Effect of neonatal capsaicin treatment on orthodontic tooth movement in male Sprague-Dawley rats

Julian E. Davila,[a] James R. Miller,[b] James S. Hodges,[c] John P. Beyer,[d] and Brent E. Larson[e]
Indianapolis, Ind, and Minneapolis, Minn

Introduction: In this study, we examined the effect of neonatal administration of capsaicin on the magnitude of orthodontic tooth movement in rats. **Methods:** Twelve timed pregnant Sprague-Dawley rats were randomized between the capsaicin group and the vehicle group. The pups received treatment with either capsaicin or vehicle on day 2 of life. Capsaicin treatment has been shown to produce a selective destruction of fine myelinated and unmyelinated Aδ and C sensory nerve fibers, causing an inhibition of the effects from neurogenic inflammation. Tooth-movement experiments began at 12 weeks of age. A mesial tipping force was applied to the maxillary first molar by using a 3-mm length of Sentalloy closed-coil spring (Dentsply GAC Intl, Bohemia, NY) activated from a bonded molar cleat to the maxillary incisors; this appliance delivers a constant tipping force of 50 g. Diastema measurements between the first and second molars were made at 2 and 4 weeks after appliance placement. Measurements were made indirectly from stone models by using a charge-coupled device microscope camera and Optimas 5.2 measurement software (Media Cybernetics, Bethesda, Md). Two-way repeated-measures analysis of variance (ANOVA) was used to analyze the differences between the groups. **Results:** The capsaicin-treated rats and the controls did not differ in the amount of tooth movement at the collected time points ($P > 0.05$). Similarly, the magnitude of change of tooth movement from 2 to 4 weeks did not differ between the groups ($P > 0.05$). An increase in average diastema size was observed between 2 and 4 weeks after appliance activation in both treatment groups ($P < 0.0001$). **Conclusions:** These results suggest that neonatal capsaicin desensitization in the rat does not affect the rate of orthodontic tooth movement after the application of a 50-g tipping force to the maxillary first molar. This might be due in part to the development of compensatory mechanisms in the chronically desensitized rat. Further studies are necessary to determine the reproducibility and histologic characteristics of this treatment. (Am J Orthod Dentofacial Orthop 2011;139:e345-e352)

Recent experimental studies have suggested that peripheral nerve fibers play a regulatory role in the control and development of local inflammatory reactions observed during orthodontic tooth movement (OTM).[1-5] Calcitonin gene related peptide (CGRP) and substance P are two known multi-potent neuropeptides that contribute to the neurogenic component of inflammation by having multiple vascular, inflammatory, and cellular effects. An increased density of CGRP- and substance P-immunopositive nerve fibers has been observed in the pulp and periodontal tissues of mechanically stressed teeth. This coincides with the vascular and cellular changes observed during OTM.[4-7] Conversely, the deprivation of sensory nerve supply has been shown to attenuate the local inflammatory responses after the application of an orthodontic force.[2,3] Miller et al[8] evaluated the effect of surgical transection of the maxillary nerve on OTM. Although no significant differences were found in the amount of tooth movement after the application of an orthodontic force, the denervated group had a smaller increase in the magnitude of tooth movement compared with the controls. Duan et al[9] showed that denervation of dental tissues reduces the amount of bone formation. Collectively, these studies have suggested that neurogenic

[a]Private practice, Indianapolis, Ind.
[b]Assistant professor, Division of Orthodontics, University of Minnesota, Minneapolis.
[c]Senior research associate, Division of Biostatistics, University of Minnesota, Minneapolis.
[d]Associate clinical specialist, Division of Orthodontics, University of Minnesota, Minneapolis.
[e]Program director, Division of Orthodontics, University of Minnesota, Minneapolis.
The authors report no commercial, proprietary, or financial interest in the products or companies described in this article.
Reprint requests to: Julian E. Davila, 8140 Oaklandon Rd, Indianapolis, IN 46236; e-mail, jdavila98@yahoo.com.
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mechanisms might have a significant effect in the cellular processes that mediate tooth movement.

