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Nerve Growth Factor and Sensory Neuropeptide Levels in Plasma and Saliva of Various Orofacial Pain Patients

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Nerve growth factor (NGF) and sensory neuropeptides are involved in the process of nociception at peripheral nerve fibers and wide spread in central nervous system. The aims of this study were to investigate NGF and sensory neuropeptides (substance P [SP] and calcitonin gene-related peptide [CGRP]) levels in human plasma and saliva, and the associations between these sensory neuropeptides levels and chronic orofacial pain symptoms. NGF, SP, and CGRP levels in plasma and resting whole saliva samples collected from 67 orofacial pain patients (joint pain, dental or periodontal pain, mucosal pain) and 36 pain free control subjects were measured by enzyme immunoassay. The characteristic pain intensity of each subject was measured using the Graded Chronic Pain Scale and the flow rate of resting whole saliva was measured. Joint pain patients group showed significantly higher plasma NGF level compared to each of dental pain patients ($p<0.01$), mucosal pain patients ($p<0.01$), and control group ($p<0.01$). Plasma NGF level of dental pain patients group was significantly higher than that of control group ($p<0.01$). Saliva SP level of dental pain patients group ($p<0.05$) and saliva CGRP level of mucosal pain group ($p<0.05$) were significantly higher than that of control group. Plasma and saliva SP levels of joint pain patients was significantly associated with pain intensity (plasma: standardized coefficient=0.599, $p<0.01$, saliva: standardized coefficient=0.504, $p=0.05$). In dental pain patients group, plasma SP (standardized coefficient=0.559, $p<0.01$), saliva SP (standardized coefficient=0.520, $p<0.01$) and saliva CGRP (standardized coefficient=0.599, $p<0.01$) levels were significantly associated with age. In mucosal pain patients group, plasma SP (standardized coefficient=0.495, $p<0.05$), saliva SP (standardized coefficient=0.500, $p<0.05$), and saliva CGRP (standardized coefficient=0.717, $p<0.01$) levels were significantly associated with age. NGF and neuropeptides may play a role in the maintenance of various orofacial pain symptoms. The examination of those levels in plasma and saliva helps understanding the mechanism of orofacial pain, and furthermore, can be applied to the diagnosis and therapy of orofacial pain.

Key words: Plasma, Saliva, Nerve growth factor, Substance P, Calcitonin gene-related peptide

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Ⅰ. INTRODUCTION

Orofacial pain can be defined as pain related to the face or mouth. In the acute form, it is most commonly related to tooth or periodontal tissue, but it often appears as chronic clinical conditions such as burning mouth, temporomandibular disorders and headache. These pain conditions commonly cause interference in daily living activity and frequently result in dysfunction at home or work. Orofacial pain is one of the most common regional pain syndromes. Lipton et al.[1] investigated prevalence and distribution of orofacial pain in the united states. They reported that an estimated 39 million adults in the U.S. civilian population have recently experienced or currently suffer at least one type of orofacial pain.

There are some difficulties in diagnosis and treatment of orofacial pain, because the symptoms appear in various patterns and it relates to complex regional anatomy of the face and the mouth. For same reasons, the mechanism of orofacial pain has not been defined well. But it seems to be evident that some neuropeptides play a role in chronic orofacial pain condition. Neuropeptides act not only as local neurotransmitters on closely adjacent neuroeffector structures but also as hormones in their own right, being released into the bloodstream, even into the saliva, to act at sites distant from their point of release. Such diverse distribution methods and successively more diverse sites of action have suggested a large number of biological functions for these substances, including control of pain pathways which require the concerted action of many different physiological and anatomical systems. Substance P (SP) was significantly elevated in the cerebrospinal fluid of patients with fibromyalgia.[2] Calcitonin gene-related peptide (CGRP) also has been implicated in the pathogenesis of inflammatory joint diseases and joint pain.

