Pathognomonic Hypersensitivity of the Oral Mucosa and Tongue Induced by Diabetes Mellitus Accompanied by Saliva Reduction in Rats

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Aims: To clarify the mechanisms of hypersensitivity and spontaneous pain in intraoral structures in rats with diabetes mellitus (DM) accompanied by reduced saliva. **Methods:** Adult male Sprague-Dawley rats received a single injection of streptozocin (50 mg/kg) to induce DM. Saliva volume, intraoral hypersensitivity to menthol and capsaicin solutions, and head-withdrawal thresholds (HWTs) to noxious heat and mechanical stimulation of the tongue and whisker pad were measured. **Results:** On day 7 after streptozocin injection, rats with DM had a significantly reduced spontaneous saliva volume, polydipsia, capsaicin aversion of the intraoral mucosa, and a reduced HWT to noxious mechanical stimulation of the whisker pad skin. The HWT to noxious mechanical stimulation of the tongue reduced further on day 14 after streptozocin injection. These symptoms are similar to the orofacial and intraoral complaints of patients with DM. Meanwhile, reduction of HWT to noxious heat stimulation of the tongue and whisker pad were not observed. These results indicate that spontaneous intraoral mucosal pain and mechanical facial hypersensitivity are antecedent symptoms before mechanical hypersensitivity of the tongue. **Conclusion:** The mechanisms of saliva reduction, spontaneous intraoral mucosa pain, and mechanical hypersensitivity of intraoral and facial structures induced by DM involve both peripheral and autonomic neuropathies. Tongue hypersensitivity to noxious mechanical stimulation might be aggravated by xerostomia. *J Oral Facial Pain Headache 2021;35:54–61. doi: 10.11607/ofph.2790*

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Diabetes mellitus (DM) is an endocrine disease characterized by a deficit in the production of insulin with consequent alterations in the assimilation, metabolism, and balance of blood glucose concentration.[1] Symptoms of DM commonly include hyperglycemia, polyuria, polydipsia, weight loss, fatigue, and delayed wound healing. DM has three major microvascular complications: retinopathy, nephropathy, and neuropathy.[2] Patients with diabetic peripheral neuropathy experience abnormal sensations such as paresthesia, allodynia, hyperalgesia, and spontaneous pain.[3] Neuropathic pain in patients with DM typically includes mechanical, thermal, and chemical hyperalgesia.[4] Approximately 5% of all patients who visit dental clinics have DM.[5] Oral complaints related to DM include dry mouth, tooth decay, periodontal disease, oral candidiasis, a burning sensation in the mouth, and salivary dysfunction.[6] Orofacial pain (eg, oral sores, toothache pain) is more severe in patients with DM compared to nondiabetic patients.[7] Patients with DM experience a burning sensation in the tongue,[8] which could be due to a higher degree of irritation in the lingual mucosa.[9]

However, the role of diabetic neuropathy in spontaneous pain and the hypersensitivity of intraoral structures is yet to be clearly understood. Peripheral neuropathy causes pain, whereas autonomic neuropathy may impair salivary flow rate.[10] In patients with type 1 DM, neuropathy and dry mouth are associated with decreased salivary flow rates.[11] There are also reports of a higher prevalence of xerostomia (ie, the subjective sensation of dry mouth), lower salivary flow rate,[1] and hypersensitivity of the tongue in patients with DM.[8] In animal studies, dry-tongue model

rats demonstrated mechanical hypersensitivity of the tongue and sensitization of neurons in the trigeminal ganglion and the trigeminal spinal subnucleus caudalis.[12,13] Preclinical studies using animal DM models have been crucial to understanding the intraoral sensory changes in patients with DM, with streptozocin (STZ) being the most commonly used agent to induce type 1 DM. Diabetic neuropathic pain in STZ-DM rodents manifests as mechanical allodynia and thermal hypersensitivity.[14] However, only a few studies have demonstrated facial hypersensitivity in DM rodents.[15–18]

Furthermore, no animal study has investigated the changes in intraoral sensation and saliva secretion in DM. Thus, this study aimed to investigate the mechanisms and manifestations of spontaneous pain and hypersensitivity of intraoral structures, as well as saliva flow, using STZ-DM rat models.

