Effect of Capsaicin Cream on the Secretion of the Submandibular and Parotid Gland in the General Population with Different Chilli-eating Habits

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Objective: *To investigate the effect of capsaicin cream on the secretion of the submandibular gland (SMG) and the parotid gland (PG) in the general population, with different chilli-eating habits.*

Methods: *In two groups with different chilli-eating habits, the salivary flow rate of the SMG and the PG was detected at statics and different times, after application of capsaicin cream.*

Results: *In both groups, the topical application of capsaicin cream could significantly increase the salivary secretion of SMG ($P < 0.05$), but the increase in the salivary flow rate of the SMG between the two groups had no significant difference ($P > 0.05$). On the other hand, although the salivary flow rate of PG also increased after stimulation, the increase had no statistical difference ($P > 0.05$).*

Conclusion: *The application of capsaicin cream can effectively promote the secretion of the SMG and the PG, and its effect is independent of chilli-eating habits, which indicates that topical application of capsaicin cream can be considered as a potential treatment for the hypofunction of the salivary gland.*

Key words: *capsaicin, chilli, parotid gland, salivary secretion, submandibular gland, transient receptor potential vanilloid subtype 1, vanilloid receptor 1*

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Saliva is essential to maintain the normal function of the oral cavity. Hyposecretion of salivary glands can significantly affect the oral physiological functions and damage the oral defence mechanism. Unfortunately, effective and convenient treatments for hyposecretion of the salivary glands remain scarce.

There are reports that the application of capsaicin to the tongue or palate caused salivation[1]. We previously demonstrated that dermal application of capsaicin promoted salivary secretion of the submandibular gland *in vivo*[2], which suggests that capsaicin can be considered as a new option for xerostomia treatment.

However, desensitisation after long-term application of capsaicin is also seen[3]. It is unclear whether chilli addiction will result in desensitisation and influence the effect of capsaicin on the promotion of salivation of the submandibular and the parotid gland. This study was designed to investigate the effect of capsaicin cream on the secretion of the submandibular gland (SMG) and the parotid gland (PG) in the general population, with different chilli-eating habits.

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Materials and methods

Human participants and ethics

Sixty participants were recruited in this study. The participants were asked about their chilli-eating habits and divided into two groups: the chilli-addiction group whose estimated daily intake of chilli was equal or greater than 20 g and the chilli-avoidance group who never ate any chilli. The participants of the chilli-addiction group were from Changsha, Hunan Province, and the chilli-avoidance group were from Hangzhou, Zhejiang Province. In each group, 15 females and 15 males were included. Participants with a history of oral and maxillofacial diseases or systemic disease were excluded. The mean age in the chilli-addiction group and chilli-avoidance group was 23.3 years old and 25.2 years old, respectively. The research protocol was approved by the Peking University Institutional Review Board, and all participants signed an informed consent document for sample collection.

Measurement of salivary secretion

Participants were instructed not to eat, drink or smoke for 60 min before saliva collection at 9:00 to 11:00. Participants swallowed, in order to clean the residual saliva in the oral cavity, then two specialised cupulas were placed around the opening orifices of the PG and the SMG and were connected with 20 ml syringes through perfusion tubes. The syringes were adjusted to produce the appropriate negative pressure for collecting saliva of the ipsilateral PG and SMG simultaneously. Capsaicin cream (0.075%) was smeared to the skin covering the PG (about 5 × 4 cm^2) and the SMG (about 3 × 2 cm^2). Saliva was continuously collected for 5 min during the rest state and 10, 30, 60 min after capsaicin stimulation. The saliva collection devices were pre-weighed (weight 1) and re-weighed after collection (weight 2). The saliva flow rate (g/5 min) was calculated as weight 2 - weight 1.

Data analysis

Data are expressed as mean ± standard deviation (SD). Statistical analysis involved one-way ANOVA and multi-way ANOVA, with the use of SPSS version 13.0 (SPSS, Illinois, USA). A $P < 0.05$ was considered statistically significant.

Results

The change in salivary flow rate was demonstrated in figures 1 and 2. In the chilli-avoidance group (Fig 1), the salivary flow rate of the SMG was significantly higher than that of the PG ($P < 0.05$). Ten minutes after the application of capsaicin cream, the salivary flow rate of the SMG increased ($P < 0.05$), which was still effective at 30 min after application ($P < 0.05$). At 60 min after application, the flow rate reversed to a normal level. However, the salivary flow rate of the PG increased slightly after the application of capsaicin cream and the increment had no statistical significance (one-way ANOVA, $P > 0.05$). In the chilli-addiction group, similar results with the chilli-avoidance group could be observed (Fig 2).

