Responses by humans to oral chemical irritants as a function of locus of stimulation

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Different areas of the mouth varied in responsiveness to chemical irritation. Subjects were stimulated with 7-mm filter-paper disks containing capsaicin or piperine, which are irritant components of red and black pepper, in seven different regions of the mouth. They reported intense sensations from stimulation of the tip of the tongue, side of the tongue, and posterior palate, all of which contain gustatory receptors, and less intense sensations from the cheek and anterior palate. Capsaicin produced relatively more intense responses from the lip and posterior tongue than did piperine. Sensations produced by stimulation of these small areas grew over time. The patterns of qualitative adjectives used to describe the sensations arising from the two compounds were not the same. These results suggest that irritative chemical stimuli may be qualitatively differentiable.

A fundamental characteristic of sensory systems with spatially distributed arrays of receptors is variation in sensitivity to different stimuli across the spatial array. In the skin senses, for example, variations in sensitivity to thermal, pressure, vibrotactile, and pain stimuli have been "mapped" across the body surface (Geldard, 1972; Kenshalo, 1960; Kenshalo, Decker, & Hamilton, 1967; Stevens, Marks, & Simonson, 1974; Wilska, 1954). Spatial variation in responsiveness is also a characteristic of the mouth. Collings (1974) and Sandick and Cardello (1981) compared the responsiveness of oral areas to tastants, and Green (1984) studied spatial differences in oral responsiveness to thermal stimuli. However, little attention has been paid to the assessment of spatial variation in oral responsiveness to irritative compounds. Previous research is limited to two reports. In one the tongue was stimulated only at the tongue tip and root (Dunér-Engström, Fredholm, Larsson, Lundberg, & Saria, 1986), and in the second, the whole mouth was stimulated without localization of stimuli (Lawless, 1984). One goal of the present study was to assess differences in oral responsiveness to irritants over more areas and with a higher degree of stimulus control than in previous studies.

The importance of understanding spatial variation lies not only in psychophysical documentation, but in the implications for anatomical and physiological correlates of such variation. Spatial variation in responsiveness must

arise from differences in receptor type, receptor density, or aspects of the receptor environments, such as depth in the epithelium, that could influence the accessibility of stimuli to receptors.

Differences in spatial patterns of responsiveness across the parts of the mouth could also give rise to qualitative differentiation of irritative stimuli. An unresolved question is whether there are perceptually different qualities of irritation, or whether all types of irritation feel the same. To further address this possibility, we had subjects describe the sensory qualities elicited by localized stimulation in addition to judging perceived intensity.

METHOD

Subjects

Eight male and 12 female paid volunteers, 18-27 years of age, served as subjects. One male and 2 females were smokers. Before participating, all were informed of the general nature of the study and of their right to terminate their participation at any time.

Stimuli

Stimulation with wetted swatches of filter paper has been found to be a reliable technique for localizing tastants to particular parts of the oral epithelium (Collings, 1974). Stimuli were administered on 7-mm disks of Whatman Qualitative Grade 1 filter paper to which either 2.5 μ g capsaicin (Sigma Grade 1) or 230 μ g piperine (Sigma) in ethanol solutions had been added. These concentrations had been found in pilot work to produce equally intense sensations on the tip of the tongue. The ethanol evaporated from the paper prior to the application of the stimulus to the tongue.

Procedure

Subjects were instructed in magnitude estimation and were given practice in judging the weights of visually identical jars of 100, 200, 400, and 800 g, presented in random order three times each.

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Figure 1. Mean perceived intensity of capsaicin stimuli for the seven loci in the mouth over time. The data were normalized such that the initial rating of the stimulus on the tip of the tongue was set equal to 100.

Figure 2. Mean perceived intensity of piperine stimuli for the seven loci in the mouth over time.

No standard was identified and no modulus was assigned either during practice or during the experiment proper.