Salivary glands secrete a large number of proteins and peptides, which have functions in host defense, immunoregulation, and maintenance of mucosal tissue and dental health. Some of the peptides found in serum or spinal fluid also are present in saliva. The salivary glands are integrated into the neuroendocrine system through complex regulatory pathways, and investigation of salivary neuropeptide concentration can give a key to diagnosis, treatment and predicting prognosis of orofacial pain. Several studies investigated the concentrations of SP and CGRP in saliva and serum of the headache patients, and showed the significant differences between normal controls and headache patients.[3,4]

Nerve growth factor (NGF) is a peptide known as a neurotrophin. In addition to the neurotrophic activity, NGF plays an important role in hyperalgesia since the concentration of this molecule was found to be increased by inflammatory injury and up-regulated in response to noxious stimuli.[5,6] NGF has been thought to be related to pain, behavioral changes, and neuropsychiatric disorders affected by the endocrine mechanism.[7,8] A number of studies were performed on NGF in chronic pain disorders. NGF has a potentiating effect on nociceptive sensory input and NMDA-evoked responses suggests its involvement in central sensitization.

The aims of this study were to investigate NGF and sensory neuropeptide (SP and CGRP) levels in both the plasma and saliva of various types of orofacial pain patients, to analyze the association between pain intensity and each NGF and sensory neuropeptide level, and to analyze the relationships among NGF and neuropeptide levels in plasma and saliva samples.

Ⅱ. METHODS

1. Subjects

Sixty-seven patients with orofacial pain who had visited in the Orofacial Pain Clinic of Seoul National University Dental Hospital from December 2002 to March 2005 and attended the Senior Hall located in Chongro-Ku of Seoul city were evaluated. Inclusion

criteria was patients who had joint pain, dental or periodontal pain, intraoral mucosal pain during past six months.

Thirty-six healthy control subjects were also evaluated. The control subjects did not have any history of orofacial pain within the previous six months.

The exclusion criteria for both groups were smokers, and systemic diseases. The project was approved by an institutional review board, and each subject gave informed consent.

The characteristics and demographic features of both orofacial pain patient and control group are shown in Table 1.

2. Characteristic pain intensity

The characteristic pain intensity of CDH was assessed using a structured questionnaire of the Graded Chronic Pain Scale.[9] The pain intensity was calculated by averaging 0-10 ratings of present pain, average pain, and worst pain in the past 6 months. This average was multiplied by 10 yielding a 0-100 score.

3. Collection of saliva and plasma

Resting whole saliva were obtained between 9 and 11 a.m. Subjects were prohibited from eating and drinking for an hour before collection. Subjects were seated under observation for 5 minutes, and right before starting the collection process the mouth was prepared by rinsing with diluted water and swallowing the residual saliva. Samples were collected through self-drainage into a sterilized tube for 10 minutes. The salivary flow rate was measured in ml/min.

Plasma samples were collected from the antecubital vein and transferred to Lavender tubes (Becton Dickinson Vacutainer System, Rutherford, NJ, USA) with EDTA.

4. Quantification of NGF, SP, and CGRP

The plasma and saliva concentrations of NGF, SP, and CGRP were measured by means of a commercially available enzyme-linked immuno-assay (EIA) kit according to the manufacturers' instructions (NGF: Promega Corp., Madison, WI, USA; SP: R&D system Inc., Minneapolis, MN, USA; CGRP: Spi-Bio Inc., Montigny le Bretonneux, France). Plates were measured with a plate reader (Power Wave, Bio-Tek Instrument Inc., Winooski, VT, USA). The person conducting the EIA measurement was blind to the identity and experimental group of the subjects.

5. Statistical analyses

One-way ANOVA was conducted to analyze the differences in the NGF, SP and CGRP level of plasma and saliva among each group of orofacial pain patients and control subjects. Post-hoc test was performed to compare each pair of orofacial pain patient groups. Multiple linear regression analysis was done to show the associations

Table 1. NGF, SP, and CGRP levels in plasma and saliva among each group of orofacial patients and control subjects

	Joint pain (n=17)	Dental pain (n=27)	Mucosal pain (n=23)	Control (n=36)
Age (yrs)	47.9 ± 11.3	62.3 ± 14.0	60.4 ± 15.0	44.3 ± 14.2
Gender (women)	12 (70.6 %)	14 (51.9 %)	17 (73.9 %)	19 (52.8 %)
Saliva flow rate (ml/min)	0.53 ± 0.21	0.43 ± 0.25	0.47 ± 0.25	0.45 ± 0.23
Pain intensity	52.1 ± 15.4	50.3 ± 25.8	41.5 ± 25.5	NA

between explanatory variables (age, gender, pain intensity, saliva flow rate) and each plasma and saliva NGF, SP, and CGRP level in three types of orofacial pain.