Chemical denervation with capsaicin treatment is a suitable method for analyzing the efferent actions of sensory nerves.[10-13] Capsaicin has been extensively used as a tool in sensory neuron biology.[14] Its neurotoxic actions, when applied systemically in high doses to neonatal rats, have been well documented. Studies by Jancsó et al[15-18] have demonstrated that the administration of capsaicin to newborn rats results in the selective degeneration of B-type primary sensory dorsal root ganglion cells, giving rise to unmyelinated (Aδ and C) and myelinated fibers of small diameter. This produces depletion of neuropeptides from the central and peripheral parts of primary sensory neurons, causing inhibition of the effects from neurogenic inflammation.[13,19] The capsaicin receptor, transient receptor potential vanilloid 1 (TRPV1), is a well-characterized cation channel expressed predominantly in unmyelinated sensory C fibers and activated by various noxious stimuli.[20] TRPV1 is activated not only by capsaicin but also by protons or heat (with a threshold of approximately $>43°C$), both of which cause pain in vivo.[20,21] Systemic administration of capsaicin to neonatal mice has been documented as a well-established method to ablate TRPV1-expressing sensory neurons.[15] More recent studies have shown a relationship between TRPV1 receptors and inflammatory mediators released from the cyclooxygenase pathway, such as prostaglandin E_2 (PGE_2) and prostaglandin I_2 (PGI_2). Moriyama et al[22] found that, in the presence of PGE_2 and PGI_2, the temperature threshold for TRPV1 activation was reduced below 35°C, so that temperatures near body temperature were sufficient to activate TRPV1. In addition, an increase in the potentiation or sensitization of TRPV1 activity was observed through PGE_2 and PGI_2 receptor activation, leading to thermal hyperalgesia and inflammatory nociceptive responses.[22,23] These studies further document the potential role of vanilloid capsaicin receptors in the inflammatory response.

The purpose of this study was to evaluate the effect of capsaicin-induced sensory denervation on the rate of OTM in Sprague-Dawley rats. These results would be of clinical importance, especially in patients when combined orthodontic and extensive surgical treatment is planned and sensory innervation is severed. Sensory nerve damage and paresthesia have been common findings in patients undergoing Lefort[24] and mandibular ramus surgical procedures.[25] If capsaicin-induced sensory denervation is shown to inhibit the rate of OTM, this would not only open a new avenue of research, but also suggest that special considerations should be taken in the orthodontic treatment of our orthognathic surgical patients who have been deprived of their sensory innervation.

In this study, we attempted to answer the question: "Will teeth under a constant orthodontic force move at the same rate if their sensory input is compromised by capsaicin desensitization at a neonatal age?"

MATERIAL AND METHODS

The animals used in this study were 12-week-old (weight, 350 ± 25 g) male Sprague-Dawley rats raised and treated as described below in the animal facilities at the University of Minnesota. The animals were housed in accordance with National Institutes of Health guidelines and kept in a vivarium maintained at 22°C with a 12-hour alternating light and dark cycle. They were fed powdered rodent chow and water ad libitum throughout the study. All procedures were approved by the Animal Care and Use Committees at the University of Minnesota.

Twelve timed pregnant Sprague-Dawley rats were housed individually until delivery. Six pregnant rats were randomly assigned to the capsaicin group, and the remaining six rats were assigned to the vehicle group. One hundred fifty-six pups were obtained from the twelve pregnant rats. The average litter size was 13 pups. Six litters were assigned to the capsaicin group (75 pups), and the remaining six litters were assigned to the control group (81 pups). Average weight at day 2 after birth was 7.4 g.

Pups from the mothers assigned to the capsaicin group were injected with capsaicin (50 mg/kg, 5 μL/g; Sigma, St. Louis, Mo) on the second day of life, according to the protocol of Jancsó and Király.[15] Capsaicin (1%) was dissolved in a mixture of 10% ethanol and 10% Tween 80 (Sigma Ultra) in 0.9% sodium chloride. The pups were injected subcutaneously in the dorsal thoracic region by pinching the skin on the back and inserting a 30-gauge needle on a 1-mL syringe. The pups in the control group received subcutaneous injections of the vehicle without capsaicin at day 2 after birth. The pups were returned to their respective mothers after treatment to ensure nurturing. The animals were weaned and sex differentiated at 28 days of age.

