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Dental deafferentation as an etiologic factor of taste dysfunction in male Wistar rats

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ABSTRACT

Objective: To evaluate the influence of dental deafferentation (DD) on the sense of taste in male Wistar rats using the taste reactivity test (TRT). **Materials and methods:** An experimental study was conducted on ten Wistar rats, following ARRIVE 2.0 guidelines. They were randomized and assigned to a control or experimental group, and both groups' cannulae for the TRT were implanted. In the experimental group, exodontia of the three upper molars on the right side was performed. On the third day, TRT was started (day 1) by infusing 1 M of a sweet substance (ingestive) and 3 mM of a bitter substance (aversive) at a rate of 1 mL in 1 minute. This TRT was repeated on days 7, 14 and 21. Ingestive and aversive responses were scored for 1 minute. The data were processed in the SPSS v. 26 statistical package. The Mann-Whitney U test was used to identify differences, and the magnitude of the difference was calculated using Rosenthal's r. **Results:** Ingestive responses to sucrose were obtained on day 1 ($p > 0.05$); different responses were obtained on the other days: day 7 ($p = 0.05$), day 14 ($p = 0.009$), and day 21 ($p = 0.009$). Likewise, aversive responses to denatonium benzoate (DB) were obtained on days 1, 7, and 21 ($p > 0.05$); this was different on day 14 ($p = 0.05$). **Conclusions:** We found a difference in median ingestive responses to sucrose and aversive responses to DB in male Wistar rats due to DD.

Keywords: tooth extraction, taste perception, cannula, Wistar rats.

INTRODUCTION

Sense of taste is essential for life because, apart from preventing the ingestion of toxic substances, it activates the neural pathways for digestion, absorption, and storage of nutrients. A dysfunction of taste perception can have an impact on the quality of life by affecting appetite, body weight, and psychological well-being (1). As a consequence, a change in the perception of this sense can influence a person's health and the risk of chronic diseases such as obesity (2), atherosclerosis, diabetes, liver diseases, hypertension (3), cancer (4), etc.

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There are several factors that can affect taste perception, such as malnutrition, cancer, chronic hepatitis, renal dysfunction, AIDS, encephalocranial trauma, exposure to toxic chemicals, exposure to industrial agents, medication, aging, oral and perioral infections, Bell's palsy, use of dental prostheses, root canal treatments etc. (5). It has been reported that it can also be caused by exodontia of the mandibular wisdom teeth (6, 7), or as a sequel by the administration of dental anesthesia for the surgical procedure (8, 9). However, taste deficits following exodontia of other teeth (upper molars, incisors, etc.) or root canal treatments cannot be explained by damage to the chorda tympani or glossopharyngeal nerve, as the nerve fibers of these nerves do not innervate or go through the anterior surgical site (10-12).

Dental deafferentation (DD) is defined as the elimination or reduction of peripheral afferent neural inputs related to dental and masticatory apparatuses. Examples of DD include tooth loss, local and/or generalized periodontal loosening, inadequate surgical or prosthetic restorations, orthodontic treatments, root canals, defective mastication, etc. (11, 13).

Humans and animals, such as rats and mice, tend to over-consume high-calorie foods. «Reward» has been subdivided into three interdependent psychological processes: hedonia (liking a food), reinforcement (forming associations between stimuli, actions and/or the food) and motivation (wanting the food) (14). *Wanting* is assessed in animals by means of intake tests, such as total mass or volume consumed during a designated period; however, avoiding the consumption of a solution does not necessarily imply that you do not like it, nor does exacerbated consumption imply greater liking for a substance. Consequently, intake measures alone are interpretatively limited. To correct this problem, Grill and Norgren developed the taste reactivity test (TRT), capable of probing *liking* in the absence of *wanting* (15). Taste reactivity (TR) refers to stereotyped orofacial responses provoked by a taste stimulus in animals, including rodents and human beings. To apply this procedure in animals, intraoral cannulae are surgically placed by which taste stimuli can be directly infused and responses can be videotaped for frame-by-frame analysis. TR can be classified as ingestive, aversive, or ambiguous (16, 17).

