

Effects of Fluoxetine and Venlafaxine on the Salivary Gland – Experimental Study

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1. Introduction

Depression is the most common form of affective disorders and may range from discrete to severe. Various studies have worked with the hypothesis that depression arises from the deficiency of monoamines (noradrenaline, serotonin and dopamine), the most adequate treatment being to raise the supply of these neurotransmitters in the central nervous system (CNS). Statistical data have shown that depression has increased as a result of the longer life expectancy and is common among the elderly population (Glassman et al., 1984).

The treatment of psychiatric disorders and affective disturbances mainly involves antidepressant, antipsychotic and anxiolytic drugs. Studies relate that patients with psychiatric alterations that make use of these drugs complain of a dry mouth (Thomsom et al., 2000). Depressive alterations accompanied by the symptom of a dry mouth are 20% more frequent in women than in men (Bogetto et al., 1998) and the most affected age group ranges from 30 to 59 years (Scully, 2003).

Antidepressants have an affinity for the adrenergic and cholinergic receptors present in the salivary glands and present an anticholinergic effect. The action of antidepressant drugs may be related to this affinity and the reduction of the cholinergic and sympathetic influx to the CNS. The main side effect of these drugs is inhibition of the secretagogue effect caused by cholinergic stimulation, thus causing hyposalivation (Grégio et al., 2006). Other side effects include: nausea, dizziness, somnolence, sweating and tremors (Horst & Preskorn, 1998).

Fluoxetine is a selective serotonin reuptake inhibitor (SRI) and, among others of the same class, is the result of research to find medications as effective as the tricyclic medications, but with fewer tolerability and safety problems. This drug does not inhibit the reuptake of other neurotransmitters, having no affinity for the adrenergic, muscarinic, cholinergic, H1-histaminic or dopaminic receptors (Goldstein & Goodnick, 1998). Although they are considered safe drugs and present easily attainable therapeutic doses, the SRIs present significant side effects, such as: nausea, diarrhoea, headaches, insomnia and xerostomia (Papakostas, 2008).

Venlafaxine is an antidepressant drug with a completely different chemical structure from that of other antidepressant agents. Its action mechanism resembles that of other known antidepressants, such as fluoxetine, sertraline and paroxetine, since it is directly associated with potentiating neurotransmitter activity in the CNS (Makhija & Vavia, 2002; Owens et al., 2008).

This drug is presented as a selective serotonin and noradrenalin reuptake inhibitor, and presents weak activity as a dopamine reuptake inhibitor, being clinically significant only at high doses (Goldstein & Goodnick, 1998). It does not present affinity for adrenergic receptors α_1 and muscarinic or histaminic receptors (Diaz-Martinez et al., 1998; Goldstein & Goodnick, 1998). Consequently, it is less likely to produce side effects related to these pharmacologic properties (Denys et al., 2003).

In a Cochrane systematic review (1966-2004), the adverse effects of fluoxetine (dry mouth sensation, dizziness and sudoresis) were compared with the adverse effects of the most recent antidepressants (venlafaxine, reboxetine, phenelzine, nefazodone) and they have shown to be less pronounced than in the latter (Cipriani et al., 2005).

Normal salivation is essential for oral health due to its important contributions to the oral defence mechanisms. Diminished salivary secretion could lead to caries disease and deterioration of the mucosa (Mandel & Wotman, 1976; Mandel, 1980; Narhi, 1994).