At weaning, 61 rats (81%) survived in the capsaicin group, and 77 rats (95%) survived in the control group. Only male rats were included in our study, since a previous study indicated that OTM varies depending on the phase of the estrous cycle in female rats.[26] Specifically, cyclic changes in the estradiol level have been found to be associated with the estrous-cycle-dependent variations in tooth movement through its effects in bone resorption. A total of 73 male animals who survived

the treatments were used in our study: 35 rats from the capsaicin group and 38 from the control group.

The animals' responsiveness to noxious chemical stimuli was determined at 6 weeks of age by using the standard eye-wipe test, a method described by Szolcsány and Jancsó.[27] A cotton-tipped applicator saturated with a solution of 0.01% (w/v) capsaicin was applied to the cornea in one eye, and the number of wiping motions that occurred in the subsequent 30 seconds was counted. This method has proved to be highly reliable in determining the effectiveness of capsaicin desensitization.[13,27] In normal animals, this treatment induces a brief period of scratching or redness. The lack of a wiping response or casual wiping indicates desensitization.

General anesthesia for the placement of the orthodontic appliances was induced with the administration of 50 mg per kilogram of ketamine hydrochloride and 10 mg per kilogram of xylazine hydrochloride injected as one bolus dose intraperitoneally. If anesthesia was not effective within 15 minutes, a second injection of 150 μL of nembutal was given intraperitoneally. This gave adequate anesthesia for approximately 30 to 45 minutes. The rats were weighed before each anesthesia event to monitor their ability to thrive during this experiment.

The rat model used in this study was modified from a model described initially by King et al.[28] This model was used in a recent experimental study by Miller et al,[8] with a detailed description of the method for the orthodontic appliance used in this study. A schematic representation of the orthodontic appliance is shown in Figure 1.

Tooth movement measurements were taken at 2 and 4 weeks after appliance placement. The rats were anesthetized in a manner similar to that described by Miller et al.[8] Impressions of the diastema distal to the maxillary first molar were taken with Vinyl Polysiloxane Imprint II wash material low viscosity and Garant mixing tips (both, 3M ESPE, St Paul, Minn) with intraoral injectable attachment tips. This material was allowed to set for 4 minutes before removing it from the mouth. Impressions were stored for 1 day in a temperate room before pouring with stone. According to the manufacturer's specifications, no appreciable expansion or contraction will be observed with these storage times or conditions. The stone used to pour the impressions was Fujirock II (GC America Inc, Alsip, Ill). The stone was allowed to sit for 24 hours before separation from the impression material.

In preparation for the measurement procedures, the stone models were randomized and assigned code numbers. All measurements were done by one examiner (J.D.) who was blinded to the experimental conditions. A Navitar macro zoom 18-108 lens (Navitar Inc, Rochester, NY) attached to an MTI 3 charge-coupled device camera (DAGE-MTI Inc, Michigan City, Ind) was used to measure

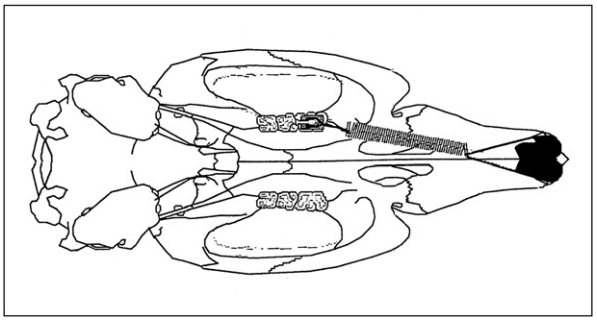

Fig 1. Schematic representation of the orthodontic appliance.

the diastemas. A laminated millimeter ruler was digitized at a constant focal length for calibration purposes. Diastemas were measured indirectly from acquired images of the stone models with the camera and Optimas 5.2 measurement software (Media Cybernetics, St. Louis, Mo). A measurement tool in the software program allowed us to calculate linear distances on the stone models from the calibrated ruler algorithm. Pilot experiments showed that this technique provided reproducible and accurate measurements.