The objective of this study was to evaluate the influence of DD on the sense of taste in male Wistar rats using TRT.

MATERIALS AND METHODS

Experimental study that followed ARRIVE 2.0 (Animal Research Reporting of *In Vivo* Experiments) guidelines. It was conducted with ten Wistar rats in good systemic health conditions, which were obtained from the animal care laboratory of the Facultad de Medicina of Universidad Peruana Cayetano Heredia (UPCH). Rats were housed in individual 35 × 23 × 18 cm cages, where they received habitual feeding, consisting of grain diet and proportioned *ad libitum* and unlimited access to water. In addition, during the experiments, they were kept in optimal conditions of a 12-hour day-night cycle, with constant temperature (22°C) and humidity (60-70% RH).

Sample size calculation was performed using OpenEpi software based on a previous research study (18) which established that the mean difference in the number of aversive responses to 0.003% quinine in TRT between the control group, and the glossopharyngeal nerve section group was 8.2 (SD 3.4 and 2.1, respectively). Moreover, by using a power of 90% and a significance level of 5%, we were able to calculate that three rats in each group would be sufficient to reject the null hypothesis. This number was increased to five in each group to compensate for the possible loss of cannulae or death during the experimental phase. Rats were randomized and assigned to one of two groups: control and experimental.

To ensure homogenization of the groups, all research subjects were male, aged 8 to 12 weeks and with a statistically non-significant weight when comparing the control group with the experimental group (Table 1).

Table 1. Weight of the research subjects before starting the study.

	Group	n	Mdn	Q1-Q3	Range	U	p
Weight (g)	Control	5	133	129.5-163	44	8	0.35**
	Experimental	5	126	123-165	52		

Mdn: median: Significance level p < 0.05: * significant; ** not significant.

Implantation of intraoral cannulae for TRT in both groups was done under deep sedation, using a combination of ketamine 40 mg/kg and xylazine 5 mg/kg intraperitoneally. Once the rats did not respond to paw pinch, surgery was initiated using a technique similar to that of Parker (19, 20), but using Clay Adams PE-50 cannulae. To prevent loss or

obstruction of the cannula, the same procedure was followed on the opposite side. At the same time, taking advantage of anesthesia, the experimental group underwent extraction of the three upper molars on the right side. Rats were individually housed in cages immediately after surgery. An injection of the analgesic meloxicam 1 mg/kg and penicillin-streptomycin 0.1 mg/kg subcutaneously was administered. To maintain the permeability of the cannulae, distilled water was infused every three days. For infusion of solutions used in the TRT, a 23G × 1" cut needle was connected to the cannula protruding from the nape, which in turn was adapted to a 30 cm DIS extension and a three-way stopcock with a 50 cm extension. Finally, a 3 cc syringe with the solution to be infused was connected to the three-way stopcock.

On the third day of surgery, TRT started (day 1) in a trapezoidal mirrored cabinet, in which rats from both groups were individually placed and the orofacial and body reactions to the intraoral infusion of two flavoring agents were recorded with a video camera at 60 frames per second: 1 M sucrose (ingestive) and 3 mM denatonium benzoate (DB), which is aversive, at a rate of 1 mL in 1 minute. This TRT was repeated on days 7, 14 and 21. The total number of ingestive and aversive responses during the one-minute infusion period and during the following 30 seconds was recorded.

The ingestive responses considered in this research were as follows: 1) mouth movements: rhythmic low-amplitude openings of the mandible, usually during fluid swallowing; 2) tongue protrusion (medial and lateral): rhythmic protrusions of the tongue in the midline, covering the upper incisors, and non-rhythmic extensions of the tongue, which emerges on both sides of the mouth, resulting in an asymmetrical separation of the lips; 3) forepaw licking: rhythmic high-amplitude extensions of the tongue in the midline directed at the forepaws (Figure 1).

