Short Communication

Perception of pungent, gustatory and olfactory stimuli in patients with congenital insensitivity to pain with anhidrosis

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Abstract: Congenital insensitivity to pain with anhidrosis (CIPA) is a rare disease caused by a mutation in the nerve growth factor (NGF) receptor, which results in an absence of A δ and C fibers. It can be considered that this defect may also lead to deterioration of oral sensations. The aim of the present study was to clarify the ability of CIPA patients to perceive pungent, gustatory, and olfactory stimuli, which is essential for eating function, and the impact of the defect on dietary habits. Sensitivities to capsaicin and the five basic tastes were evaluated by measuring their threshold values, and dietary habits were examined using a questionnaire. Additionally, odor identification ability was evaluated using the odor stick method. The detection threshold for capsaicin and the recognition threshold for sour taste were significantly higher in the patients than in healthy volunteers. The questionnaire responses showed that the patients consumed spicy food more often. All patients were able to identify the tested odors, except those to which they had not been well accustomed. Since the abilities of CIPA patients to perceive taste and smell were not basically impaired, despite their lower sensitivity to capsaicin, it was suggested that their dietary habits were only minimally affected, except for intake of pungent foods.

Keywords: congenital insensitivity to pain with anhidrosis, dietary habits, perception, pungency, smell, taste

Introduction

Congenital insensitivity to pain with anhidrosis (CIPA), known as hereditary sensory and autonomic neuropathy (HSAN) Type IV, is a rare autosomal recessive disorder caused by a mutation in the neurotrophic receptor tyrosine kinase 1 gene encoding the tyrosine kinase receptor A (TrkA) for nerve growth factor (NGF). Since the NGF/TrkA system does not function normally in CIPA, patients congenitally lack peripheral nerves, such as A δ and C fibers conveying pain sensation, and sympathetic postganglionic nerves [1]. Thereby, CIPA patients present with pain insensitivity, lack of thermal sensitivity, absence or decline of perspiration (anhidrosis), and intellectual disability. As self-mutilations due to indolence frequently involve oral structures, dental management including mouth guard application has been taken [2].

Because the oral functions involved in eating have a great impact on the quality of life, comprehensive studies on the sensations relevant to food intake in CIPA patients are required in order to understand any problems in their dietary habits. Therefore, the present study was conducted to investigate the perception of pungent, gustatory and olfactory stimuli in CIPA patients. To evaluate perceptual abilities, the thresholds for capsaicin, a typical pungent stimulus, and the five basic tastes, and odor identification ability were measured. In addition, a questionnaire survey of dietary habits was conducted to assess whether the patients' actual dietary habits were

influenced by the defect.

Materials and Methods

Nineteen CIPA patients were recruited from among attendees at the annual meeting of the Japan Association of Patients with CIPA and outpatients attending Tokyo Medical and Dental University Dental Hospital. Patients with significant damage to oral tissues or with moderate to severe intellectual disability were excluded. Fifty-three healthy participants were also recruited from among the students and faculty members of the university as well as hospital outpatients. None of them were smokers or receiving medication, and none had any complaints related to oral sensation or smell. This study was performed between 2010 and 2017 with the approval from the Ethics Committee of Faculty of Dentistry, Tokyo Medical and Dental University (approval number 963). Written informed consent was obtained from all participants or their parents.

Eleven patients (8 males and 3 females, 14.6 ± 6.5 yr) and 31 healthy participants (12 males and 19 females, 27.5 ± 4.6 yr) participated in measurement of the detection threshold for capsaicin, using topical tongue-tip application of a filter paper disc 6 mm in diameter infiltrated with capsaicin solution. Only 6 (0.001, 0.003, 0.01, 0.03, 0.1, and 0.3 mM) out of 12 concentration levels of capsaicin (Table 1) were used for CIPA patients because a preliminary test had shown that their thresholds were much higher, and the measurement had to be completed within a short time to ensure their attention and cooperation.

The recognition thresholds for each basic taste were measured by the whole-mouth method in six patients (4 males and 2 females, 20.0 ± 8.9 yr) who were able to perceive all tastes in the preliminary test, and in 31 healthy participants (12 males and 19 females, 27.5 ± 4.6 yr). All participants refrained from eating and drinking anything except for water for 2 h prior to the examination. After tasting 3 mL of each test solution (Table 1), the subjects were asked to choose an answer from seven options: "no taste", "some taste but unable to identify the respective taste", "sweet", "sour", "salty", "umami", or "bitter". The lowest concentration at which the participant could correctly identify the taste was taken as the recognition threshold.

