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ORIGINAL ARTICLE

Impaired somatosensation in tongue mucosa of smokers

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Abstract Smoking has been indicated as a risk factor for oral diseases and can lead to altered sense of taste. So far, the effects of sensory changes on the tongue are not investigated. In this study, quantitative sensory testing was used to evaluate somatosensory function in the lingual region. Eighty healthy volunteers were investigated (20 smokers, 20 non-smokers). Subjects were bilaterally tested in innervation areas of lingual nerves. Thresholds of cold and warm detection, cold and heat pain, and mechanical detection were determined. As control for systemic, extraoral effects of smoking, tests were additionally performed in 40 volunteers (20 smokers, 20 non-smokers) on the skin of the chin innervated by the mental branch of the trigeminal nerve. Cold ($p<0.001$), warm detection thresholds ($p<0.001$), and thermal sensory limen ($p<0.001$) showed higher sensitivity in non-smokers as compared to smokers. Heat pain and mechanical detection, as well as all tests in the skin of the chin, showed no significant differences. The impaired temperature perception in smokers indicates a reduction of somatosensory functions in the tongue, possibly caused by nerve degeneration associated with smoking. Possible systemic effects of smoking do not seem to affect extraoral trigeminal branches.

Keywords Smoking · Trigeminal · Quantitative sensory testing · Lingual

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Introduction

The lingual nerve is a branch of the mandibular nerve, itself a branch of the trigeminal nerve. It also carries fibers from the chorda tympani nerve (branch of the facial nerve), which returns taste information from the anterior two thirds of the tongue. The lingual nerve supplies general sensation to the mucosa of the anterior two thirds of the tongue, the sublingual mucosa and the mandibular lingual gingival [23, 29].

It has been realized and generally accepted that smoking is an important risk factor for oral diseases [13, 19, 28]. Furthermore, smoking affects the acuity of smell and taste. Previous studies reported that olfactory function improved upon cessation of smoking [11], and non-smokers were able to detect salt concentrations 12–14 times lower than the lowest concentration heavy smokers were able to detect [12]. Investigation of the effects of tobacco smoke on the olfactory epithelium in rats have shown that cigarette smoking leads to smell loss in smokers, which is triggered by increased olfactory sensory neurons death, which eventually overwhelms the regenerative capacity of the epithelium [26]. Histopathological analysis of nasal mucosa in exposed rats revealed structural changes of olfactory epithelium, especially in the rats exposed to both ethanol and tobacco smoke [25]. A new case report has shown that nicotine

induces osteonecrosis [14]. Somatosensory changes of the lingual nerve in smokers have not been investigated so far.

Sensory dysfunction in humans can be objectively quantified by electrophysiological recordings of trigeminal somatosensory-evoked cortical potentials [9] and brainstem reflexes [1, 10]. Brain imaging studies such as functional magnetic resonance imaging are able to assess sensory functions as well [3, 6]. These methods are complex and time consuming. Clinical assessment of the trigeminal small Aδ and C fiber function may be achieved with the protocol of quantitative sensory testing (QST). This protocol measures the detection and pain threshold of accurately calibrated sensory stimuli. Thermal and mechanical stimuli are chosen because they relate to distinct neuroanatomic pathways with Aβ, Aδ, and C fiber populations. Abnormal results may signal dysfunction anywhere along the sensory pathway between the receptor apparatus, the primary sensory cortex, and the association cortex [17, 22].

The aim of the present study was to analyze the effects of smoking related to gender and age. Beyond local irritant effects of smoking in the mouth, central mechanisms of nicotine that may indirectly affect lingual somatosensation were considered. Nicotine has been shown to activate nociceptors through neuronal nicotinic acetylcholine receptors (nAChRs) that excite neurons in the spinal and trigeminal dorsal horn [5, 7, 21]. To evaluate systemic effects of smoking on all innervation areas of the trigeminal nerve, QST was additionally performed on the chin skin innervated by the mental nerve. This study reports that smokers display significantly diminished perception of temperature, which is not explained by central effects.