The aversive responses were as follows: 1) triangular mouth openings: wide-openings of the jaw revealing the upper and lower incisors with concomitant retraction of the corners of the mouth; 2) head movement: burst of high-frequency side-to-side head movements; 3) forepaw movement: burst of high-frequency movements of one or both forelimbs; 4) fluid ejection: accumulation of fluid outside the mouth, fluid drips into the TRT cabin (21) (Figure 1).

Finally, for the analysis, the reactions recorded during the last 30 seconds of the infusion phase and during the first 30 seconds of the post-infusion phase were scored. The information obtained was inserted in an MS-Excel spreadsheet. It was then processed in the SPSS version 26 statistical package. Since not all variables had a normal distribution, and there are fewer than 50 data in each group, a nonparametric test (Mann-Withney U) was used to identify differences between two independent samples. Finally, the magnitude of the difference was calculated using Rosenthal's r.

All experiments were approved by the Research Ethics Committee of the Facultad de Medicina of Universidad Nacional Mayor de San Marcos (study code no. 0054-2022).

RESULTS

Results are presented with 95% confidence interval. All the time, the significance level was set at $p \leq 0.05$ (Table 2). In the comparison of the number of responses to TRT between the control and experimental groups on day 1, no statistically significant differences were found in the ingestive and aversive responses to sucrose ($p = 0.18$ and 0.43, respectively). Similarly, no statistically significant differences were found in aversive and ingestive responses to DB ($p = 0.47$ and 0.14, respectively). In all cases, a magnitude of difference (Rosenthal's r) < 0.5 was maintained, which is considered a small effect.

When comparing the number of responses to TRT on day 7, no statistically significant differences were found in aversive responses to DB and sucrose ($p = 0.35$ and 0.16, respectively). In contrast, statistically significant differences were found in the ingestive responses to sucrose, where the scores of the control group (Mdn = 197; Range = 120) were higher than those of the experimental group (Mdn = 95; Range = 81), with $U = 3$, $p = 0.05$, and a magnitude of difference of 0.623, which in Cohen's scale is considered as an intermediate effect. No ingestive responses to DB were obtained.

When evaluating the number of responses to TRT on day 14, statistically significant differences were found in the ingestive responses to sucrose, where the scores of the control group (Mdn = 205; Range = 81) were higher than those of the experimental group (Mdn = 98; Range = 100), with $U = 0$, $p = 0.009$, and a magnitude of difference of 0.83, which on Cohen's scale is considered as a great effect. In the same sense, statistically significant differences were found in the aversive responses to DB, where the scores of the control group (Mdn = 142; Range = 124) were higher than

those of the experimental group (Mdn = 34; Range = 79), with U = 3, p = 0.05, and a magnitude of the difference of 0.63, which on Cohen's scale is considered as an intermediate effect. At the same time, statistically significant differences were found in the aversive responses to sucrose, where the scores of the experimental group (Mdn = 7; Range = 23) were higher than those of the control group (Mdn = 3; Range = 5), with U = 3, p = 0.04, and a magnitude of the difference of 0.65, which on Cohen's scale is considered as an intermediate effect.

Finally, in the comparison of the number of responses to TRT on day 21, no statistically significant differences were found in aversive responses to DB (p = 0.08) or in aversive responses to sucrose (p = 1). Likewise, no ingestive responses to DB were obtained, as it occurred on days 7 and 14. In contrast, statistically significant differences were found in ingestive responses to sucrose, where the scores of the control group (Mdn = 207; Range = 159) were higher than those of the experimental group (Mdn = 85; Range = 68), with U = 0, p = 0.009, and a magnitude of difference of 0.83, which on Cohen's scale is considered as a large effect.