Ⅲ. RESULTS

The descriptive results of NGF and neuropeptide levels in plasma and saliva of each orofacial pain patients group and control subjects are shown in Table 2. Joint pain patients group showed significantly higher plasma NGF level compared to each of dental pain patients group ($p<0.01$), mucosal pain patients group ($p<0.01$), and control group ($p<0.01$). Plasma NGF level of dental pain patients group was significantly higher than that of control group ($p<0.01$). Concerning the saliva concentration, SP level of dental pain patients group ($p<0.05$) and CGRP level of mucosal pain group ($p<0.05$) were significantly higher than that of control group. (Fig. 1.)

Associations between explanatory variables (age,

Table 2. NGF, SP, and CGRP levels in plasma and saliva among each group of orofacial patients and control subjects

		Joint pain(1)	Dental pain(2)	Mucosal pain(3)	Control (0)	Significance
NGF (pg/ml)	Plasma	77.5 ± 50.0	46.8 ± 37.6	33.5 ± 17.3	21.6 ± 13.5	(0,1), (0,2), (1,2),(1,3)
	Saliva	1018.7 ± 825.5	857.7 ± 465.7	990.2 ± 534.7	891.8 ± 415.9	NS
SP (pg/ml)	Plasma	123.6 ± 64.4	150.7 ± 75.6	177.1 ± 80.6	105.0 ± 67.1	(0,3)
	Saliva	198.3 ± 78.7	269.2 ± 136.4	240.3 ± 122.5	177.5 ± 106.2	(0,2)
CGRP (pg/ml)	Plasma	204.8 ± 246.1	184.2 ± 252.7	244.2 ± 343.3	136.2 ± 92.5	NS
	Saliva	333.8 ± 227.9	420.2 ± 297.2	502.7 ± 346.9	301.5 ± 188.9	(0,3)

P-values were obtained from one-way ANOVA and post-hoc tests were performed by Tukey test

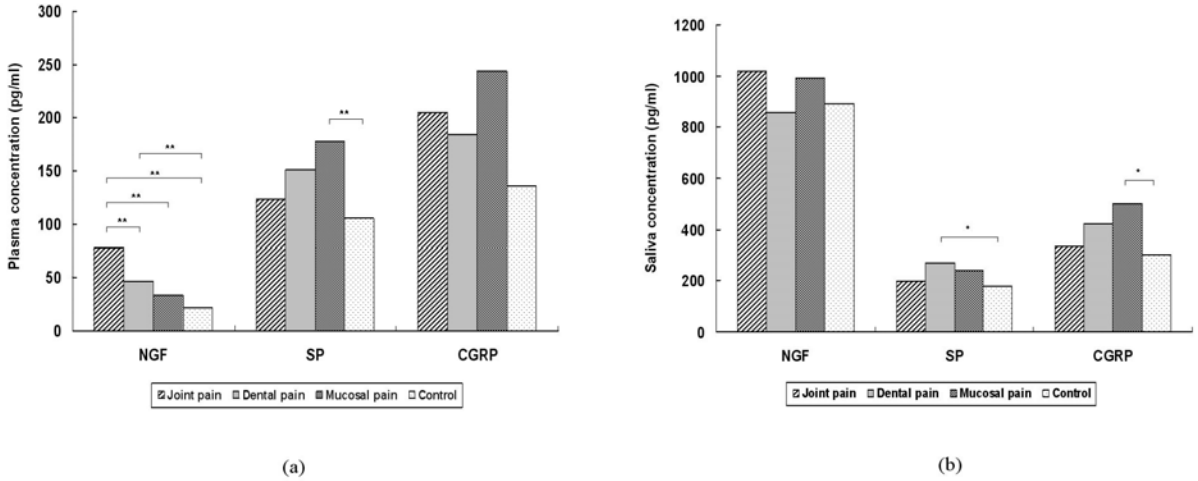

Fig. 1. NGF, SP, and CGRP levels in (a) plasma and (b) saliva among each group of orofacial patients and control subjects. (Significance *: $p<0.05$, **: $p<0.01$)