Materials and Methods

Animals

All animal experimental protocols were approved by the Animal Experimentation Committee at Nihon University (AP17D015) and were performed according to the guidelines of the International Association for the Study of Pain (PHS Law 99-158, revised 2002) and the Guide for the Care and Use of Laboratory Animals (eighth edition, National Research Council of the National Academies).

All efforts were made to minimize the number of animals used for the experiments. A total of 58 adult male Sprague-Dawley rats (sham: n = 27; DM: n = 26; exclusion: n = 3) weighing 250 to 350 g (8 to 10 weeks old) were used (Japan SLC, Hamamatsu, Japan). Twenty-nine rats were used to evaluate solution intake: 10 rats for distilled water (DW), 9 rats for menthol solution, and 10 rats for capsaicin solution. Twelve rats were used for evaluation of tongue sensitivity, and 12 rats were used for evaluation of whisker pad sensitivity. Saliva volume was measured in the same 12 rats used for measurement of whisker pad sensitivity.

Up to three rats per cage were housed in the same model type with free access to food and water, and the cages were placed in a climate- and light-controlled environment (12-hour light:dark cycle, lights on/off at 7:00/19:00, 23°C, 40% to 60% humidity) for at least 5 days before the experiments. All experimental procedures were conducted from 9:00 to 17:00.

DM type 1 was induced via an intraperitoneal injection of STZ (50 mg/kg, Tocris Bioscience) dissolved in saline.[19] Control (sham) animals were injected with saline. STZ and saline were injected under 3% isoflurane anesthesia. Seven days after STZ injection, blood samples were obtained from the tail vein, and DM was determined using a glucometer. Blood glucose levels were determined after a 12-hour fast, and > 300 mg/dL was considered DM.[19] Five rats whose blood glucose level did not exceed 300 mg/dL on day 7 after STZ injection were excluded from the experiments. All experiments were performed at baseline (the day immediately before STZ administration) and on days 7 and 14 after STZ or saline administration (Fig 1a). The investigators were blinded to all behavioral experiments.

Saliva Volume Analysis

The rats were habituated in a dim plastic tube (diameter: 7.0 cm, length: 15.0 cm) without restraint for 10 minutes daily for 7 days in advance. At the front of the tube, a small trapezial hole (height: 3.5 cm, top width: 2.0 cm, bottom width: 1.0 cm) was made to allow spontaneous protrusion of the perioral region. Rats were deprived of water for 12 hours before saliva volume measurement and habituated in the dim plastic tube for 5 to 10 minutes without any anesthetics or restraint. Then, their mandibular incisors were gently pulled down to open the mouth. Phenol red thread (Zone-Quick, AYUMI Pharmaceutical) was placed at the floor of their oral cavity under the tongue, and then the wet length of the thread was measured for 30 seconds. The thread, except for the tip, was covered by a polyethylene tube (SP45, Natsume Seisakusho; ID: 0.58 mm, OD: 0.96 mm, length: 3.0 cm) to avoid contact with the mucosa and lower lip. The mean value of three measurements, taken at intervals of 1 to 3 minutes, was determined.

Analysis of Water, Menthol Solution, and Capsaicin Solution Intake

After 12 hours of water deprivation, rats were habituated in a Plexiglas chamber (40 [width] × 24 [length] × 20 [height] cm^3) for 30 minutes and were allowed to move freely in the chamber during the test session. A plastic dish (diameter: 3.5 cm, height: 1.0 cm) was set at the corner of the chamber, and the duration of intake of DW, menthol (transient receptor potential melastatin 8 [TRPM8] agonist) solution, or capsaicin (transient receptor potential vanilloid 1 [TRPV1] agonist) solution in the plastic dish was measured for 20 minutes from the first intake. Each rat was included in one solution test (DW, menthol, or capsaicin) on day 0 (pre-value before STZ or saline injection: baseline) and days 7 and 14 after STZ or saline injection. The 10.0 μM menthol (ChromaDex) solutions were prepared from a stock solution of 10.0 mM menthol in 6.25% ethanol and 6.56% polysorbate 80 (TWEEN 80, Sigma-Aldrich) by diluting with DW. The 1.0 μM capsaicin (Wako Chemicals) solutions were prepared from a stock solution of 10.0 mM capsaicin

in 50% ethanol by diluting with DW. The duration of DW, menthol, or capsaicin solution intake was measured before STZ or saline injection, with the baseline duration for each solution set at 100%. The duration of the intake of each solution on days 7 and 14 after injection was represented as relative values (%) vs the baseline duration. There were no differences in the duration of drinking among the 10.0 μM menthol, 1.0 μM capsaicin, and DW groups in naïve rats in the preliminary drinking test (data not shown).