Statistical analysis

Data from the eye-wipe test were expressed as mean ± standard error of the mean. The mean nociceptive thresholds were compared between groups by using a mixed-effects analysis of variance (ANOVA) in which the groups were a fixed effect, litters in the groups were a random effect, and rats in the litters were a second random effect. The means and standard errors of body weight were similarly calculated at baseline and on days 14 and 28. Differences in body weight between groups and time points were analyzed by using mixed-effects ANOVA with rats as the random effect. The diastema measurements were collected in triplicate from the stone models with the camera and the software program. The averages of the 3 measurements were calculated for each rat at both 14 and 28 days. Repeated measures ANOVA was used to analyze the differences between groups. The analysis was a mixed linear model with rats as the random effect and included these fixed effects: treatment group, time, and their interaction. The analyses were done with a statistical software package (version 8.2, SAS, Cary, NC) by using the mixed procedure and the restricted-likelihood method.

RESULTS

Ophthalmic administration of capsaicin evoked a characteristic wiping response in the vehicle-treated

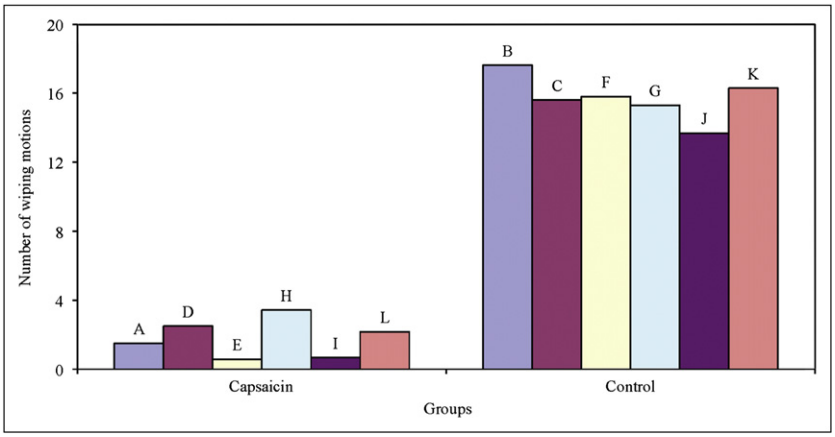

Fig 2. Comparisons of the number of wiping responses among litters in the treatment groups.

rats at 6 weeks of age. Although ophthalmic instillation of capsaicin in the capsaicin-treated rats also evoked a wiping response, the number of wipes (1.8 wipes on average) was significantly less than in the corresponding vehicle-treated rats (15.7 wipes on average) of the same age ($P < 0.0001$) (Fig 2).

Seventy-three animals started the tooth movement experiment at 12 weeks of age. Of these, 6 animals (2 capsaicin-treated and 4 vehicle-treated rats) had debonded appliances 2 weeks after their placement. These animals were excluded from the analysis. One additional animal from the capsaicin group had a debonded appliance on day 28; therefore, 28-day measurements were not taken for this animal. The major reason for bond failure was the debonding of the molar cleat from the occlusal surface of the molar at the enamel-resin interface. A total of 66 animals (90%) had intact appliances on day 28: 32 from the capsaicin group and 34 from the control group.

Sixty-six animals completed this study. Analysis of weight data indicated that the rats lost on average 7.8 g (2.2% decrease) in the first 2 weeks after appliance placement and gained 21.3 g in the subsequent 2 weeks. Averaging over the 2 groups, the differences in weight were significantly different among the 3 measurement times (time main effect, $P < 0.0001$). Weight gain differences between the treatment groups were not significant (group main effect, $P = 0.16$). In addition, no significant difference in body weight change was found between the 2 treatment groups during the experiment (group-by-time interaction, $P = 0.41$) (Fig 3). The initial reduction in body weight could be associated with the discomfort that the animals experienced as a result of initial appliance activation. However, a significant increase in body weight was observed at day 28; this was consistent with the biocompatibility of the appliance system and the ability of the animals to thrive.