Seven places in the mouth were independently stimulated with two irritants: (1) the midline dorsal surface of the tip of the tongue, (2) the side of the tongue (3 cm posterior to the tip), (3) the posterior tongue below the soft palate on the midline in the region of the circumvallate papillae, (4) the inside of the lower lip in front of the incisors, (5) the inside of the cheek opposite the molars, (6) the posterior (soft) palate approximately 1 cm behind the hard palate on the midline, and (7) the midline of the hard palate medial to the canine teeth. Subjects participated in four sessions, two for each irritant compound. Half the subjects received capsaicin first, and half received piperine first. Either three or four loci were stimulated in each session, in a randomly determined sequence.

Before each test, the subject rinsed with distilled water and expectorated. Then the experimenter, using forceps, placed a stimu-

lus paper on a site. The mouth was then closed, and the tongue was kept away from treated surfaces (if a tongue site was being stimulated, the tongue was kept away from all surfaces). Every 30 sec for 5 min, the subjects were given response sheets on which they (1) recorded their magnitude estimates of the intensity of irritation and (2) indicated on checklists the most appropriate descriptor from each of four general categories: taste, thermal, tactile, and flavor. Taste choices were *sweet*, *sour*, *salty*, *bitter*, and *metallic*. Thermal choices were *burning*, *very hot*, *hot*, *very warm*, and *warm*. Tactile choices were *biting*, *pricking*, *piercing*, *itching*, and *stinging*. Flavor choices were *peppery*, *spicy*, *tangy*, *astringent*, and *flavorful*. We chose the descriptors on the basis of previous work (Lawless, 1984). Responses of *other* or *no sensation* were also permitted. The subjects were not provided with definitions of the descriptors.

At the end of each test, the subject expectorated into a 30-ml cup, clearing the mouth of saliva. Whole-mouth clearing has been found to be as reliable as other salivary measurement procedures (Navazesh & Christensen, 1982). Cups were weighed to the nearest .01 g. A minimum intertrial interval of 5 min was imposed between tests within sessions. A test was never begun if the subject reported residual sensations from the previous test. During the intertrial intervals, questionnaires were administered to the subjects to assess personality variables and preference for and frequency of eating hot and spicy foods. These data are not reported here.

Data were normalized to set the initial perceived intensity estimate for capsaicin at the tip of the tongue to 100 for each subject.

RESULTS

The mean perceived intensities of irritation are shown for the seven loci over time in Figure 1 (capsaicin) and Figure 2 (piperine). For both compounds, irritation increased over time [$F(9,171) = 17.14, p < .01$] and was described by an exponential approach to an asymptote in the equation

$$R = R_{\max} - e^{-kt},$$

where $R_{\max}$ is the asymptote and k is a rate constant (Riggs, 1963). Table 1 gives these constants for each curve, fitted by an iterative procedure from RS-1 (BBN Research Systems, 1983) (r^2 s exceeded .9).

Table 1
Parameter Estimates for Capsaicin and Piperine

Locus	$R_{\max}$		k Rate Constant	
	M	SEM	M	SEM
Capsaicin				
Tip of tongue	342	11	.53	.04
Lip	266	7	.59	.04
Side of tongue	214	6	.57	.05
Posterior palate	212	5	.50	.03
Back of tongue	149	4	.45	.03
Anterior palate	125	17	.37	.10
Cheek	86	2	.68	.06
Piperine				
Tip of tongue	278	8	.60	.05
Lip	127	8	.43	.06
Side of tongue	156	8	.60	.09
Posterior palate	165	12	.42	.06
Back of tongue	60	2	.79	.10
Anterior palate	40	2	1.28	.29
Cheek	60	2	.83	.08

Table 2
Saliva Flow (in Grams)

Locus	Capsaicin		Piperine	
	<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>
Tip of tongue	7.9	1.3	5.1	0.6
Lip	2.3	0.3	2.2	0.2
Side of tongue	3.8	0.7	3.2	0.5
Posterior palate	3.2	0.4	2.2	0.2
Back of tongue	3.0	0.4	1.9	0.2
Anterior palate	2.6	0.4	1.6	0.2
Cheek	2.3	0.4	1.9	0.3

Note—Values are means for whole-mouth flow over 5 min.