Methods

Subjects

Forty smokers (20 female, 20 male; 20 to 56 years) and 40 non-smokers (20 female, 20 male; 19 to 62 years) were investigated by QST on the tongue. Due to age differences of the QST parameters in the lingual region [30], 40 volunteers over 40 years and 40 subjects under 40 years participated in this study. All volunteers were right-handed. They were tested bilaterally in the lingual nerve territory on the anterior lateral two thirds of the tongue. The smokers had smoked for at least 3 pack years (more than 3 years and above 20 cigarettes a day). The non-smokers participating in this study have never smoked. Forty other volunteers (20 non-smokers, 20 smokers; 26 to 62 years) were tested bilaterally in innervation areas of mental nerve (hairy skin, lower lip; Fig. 1).

The subjects were included in this study only if a visual examination showed that their oral mucosa was healthy (without any swellings and red, white, and pigmented lesions such as candidiasis, erythroplasia, lichen planus, mucosal atrophy, leucoplakia, and black hairy tongue). Other exclusion criteria were as follows: previous lingual or orofacial injuries, neurological or psychiatric history, diabetes mellitus, and chronic medication of any kind for at least 48 h. None of the subjects had removable prostheses, and all of them did not eat, drink, or chew gum for at least 0.5 h before the examination. All participants gave their informed consent prior to their inclusion in the study according to the 1964 Declaration of Helsinki (www.wma.net). The protocol was approved by the local ethics committee.

Subjects were lying on a couch and kept their eyes closed throughout the QST procedure. In 40 volunteers, tests started on the right, and in 40 volunteers, on the left side. All investigations were performed by the same trained examiner at Aachen University in Germany.

Quantitative sensory testing (QST)

Thermal detection and pain thresholds and mechanical detection thresholds were determined using these seven parameters: cold detection threshold (CDT), warm detec-

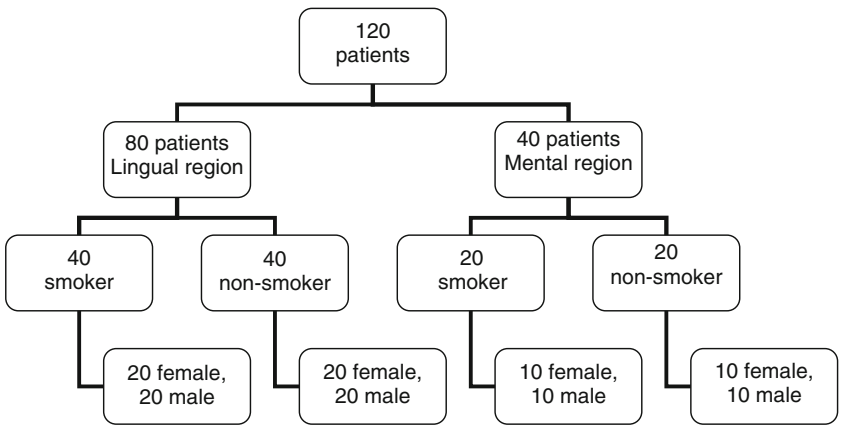

Fig. 1 Flow chart showing the groups and subgroups of patients and volunteers participating in this study

tion threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensation (PHS), cold pain threshold (CPT), heat pain threshold (HPT), and mechanical detection threshold (MDT).

Thermal stimuli were applied by a computer-controlled Peltier type thermode with a stimulation area of 16× 16 mm^2 (TSA-II, Medoc Ltd., Israel). This thermode is based on the Peltier thermo battery. When a direct current is passed between two dissimilar conductors, there is a transfer of energy in the form of heat between their junction and the environment. Depending on the direction of current flow, heat is either absorbed or lost at the junction, the reverse effect occurring at the opposite poles of the conductors. In couples formed between most conductors, the Joule heat losses overwhelm "Peltier effect" cooling [20].