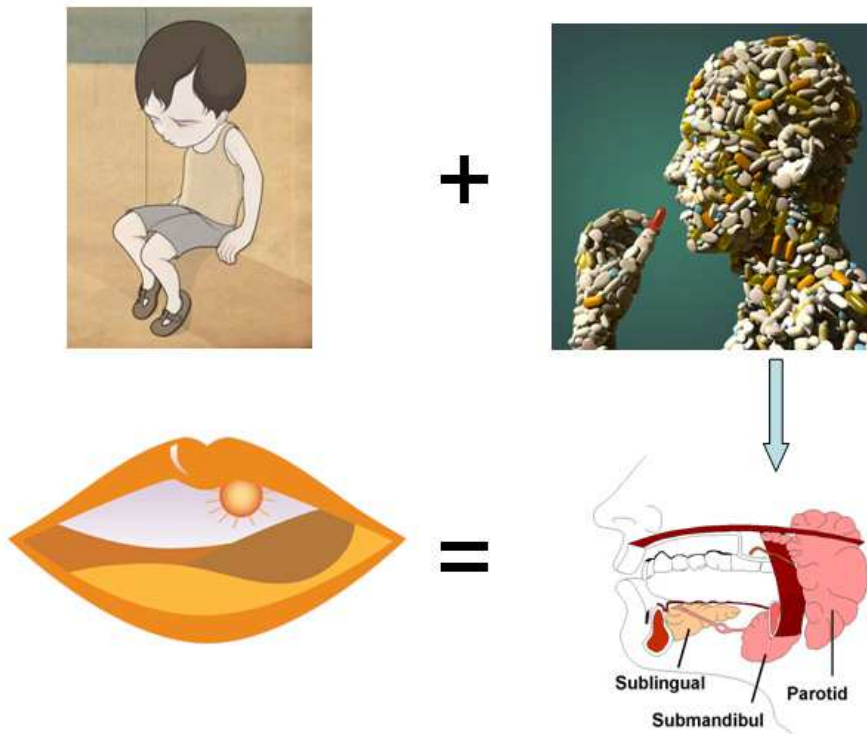


Fig. 1. Depression = affective disorders = depressive patient takes antidepressants drugs that cause dry mouth: alteration on salivary glands (parotid, sublingual and submandibular).

Salivary secretion is neurologically controlled by stimulation of reflex action. The salivary glands are enervated by the sympathetic and parasympathetic autonomic nervous system (ANS). Sympathetic enervation is linked by means of the type α_2 and β_2 adrenergic receptors (Baum, 1987), while parasympathetic enervation is linked to the muscarinic receptor M3. The primary acinar content is modified as it passes through the system of salivary gland ducts. This process occurs because the cells of the duct receive stimuli from the sympathetic and parasympathetic pathways (Scully, 2003).

Grégio et al. (2006), when studying the effects of the chronic use of the association of a benzodiazepine (Diazepam®) and an antidepressant (Tryptanol®) on the parotid glands of rats, observed hyposalivation and hypertrophy of serous cells. These findings suggested a possible inhibition of the activity of the myoepithelial cells, originating from nervous stimulation, a decrease in the number of such cells with the chronic use of psychotropic drugs or an alteration in the number of acinar and ductal cells.

The aim of the present study was to verify the action of two drugs in the antidepressant class, fluoxetine and venlafaxine, on the salivary flow rate, as well as to make a histomorphometric analysis of the rat parotid glands submitted to chronic treatment with such drugs.

2. Material and methods

This study was approved by the Research Ethics Committee of Tuiuti University of Paraná, under the registration number CEP-UTP 55/2003.

The animal model enrolled in this investigation consisted of male rats (*Rattus norvegicus albinus*, Wistar strain) obtained from the Central Animal Facility of the Pontifical Catholic University of Paraná. The animals weighed approximately 250g and were maintained in cages with water and food ad libitum on a light/dark cycle of 12 hours.

Sixty animals, divided into six groups were used, each group consisting of 10 animals (Table 1). The experimental groups received two antidepressants drugs, injectable solution of fluoxetine (lot 20040625, Galena Química e Farmacêutica Ltda., Campinas, Brazil) and venlafaxine (lot D/VN/002/02, Galena Química e Farmacêutica Ltda., Campinas, Brazil). Controlled groups S30 and S60 received solution injectable from physiological serum and the P60 group received a gel base prepared with 1% from pilocarpine hydrochloride (Gerbras Química e Farmacêutica Ltda., São Paulo, Brazil).

Groups	Drug	Treatment time	Dose	Administration via
1. Experimental (FS)	Fluoxetine	1-30 days	20mg/kg	Intraperitoneal
	Physiological Serum	31-60 days	0.1 mL	Intraperitoneal
2. Experimental (VS)	Venlafaxine	1-30 days	40mg/kg	Intraperitoneal
	Physiological Serum	31-60 days	0.1 mL	Intraperitoneal
3. Experimental (F30)	Fluoxetine	1-30 days	20mg/kg	Intraperitoneal
4. Experimental (V30)	Venlafaxine	1-30 days	40mg/kg	Intraperitoneal
5. Control (S30)	Physiological Serum	1-30 days	0.1 mL	Intraperitoneal
6. Control (S60)	Physiological Serum	1-60 days	0.1 mL	Intraperitoneal

Table 1. Controls and experimental groups in accordance with the drug, treatment, time, dose and administration.