Differences in responsiveness were observed among loci [$F(6,114) = 15.08, p < .01$]. For both compounds, the tip of the tongue was the most responsive area. The remaining areas fell roughly into two groups: a moderately responsive group—the lip, posterior palate, and side of the tongue; and a group of areas with low responses—the anterior palate, back of the tongue, and cheek.

This pattern was not the same for the two compounds, however. One major difference was that the lip was highly responsive to capsaicin (mean over time = 193), but

moderately responsive to piperine (mean over time = 81) (orthogonal planned comparison [Hays, 1981], $p < .001$). A similar two-to-one difference was also seen between responses made to stimulation of the posterior tongue by capsaicin (mean = 97) and by piperine (mean = 48; $p < .05$).

Saliva weights are shown in Table 2. Stimulation of the tongue tip evoked the largest salivary response for both compounds. Capsaicin was a more potent stimulator of saliva than was piperine in all cases except for stimulation of the lip [stimulus $\times$ locus interaction, $F(6,114) = 4.15, p < .01$; Duncan multiple range tests on individual loci, $p < .01$ in all cases but the lip].

The frequencies of choices of different descriptors for each locus are shown in Table 3 for capsaicin and Table 4 for piperine. *No taste* and *no flavor* were the most frequently chosen descriptors (58% of the taste category and 59% of the flavor category, respectively). The two compounds were similar in the overall frequencies of descriptors chosen ($r = .94$).

In spite of this similarity, a compound $\times$ locus $\times$ descriptor interaction was observed [$F(114,2166) = 1.66$,

Table 3
Descriptor Totals—Capsaicin

Attribute	Locus						
	Tip of Tongue	Lip	Cheek	Posterior Palate	Anterior Palate	Posterior Tongue	Side of Tongue
Taste							
Sweet	1	0	0	0	7	0	1
Sour	3	3	15	0	5	0	9
Salty	36	20	23	19	17	10	12
Bitter	61	21	16	33	0	26	59
Metallic	36	6	15	37	43	58	43
Other	0	0	0	0	0	0	0
No taste	63	150	131	111	128	106	76
Thermal							
Burning	97	59	8	67	14	24	49
Very hot	47	39	16	33	14	10	35
Hot	36	31	27	30	9	15	45
Very warm	16	36	35	13	32	42	25
Warm	4	24	67	40	74	66	42
Other	0	0	0	0	0	0	0
No thermal	0	11	47	17	57	43	4
Tactile							
Stinging	108	78	39	67	39	48	93
Pricking	21	11	37	45	42	33	37
Biting	17	18	19	12	6	23	20
Itching	27	9	22	20	12	22	14
Piercing	14	39	1	35	15	16	13
Other	0	3	2	1	4	2	0
No tactile	13	42	80	20	82	56	23
Flavor							
Peppery	35	29	36	25	28	33	31
Spicy	52	28	27	19	12	18	30
Tangy	14	1	5	34	0	15	11
Astringent	16	0	7	3	2	7	22
Flavorful	0	0	0	0	10	0	7
Other	0	0	0	0	0	8	0
No flavor	83	142	125	119	148	129	99