Analysis of HWRTs to Heat and Mechanical Stimulation of the Tongue

The procedures in the present study were the same as those previously described by Katagiri et al.[20] Briefly, the head-withdrawal reflex threshold (HWRT) to heat and mechanical stimulation of the left edge of the tongue (3 mm posterior to the tip of the tongue) was measured three times at 5-minute intervals under light anesthesia (0.5% to 2.0% isoflurane). The tongue was gently pulled out from the intraoral space by silicon-covered forceps without noxious stimulation, and the position was maintained during each procedure. The heart rate during isoflurane anesthesia was monitored to maintain consistency in each rat. The mean value of the HWRT measurements was calculated. The increase in velocity of the heat stimulus from a contact thermal probe (3 × 3 mm^2, Intercross) was automatically controlled from 35°C to threshold values (at a rate of 1°C /second). A cutoff value of 50°C was established to prevent tissue damage. The velocity of the mechanical stimulus using flat-tip forceps (2 × 2 mm^2, PanLab) was manually controlled consecutively from 0 g to threshold values (cutoff: 55 g) at a speed of 10 g/second.

Analysis of HWL to Heat Stimulation and HWT to Mechanical Stimulation of the Whisker Pad

Rats were trained to be habituated in a dim plastic tube without restraint following the same protocol as for saliva volume measurements. The whisker pad skin, excluding the orbital region to avoid visual recognition of the stimuli, was allowed to protrude from the small trapezial hole of the tube. After 5- to 10-minute habituation, head-withdrawal latencies (HWLs) and head-withdrawal thresholds (HWTs) to heat and mechanical stimulation, respectively, of the left whisker pad skin were measured. Rats were free to escape from the stimuli.

Heat sensitivity of the whisker pad skin was assessed using a radiant heat stimulator (Intercross 2000, Intercross). The radiant heat probe was placed 3 mm away from the whisker pad skin, and the HWL to radiant heat stimulation was manually recorded with a chronometer. A cutoff of 15 seconds was established to prevent tissue damage. Radiant heat stimuli were applied three times at 5-minute intervals, and the mean value of the HWL was determined.

Mechanical sensitivity of the whisker pad skin was assessed using von Frey filaments (15, 25, 35, 45, 55, and 60 g). The HWT to mechanical stimulation of the whisker pad skin was defined as the minimum pressure needed to evoke an escape more than three times to five stimuli. A cutoff of 60 g was established to prevent tissue damage. Different procedures were used to measure the noxious reflexes between the tongue and whisker pad because of anatomical and functional differences.

Statistical Analysis

Statistical analyses were performed using Mann-Whitney U test and compared between the sham and DM groups at baseline and on days 7 and 14 after STZ injection (Prism version 7.02, GraphPad Software). The data are expressed as mean ± standard error of the mean (SEM). The significance level was set at $P < .05$.

Results

Blood Glucose Level, Body Weight, and Saliva Volume

Blood glucose levels significantly increased on days 7 and 14 after STZ injection compared to sham rats (Fig 1b; sham [n = 4]: baseline = 75.25 ± 2.32, day 7 = 101.00 ± 9.30, day 14 = 76.75 ± 2.98; DM [n = 8]: baseline = 73.63 ± 2.60 [$P = .5434$], day 7 = 344.50 ± 22.92 [$P = .0040$], day 14 = 320.50 ± 32.58 [$P = .0040$]).

There was a significant loss in body weight in STZ-DM rats compared to sham rats on days 7 and 14 (Fig 1c; sham [n = 7]: baseline = 281.20 ± 5.20, day 7 = 326.14 ± 4.50, day 14 = 351.86 ± 9.85; DM [n = 8]: baseline = 288.63 ± 2.82 [$P = .0873$], day 7 = 290.88 ± 6.55 [$P = .0056$], day 14 = 283.13 ± 6.81 [$P = .0006$]).