2.1 Sialometry

According to described methodology of Onofre et al. (1997), saliva samples were collected 30 hours after the end of treatment. The animals had received two drops of 4% pilocarpine hydrochloride eye drops (Allergan pilocarpina® 4%, Allergan Produtos Farmacêuticos Ltda., Guarulhos, Brazil), to stimulate salivation. After one minute, saliva was collected in a collecting pot that was weighed on a high precision scale - Belmark® U210A (Bel Engenharia, Piracicaba, Brazil), obtaining thus a salivary flow rate (SFR).

The values of amount of saliva were obtained in accordance with the described formula below (Banderas-Tarabay et al., 1997; Olsson et al., 1991).

$$\begin{aligned} & \text{weight of pot after collection (g) - weight of pot before collection (g) =} \\ & = \frac{\text{weight saliva}}{\text{time (1 min)}} = \text{salivary flow rate (ml/min)} \end{aligned} \quad (1)$$

2.2 Parotidean gland exsiccation and size measurement

Glands were obtained from each group right after the saliva collection. Rats were weighted and anaesthetised by intraperitoneal administration of 100 mg/kg sodium thiopental (Thionembatal®, Abbott Laboratórios do Brazil Ltda.) and killed.

The right and left parotid glands were dissected and carefully removed. Fresh gland masses were determined with a BelMark® U210A precision scale. After this, the millimetric longitudinal dimensions were achieved using a high precision digital calliper - Mitutoyo 500 Mical® (Mitutoyo Co., Tokyo, Japan). The average of the glands size and the glands mass was carried through, for attainment of variable so size (GS) and mass (M) for each rat. After the measurement of the part, gland tissue was fixed in 10% neutral formalin solution and embedded in paraffin. Four μm sections were obtained and submitted for routine haematoxylin-eosin (in accordance with the routine of the Laboratory of Experimental Pathology of the PUCPR).

The microscopy Olympus® BX50 (Olympus Corporation, Ishikawa, Japan) was used with the objective of 40X and 100X (oil immersion). The images were captured with a digital camera - Sony® CCD-IRIS DXC-107A (Sony Electronics Incorporation, Tokyo, Japan) connected to the microscope and a microcomputer. With a programme for analysis of images (Image-Pro® Plus, Cybernetics, Silverspring, U.S.A.), the histological analysis front to the use of antidepressants was evaluated.

2.3 Histomorphometry of parotid glands

To establish the comparisons among the groups with regard to the cellular volume (CV), the variable presented had been used in the study of Onofre et al. (1997).

Processed gland volume (vp) was calculated for each animal using the following equation:

$$V_p = m / d \times r_f \quad (2)$$

M is fresh mass, d is density and rf is the shrinkage caused by histological processing. For these calculations we used $d=1.089 \text{ g/cm}^3$ and $r_f=0.7$ using the method of Onofre et al. (1997).

For the stereological evaluation of acinar volume density (V_{vi}) and total volume (V_{ti}) an objective of 40X it was used connected to the programme Image-Pro® Plus, where it obtained a vertical grating with ten horizontal lines and ten vertical lines, determining one hundred points of which forty had been chosen randomly. In these, 40 chosen points had counted how many points coincided with acini (P_i). The V_{vi} by means of the formula was calculated then:

$$V_{vi} = P_i / Pt \quad (3)$$

Pt mentions the number to it of selected points 40.

Having obtained the V_{vi} and processed gland volume (V_p) values, we calculated the total acinar volume (V_{ti}) by the formula:

$$V_{ti} = V_{vi} \times V_p \quad (4)$$

Nuclear volume was determined from the measurement of the orthogonal diameters of 50 nuclei per gland using a microscopy technique as stated before. We calculated the mean radius of the geometric mean diameter by:

$$r_2 = d_1 \times d_2 \quad (5)$$

The nuclear volume was calculated by the formula for the volume of a sphere:

$$V = 4/3 \times \pi \times r^3 \quad (6)$$

The cytoplasmic volume was calculated as of the nucleus densities and the cytoplasm of acinar cells (Weibel, 1969). In this respect, the points over nuclei (P_n) were counted and over the cytoplasm (P_{cyti}) in 40 histological fields of the cells under study. The corrected nuclear volume density (p_{ncorr}) was calculated by the equation:

$$p_{ncorr} = (P_n / P_n + P_{cyti}) / K_o \quad (7)$$

K_o is the correction factor and is calculated by the formula:

$$K_o = 1 + 3t / 2d \quad (8)$$

d is the mean nuclear diameter and t is section thickness.