Table 4
Descriptor Totals—Piperine

Attribute	Locus						
	Tip of Tongue	Lip	Cheek	Posterior Palate	Anterior Palate	Posterior Tongue	Side of Tongue
Taste							
Sweet	1	0	0	1	0	4	3
Sour	0	3	4	0	10	2	5
Salty	9	19	5	11	13	12	18
Bitter	46	21	35	39	23	24	46
Metallic	45	19	22	35	13	26	14
Other	0	0	0	0	1	0	0
No taste	99	138	134	114	140	132	114
Thermal							
Burning	64	15	12	21	5	3	21
Very hot	53	14	5	21	2	9	21
Hot	43	45	6	37	5	10	40
Very warm	18	25	21	40	6	9	32
Warm	17	68	60	61	74	118	77
Other	0	0	3	0	3	0	0
No thermal	5	33	93	20	105	51	9
Tactile							
Stinging	105	68	34	50	17	20	62
Pricking	14	26	22	45	13	50	55
Biting	11	3	4	12	3	9	10
Itching	34	31	32	48	29	32	32
Piercing	17	7	3	19	0	2	2
Other	1	2	7	5	0	6	9
No tactile	18	63	98	30	138	81	30
Flavor							
Peppery	63	39	32	40	20	34	40
Spicy	42	34	34	27	7	17	48
Tangy	10	17	9	19	1	10	11
Astringent	0	0	0	9	0	6	11
Flavorful	1	0	0	9	5	3	0
Other	1	0	0	0	1	0	0
No flavor	83	110	125	96	166	130	90

$p < .01$]. Locus $\times$ descriptor and compound $\times$ descriptor interactions were also seen [$F(114,2166) = 5.64$ and $F(19,361) = 3.20$, respectively, $ps < .01$]. There was a complex pattern of descriptor choices for different loci and compounds. In the taste category, capsaicin evoked more *metallic* and fewer *no taste* choices. In the thermal category, capsaicin evoked more *burning* and *very warm* responses, whereas piperine evoked more *warm* and *no thermal* responses (see Figure 3). In the tactile category, capsaicin evoked more *stinging*, *biting*, and *piercing* choices, whereas piperine evoked more *itching* and *no tactile* choices than did capsaicin (Figure 4).

A principal-components analysis of the totals from Tables 3 and 4 (excluding descriptors with less than 5% total frequency) yielded six factors that accounted for 90% of the variance. The first was a general intensity factor, which correlated with 10 of the descriptors at $r \geq .5$ and accounted for 29% of the variance. The second was a burning pain factor which correlated with 8 descriptors (22% of the variance). The third correlated with the *bitter* and *metallic* descriptors and negatively with *no taste* (14%). The fourth factor correlated with *tangy* and *pricking* (9%), the fifth with *very warm* and *biting* (9%), and the sixth with *salty* (8%).

DISCUSSION

Our results address the following issues: (1) the nature of spatial differences in oral responsiveness to irritants, (2) the possibility of qualitative differentiation of irritants, (3) patterns of temporal summation, and (4) the relationship of subjective intensity ratings to the magnitude of the evoked salivary reflex.

Two major findings concerned the spatial pattern of responsiveness. First, different oral loci are differentially responsive to oral chemical irritation. The present results showed the tip of the tongue to be most responsive; Duner-Engstrom et al. (1986) also found the anterior tongue to be more responsive than the posterior. Green (1984) observed a similar pattern of responsiveness to thermal stimulation of the tongue and lip. He found the tongue tip to be more responsive than the tongue dorsum and the lip under most conditions.

The responsiveness of the tongue tip relative to other areas is predictable in light of anatomical and physiological observations. This area shows a higher density of fungiform papillae (Miller, 1986) than other areas of the tongue. The fungiform papillae, in addition to providing a supporting matrix for taste buds, are also richly inner-

Figure 3. Mean frequency of choices (percent) allotted to selected thermal descriptors for capsaicin (open bars) and piperine (hatched bars).

Figure 4. Mean frequency of choices (percent) allotted to selected tactile descriptors for capsaicin (open bars) and piperine (hatched bars).

vated by lingual trigeminal afferents (Beidler, 1969; Cheal & Oakley, 1977; Farbman & Hellekant, 1978; Miller, 1974; Whitehead, Beeman, & Kinsella, 1985). Many of these fibers terminate in extremely superficial layers of the extragemmal cells surrounding the taste buds, making them well suited to interaction with the oral chemical milieu (Whitehead et al., 1985). Furthermore, they often show substance P immunoreactivity, suggesting a role in nociception (Nagy, Goedert, Hunt, & Bond, 1982; Nishimoto et al., 1982). The substance P-containing fibers of the glossopharyngeal nerve (Yamasaki, Kubota,

& Tohyama, 1985) innervating the posterior tongue may be less responsive than the anterior trigeminal fibers, or, alternatively, there may be more restricted access of irritant molecules to receptors on the posterior tongue.