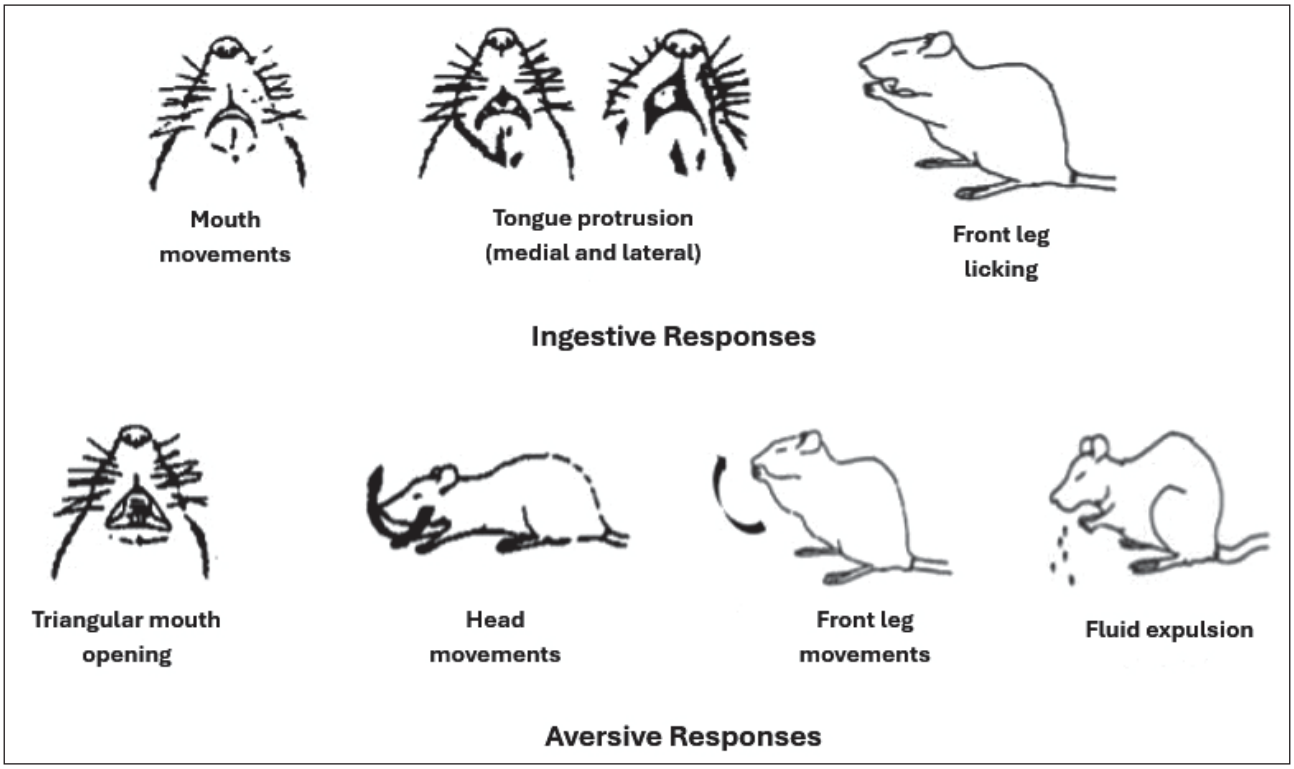

Figure 1. Behavior during the taste reactivity test. Adapted from Grill et al. (18).

Table 2. Comparison of the number of TRT responses.