The corrected cytoplasm volume density is:

$$p_{cyticorr} = 1 - p_{ncorr} \quad (9)$$

By dividing $p_{cyticorr}$ by p_{ncorr} the cytoplasm/nucleus ratio (RC/N) of the acinar cells was obtained. On the basis of nuclear volume (V_{ni}) and the C/N ratio, the cytoplasmic volume (V_{cyti}) was calculated by the equation:

$$V_{cyti} = V_{ni} \times RC/N \quad (10)$$

This then permitted calculating the cell volume by:

$$V_c = V_{ni} + V_{cyti} \quad (11)$$

2.4 Statistical analysis

To rest the presupposition of normality of the variables for each group, the Komolgorov-Smirnov test was used. The Levene test verified the homogeneity of the variances among the groups. When the analysis of variance Anova found differences among the means of the groups and treatments, the Tukey HSD multiple comparisons test was used for the variables that presented homogeneity of variances among the groups. For the variables that did not present homogeneity of variances among the groups, the Games-Howell test was used.

For all the tests the level of significance of 5% ($p < 0.05$) was applied.

3. Results

All the groups presented normality of distribution of the data for the variables GS, M, SFR and CV of the studied glands ($p > 0.05$), with the exception of the variable SFR in the group S60, the variable GS in groups F5 and S30 and the variable M in the group F30.

The variables GS and M showed homogeneity of variance ($p > 0.05$) and the variables SFR and CV did not present homogeneity of variance ($p < 0.05$).

3.1 Groups treated for 30 days

There was a statistically significant difference between the means of the variable GS among the following groups: F30 ($p = 0.0002$), V30 ($p = 0.0112$), when compared with group S30 (control).

For the variable M, there was a statistically significant difference for the following groups: F30 and V30 ($p = 0.0011$), F30 and S30 ($p = 0.0190$), the highest mean being found for the group F30 and the lowest mean for the group V30.

There was a statistically significant difference for the variable CV between the following groups: F30 (Figure 3) and S30 ($p = 0.0005$), V30 and S30 ($p = 0.0004$).

The variable SFR presented a statistically significant difference between groups: F30 and S30 ($p = 0.0031$).

Table 2 shows the means and standard deviations of the studied variables in accordance with the groups treated for 30 days.

Groups	C30		F30		V30	
	Mean	SD	Mean	SD	Mean	SD
SFR (mL/min) ^δ	0.051	0.026	0.014	0.006	0.026	0.022
CV (mm ³) ^δ	6965.683	3792.951	10384.311	4869.539	11945.927	7891.179
Gland size (mm)	7.036	0.506	9.501	1.404	8.696	1.409
Mass (mg)	0.075	0.010	0.103	0.032	0.064	0.018

serum - 30 days), F (fluoxetine - 30 days) and V (venlafaxine -30 days). SD = standard deviations.

δ: Values obtained from the study by Da Silva et al. (2009).

SFR - Stimulated salivary flow rate.

CV - Cellular volume.

* Statistically significant difference among groups ($p < 0.05$).

Table 2. Values of studied variables in accordance with groups treated with C (physiological