Our second important finding was that the two oral irritants were different in the spatial patterns of response they evoked. Capsaicin stimulated a greater response from the lip and posterior tongue than did piperine. These results are similar to previous observations based on frequencies of reports of irritation of areas following whole-mouth stimulation (Lawless, 1984). There are also some

similarities in the patterns of stimulation by the two irritants, with several oral areas being effectively stimulated by both compounds.

Differences in the spatial pattern of response to various irritant compounds provide an additional mechanism by which irritants might differ in perceived quality (as opposed to intensity). Consumers of hot and spicy foods often claim that different types of pepper burn different areas of the mouth. The locus $\times$ compound $\times$ descriptor interaction noted in our descriptor frequency counts suggests differences in perceived quality in addition to variations in spatial pattern. Previous results provide indirect evidence for the possibility of qualitative differentiation. First, the course of decay of sensation over time differs for capsaicin and piperine (Stevens & Lawless, 1986). Second, capsaicin's and piperine's patterns of interaction with the four basic tastes are different (Lawless & Stevens, 1984). Third, studies of sensory interactions with sequential stimulus presentation suggest at least partial specificity of receptors for these two compounds (Stevens & Lawless, 1987).

It is possible that qualitative differences in the current data may be explained in part by intensity differences and that higher concentrations of piperine may attenuate the differences we observed. However, complete equation of intensity is problematic. Due to the differences in growth of sensation with locus, concentration, and time, intensity equivalence could be achieved only at specific loci and specific time intervals. Qualitative differences may also be explained by side-bands, that is, sensations other than the burning pain and irritation characteristic of these stimuli. Although *no taste* and *no flavor* were the most frequently chosen descriptors, they were not universal. In particular, we were surprised to find *salty* chosen 8% of the time. This suggests that these compounds provide some minor but perceivable sensations in the classical gustatory qualities, and that these sensations may contribute to qualitative differences.

One unexpected result was that the perceived intensity of irritation grew over time and appeared to approach an asymptote; it did not decay within the time period we examined. This is in contrast to the decay in sensation that begins within about 1 min in whole-mouth "sip-and-spit" methods of stimulation (Lawless, 1984; Stevens & Lawless, 1986). It could be argued that the growth in sensation is due to spreading of the stimulus, perhaps through salivary wetting. In other words, what appears to be a case of temporal summation could instead be a case of spatial summation. We find this suggestion questionable for several reasons. First, one other study in which small localized areas were stimulated showed growth of intensity over time; in that study, a flow chamber was used to stimulate the tongue surface (Lawless & Gillette, 1985). With a flow chamber in contact with the extended tongue, salivary spreading can be ruled out. Second, the loci we studied were chosen (after extensive pilot work) to avoid areas in which salivary pooling would occur. Third, if salivary spread were a factor, one might expect reports of throat burn, which did not occur. Fourth, if salivary

spread were a factor, there should have been greater perceived intensity in the "wetter" areas. Instead, we found that capsaicin produced a higher intensity estimate on the lip (a relatively dry spot) than on the side of the tongue (relatively more prone to wetting).

"Subjective" estimation of perceived intensities of irritation was largely paralleled by the "objective" measure of evoked salivary flow, as observed in other studies (Duner-Engstrom et al., 1986; Lawless, 1984). However, our results uncovered one important exception to this general relationship: although capsaicin was significantly higher in perceived intensity on the lip, stimulation of the lip evoked equivalent salivary flow for the two compounds. Therefore, proportionality of the magnitude of the salivary reflex response and the magnitude of sensation intensity should not be universally assumed.

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