No measurements were made at the time of appliance placement; it was assumed that all first and second molars in rats start with no diastema. Analysis of diastema size indicated that, averaged over the collected time points (2 and 4 weeks), the treatment groups did not significantly differ from one another in diastema size (group main effect, $P = 0.90$). Averaged over the treatment groups, the diastema increased significantly between the 2- and 4-week measurements (time main effect, $P < 0.0001$) by a factor of 3.8 on average (Table I). In addition, the magnitude of change from 2 to 4 weeks did not depend on the treatment groups (group-by-time interaction, $P = 0.97$) (Fig 4). The results of the mixed-effects ANOVA with diastema size as the dependent variable are given in Table II.

DISCUSSION

The eye-wipe test was used at 6 weeks of age to determine the animals' responsiveness to noxious chemical stimuli. It was observed that the capsaicin-treated rats responded significantly less (2 wipes/30 seconds) than the vehicle-treated rats (16 wipes/30 seconds). These results were similar to those reported by Hammond and Ruda.[13] All six litters in the capsaicin-treated group demonstrated a consistent inhibited response to ophthalmic administration of capsaicin. In the vehicle-treated group, all six litters demonstrated a consistent heightened response to ophthalmic administration of capsaicin, thus corroborating the effectiveness of the eye-wipe test in determining uniform desensitization. These findings correlate with the general loss of sensory neurons originating from the dorsal horn of the spinal cord, which, according to Hammond and Ruda, can be observed as early as 10 days of age in neonatally treated rats. It was assumed that this systemic response indicates

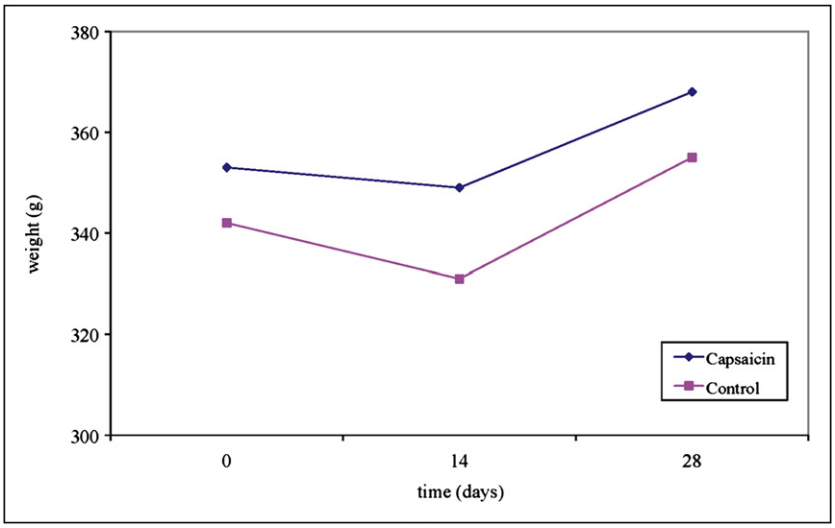

Fig 3. Changes in body weight during the experiment.

neuronal desensitization in local peripheral tissues such as the dental pulp and periodontium.