Starting from a baseline of 32°C, temperature was decreased or increased by 1°C/s in order to determine CDT, WDT, CPT, and HPT. Temperature stimuli stopped as soon as volunteers pressed a computer mouse button to indicate the corresponding thermal perception. The range of stimulating temperatures was from 0°C to 50°C. CDT and WDT were specified as difference of temperatures (dT) from baseline (32°C); CPT and HPT were defined as absolute temperatures (°C) [30]. Due to the common definition of CDT as a temperature difference, CDT values are negative. Thus, a less negative value indicates an arithmetic increase of CDT and vice versa. Arithmetic means of thermal thresholds were calculated from three separate temperature ramps. TSL was determined by alternating warm and cold stimuli. From the 32°C baseline, temperature increased until the subject indicated warm perception. Thereafter, the temperature decreased until the subject's indication of cold perception. The alternating stimulation was repeated twice. The mean difference between temperatures causing warm and cold perceptions was defined as TSL. In the same test, possible PHSs (a subjective feeling of heat upon cooling) during cold stimuli were registered.

MDT was measured with modified von Frey filaments with forces of 0.08, 0.2, 0.4, 0.7, 1.6, 4, 6, 10, 14, 20, 40, 60, 80, 100, 150, 260, 600, 1,000, 1,800, and 3,000 mN (Touch-Test Sensory Evaluators, North Coast Medical, Morgan Hill, CA, USA). MDT was determined by the method of limits starting with a clearly noticeable filament of 16 mN [30]. The examination for each region took about 45 min including a demonstration of each test at a practice area.

Statistical analysis

Intraindividual side-to-side comparisons of QST parameters were evaluated with the Wilcoxon signed rank test. For all QST parameters, differences between smokers and non-smokers and age and gender were performed using three-way analysis of variance (F, p value) with the factors group smokers/non-smokers, age (≤40 and >40 years), and gender with Bonferroni corrections and subsequent Student–Newman–Keuls test when applicable (q, p value). Significance was accepted at $p<0.007$. Due to data distribution, log-transformation was executed in the following QST parameters: WDT, TSL, and MDT.

The relationship between smoking duration and threshold was established with the Spearman rank order correlation. Statistical analysis was performed by the Software SigmaStat 3.0 (SPSS Inc., USA).

Results

Left and right sides of innervation areas of lingual and mental nerves did not show any significant differences in all volunteers.

Differences between smokers and non-smokers in innervation areas of the lingual region

Significant differences between smokers and non-smokers in the lingual region were found with respect to CDT ($F=33.9$, $p<0.001$), WDT ($F=76.0$, $p<0.001$), and TSL ($F=45.8$, $p<0.001$; Table 1 and Fig. 2). These results show that the thermal sensitivity is reduced in smokers in comparison to non-smokers.

Gender-related differences were found in WDT ($F=10.1$, $p<0.002$).

WDT ($F=10.2$, $p<0.002$) and TSL ($F=17.6$, $p<0.001$) showed significant differences between subjects ≤40 and >40 years (Tables 1 and 2).

MDT indicated a statistically significant interaction between smokers/non-smokers and age ($F=15.1$, $p<$

Table 1 Differences between smoker and non-smoker in innervation area of lingual nerves ($n=80$)

	Smoker ($n=40$)	Non-smoker ($n=40$)	p value
Mean age (years)	38.3±11.4	37.7±9.7	
Parameter			
CDT (°C)	−4.1±1.9	−2.6±1.3	<0.001
WDT (°C)	5.1±2.6	2.7±1.5	<0.001
TSL (°C)	7.6±3.7	4.5±2.0	<0.001
PHS (x/3)	0	0	
CPT (°C)	13.4±8.2	10.7±8.5	
HPT (°C)	47.9±3.1	47.9±2.7	
MDT (mN)	0.14±0.1	0.16±0.1	