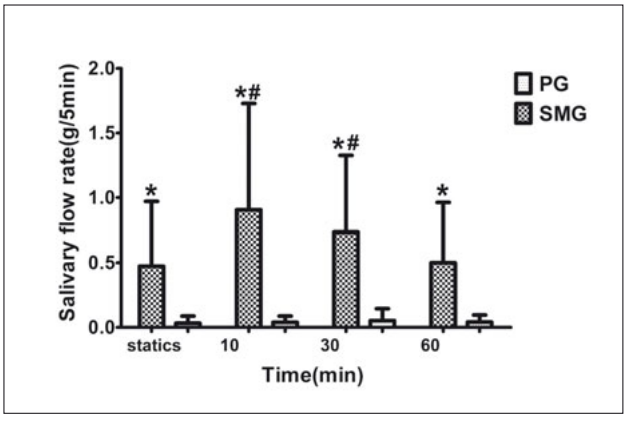

Fig 1 Effect of capsaicin cream on salivary flow rate of the SMG and the PG in the chili-avoidance group: *$P < 0.05$, the salivary flow rate of the SMG was significantly higher than that of the PG; #$P < 0.05$, the salivary flow rate of the SMG was increased after the application of capsaicin cream.

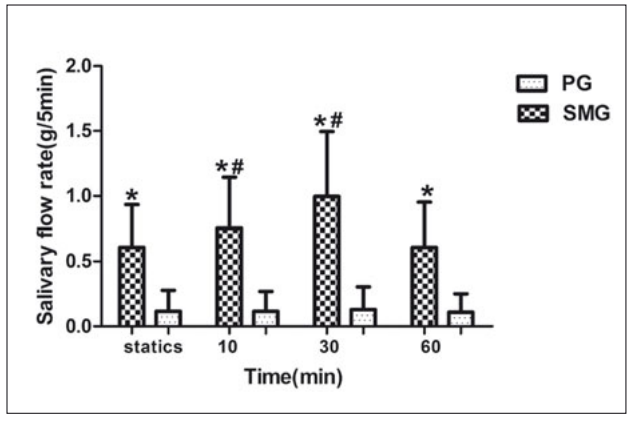

Fig 2 Effect of capsaicin cream on salivary flow rate of the SMG and PG in the chili-addiction group: *$P < 0.05$, the salivary flow rate of SMG was significantly higher than that of the PG; #$P < 0.05$, the salivary flow rate of the SMG was increased after the application of capsaicin cream.

In both groups, the effect of capsaicin cream on promoting the secretion of the SMG demonstrated different patterns. In the chilli-avoidance group, the promoting effect of capsaicin cream was strongest at 10 min after its application. At 30 min after application, the flow rate was still increased but its increasing range was weaker than that at 10 min. In contrast, in the chilli-addiction group, the effect of promoting secretion of capsaicin cream began at 10 min after application and reached peak levels at 30 min. The results of the statistical analysis indicated that the increase in the salivary flow rate of the SMG between the two groups had no significant difference (multi-way ANPVA, $P > 0.05$), which means the chilli-eating habit had no influence on the effect of promoting secretion of capsaicin in the SMG. When comparing the increase in salivary flow rate of the PG between the two groups, it showed that the increase in salivary flow rate of the chilli-avoidance group was significantly higher than that of the chilli-addiction group (multi-way ANOVA, $P < 0.05$).

Discussion

Saliva is mainly secreted from the major salivary gland including the parotid and the submandibular gland. About 60% to 65% rest saliva is secreted by the submandibular gland, while most stimulated saliva is from the parotid gland[4]. Several kinds of diseases such as Sjögren syndrome, age-related degeneration of the salivary glands or radiotherapy, can damage the secretion function of the gland. The reduction of quantity and quality of saliva is a considerable cause of oral diseases such as xerostomia, dysphagia, dental caries, oropharyngeal infections and mucositis, meaning the patients' living quality is seriously impacted[5].

At present, the treatment for xerostomia is restricted in terms of the symptomatic approach and due to lack of effective therapy. Effective and convenient treatment is expected by doctors and patients. In this study, the effect of capsaicin cream on the salivary secretion of the SMG and the PG was investigated based on former research. The results revealed that salivary secretion was increased by topical application of capsaicin cream. This saliva-promoting effect was especially significant in the SMG. Also, the application of capsaicin cream is relatively convenient, by smearing it on the superficial skin of the glands, which makes it a promising option for the treatment of hypofunction of the salivary glands.

Multiple factors including timing, gender, age, environment and circadian rhythm may influence the resting salivary flow rate. In this study, the saliva collection was strictly restricted under the same conditions as much as possible, in order to minimise the deviation. A specially-designed device which can attach to the surrounding orifice of the parotid and submandibular glands, through negative pressure, was used to collect saliva. This device ensured the saliva collection from a single gland and avoided interference from other glands. By considering the variation and limited volume of the parotid gland secretion, the weighing method was applied to measure the salivary flow rate, which may eliminate the error caused by the visual interpretation of saliva volume.