A significant reduction in spontaneous saliva volume in DM rats compared to sham rats on days 7 and 14 after STZ injection was also observed (Fig 1d; sham [n = 4]: baseline = 20.33 ± 3.94, day 7 = 23.75 ± 6.84, day 14 = 25.33 ± 3.83; DM [n = 8]: baseline = 17.69 ± 1.77 [$P = .6828$], day 7 = 5.09 ± 2.68 [$P = .0263$], day 14 = 3.21 ± 1.98 [$P = .0061$]). These symptoms are consistent with those of DM in humans.[1]

Duration of Distilled Water, Menthol, and Capsaicin Solution Intake

The ratio of duration of DW intake for 20 minutes compared to the baseline duration was significantly higher in DM rats than in sham rats (Fig 2a; sham [n = 6]: baseline = 100.00 ± 0.00, day 7 = 106.41 ± 5.72,

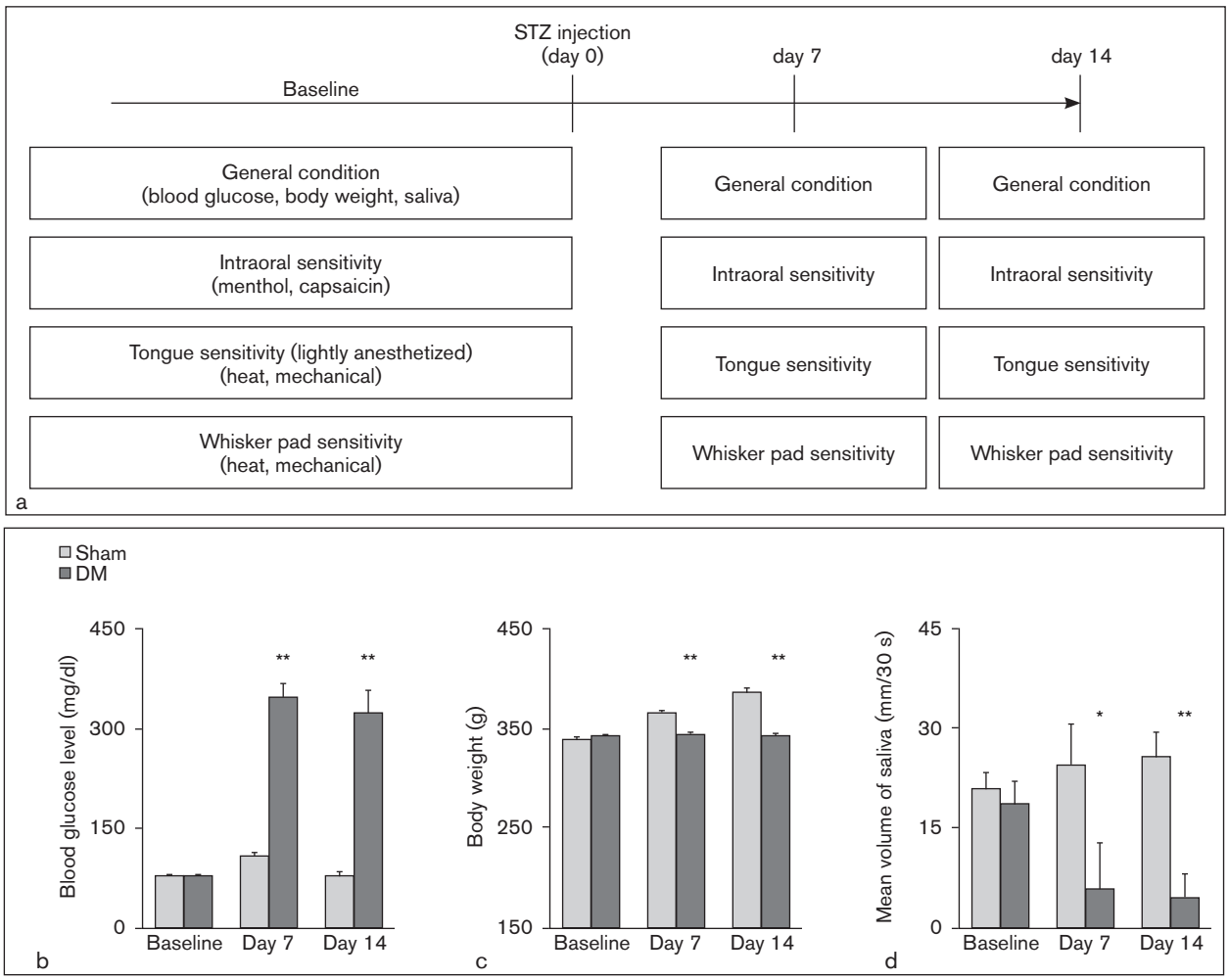

Fig 1 **(a)** Experimental design. **(b)** Mean blood glucose levels, **(c)** body weight, and **(d)** saliva volume over the course of the study. *P < .05, **P < .01 for sham vs diabetes mellitus (DM) rats.

day 14 = 105.48 ± 10.07; DM [n = 4]: baseline = 100.00 ± 0.00 [P > .9999], day 7 = 254.35 ± 55.69 [P = .0095], day 14 = 221.24 ± 36.90 [P = .0190]).