Data are presented as mean±SE

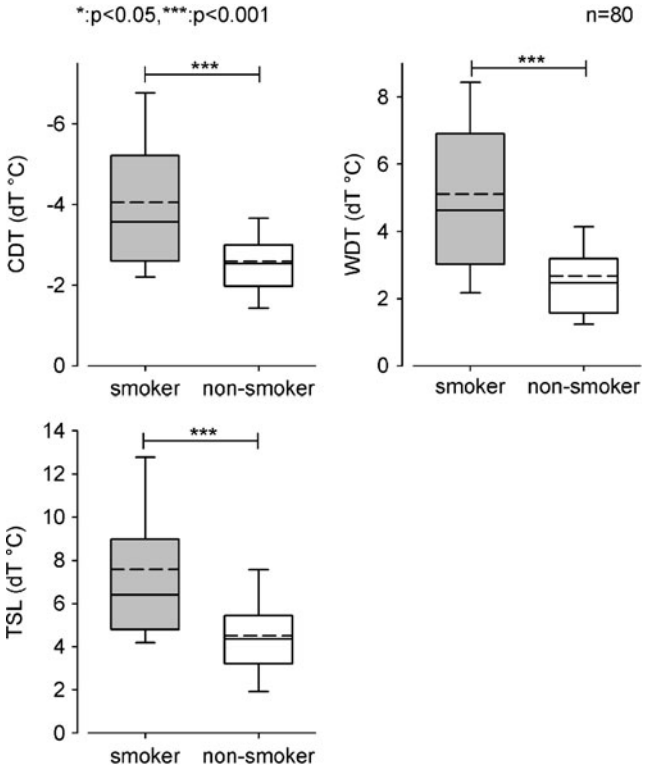

Fig. 2 Differences between smokers and non-smokers in innervation areas of lingual nerve. Cold detection threshold (CDT), warm detection threshold (WDT), and thermal sensory limen (TSL) were determined from 80 QST experiments in healthy volunteers (40 women, 40 men; 20 smokers, 20 non-smokers each). CDT and WDT are given as differences from baseline (32°C; dT). Data on smokers (*grey*) and non-smokers (*white*) are presented as *box plots* (*solid line*: median, *dashed line*: arithmetic mean). Significant differences between smokers and non-smokers are indicated by *asterisks* (*$p<0.05$, ***$p<0.001$; Mann–Whitney rank sum test)

0.001). Subsequent Student–Newman–Keuls test demonstrated significant differences between smokers (mean, 0.12) and non-smokers (mean, 0.17) in subjects ≤40 ($q=5.5$, $p<0.001$)years.

Table 2 Differences between female and male and between subjects ≤40 and >40 years in innervation area of lingual nerves ($n=80$)

Parameter (mean)	Female	Male	≤40 years	≥40 years
CDT (°C)	−3.1	−3.6	−3.0	−3.6
WDT (°C)	*3.5*	*4.3*	*3.4*	*4.4*
TSL (°C)	5.5	6.5	*5.3*	*6.8*
PHS (x/3)	0	0	0	0
CPT (°C)	12.4	11.6	12.7	11.4
HPT (°C)	47.4	48.4	47.7	48.1
MDT (mN)	0.15	0.15	0.15	0.15

Values in italic indicate gender- or age-related significant differences

Dependency of smoking duration and parameters

WDT, CPT, and MDT were related to smoking duration (Spearman rank order correlation; Fig. 3). CPT negatively correlated with smoking duration, demonstrating impairment of cold sensitivity with increasing duration. WDT and MDT positively correlated with smoking duration, pointing to impairment of sensory functions with increasing smoking duration.

QST on the innervation area of the mental nerve in 40 further volunteers revealed no significant differences between smokers and non-smokers in all parameters (Table 3).