Another observation in the capsaicin-treated rats was the development of spontaneous cutaneous lesions, characterized previously by Maggi et al.[29] These skin lesions in the form of wounds, scabs, and areas of alopecia were identified in 82% of the rats desensitized to capsaicin, beginning at 4 weeks of age in a mild expression. The spontaneous skin lesions were almost entirely restricted to the head; the areas most frequently affected were the snouts and the periocular and retroauricular regions. No spontaneous cutaneous lesions were seen in the vehicle-treated rats. It has been reported that capsaicin-sensitive nerves play a trophic role in maintaining tissue integrity in the rat skin and contribute to its ability to react and repair in response to injuries.[29] It is probable that normal injurious factors (such as grooming) induce a repeated mechanical microtrauma that, by acting on the dystrophic skin, generates the spontaneous lesions observed in rats desensitized to capsaicin. The cutaneous lesions in the capsaicin-treated rats increased in number and severity by week 7 of life. At this stage, the Department of Research Animal Resources at the University of Minnesota recommended treating the rats with trimethoprim-sulfamethoxazole (SMZ-TMP, bactrim pediatric suspension) added to their drinking water. This antibiotic regimen was administered to 29 rats (82%) from the capsaicin group, all that showed moderate to severe cutaneous lesions in the head. Antibiotic treatment was continued for 15 days. The 2-week antibiotic regimen and increasing the amount of environmental enrichment in the animal cages reduced the severity of the cutaneous lesions. The Department of Research Animal Resources recommended discontinuing the antibiotic treatment at week 9 of life and monitoring the healing of the facial lesions. By week 12, most lesions were completely resolved, and experimental OTM began. SMZ-TMP is a sulfonamide derivative antibiotic that has a broad spectrum of activity. Given orally, it is rapidly and extensively absorbed, and widely distributed. Serum half-life is 9 hours with SMZ, and 6 to 17 hours with TMP. There have been no reports in the dental literature of direct effects or complications of this drug in the paradental tissues or bone remodeling. Therefore, it was assumed that administration of this drug to the capsaicin-treated rats should have no effects on the experimental OTM.

Table I. Comparisons of tooth movement (mm) in the groups

	Time points	
Group	*Week 2*	*Week 4*
Capsaicin	0.230 ± 0.062	0.874 ± 0.063
Control	0.221 ± 0.061	0.862 ± 0.061

Data are expressed as mean ± SEM.
The groups did not differ at either time ($P = 0.99$ at 2 weeks, $P = 0.89$ at 4 weeks, testing contrasts in ANOVA's group-by-time interaction) or averaged over times ($P = 0.93$ for the main group effect).

The results of this study suggest that sensory denervation induced by neonatal capsaicin did not affect the rate of OTM. The amount of tooth movement did not differ between the capsaicin-treated rats and

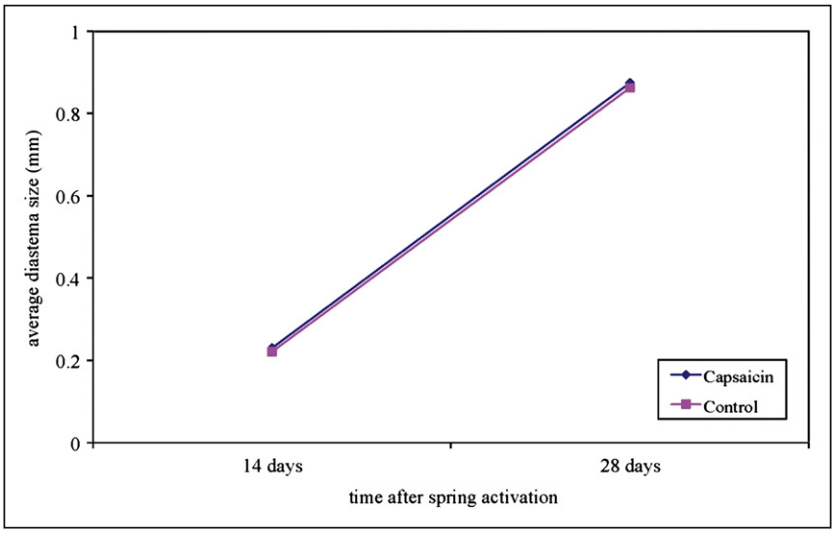

Fig 4. Average diastema size after 14 and 28 days of appliance activation.