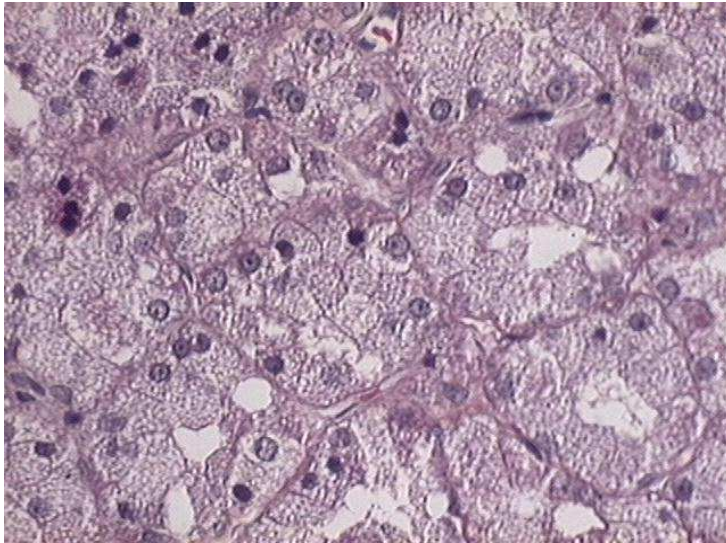


Fig. 2. Histological aspect of the salivary gland of the fluoxetine 30 group showing disorganised glandular parenchyma. There was a loss of borders to the serous cells, which were also increased in size, with a consequent reduction or disappearance of the central lumen (H.E.; original magnification: 400X).

Figures 3 and 4 show rat parotid glands from groups venlafaxine 30 and saline 30, respectively.

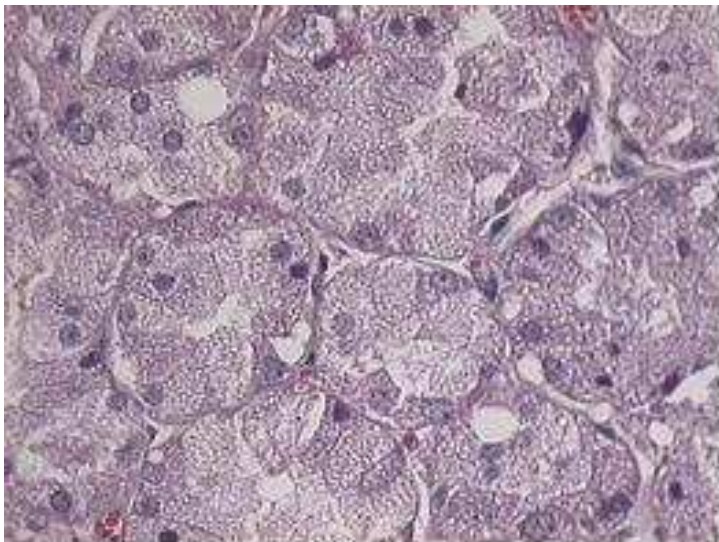


Fig. 3. Histological aspect of the salivary gland of the venlafaxine 30 group. There was a loss of borders to the serous cells, which were also increased in size, with a consequent reduction or disappearance of the central lumen (H.E.; original magnification: 400X).

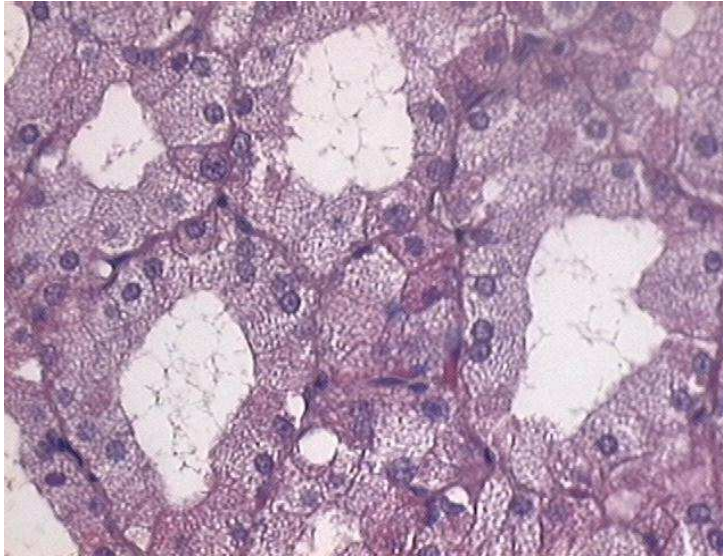


Fig. 4. Group saline 30. Well-structured glandular parenchyma divided into lobules. Inside the lobules, intercalary ducts were covered by cuboidal cells while striated ducts were found covered by columnar cells. (H.E.; original magnification: 400X).

3.2 Groups treated for 60 days

Table 3 shows the means and standard deviations of the studied variables in accordance with the groups treated for 60 days.

For SFR, there were statistically significant differences between the following groups: V60 and C 60 ($p=0.000$).

The variable GS did not show statistically significant differences among the groups. There were statistically significant differences for the variable M between groups VS and S60 ($p=0.0132$).

The variable CV did not showed statistically significant differences between groups C60, F60 and V60.