The ratio of the duration of menthol (TRPM8 agonist) solution intake compared to the baseline duration was also significantly higher in DM rats than in sham rats on days 7 and 14 (Fig 2b; sham [n = 5]: baseline = 100.00 ± 0.00, day 7 = 105.73 ± 9.98, day 14 = 102.86 ± 4.99; DM [n = 4]: baseline = 100.00 ± 0.00 [P > .9999], day 7 = 253.46 ± 35.61 [P = .0159], day 14 = 218.59 ± 31.28 [P = .0159]). These results indicate that the STZ-DM rats had polydipsia, which is one of the main symptoms of DM,[2] and that intraoral sensitivity to menthol did not change under the DM condition.

However, there were no significant differences in the ratio of capsaicin (TRPV1 agonist) solution intake duration compared to baseline duration between sham and DM rats (Fig 2c; sham [n = 6]: baseline = 100.00 ± 0.00, day 7 = 96.89 ± 2.71, day 14 = 98.43 ± 6.58; DM [n = 4]: baseline = 100.00 ± 0.00 [P > .9999], day 7 = 98.65 ± 4.29 [P = .7381], day 14 = 113.54 ± 5.44 [P = .1476]).

Although STZ-DM rats showed an increase in water intake, they avoided the capsaicin solution. However, there were no significant differences in the intake of DW, 10.0 μM menthol, and 1.0 μM capsaicin solutions in naïve rats (data not shown); thus, these concentrations were chosen in the present study.

These results indicate that the STZ-DM rats have spontaneous pain in the intraoral structures when taking capsaicin. It should be noted that differences in the amount of solution intake in each rat caused by differences in general oral function could not be controlled by handlings.

Mechanical Hypersensitivity of the Tongue

No changes were found in HWRT to heat stimulation of the tongue in DM rats compared to sham (Fig 3a; sham [n = 6]: baseline = 50.59 ± 0.24, day 7 = 49.63 ± 0.51, day 14 = 50.99 ± 0.33; DM [n = 6]: baseline = 50.14 ± 0.45 [P = .4848], day 7 = 49.32 ± 0.24 [P = .8182], day 14 = 50.87 ± 0.26 [P = .4177]).

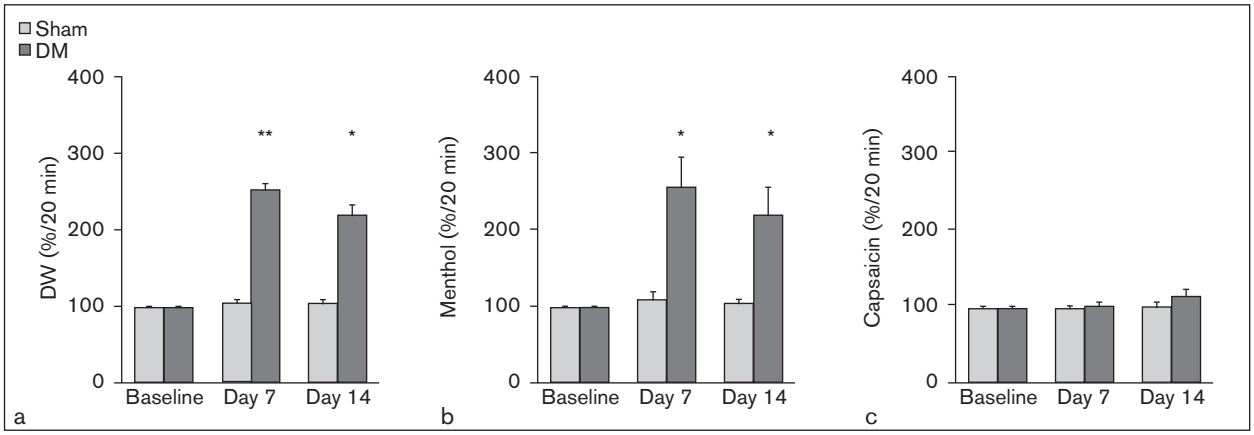

Fig 2 Relative duration of **(a)** distilled water (DW), **(b)** menthol, and **(c)** capsaicin solution intake for 20 minutes. *$P < .05$, **$P < .01$ for sham vs diabetes mellitus (DM) rats.