	Responses	Group	n	Median	Q1-Q3	Range	U	p	Rosenthal's r
Day 1	Ingestive (sucrose)	Control	5	184	98-226	150	6	0.180**	0.42
		Experimental	5	235	145.5-266.5	153			
	Aversive (DB)	Control	5	61	36-179.5	183	9	0.140**	0.23
		Experimental	5	135	84.5-178	136			
	Ingestive (DB)	Control	5	0	0-0	0	7.5	0.470**	0.47
		Experimental	5	0	0-2.5	3			
	Aversive (sucrose)	Control	5	2	0-9	12	9	0.430**	0.25
		Experimental	5	0	0-3	3			
Day 7	Ingestive (sucrose)	Control	5	197	121.5-211.5	120	3	0.050*	0.62
		Experimental	5	95	73-141.5	81			
	Aversive (DB)	Control	5	142	94-251.5	217	8	0.350**	0.30
		Experimental	5	186	172.5-269	107			
	Ingestive (DB)	Control	5	0	0-0	0			
		Experimental	5	0	0-0	0			
	Aversive (sucrose)	Control	5	6	3-12	12	6	0.160**	0.44
		Experimental	5	12	7.5-20	17			
Day 14	Ingestive (sucrose)	Control	5	205	168-221	81	0	0.009*	0.83
		Experimental	5	98	43.5-128.5	100			
	Aversive (DB)	Control	5	142	57.5-158	124	3	0.050*	0.63
		Experimental	5	34	26.5-84	79			
	Ingestive (DB)	Control	5	0	0-0	0			
		Experimental	5	0	0-0	0			
	Aversive (sucrose)	Control	5	3	2-4.5	5	3	0.040*	0.65
		Experimental	5	7	4.5-23.5	23			
Day 21	Ingestive (sucrose)	Control	5	207	139-252	159	0	0.009*	0.83
		Experimental	5	85	70-109	68			
	Aversive (DB)	Control	5	179	103.5-249	204	4	0.08**	0.56
		Experimental	5	90	45-120.5	113			
	Ingestive (DB)	Control	5	0	0-0	0			
		Experimental	5	0	0-0	0			
	Aversive (sucrose)	Control	5	7	4.7-8.5	7	12.5	1.000**	0
		Experimental	5	6	4-12.5	13			

Significance level $p < 0.05$: * significant; ** not significant.

DISCUSSION

Multiple DD studies have been conducted in rodents to reduce their chewing ability by molar extraction (22, 23), root canal treatment (24), soft diet feeding (25, 26), or bite plate placement (27, 28). In this research study, DD was provoked in the study subjects by exodontia of the three upper molars on the right side.

A little-known aspect is that DD affects the sense of taste because trigeminal and gustatory somatosensory inputs converge in the cortex, thalamus, parabrachial nucleus, etc., and anatomical studies have revealed projections from the V pair to the face-lateral region of the nucleus of the solitary tract (NST), the first gustatory relay at the central level, which receives projections from the chorda tympani (CT) nerve of

the facial (29, 30) or glossopharyngeal (GL). In one study, it was determined that responses to flavorings applied to the rat tongue were electrophysiologically registered in NST units while manipulating the lingual and mandibular nerves. The section of either of these nerves resulted in a significant decrease in the taste response; however, it was even greater when the tooth nerve was cut. Therefore, the parameters of the texture properties of food monitored by the teeth that function as force sensors clearly contribute to «taste» signaling (31).

The relationship between DD and cognitive problems such as Alzheimer's dementia, spatial memory impairment, Parkinson's disease, heart disease, osteoporosis, depression and anxiety has been studied (11). However, there are a few studies that analyze the relationship between DD and taste dysfunction without direct injury to the chorda tympani or glossopharyngeal nerve. The study by Boucher et al. (10) is interesting because it correlates taste dysfunctions and DD in humans by electrogustometry (EGM). In this study it was determined that the greater the number of missing teeth, the higher the EGM threshold, regardless of the age of the subject. As it is known, the higher the threshold, the lower the taste sensation. However, taste deficits following other types of DD, such as exodontia of other teeth (upper molars, incisors, etc.) or root canal treatments, cannot be explained by damage to the CT or GL nerve, because the nerve fibers of these nerves do not innervate or go through the anterior surgical site (10, 12).