gender, pain intensity) and the concentrations of NGF and neuropeptides in each orofacial pain patients groups are shown in Table 3 and Table 4. Salivary flow rate was added to explanatory variables in analysis of saliva levels of NGF and neuropeptides in each orofacial pain patients group. Plasma and saliva SP levels of joint pain patients group showed significant association with pain intensity (plasma: standardized coefficient=0.599, $p<0.01$, saliva: standardized coefficient=0.504, $p=0.05$). In dental pain patients group, plasma SP (standardized coefficient=0.559, $p<0.01$), saliva SP (standardized coefficient=0.520, $p<0.01$) and saliva CGRP (standardized coefficient=0.599, $p<0.01$) levels were significantly associated with age. In mucosal pain patients group, plasma SP (standardized coefficient=0.495, $p<0.05$), saliva SP (standardized coefficient=0.500, $p<0.05$), and saliva CGRP (standardized coefficient=0.717, $p<0.01$) levels were significantly associated with age. Gender was not significantly associated with any of NGF and neuropeptides levels in every orofacial pain patients group, except plasma NGF concentration in dental pain patients group (standardized coefficient=0.414, $p<0.05$).

Table 3. Associations between explanatory variables (age, gender, pain intensity) and each plasma NGF and neuropeptide level of three orofacial pain groups by multiple linear regression analysis

Joint pain

Explanatory variables	Plasma NGF		Plasma SP		Plasma CGRP	
	Standardized coefficient	P-value	Standardized coefficient	P-value	Standardized coefficient	P-value
Age (yrs)	-0.039	0.893	0.254	0.246	0.136	0.643
Gender (women)	0.285	0.335	-0.101	0.636	0.030	0.917
Pain intensity	0.140	0.610	0.599	0.009	-0.284	0.310

Dental pain

Explanatory variables	Plasma NGF		Plasma SP		Plasma CGRP	
	Standardized coefficient	P-value	Standardized coefficient	P-value	Standardized coefficient	P-value
Age (yrs)	-0.329	0.084	0.559	0.003	-0.004	0.984
Gender (women)	0.414	0.036	-0.115	0.513	-0.054	0.804
Pain intensity	-0.076	0.692	0.152	0.399	-0.185	0.403

Mucosal pain

Explanatory variables	Plasma NGF		Plasma SP		Plasma CGRP	
	Standardized coefficient	P-value	Standardized coefficient	P-value	Standardized coefficient	P-value
Age (yrs)	0.137	0.564	0.495	0.022	0.064	0.794
Gender (women)	0.176	0.450	0.181	0.362	-0.106	0.658
Pain intensity	-0.246	0.289	0.242	0.220	0.062	0.793

Table 4. Associations between explanatory variables (age, gender, saliva flow rate, pain intensity) and each saliva NGF, and neuropeptide level of three orofacial pain groups by multiple linear regression analysis

Joint pain

Explanatory variables	Saliva NGF		Saliva SP		Saliva CGRP	
	Standardized coefficient	P-value	Standardized coefficient	P-value	Standardized coefficient	P-value
Age (yrs)	-0.289	0.271	0.254	0.328	0.485	0.089
Gender (women)	0.252	0.336	0.007	0.979	-0.049	0.854
Saliva flow rate (ml/min)	-0.410	0.108	-0.067	0.780	0.057	0.822
Pain intensity	0.074	0.760	0.504	0.054	0.141	0.581