Table II. Results of mixed-effects ANOVA for treatment group, time, and their interactions with diastema size as the dependent variable

Effect	*Num DF*	*Den DF*	*F statistic*	P *value*
Treatment group	1	10	0.02	0.8961
Time	1	64	199.32	<0.0001
Group*time	1	64	0.00	0.9683

No differences were found between the 2 treatment groups (group main effect, $P = 0.8961$).
Diastema size increased significantly between the 2 time points (time main effect, $P < 0.0001$).
The difference between times does not depend on the groups (group-by-time interaction, $P = 0.9683$).
Num DF, degrees of freedom of the numerator; *Den DF*, degrees of freedom of the denominator.

vehicle-treated rats at either 14 or 28 days. Thus, these findings do not directly support previously suggested roles of peptidergic nerve fibers in the modulation of local inflammatory responses and bone remodeling during the application of orthodontic force. It is apparent that other factors must be considered to reconcile our data with previous reports.

There are other considerations. Previous studies have suggested that failure of the sensory pathway induced at birth by capsaicin treatment could be partly compensated for, over time, by adaptive mechanisms.[10,11] Neonatal capsaicin treatment induces a chronic state of sensory denervation, and compensatory mechanisms might develop to reduce any effects on bone metabolism. Postjunctional receptor supersensitivity and activation of alternative sources of peptides are some examples of these adaptive mechanisms.[10] The thyroid has been shown to become a major source of CGRP in old rats.[30] Such an alternative source of circulating peptides in denervated rats might produce partial compensation for the loss of CGRP-containing nerve fibers. Thus, bone remodeling processes involved in tooth movement might not be affected significantly in capsaicin-treated rats because of the development of compensatory mechanisms.

Additionally, the sympathetic nervous system has been shown to play an important role in blood vessel regulation and the focal metabolism of bone. Data from surgical denervation studies should be interpreted carefully, since major sensory nerves also carry sympathetic fibers; therefore, such denervation might not have affected only sensory nerves but also sympathetic branches. There might also be an important interaction between these two systems that contributes to the regulation of bone remodeling processes.[10,31]

Although it has been demonstrated that capsaicin-induced sensory denervation in rats causes a reduction in local bone remodeling, the effects observed can be considered to be not dramatic. Hill et al[10] reported a 21% reduction in bone resorption when rats treated with capsaicin at birth were subjected to a wave of synchronized resorption in adulthood. Sensory denervation

did not prevent the entire response as might have been expected if neural influences were the dominant regulating factors in local bone remodeling. In comparison, another study with a similar experimental model showed a dramatic decrease (92%) in bone surface that was occupied by osteoclasts in rats pretreated with an inhibitor of prostaglandin synthesis.[32] Prostaglandins are known regulators of the inflammatory response, produced locally from arachidonic acid catabolism. It is probable that even after the induction of sensory denervation, there is enough redundancy in the cascade of events leading to inflammation so that other mechanisms that mediate tooth movement take precedence.

Neonatal capsaicin-induced sensory denervation did not produce a significant effect on the rate of OTM in rats after the application of a 50-g tipping force to the maxillary first molar. This finding can be explained by enough redundancy in the cascade of events leading to the inflammatory response so that other mechanisms take precedence or by the development of compensatory mechanisms in chronically desensitized rats.

Our study did not include immunohistochemical analysis of the paradental tissues. Further studies that include immunohistochemistry for substance P and CGRP or assessment of TRPV1 receptor activity are necessary to evaluate the reproducibility and histologic characteristics of this treatment, and to elucidate the precise mechanisms involved in the cellular responses that mediate OTM.

CONCLUSIONS

1. Neonatal capsaicin desensitization in male Sprague-Dawley rats did not affect the rate of OTM after the application of a 50-g tipping force to the maxillary first molar.
2. An increase in average diastema size was observed from 2 to 4 weeks after appliance activation in both treatment groups. No significant difference was found in the magnitude of change of tooth movement from 2 to 4 weeks between the two treatment groups.
3. Ophthalmic administration of capsaicin evoked a characteristic wiping response in vehicle-treated rats at 6 weeks of age. This response to chemical noxious stimuli was significantly less in the capsaicin-treated animals, confirming the uniform sensory desensitization in the capsaicin-treated group.

OTM appears to be unaffected when sensory innervation to the teeth and their paradental structures is compromised. According to this study, orthognathic surgical procedures and tooth devitalization procedures should not affect the timely movement of teeth through alveolar bone.

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