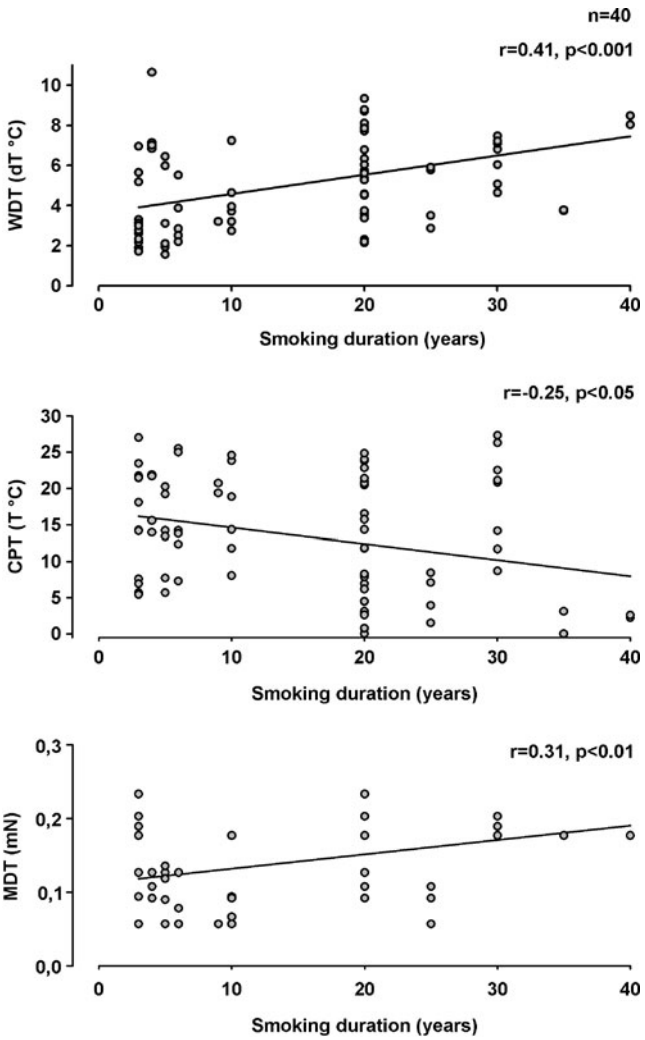

Fig. 3 Correlation between smoking duration and QST parameters in innervation areas of lingual nerve. Warm detection threshold (WDT), cold pain threshold (CPT), and mechanical detection threshold (MDT) were determined from 40 QST experiments in smokers (20 women, 20 men). WDT is given as differences from baseline (32°C; dT). Data were analyzed by Spearmen correlation. Each *point* represents the results of one subject. The *lines* show linear regression curves

Table 3 Differences between smoker and non-smoker in innervation area of mental nerves (n=40)

	Smoker (n=20)	Non-smoker (n=20)
Mean age (years)	40.5±8.6	41.9±9.9
Parameter		
CDT (°C)	−1.4±0.5	−1.2±0.4
WDT (°C)	2.3±0.8	1.9±0.6
TSL (°C)	2.9±1.1	2.3±0.6
PHS (x/3)	0	0
CPT (°C)	16.2±9.5	17.5±10.3
HPT (°C)	43.5±3.7	43.2±4.6
MDT (mN)	0.16±0.04	0.16±0.04

Data are presented as mean ± SE

Discussion

The QST protocol has been developed as a comprehensive test battery for somatosensory functions across the full spectrum of primary afferents [17]. A recent study has adapted the standardized QST protocol to the lingual region [30]. This study investigated seven QST parameters with respect to differences related to gender, smoking, and age. These parameters assess the function of Aβ, Aδ, and C fibers.