Dental pain

Explanatory variables	Saliva NGF		Saliva SP		Saliva CGRP	
	Standardized coefficient	P-value	Standardized coefficient	P-value	Standardized coefficient	P-value
Age (yrs)	-0.209	0.291	0.520	0.006	0.599	0.001
Gender (women)	0.368	0.084	-0.107	0.551	0.173	0.313
Saliva flow rate (ml/min)	-0.155	0.543	0.207	0.353	-0.025	0.906
Pain intensity	-0.231	0.362	0.332	0.140	0.143	0.491

Mucosal pain

Explanatory variables	Saliva NGF		Saliva SP		Saliva CGRP	
	Standardized coefficient	P-value	Standardized coefficient	P-value	Standardized coefficient	P-value
Age (yrs)	-0.210	0.317	0.500	0.031	0.717	0.001
Gender (women)	0.401	0.059	0.118	0.580	0.202	0.209
Saliva flow rate (ml/min)	-0.291	0.199	0.318	0.180	-0.130	0.452
Pain intensity	-0.268	0.234	0.193	0.408	0.131	0.447

Ⅳ. DISCUSSION

It has been clearly defined that NGF is a survival factor during the embryonic development of sympathetic and sensory neurons, moreover it is also responsible for some peripheral and central pain conditions. NGF causes hyperalgesia when administered either locally or systemically in many species.[10] NGF has been shown not only to cause acute hyperalgesia but also to be involved in the development of allodynia and second pain response.[11] NGF-induced hyperalgesia seems to involve an enhanced production of SP and CGRP in nociceptive peripheral endings.[5] Several lines of experimental evidence support the involvement of SP and CGRP in the central mechanism as well as peripheral process underlying sensitization in painful conditions.[12]

There are several previous reports that evaluated concentrations of NGF and neuropeptides in plasma

or cerebrospinal fluid and presented elevation of NGF and neuropeptides, but most of the studies were focused on episodic headache such as classical migraine. In our study, plasma NGF levels of joint pain patients and dental pain patients groups, plasma SP level of mucosal pain patients group, saliva SP level of dental pain patients group, and saliva CGRP level of mucosal pain patients group were significantly elevated compared to the healthy controls. These findings suggest that NGF and neuropeptides have an important role in the maintenance and progression of other types of orofacial pain.

Previous studies have reported an upregulation of NGF in the synovial fluid of patients with arthritis,[13,14] and Pelegrini-da-Silva et al.[15] verified that the injection of NGF induces spontaneous nociceptive behavior in the temporomandibular joint (TMJ) of rats. These results support that inflamed peripheral tissue enhance production of NGF, and vice versa, NGF initiates or maintains tissue inflammation. In addition, NGF has been shown not only to cause acute peripheral hyperalgesia but also to be involved in the development of allodynia and second pain response.[6] The potentiating effect of the NGF on nociceptive sensory input suggests its involvement in the central sensitization.[11] Elevation of NGF concentration in plasma or saliva of patients with chronic pain condition is consequence of both peripheral and central mechanism of chronic orofacial pain. Especially, joint pain patients group showed significant high NGF level compared to each of dental pain patients group, mucosal pain patients group, and control group in our study. In consideration of the characteristics of TMJ disease, joint pain rather than dental or mucosal pain is regarded to have more chronic aspects. It is assumed that the chronicity of joint pain is related to this result. Regarding chronicization of orofacial pain, some possible mechanisms were proposed involving NMDA receptor activation and increased and maintained production of NGF,[16] but there is no definite idea about the detail.

SP is also an abundantly found neuropeptide in the peripheral and central nervous system and evidence shows that its level increases with noxious stimulation suggesting that SP may play a role in both peripheral and central sensitization of pain. Our results showed that pain intensity of the joint pain patients was significantly associated with SP levels in both plasma and saliva. However, other orofacial pain group such as dental or periodontal pain patients and mucosal pain patients groups were not significantly associated with pain intensity. We speculated that TMJ pain is more progressed into central sensitization than other localized pain group and NGF and sensory neuropeptides levels are more highly associated with intensity of patient's subjective pain.

