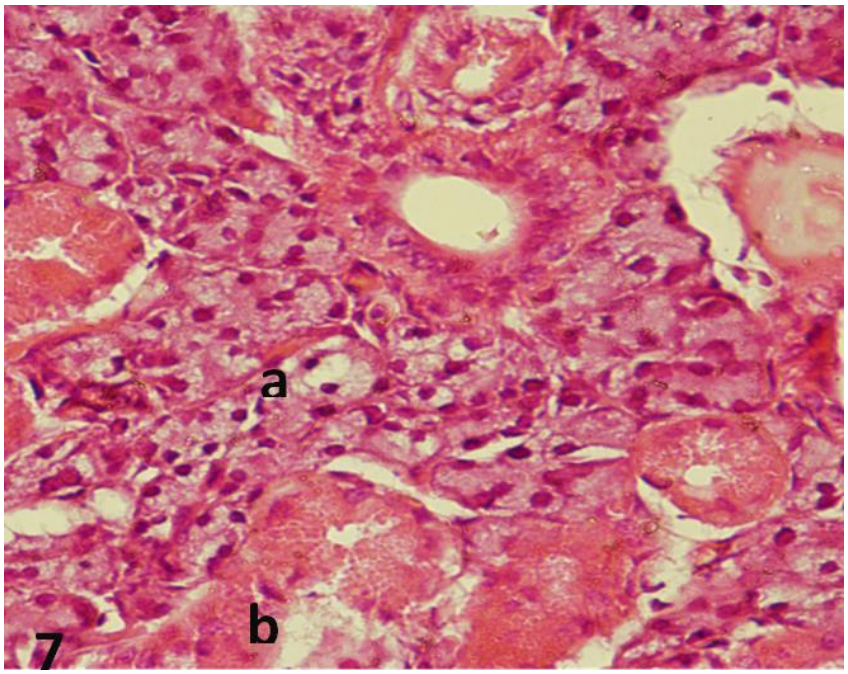

Figure 7 Sertraline group in the fourth week showing faintly stained cytoplasm and intracellular vacuolization with a moderate reduction in the granular content of serous portions (a) and granular tubule (b).

Throughout the experimental period, the mucous portions and excretory ducts showed mild distension with secretory material, while the striated duct was unchanged, and the blood vessels appeared dilated and congested (Figure 8).

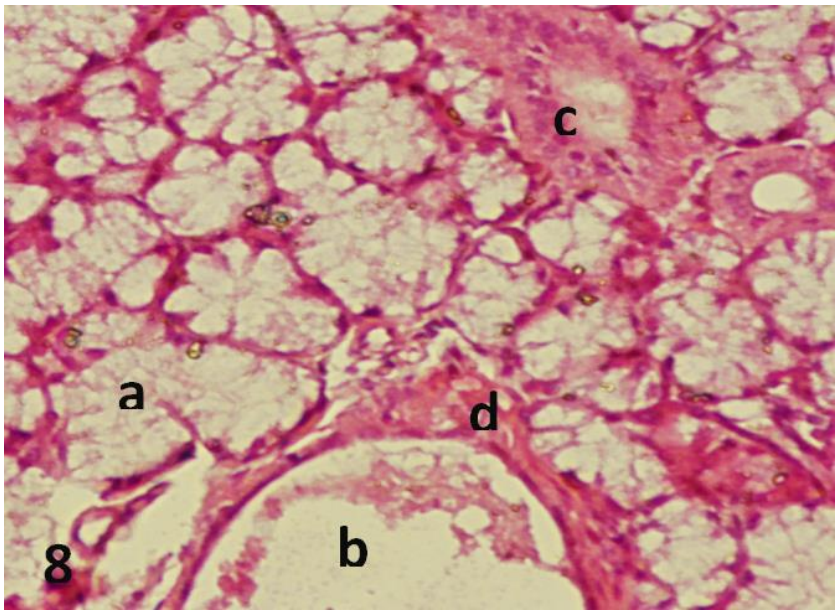

Figure 8 Sertraline group in the eighth week showing mild distension of the mucous portions (a) and excretory ducts with secretory material (b), unchanged striated ducts (c), and dilated congested blood vessels (d). (Hematoxylin and eosin stain; magnification 200x).

4. DISCUSSION

The primary function of the salivary glands is to secrete saliva, which has a protective influence against the development of oral infections and dental caries (Atkinson and Wu, 1994; Dawes, 1987; Hopcraft and Tan, 2010; Mandel and Wotman, 1976; Schubert and Izutsu, 1987). Because the administration of antidepressants has been associated with dry mouth and xerostomia (Clemmesen, 1988; Marton et al., 2004; Nelson et al., 1984; Sreebny et al., 1989; Wolff et al., 2008), it is worth conducting a study (using a light microscope) on the effect of these drugs on the structure of the rat submandibular gland, which contributes to about 60% of the secreted saliva (Bhaskar, 1980).