Furthermore, HWRT to mechanical stimulation of the tongue significantly decreased in DM rats compared to sham rats on day 14 after STZ injection (Fig 3b; sham [n = 6]: baseline = 105.57 ± 1.00, day 7 = 108.38 ± 2.86, day 14 = 103.93 ± 1.40; DM [n = 6]: baseline = 105.37 ± 1.81 [P = .7835], day 7 = 108.42 ± 1.94 [P = .6991], day 14 = 78.97 ± 5.86 [P = .0087]).

Mechanical Hypersensitivity of the Whisker Pad Skin

DM rats also did not show hypersensitivity of the whisker pad skin to heat stimulation compared to sham (Fig 4a; sham [n = 4]: baseline = 11.90 ± 0.76, day 7 = 11.26 ± 0.23, day 14 = 11.00 ± 0.56; DM [n = 8]: baseline = 12.19 ± 0.64 [P = .9333], day 7 = 12.70 ± 0.58 [P = .727], day 14 = 11.49 ± 0.63 [P = .4606]).

Similar to hypersensitivity to mechanical stimulation of the tongue, HWT to mechanical stimulation of the whisker pad skin was significantly lower in DM rats compared to sham rats on days 7 and 14 after STZ injection (Fig 4b; sham [n = 4]: baseline = 45.00 ± 0.00, day 7 = 40.00 ± 2.89, day 14 = 40.00 ± 2.89; DM [n = 6]: baseline = 41.67 ± 2.11 [P = .4667], day 7 = 25.17 ± 2.59 [P = .0190], day 14 = 21.67 ± 2.11 [P = .0048]).

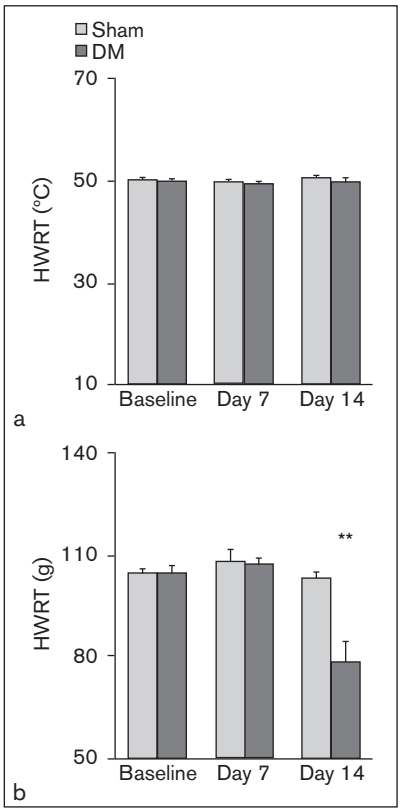

Fig 3 Head-withdrawal reflex thresholds (HWRT) to **(a)** heat and **(b)** mechanical stimulation of the tongue. **$P < .01$ for sham vs diabetes mellitus (DM) rats.

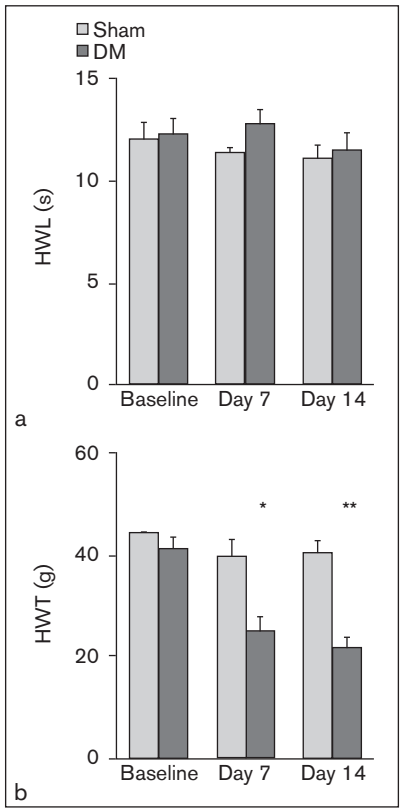

Fig 4 (a) Head-withdrawal latency (HWL) to heat stimulation of the whisker pad skin. **(b)** Head-withdrawal threshold (HWT) to mechanical stimulation of the whisker pad skin. *$P < .05$, **$P < .01$ for sham vs diabetes mellitus (DM) rats.

