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Opposite effects of antidepressants on unstimulated and stimulated salivary flow

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Summary In this study, effects on both stimulated and non-stimulated salivary flow as well as salivary components of different antidepressant drugs were compared. Rats received imipramine (IMI; 10 mg/ml), fluoxetine (FLU; 20 mg/ml) or moclobemide (MOC; 30 mg/ml) by gavage. The drugs were administered 24, 5 and 1 h before saliva collection (sub-acute treatment) or as a once a day treatment for 14 days (chronic treatment). Animals were sedated with thiopental and saliva was collected using pre-weighed cotton balls inserted in the mouth for 1 min before and after pilocarpine stimulus. Pilocarpine-stimulated saliva was also collected for biochemical assays of total proteins, amylase, phosphate and calcium, performed through automated colorimetric methods. Non-stimulated salivary flow was decreased by sub-acute IMI 10 mg/kg treatment. Pilocarpine-stimulated salivary flow was significantly increased by acute treatments with IMI, FLU and MOC in comparison to the control group. The same opposite pattern of effects on non-stimulated and pilocarpine-stimulated salivation was seen after chronic treatment with the antidepressants. Increased levels of calcium following sub-acute treatment with IMI and after prolonged treatment with FLU and MOC were detected. In the assayed samples, phosphate was found to be increased following chronic treatment with FLU or MOC. These results may explain the discrepant effects of the antidepressants on salivation described in pre-clinical and clinical studies.

Saliva and its components are indispensable for maintenance of oral health.[1] Many drugs affect the output or composition of saliva.[2] Psychoactive agents are among the most probable to induce salivary output changes. Reduction in measured salivary output is referred to as hyposalivation and may be perceived by the patients as xerostomia, while increased salivary output, hypersalivation, may be described as sialorrhea.[3] Antidepressants are the most frequently prescribed psychoactive substances, nowadays, and as much as 30–60% of the patients taking these medications refer xerostomia as an important side effect. Reduction of

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salivary flow may vary between patients who receive different antidepressant classes. Those with xerostomia present 30—60% reduction of salivary flow.[4–8] The xerostomic effect of antidepressants is related to reduction of stimulated salivary flow[7] or to basal salivation.[8] In experimental studies with laboratory animals, there is a large variability in saliva flow rates after antidepressant treatments, according to the type of antidepressant agent used, the method of evaluation (non-stimulated or stimulated saliva collection) or by considering whole-saliva or parotid flow.[9]

In pre-clinical assays, non-stimulated or stimulated whole-saliva or individual gland flow are usually performed in rats through dissection of the parotid, sub-mandibular, and sublingual glands,[10–12] after ligation of salivary gland duct[13] or by its cannulation.[14–19] For all of these methods, invasive surgical procedures are required. There are also other non-surgical techniques for saliva collection, which often require tracheobronchial intubation of the animals.[20] Therefore, besides being invasive many procedures cause destruction or irreversible damage to the tissues.

As in the clinical studies,[21] a non-invasive sialometric method in experimental laboratory uses cotton balls placed on the floor of the mouth. The salivary flow in rats may be determined through the difference in weight of the cotton before and after collection from either non-stimulated or stimulated salivary flow. However, it can only be used for salivary flow determination as the amount collected is not enough for analysis. Another non-invasive method for saliva collection in rats was proposed, in which anaesthetized animals, receiving a sialogogue agent are placed heads-down onto a downward-sloped bench and saliva flows into flasks. This method allows a high amount of saliva collection for analysis of its constituents.[22] One concern about this method is related to a possible interaction between the sialogogue agent and the antidepressant drug.

Because of the great variability of effects of antidepressant drugs in clinical research, our aim was to analyze and compare the effects on non-stimulated and stimulated salivary flow of different antidepressant drugs and its effects on salivary components, using a pre-clinical model.

Male Wistar rats (n = 40) were maintained in groups of five animals per cage (polyethylene 50 cm × 36 cm × 18 cm). The animals were kept at room temperature of 22 ± 2 °C and light cycle from 7 a.m. to 7 p.m., receiving rat chow (Nutrilab®, Brazil) and water *ad libitum*. The experimental procedures comply with national and international guidelines for the use of animals. The Ethics Committee for Animal Research of FFFCMPA approved the research.

The animals were divided into four treatment groups, 10 animals each. Saline, imipramine (IMI; Tofranil®, Biogalênica) 10 mg/ml, fluoxetine (FLU; Prozac®, Elli Lilly) 20 mg/ml or moclobemide (MOC; Aurorix®, Roche) 30 mg/ml, suspended in saline. All solutions were administered by oral gavage, 1 ml/kg. These doses were chosen because they show anti-immobility action in rats submitted to the forced-swimming test commonly used in antidepressant agents' trials.

To follow the same administration schedule used in antidepressant screening trials with the forced-swimming test[27], drugs were administered 24, 5 and 1 h before saliva collection. Following the sub-acute salivation test, the animals received treatment with the same drugs once a day, for 14 days, until the next salivation testing. The same intensive schedule of drug administration was given on the 15th day, before chronic salivation testing.

On the day of the experiments, 0.5 cm cotton balls were prepared and individually placed into previously labelled closed glass flasks, which were weighed in an analytic electronic scale (Sartorius 2662). For each animal, two such sets were prepared, one for non-stimulated salivation and another for pilocarpine-stimulated salivation measurements.

An hour after the last antidepressant dose in sub-acute administration, animals were sedated with thiopental 30 mg/kg, intraperitoneally, and kept in lateral decubitus. The first cotton ball was inserted under the rat's tongue for 1 min. The cotton was then returned to its flask and weighed. Seventy-five minutes after the last treatment dosing, pilocarpine 0.1 mg/kg (Merck®, Brazil) was administered subcutaneously, and after 10 min the procedure of saliva collection with the cotton was repeated. The dose of pilocarpine was selected in a pilot study and corresponds to the maximum sialogogue dose with minimum systemic toxicity for the rats.

Twenty minutes after pilocarpine administration, the animals were placed heads-down on a 20 cm deep acrylic bench divided into four 12 cm (wide) sections, separated by 4 cm (high) divisions. The height of the bench in the anterior sides is 8 cm and the posterior side is inclined upward in 8°. With the animals' heads lower than their bodies the saliva drops fell directly into the collecting flasks, placed in front of the bench (modified from Bernarde et al.[22]). The saliva collected in the flasks was stored at −30 °C until biochemical assays. Quantitative determination of total proteins, amylase, phos-