Groups /Variables	C60		F60		V60	
	Mean	SD	Mean	SD	Mean	SD
SFR (mL/min) ^δ	0.052	0.029 ^a	0.036	0.017	0.020	0.004 ^a
CV (mm ³) ^δ	6505.564	3343.475 ^b	6809.347	3189.246 ^c	7525.112	3196.085
Gland size (mm)	7.885	0.628	8.350	0.077	8.040	0.949
Mass (mg)	0.074	0.021	0.095	0.014	0.101	0.016

δ: Values obtained from the study by Da Silva et al (2009).

SFR - Stimulated salivary flow rate.

CV - Cellular volume.

a,b,c, groups followed by the same letter differed statistically from each other.

* Statistically significant difference among groups (p<0.05).

Table 3. Values of studied variables in accordance with groups treated with C (physiological serum -60 days), F (fluoxetine - 60 days) and V (venlafaxine -60 days). SD = standard deviations.

4. Discussion

The anticholinergic effects of drugs that act on the CNS have not yet been completely explained. The majority of authors opt for defining the autonomic capacity of these drugs in linking to the adrenergic and cholinergic receptors, altering the quality and quantity of salivary flow. But several other factors must be considered, because in addition to interaction with and affinity to the sympathetic and parasympathetic CNS and ANS, other neurotransmitters, proteins and amino acids are capable of resulting in alteration of activity in the salivary glands (Scully, 2003).

This study observed that fluoxetine (F30) produced an increase in GS and M of the rat parotid salivary glands, in addition to increasing CV in comparison with the control group S30. This effect probably occurred because the drugs with central action promote an action of salivary gland hypertrophy (Grégio et al., 2006). This result corroborates those of Martinez-Madrigal & Micheau (1989), who characterised hypertrophy of the glands by widening of the acini and accumulation of secretion granules, caused by drugs with central action.

The anticholinergic action of psychotropic drugs (Martinez-Madrigal & Micheau, 1989; Scully, 2003) was proved once again, because in the group treated with fluoxetine for 30 days (F30), the animals' SFR was lower in comparison with the control group (S30), thus justifying the increase in GS and M, as there was retention of saliva in the acini lumen and little of it being released.

The antidepressants SRIs when compared to the tricyclic drugs have not presented significant effect on the flow rate, probably due to lack of anticholinergic activity. The flow reduction could occur through the serotonin receptor action presented at the peripheral microcirculation (Hunter & Wilson, 1995; Siepmann et al., 2003). According to Schubert & Izutsu (1987), the salivary flow can be affected by drugs through alteration of the blood flow to the salivary glands. For Grubb & Karas (1998) the serotonin has important physiology participation in the autonomic regulation since the CNS controls the sympathetic, the parasympathetic and the serotonin mechanisms, and therefore probably a decrease or

activation of the release of serotonin at the CNS would result in the alteration of both sympathetic and parasympathetic systems. This hypothesis contributes to our finding regarding the reduction of the SFR caused by fluoxetine.

The uncertainty with regard to the exact biochemical mode of action of antidepressants frequently causes the development of new drugs to be empirical. This leads to the introduction of a heterogeneous group of compounds (to which venlafaxine belongs), the atypical antidepressants. In practice, the most recent drugs may definitively be superior to the tricyclic drugs in terms of side effects and acute toxicity, but they have not been shown to have a faster action or be more effective (Goldstein & Goodnick, 1998; Siepmann et al., 2003).

With regard to the results obtained for venlafaxine (V30), both GS and CV had higher values in comparison with the control group, and in addition there was diminished SFR when compared with the control (S30), once again demonstrating the anticholinergic action of psychotropic drugs and the effect of acinar cell hypertrophy (Grégio et al., 2006; Martinez-Madrigal & Micheau 1989).

Venlafaxine has fewer anticholinergic and adrenergic α -blocker effects than the other antidepressive (Denys et al., 2003). This would cause a reduction in the adverse effects, because at low doses this drug predominantly blocks serotonin and noradrenalin reuptake, and at high doses it also inhibits dopamine reuptake. This hypothesis reinforces the great expectation in the use of venlafaxine in comparison with fluoxetine, and is in agreement with the present study findings, since the value of SFR for venlafaxine (V30) was higher when compared with the SFR value for fluoxetine (F30). Furthermore, fluoxetine has metabolite of prolonged action and is pharmacologically active (Goldstein & Goodnick, 1998).