Saliva SP level of dental or periodontal pain patients group and saliva CGRP level of mucosal pain patients group were significantly elevated. As periodontal or mucosal tissue is a barrier facing outside, it is possible that inflamed tissue and its inflammatory substances are directly exposed to oral cavity in case of tissue destruction, like periodontitis or oral ulcer. It is presumed that the elevations of SP and CGRP are influenced by immediate release of SP and CGRP into saliva. SP and CGRP are released from nociceptive afferents during repeated stimulation.

Some of saliva neuropeptides levels were significantly associated with age (saliva SP and CGRP of dental and mucosal pain patients group), but not with salivary flow rate. Besides, some plasma neuropeptides levels (plasma SP of dental and mucosal pain patients group) also had significant correlation with age. These results suggested that the elevation of neuropeptide concentrations does not result from hyposalivation caused by aging, but from other systemic mechanism.

Most of the studies that have been conducted in the past to assess the role of neuropeptides and neurotrophins in chronic pain mechanisms have centralized on the plasma concentration level. However collecting saliva has advantages such as cost effectiveness and the easy non-invasive nature

of collection and the relationship between oral fluid and plasma levels make oral fluid a valuable clinical tool. The value of whole saliva as a specimen for the diagnosis of hereditary disorders, autoimmune diseases, malignant and infectious diseases, and endocrine disorders, as well as in the assessment of therapeutic levels of drugs and the monitoring of illicit drug use has been readily proved through many studies, since it is readily collected and contains serum constituents. In the same manner measuring neuropeptide levels in saliva has advantages over analyzing serum as a diagnostic tool for various types of orofacial pain.

Collectively, NGF and neuropeptides may play a role in the maintenance of various orofacial pain symptoms. The examination of those levels in plasma and saliva helps understanding the mechanism of orofacial pain, and furthermore, can be applied to the diagnosis and therapy of orofacial pain.

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국문요약

다양한 구강안면통증환자의 혈장 및 타액에서의 신경성장인자와 감각성 신경펩티드 농도에 관한 연구

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장민욱 · 정성창 · 정진우

신경섬유 말단에서의 유해자극 인지과정에는 신경성장인자 (nerve growth factor [NGF])와 감각성 신경펩티드가 관여하고, 또한 이들은 중추신경계에도 광범위하게 분포되어 있다. 본 연구는 인체 혈액과 타액에서 NGF와 감각성 신경펩티드 (substance P [SP], calcitonin gene-related peptide [CGRP])의 농도를 조사하여 다양한 구강안면통증 증상들과의 관계를 알아보고자 시행되었다. 67명의 구강안면통증 환자 (관절 통증, 치아 혹은 치주 통증, 점막 통증)와 36명의 건강한 성인에서 혈장과 안정시 전타액을 채취하여 효소면역분석법 (enzyme immunoassay)을 이용하여 NGF, SP, CGRP의 농도를 측정하였다. 만성통증척도 (Graded Chronic Pain Scale) 설문지를 이용하여 각 피실험자들의 통증강도를 조사하였으며 안정시 전타액의 타액분비율 또한 측정하였다. 관절 통증 환자군은 치아 통증 환자군, 점막 통증 환자군, 대조군 각각에 비하여 유의하게 높은 혈장 내 NGF 농도를 나타내었다. 치아 통증 환자군의 혈장 내 NGF 농도는 대조군에 비하여 유의하게 높았다. 치아 통증 환자군의 타액 내 SP 농도와 점막 통증 환자군의 타액 내 CGRP 농도 또한 대조군에 비하여 유의하게 높았다. 관절 통증 환자군의 혈장 및 타액 내 SP 농도는 통증 강도와 유의한 상관관계를 보였다. 치아 통증 환자군과 점막 통증 환자군에서, 혈장 내 SP 농도, 타액 내 SP 농도, 타액 내 CGRP 농도는 연령에 따라 증가하였다. 혈장과 타액에서의 신경성장인자와 신경펩티드 검사는 다양한 구강안면통증의 특성과 예후를 평가하는데 도움을 줄 수 있으리라 생각된다.

주제어: 구강안면통증, 혈장, 타액, 신경성장인자, 감각성 신경펩티드