TRT is mostly used in conditioned taste aversion paradigms (32). However, it is also used in a wide range of experimental situations, including research on taste palatability, satiety, sodium depletion (16), and in studies related to learning and memory using consummatory behavior and classical conditioning (33). In the pioneering research study of Grill and Norgren (34, 35), behaviors that make up the hedonic (ingestive) and aversive pattern in adult rats were thoroughly described. Initially, four orofacial components and five body response components were identified. The hedonic (ingestive) pattern includes rhythmic mouth movements (MM), medial tongue protrusions (MTP) and lateral tongue protrusions (LTP). In contrast, the aversive pattern incorporates triangular mouth openings (TMO), chin rubbing against the floor, rapid head movements (HM), forward foreleg movements (FFM) and washing with both forelegs over the muzzle (WFL). Some later studies have narrowed the pattern of aversive responses to TMO, FFM and FB, and have added front paw licking (FPL) to the hedonic pattern (18). In our research study, MM, tongue protrusion (including MTP and LTP) and WFL were considered as ingestive patterns. The aversive pattern included TMO, HM, FFM and fluid expulsion.

Since the number of aversive responses to sucrose and ingestive responses to DB in the TRT were negligible, only ingestive responses to sucrose and aversive responses to DB were considered in the final analysis. In this study, it was observed that the number of ingestive reactions to sucrose decreased significantly from the first week in the experimental group with respect to the control group, statistically significantly in all cases. In contrast, aversive reactions to DB were variable, increasing in the experimental group in the first week and decreasing in the second and third week when compared to the control group, with statistically significant differences being found on the second week. On the first day of TRT, no statistically significant differences in ingestive responses to sucrose or aversive responses to DB were found because it is presumed that little time passed by to have changes in the sense of taste for DD.

These results cannot be compared with other research studies because, in the literature review, no studies measuring these variables were found, and aversive responses were not measured with DB. However, there are reports of TRT in murines subjected to section of the CT nerve from the VII pair (carries taste information from the anterior 2/3 of the tongue) or GL (carries taste information from the posterior 1/3 of the tongue), which could be considered another form of deafferentation. For example, in the study by Grill and Schwartz (36), when comparing ingestive responses by sucrose infusion at different concentrations in rats with CT and GL nerve section versus the control group, they observed that the ingestive score increased significantly with increasing sucrose concentration in the control group ($F2.6 = 6.3$; $p < 0.05$); in contrast, CT + GL rats showed significantly fewer total ingestive responses than intact rats at each sucrose concentration tested ($F2,6 = 6.7, 5.6, 7.8$; $p < 0.05$). All taste aversion studies that employed TRT were conducted with quinine hydrochloride; however, DB is three thousand times more bitter than quinine.

In the study by King et al. (37), in which rats were exposed to one of three surgical conditions (section of the LG bilaterally, removal of 8-10 mm of the LG bilaterally, and control group in which only LGs

were exposed), TRT was used by infusion of quinine (3 mM) or distilled water at 17, 52, or 94 days after surgery. Scored aversive behaviors included TMO, chin rubbing, HM and FFM. A two-factor analysis of variance indicated significant main effects of stimulus ($F_{(1,65)}$ = 92.55; p < 0.001) and nervous condition ($F_{(6,65)}$ = 7.26; p < 0.001), as well as a significant interaction ($F_{(6,65)}$ = 7.713; p < 0.001). When water was the stimulus, very few aversive behaviors occurred, regardless of the GL condition. In contrast, quinine infusion provoked many aversive behaviors, but only in animals with intact nerves. Among the limitations of the study, we have the lack of homogenization of the sample, a situation that we tried to remedy with the initial weight of the research subjects.

CONCLUSIONS

In this investigation, a difference was found in the medians of ingestive responses to sucrose and aversive responses to DB in male Wistar rats as a consequence of DD, being lower in the experimental group on day 7 (ingestive to sucrose), day 14 (ingestive to sucrose and aversive to DB) and day 21 (ingestive to sucrose), and higher in the experimental group on day 14 (aversive to sucrose). It is suggested to extend this line of research through the evaluation of taste function by means of a histomorphometric study of the goblet papilla in albino rats.

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