In the questionnaire study, 10 patients (6 males and 4 females, 17.7 ± 4.2 yr) and 25 healthy participants (10 males and 15 females, 25.8 ± 4.6 yr) answered 7 questions regarding their dietary habits (Table 2).

Eight patients (6 males and 2 females, 16.1 ± 9.0 yr) and 12 healthy participants (4 males and 8 females, 22.6 ± 9.9 yr) participated in the identification test for eight types of odor, which are familiar even to children, using the Odor Stick Identification Test for Japanese (Daiichi Yakuhin Sangyo Ltd., Tokyo, Japan).

Statistical analyses were performed using IBM SPSS Statistics 25.0 (Japan IBM Co., Tokyo, Japan). The differences in measured values between the patients and the healthy volunteers were evaluated using the Mann-Whitney *U*-test, chi-squared test, or the Fisher's exact test. A *P*-value of <0.05 was considered statistically significant.

Results

Measurements of the detection thresholds for capsaicin demonstrated significantly higher thresholds in the patients than in the healthy volunteers

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Table 1 Concentration levels of each solution used for measurement of thresholds

Concentration levels	Pungent Capsaicin (mM)	Sweet Sucrose (M)	Sour Citric acid (M)	Salty NaCl (M)	Umami MSG (M)	Bitter Quinine (mM)
12	0.5					
11	0.3					
10	0.1					
9	0.05	1	0.05	0.5	0.5	0.3
8	0.03	0.5	0.03	0.3	0.3	0.1
7	0.01	0.3	0.01	0.1	0.1	0.05
6	0.005	0.1	0.005	0.05	0.05	0.03
5	0.003	0.05	0.003	0.03	0.03	0.01
4	0.001	0.03	0.001	0.01	0.01	0.005
3	0.0005	0.01	0.0005	0.005	0.005	0.003
2	0.0003	0.005	0.0003	0.003	0.003	0.001
1	0.0001	0.003	0.0001	0.001	0.001	0.0005

MSG, monosodium glutamate; Quinine, quinine hydrochloride

Table 2 Responses to the questionnaire on dietary habits

Question	Options	Rarely		Sometimes		Often		Usually		P-value
		n	(%)	n	(%)	n	(%)	n	(%)	
Q1. How often do you eat sweet food?	Healthy	0	(0)	5	(20)	10	(40)	10	(40)	0.163
	CIPA	0	(0)	0	(0)	4	(40)	6	(60)	
Q2. How often do you eat sour food?	Healthy	1	(4)	7	(28)	11	(44)	6	(24)	0.737
	CIPA	0	(0)	3	(30)	6	(60)	1	(10)	
Q3. How often do you eat salty food?	Healthy	1	(4)	5	(20)	12	(48)	7	(28)	0.088
	CIPA	0	(0)	1	(10)	3	(30)	6	(60)	
Q4. How often do you eat umami-rich food?	Healthy	0	(0)	2	(8)	19	(76)	4	(16)	0.096
	CIPA	0	(0)	0	(0)	6	(60)	4	(40)	
Q5. How often do you eat bitter food?	Healthy	7	(28)	11	(44)	7	(28)	0	(0)	0.724
	CIPA	2	(20)	5	(50)	3	(30)	0	(0)	
Q6. How often do you eat spicy food?	Healthy	1	(4)	4	(16)	18	(72)	2	(8)	0.056
	CIPA	0	(0)	1	(10)	5	(50)	4	(40)	
	Options	Lightly		Moderate		Heavily				P-value
		n	(%)	n	(%)	n	(%)			
Q7. How do you season your usual meal?	Healthy	7	(28)	16	(64)	2	(8)			0.138
	CIPA	0	(0)	8	(80)	2	(20)			

CIPA, congenital insensitivity to pain with anhidrosis. The significance of differences was determined using the Mann-Whitney *U*-test for Q1-Q6 and chi-squared test for Q7. **Fig. 1** (a) Detection thresholds in concentration levels of capsaicin solution in the healthy volunteers and CIPA patients. (b) The recognition thresholds for the five basic tastes in the two groups. The thresholds in the two groups are displayed as box plots and the *P*-values determined using the Mann-Whitney *U*-test are presented above. The whiskers indicate the lowest and highest values, and the boxes represent the 25-75% data ranges. The horizontal lines within the boxes represent medians, and the “x” symbols indicate the means.