The present study revealed that the administration of clomipramine and sertraline could induce degenerative and atrophic changes in the rats' submandibular salivary gland. Such changes appeared as intracellular vacuolization and cell shrinkage in the serous acini, supporting the results reported by Dissing and Nauntofte (1990) and Brodkin et al. (1996), who studied the parotid following amitriptyline administration. Of note is that the observed intracytoplasmic vacuolization that occurred four weeks after tricyclic drug administration could reflect the lack of balance between water intake and water secretion by the cell (Kyriacou et al., 1988) On the other hand, Wright (1961) attributed the presence of such vacuoles to the accumulation of lipid droplets from unutilized fatty acid as a result of the decreased cellular activity.

The observed reduction in the size of serous acini and the loss of their typical form with ill-defined cell boundaries is in agreement with the results of da Silva et al. (2009) who studied the effect of fluoxetine and venlafaxine antidepressants on rat parotid glands. Additionally, the present results are in line with the findings of Jick and Li (2008), who observed dilated and congested blood vessels following antidepressant administration. Moreover, the observed thickened connective tissue stroma with clomipramine could be related to the increased expression of the basic fibroblast growth factor, with a broad neurotrophic activity resulting from the administration of antidepressants (Mallei et al., 2002). All these changes might explain the subjective complaint of dry mouth, oral discomfort, and decreased salivary flow reported in patients receiving antidepressants (Daly, 2016; Dechant and Clissold, 1991; Hunter and Wilson, 1995; Johnsson et al., 2016; Marton et al., 2004; Sreebny et al., 1989; Wolff et al., 2008).

The observed atrophic changes appeared to be progressive and much more pronounced with the tricyclic group rather than with the SSRIs group. This result is in agreement with the persistent significant inhibition of salvation reported during long-term treatment with tricyclic drugs (Bertram et al., 1981; Clemmesen, 1988; Hunter and Wilson, 1995). It could be attributed to their potent anticholinergic effects as well as muscarinic receptor blockade (Clemmesen, 1998; Hunter and Wilson, 1995), resulting in a

lack of parasympathetic neurotransmitter and impulses, which have an important function in maintaining the normality of the acini, granular tubules, and striated ducts (Ohlin, 1963).

On the other hand, SSRIs proved to have a less potent anticholinergic effect as well as less affinity for muscarinic receptors (Thomas et al., 1987). Hence, it could inhibit the neuronal reuptake of serotonin, facilitating serotoninergic transmission (Dechant and Clissold, 1991). This mechanism of action appears to account for the mild degenerative and atrophic changes observed with drugs of this class.

The observed difference in the effects of the two drugs is in agreement with other comparative trials by Dominguez et al. (1985) and Feighner (1985) who reported a significant reduction in salivary flow with tricyclic drugs (imipramine and amitriptyline) rather than the SSRIs (fluvoxamine and fluoxetine). Additionally, sertraline has been reported as an effective drug with much less adverse effects (Muijsers et al., 2002; Schramm et al., 2007; Turner et al., 2008).

In the present study, the serous portions and granular tubules appeared to be more affected and more sensitive to antidepressant administration than the rest of the glandular tissues. This could be explained by variations in the neuroeffector arrangements not only from gland to gland but also between the cell types within the same gland (Flint et al., 2014; Garrett, 1987). The neuroeffector sites have been detected more frequently in association with the acini, myoepithelial cells, and muscular blood vessels and, to a lesser extent, with the striated and collecting ducts of the human submandibular and parotid glands (Garrett, 1967).

It is well known that the neurologic functions involved with salivation include parasympathetic impulses, which cause the flow of serous secretion from both acini and granular tubules (Kyriacou et al., 1988), and sympathetic stimuli, which produce only small amounts of mucinous saliva (Schubert and Izutsu, 1987). Thus, with exclusion of normal parasympathetic impulses, it is possible that reflex sympathetic impulses may cause secretion of a viscous saliva (Kyriacou et al., 1988; Kyriacou and Garrett, 1988). This could explain the observed distension of the mucous portions, as well as the accumulation of mucosubstances and the distension of the ducts, which could be attributed to lack of water mobilization (Garrett et al., 1981) resulting from atrophied serous portions and granular tubules evoked by the antidepressants. Additionally, Mandel and Wotman (1976) suggest that the quality of secretion, especially mucin content, is more important than the quantity in persons who experience a dry mouth.

5. CONCLUSION

This study provides evidence that clomipramine can induce progressive and pronounced degenerative and atrophic changes in the submandibular salivary gland when compared to sertraline, which showed limited degenerative and atrophic changes. Thus, sertraline is preferable to clomipramine (a tricyclic drug) because it has less deleterious effects on the submandibular salivary gland.

Disclosures

The author has no conflicts of interests.

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