Discussion

To the present authors' knowledge, no animal study has investigated the changes in intraoral sensory function and saliva volume in DM. Thus, this study investigated the mechanisms of intraoral hypersensitivity, including spontaneous pain and salivary reduction, in DM rats. The findings of the present study indicate a reduction in spontaneous saliva volume, polydipsia, oral mucosal hypersensitivity to capsaicin but not to menthol solu-

tion, and mechanical hypersensitivity in the tongue and whisker pad skin. The symptoms in STZ-DM rats were similar to those seen in patients with painful diabetic neuropathy and saliva reduction. The present findings suggest that STZ-DM rats are useful for preclinical studies on changes in orofacial sensation, especially intraoral sensory mechanisms, associated with DM.

Mechanical Hypersensitivity in STZ-DM Rats

The most common method to produce type 1 DM in rodents is systemic administration of STZ, a cytotoxic methyl nitrosourea moiety that enters pancreatic β-cells by attaching to the glucose 2 transporter, which causes cell death by DNA fragmentation.[21] The destruction of pancreatic β-cells in turn leads to insulin deficiency, hyperglycemia, and, eventually, DM. It is well established that a systemic injection of STZ induces hyperalgesia to thermal, mechanical,[22] and chemical[23] noxious stimulation of the rodent hind paw and heat hypersensitivity on the face.[16–18] The present study also demonstrated mechanical hypersensitivity in the whisker pad skin after STZ injection. These observations suggest that the symptoms in STZ-DM rats, including orofacial pain, are similar to those in patients with DM. These findings are in contrast to those of another study that demonstrated no differences in the facial mechanical threshold between STZ- and vehicle-administered rats.[17] This discrepancy could be explained by the differences in the rat strain used, as the present study used Sprague-Dawley rats, while Wistar rats were used previously. Another study also showed facial heat hypersensitivity in STZ-injected Sprague-Dawley rats[16]; in contrast, there was no significant change in heat HWL after STZ injection in the present study. This discrepancy may be caused by the difference in observation periods, as the present study used 1 to 2 weeks after STZ injection, while the previous study used 8 to 12 weeks.

Hyperglycemia is a risk factor for both peripheral and autonomic neuropathy.[24] Symptoms of diabetic peripheral neuropathy typically manifest in the peripheral nervous system first because the trigeminal ganglion[25] and dorsal root ganglion[26] are not protected by the blood-brain barrier, making them particularly vulnerable to metabolic and hypoxic damage. Patients with diabetic peripheral neuropathy present a lower density of intraoral mucosal nerve fibers[27] and hypersensitivity of the tongue[8] and oral mucosa.[28] The STZ-DM rats in the current study showed spontaneous intraoral hypersensitivity, indicating that DM rats have similar symptoms to patients with DM. The earliest changes of diabetic neuropathy occur in unmyelinated C-fibers, with initial degeneration and regeneration of C-fibers leading to neuronal ectopic firing, which results in pain, allodynia, and hyperesthesia.[29] Because unmyelinated C-fibers lack the protection offered by the myelin sheath,[26] they continue to degenerate with the progression of diabetic peripheral neuropathy.[30] Soon after, Aβ- and Aδ-fibers progressively demyelinate until degeneration occurs.[26] Together with previous data, the present findings suggest that C-fibers sensitive to mechanical stimuli in the orofacial region are susceptible to degeneration in the early stage of diabetic neuropathy in STZ-DM rats.