($P < 0.001$) (Fig. 1a). The recognition thresholds for sucrose, NaCl, and quinine were not significantly different between the two groups, while the thresholds of the patients for citric acid were significantly higher ($P = 0.031$) and those for monosodium glutamate (MSG) tended to be higher ($P = 0.075$) as compared to the respective thresholds of the healthy volunteers (Fig. 1b).

The questionnaire study showed that the patients tended to consume salty food ($P = 0.088$), umami-rich food ($P = 0.096$), and spicy food ($P = 0.056$) more frequently than the healthy volunteers (Table 2). When the participants were further classified into two groups for the response ‘usually’ as a high consumer group and the others as a low consumer group,

the patient group showed a significantly higher ratio of high consumers of spicy food than the healthy group (Fisher’s exact test, $P = 0.043$).

For the six types of odor (menthol, orange, curry, rose, sweaty socks, and condensed milk) that are familiar in daily life, the percentage of participants who identified each odor did not differ between the patients and the healthy volunteers (Fig. 2). However, the identification rate among the patients for Chinese ink and wood odor, which were unfamiliar to them, was significantly lower in comparison with the healthy volunteers (Chinese ink: $P = 0.019$, wood: $P = 0.049$).

Fig. 2 Ratio of subjects who correctly identified the eight types of odor among the healthy volunteers and the CIPA patients. (P-values obtained by the Fisher's exact test are presented above. n.s., not significant)

Discussion

As CIPA patients congenitally lack peripheral nerves conveying pain sensation [1], it had been commonly accepted that they cannot perceive information on pungent stimuli transmitted through the pain pathway [3]. However, the present study demonstrated that CIPA patients were able to perceive irritating or pain sensation induced by capsaicin through activation of transient receptor potential cation channel subfamily V member 1 (TRPV1), although the detection thresholds of them were significantly higher than those of the healthy volunteers. One explanation for this finding is that the patients may have partly retained A δ and C fibers rather than completely lacking them. Another possibility is that the patients may have perceived the capsaicin stimulus via A β nociceptive neurons, as it has been suggested that A β nerve fibers contain a certain amount of nociceptive afferent fibers [4] and the expression of TRPV1 is not limited to small-diameter neurons but also extends to larger-diameter neurons [5].

Since taste bud cells have been reported to express NGF and its receptor TrkA [6], it was anticipated that the taste sensitivities of the patients would have been affected. However, the recognition thresholds for the basic tastes except for sourness did not differ significantly between the patients and the healthy volunteers. These results suggested that the patients basically had similar ability to recognize the basic tastes as healthy individuals, and that NGF and TrkA might not play a significant role in peripheral taste function. The higher threshold for acid stimulus could be explainable by the receptor mechanisms for sourness. Because a recent animal study has suggested that gustatory nerve responses to acid may partly consist of information transmitted by TRPV1-sensitive neurons [7], patients having fewer TRPV1-expressing neurons might have lower sensitivity to sourness.

The questionnaire results demonstrated that the patients consumed spicy food more frequently than the healthy volunteers. Since the patients showed lower sensitivity to capsaicin, it was not surprising that they consumed spicy food more frequently.

This study also revealed that CIPA patients had rates of identification for familiar odors similar to those of the healthy volunteers, showing lower rates of identification for the two odors reflecting the lack of previous experience because of younger age. This finding suggests that the odor identification ability of CIPA patients is almost equivalent to that of healthy individuals.

The major limitation of this study was the small sample size of patients. This was because only patients in good physical condition with mild to almost no intellectual disability were selected. Therefore, the results may not be generalizable beyond the context of the study. Another limitation

was the difference in age between the two groups—the patient group being younger than the healthy group—because of the need to include children in the patient group to increase the total number. However, these age differences had only a minimal impact on the current outcomes for pungency and taste perception, since previous studies have reported that these abilities in children are similar to those in adults [8,9].

Although further research using a larger patient cohort may be warranted, this is the first report to have clarified that CIPA patients are basically able to sense pungent, gustatory and olfactory stimuli. Together with the results obtained through the questionnaire, these findings may provide useful knowledge for patients or their caregivers regarding dietary habits in order to enhance their quality of life.

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Conflict of interest

None.

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