The acinar cells present adrenergic α and β receptors, vasoactive intestinal peptide receptors (VIP), acetylcholine and P substance. The receptors for β adrenergic and for VIP, activate the cyclic AMP cascade, activating the G protein, which activates the adenylate cyclase enzyme. Whereas the α adrenergic receptors and the receptors for acetylcholine and P substance activate the inositol 1, 4, 5 triphosphate cascade (IP3) and of diacylglycerol. These biochemical reactions and interaction sequences influence both salivary secretion and composition (Berne et al., 2000).

Because venlafaxine is a weak serotonin and noradrenalin reuptake inhibitor, it has fewer side effects than fluoxetine (De Nayer et al., 2002). Another hypothesis which could contribute to explaining the result, besides the others mentioned before, is that the majority of types of serotonergic receptors are coupled to the G proteins, affecting adenylate cyclase activity. This enzyme, in turn, converts ATP into the second messenger, cyclic AMP (Gould & Manji, 2002) which, as a central effect, presents activation of the protein kinase A (PKA), an enzyme that regulates ionic channels, which are responsible for the entry and exit of water and electrolytes from cells (Walton & Dragunow, 2000).

On the other hand, the CV of rat parotid glands in the group treated with venlafaxine (V30) was greater than in the group treated with fluoxetine (F30). This is probably owing to the fact that venlafaxine (because it also inhibits noradrenalin reuptake and this being the mediator of the sympathetic ANS, which in turn tends to modulate the composition of

saliva) induces the protein secretion mechanism (Berne et al., 2000) which may be accumulating inside the salivary gland, resulting in cellular hypertrophy.

The groups FS and VS presented lower SFR values than the group S60, proving that after suspension of the drug, withdrawal symptoms may occur, which appear within one to 10 days and persists for up to three or four weeks. The most frequent symptoms are dizziness, vertigo, ataxia, gastrointestinal disorders, flu symptoms, sensorial disturbances, sleep alterations, psychic alterations and anticholinergic effects. As happens with other psychoactive substances, these symptoms may be the result of adaptive alterations, which most frequently involve the adjustment of the receptors to compensate for the pharmacological activity of the drug, described as a rebound effect (Goldstein & Goodnick, 1998).

The advances in research on the psychopharmacology of antidepressants have offered patients with very different pharmacokinetic profiles. In spite of this, the action mechanisms proposed for each of them remain linked to monoaminergic theories of increased amounts of neurotransmitters in the synaptic gap and the subsensitisation of presynaptic receptors (Paykel, 1992).

In terms of the number of drugs available, there has been a considerable enlargement of the therapeutic arsenal, both with expansion in the number of compounds of the same pharmacological group, and in the appearance of drugs with different action profiles from those of the original ones. The more recent compounds are more selective, leading to greater tolerability and adherence to treatment (Goldstein & Goodnick, 1998).

It is verified an effort in the sense of increasingly improving the action in receptor sites determinant of clinical efficacy, avoiding those responsible for side effects (Hunter & Wilson, 1995). However, new inquiries have become necessary due the complexity of the involved events in the saliva secretion mechanism.

5. Conclusion

It could be concluded that both fluoxetine and venlafaxine reduced the SFR and caused hypertrophy of the rat parotid gland, with fluoxetine having a more pronounced anticholinergic action.

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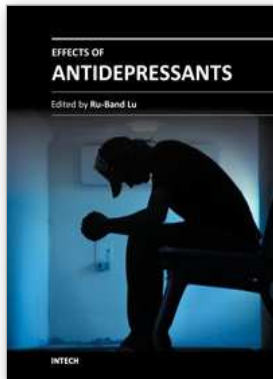
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Effects of Antidepressants

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Over the last fifty years, many studies of psychiatric medication have been carried out on the basis of psychopharmacology. At the beginning, researchers and clinicians found the unexpected effectiveness of some medications with therapeutic effects in anti-mood without knowing the reason. Next, researchers and clinicians started to explore the mechanism of neurotransmitters and started to gain an understanding of how mental illness can be. Antidepressants are one of the most investigated medications. Having greater knowledge of psychopharmacology could help us to gain more understanding of treatments. In total ten chapters on various aspects of antidepressants were integrated into this book to help beginners interested in this field to understand depression.

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