TRPV1 is a nonselective cation channel activated by capsaicin and heat[31] and is expressed predominantly in unmyelinated C-fibers and thinly myelinated Aδ-fibers.[32] TRPV1 has been determined to be involved in the processing and neurotransmission of pain and thermal stimuli in humans.[33] Additionally, several studies have indicated the involvement of TRPV1 receptors in various orofacial pain models. The majority of these studies have shown that increased expression of TRPV1 receptors in trigeminal ganglion neurons is related to the development of sensory alterations in the tongue.[34] In STZ-DM rats, TRPV1 expression was significantly increased in trigeminal ganglion neurons compared to normoglycemic ones.[18] These findings collectively suggest that increased TRPV1 expression plays a role in the development of hypersensitivity to capsaicin and heat. However, heat hypersensitivity in the tongue was not detected in the current study. This may be due to the anesthetic effects during the HWRT measurement and the different properties of nerve fibers, as a subgroup of capsaicin-sensitive A-fiber nociceptors was insensitive to heat in the present DM rats. This supports a previous finding indicating the existence of heat-insensitive capsaicin receptors.[35] There are differences in the proportion of noxious afferent fibers expressing TRPV1 between cutaneous (whisker pad skin) and mucosal tissues, including the tongue.[36]

TRPM8 has been shown to play a role in cold sensation and is activated by menthol.[37] A decrease in TRPM8 and an increase in TRPV1 function of the dorsal root ganglion were reported in the early stage of DM in STZ-DM rodent models.[38] Upregulated TRPV1 may cause downregulation of TRPM8, which aggravates pain, resulting in hypersensitivity to capsaicin.[39]

Together with these previous studies, the present results suggest that intraoral hypersensitivity to capsaicin may be the result of enhancement of TRPV1 and suppression of TRPM8 functions under DM conditions.

Dry Mouth and Tongue Hypersensitivity

Saliva production and salivary flow are mediated by the autonomic nervous system.[40] Previous studies have demonstrated a decrease in salivary secretion and an increase in the sensory abnormalities associated with

xerostomia in patients with DM compared to nondiabetic healthy patients.[1,11] When saliva secretion decreases because of chronic hyperglycemia, tongue sensitivity is altered in patients with DM and generally manifests as a burning intraoral sensation.[40] A significant saliva reduction and an increase in DW intake in STZ-DM rats was observed, indicating that the systemic administration of STZ causes severe dryness of the oral mucosa. Mechanical, but not heat, hypersensitivity of the tongue has also been reported to occur in dry-tongue model rats. Furthermore, mechanical hyperactivation of the trigeminal subnucleus caudalis neurons has been observed in dry-tongue conditions.[12] There are some differences between the dry-tongue and STZ-DM rat models. TRPV1 expression in the trigeminal ganglion neurons increased in STZ-DM rats,[18] whereas it did not change in dry-tongue rats.[13] In dry-tongue rats, mechanical hypersensitivity of the tongue occurred immediately within 3 days of dry tongue treatment,[12,13] whereas it took 14 days after STZ injection to occur in DM rats. Thus, xerostomia induced by saliva reduction may be involved in the aggravation of mechanical hypersensitivity of the tongue in DM rats. Rats with peripheral neuropathic pain in the tongue induced by lingual nerve crush also demonstrated mechanical hypersensitivity of the tongue on day 3; the tongue neuropathic pain model rats showed an increase in calcitonin gene-related peptide and phosphorylation of extracellular signal-regulated kinase associated with satellite glial cell activation in the trigeminal ganglion.[20,41] Collectively, these results and those of the present study suggest that hypersensitivity of the tongue to noxious mechanical stimulation is mainly and initially caused by diabetic peripheral neuropathy and aggravated by prolonged saliva reduction (ie, xerostomia) in DM rats.

Conclusions

The mechanisms of intraoral hypersensitivity induced by DM are involved in peripheral and autonomic neuropathy. Diabetic neuropathic pain is characterized by progressive nerve fiber loss that leads to positive clinical signs and symptoms, which are related to structural alterations in the peripheral nervous system. STZ-injected DM rats are useful for understanding the mechanisms of intraoral symptoms associated with DM and for developing appropriate diagnostic and treatment modalities for diabetic peripheral neuropathy in the early stage of DM. Although there are discrepancies in symptoms of DM between patients with DM and the present animal model, the change in intraoral sensation including spontaneous pain, not only xerostomia, observed in this animal model may help develop appropriate diagnosis and treatment strategies for intraoral neuropathic pain in patients with DM.

Highlights and Key Findings

- DM rats have reduced spontaneous saliva volume.
- DM rats have intraoral hypersensitivity to capsaicin.
- DM rats exhibit mechanical hypersensitivity of the tongue and whisker pad skin.
- STZ-DM rats are useful for investigating intraoral hypersensitivity in DM.
- STZ-DM rats are useful for investigating DM-induced xerostomia.

Acknowledgments

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