Differences between smokers and non-smokers

The present study demonstrates a significantly higher WDT, and a significantly lower CDT (more negative values) and CPT in smokers. The differences of the thermal detection thresholds were found for male as well as for female smokers alike, in comparison to gender-matched non-smokers. The findings indicate a reduction of thermal sensitivity by smoking which might be due to an impairment of Aδ and C fibers. There is evidence that nicotine may directly affect the signal transduction of C and Aδ fibers. A study on the lingual branch of the trigeminal nerve in rats suggested interaction of nicotine with some fibers of these types [27]. As likely mechanism, degenerative processes of nerve fibers responsible for the observed defects, i.e., Aδ and C fibers, can be suggested. Degeneration may be induced specifically by nicotine or unspecifically by other ingredients of tobacco smoke. For example, demyelination was observed in the retrobulbar portion of the optic nerve in rats chronically exposed to tobacco smoke [16]. It should be noted that these are Aβ and Aδ fibers, whereas no functional evidence for an impairment of Aβ fibers was found in the present study. In the tongue, their localization deep within the tissue and their thick myelination may exert a protective effect. This would explain the impairment of the unmyelinated C fibers which do not have this protective effect.

Another possible reason of thermal impairment in smokers might be due to the specific effects of nicotine mediated through a compromised microcirculation. It has been reported in a study using computerized videocapillaroscopy that cigar smoking induced significant alterations of the morphology, caliber, and number of capillaries in the lingual mucosa [18]. It is perceivable that a compromised blood supply leads to reduced function of sensory neuron and to degeneration.

Moreover, nicotine as well as other ingredients of tobacco smoke may profoundly affect the function and morphology of the tongue mucosa. Long-term nicotine administration alone was sufficient to induce significant changes in the anatomical properties of taste buds in rat fungiform papillae [24]. Keratinocytes of rats exposed to cigarette smoke exhibit an increased expression of proto-oncogene protein bcl-2, which induces apoptosis [2]. Even though the smokers participating in the present study did not show any macroscopic changes of the tongue mucosa during visual inspection, histological modifications may have contributed to the observed effects of smoking.

The reduction of thermal sensitivity by smoking could also be related to central mechanism. There is evidence that nicotine may influence perception of several sensory stimuli through central mechanisms [5, 7, 21]. A previous study used rats and mice to determine whether nicotine activates peripheral and central taste pathways and detected a previously unknown link between peripheral nAChR-dependent taste pathways and the sensory representation of nicotine in the gustatory cortex. In another study on rats, nicotine activated neurons in rat trigeminal subnucleus caudalis [4]. Finally, lesions of the insular cortex that include the primary sensory gustatory cortex promote smoking cessation [15].

The influence of tobacco smoke on human health is an important problem worldwide. Complex inflammatory processes and changes in the immune system are crucial in the pathogenesis of smoking-related disorders like chronic obstructive lung disease, lung cancer, and atherosclerosis [8]. As a test of the possibility that smoking may reduce the lingual sensitivity to cold and heat by means of systemic effects of nicotine, we performed control QST experiments on the skin outside of the oral cave. For practical reasons, another cohort of volunteers had to be recruited for these test. Fortunately, both groups were closely similar with respect to age and gender distribution. Therefore, the comparison of intraoral vs. extraoral QST results strongly suggests that smoking-related deficiencies in perception are confined to the mouth and are best explained by local alterations.

Age- and gender-related differences

The diminished sensitivities in the elderly of the present study are in line with a recent study which revealed impaired thermal thresholds in the lingual nerves [30].

Women were more sensitive than men for warm stimuli in the lingual region. The lower threshold for thermal stimuli provides evidence for a neuronal-based higher sensitivity in female's tongue [30].

In conclusion, this study using QST on the lingual mucosa reveals striking effects of smoking on the detection of non-noxious thermal stimuli but not of mechanical or painful thermal stimuli. Since these smoking-related effects were confined to the mouth and were absent in another innervation area of the trigeminal nerve, the results indicate local damage by smoking, probably involving degeneration of the little or not myelinated Aδ and C fibers of the tongue.

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Conflicts of interest The authors declare that they have no conflict of interest.

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