The process of salivary secretion is complex and accurately controlled by nervous and humoral regulation. Multiple receptors have been identified mediating the secretive reaction of salivary gland cells[6]. Known as the ligand-gated non-selective cation channel, the vanilloid receptor 1 (VR1), which is also termed the transient receptor potential vanilloid subtype 1 (TRPV1), can be activated by heat and acid, as well as capsaicin, thus resulting in calcium influx[7,8]. Increasing evidence indicates that TRPV1 is also expressed in the SMG[2,9]. Previous research from our group demonstrated that topical application of capsaicin promoted salivary secretion, upregulated the expression of TRPV1 and aquaporin 5 (AQP5), and enhanced the membrane distribution of AQP5 in the transplanted SMG[2,10]. Tight junctions (TJs), which are the cell-to-cell interactions expressed in the epithelium and endothelium, are the structural and functional foundation of water and solute transport through the paracellular pathway[11,12]. With the impact of various physiological or pathological factors, the permeability of the paracellular pathway will be altered, followed by a change in the structure of the TJs[13]. It has been demonstrated that activation of TRPV1 could increase salivary secretion by increasing TJ expression and by diminishing TJ structural and functional injury in hypofunctional SMGs. Furthermore, the TRPV1 activation directly increased paracellular permeability of TJs in SMG cells *in vitro*[14,15]. In addition, the blood flow is also one of the most important factors affecting salivary secretion. Any reduction of blood flow might reduce secretory responses. In our previous reports, rapidly increased blood flow was detected in transplanted SMG, accompanied by increased secretion after administration of capsaicin cream[16]. In this study, local expression of increased blood flow, such as a visible flare and elevated skin temperature, was also observed after application of capsaicin cream. Furthermore, a superficial anaesthetic could not block the capsaicin-induced salivation increase, which suggested that the effect of capsaicin was not mediated by

a nociceptive response[2]. All these results suggest that an increase in salivation induced by capsaicin was initiated by the direct activation of TRPV1 and tight junctions in the SMG.

Compared with the SMG, the salivary secretion of PG was increased slightly by topical application of capsaicin cream but had no statistical significance. The difference between the two glands may be explained by the distribution of TRPV1. Sobhan and his colleagues detected the expression of TRPV1 in rat major salivary glands[17]. Immunohistochemistry revealed intense expression of TRPV1 channels in myoepithelial, acinar and ductal cells in the SMG. In the PG, the TRPV1 channels were faintly expressed in ductal cells. Although acinar and myoepithelial cells exhibited intense expression, PG are known to possess few myoepithelial cells[18]. In addition, the existence of compact parotid fascia may cause resistance to capsaicin infiltration, which could also result in lower salivary increments in the PG after application of capsaicin cream.

It has been demonstrated that continuous application of capsaicin will lead to local desensitisation. A study of Simone et al showed a decreased number of nerve fibers in the epidermis and subepidermis after local application of capsaicin[19], which is mediated by an increase in intracellular calcium, followed by neurochemical, functional and immunohistochemical alterations at the peripheral ends of TRPV1-expressing cells[20]. According to the results of McMahon et al[21], topical capsaicin treatment only produces changes in the distal tips of sensory nociceptive nerve fibers, as the vast majority of axons and cell bodies in the dorsal root ganglion remain intact, even with repeated capsaicin application. Furthermore, following discontinuation of capsaicin treatment, the health of the subdermal nerve trunks and cell bodies is supported by a return in either functionality or immunostaining in the skin of the application site, over a period of weeks[21-23]. Our results indicate that the application of capsaicin cream could induce a salivary increment in both groups. Although the response to capsaicin cream was more sensitive in the chilli-avoidance group, there was no significant difference in the effect of promoting secretion of capsaicin cream between the two groups. We speculate that the chilli-eating habit is not strong enough to cause desensitisation. There is no need to evaluate the promoting effect of capsaicin cream on salivary secretion in patients with a chilli-addicted habit.

Conclusion

The application of capsaicin cream can effectively promote the salivary secretion of SMG and PG and its effect is independent of chilli-eating habits, which indicates that topical application of capsaicin cream can be considered as a potential treatment for the hypofunction of the salivary glands.

Conflicts of interest

The authors reported no conflicts of interest related to this study.

Author contributions

- Dr Yang Wang for the study design; data collection, analysis and interpretation; the preparation, revision and submission of the manuscript.
- Dr Guang Yan Yu for the study design, manuscript revision and approval of the final version.
- Dr Zhen Wang for the data collection, analysis and interpretation. Dr Zhan Gui Tang and Dr Ji An Hu for the data collection.

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