



Perceived Irritation during Ingestion of Capsaicin or Piperine: Comparison of Trigeminal and Non-trigeminal Areas

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Abstract

The aim of this study was to investigate the perception of chemosensory irritation in the oropharyngeal region during the ingestion of irritants. In two experiments subjects sipped and swallowed small samples of an ascending concentration series of capsaicin or piperine and rated the intensity of sensations of irritation perceived at four locations: the anterior tongue, the posterior tongue, the roof of the mouth and the throat. Both experiments revealed that the responsiveness to irritation from capsaicin was significantly higher in the throat than at either the front or back of the tongue. There was no difference between irritation ratings for the throat and the roof of the mouth. Compared with capsaicin, the responsiveness to piperine was more uniform along the rostro-caudal axis; for example, irritation ratings for the throat were similar to those for the anterior tongue. These results support previous findings which indicated that the oral mucosae were not uniformly sensitive to chemical irritants, and suggest further that the throat, which is innervated by both the glossopharyngeal and vagus nerves, plays an important role in the perception of chemesthetic stimuli during ingestion. *Chem. Senses* 22: 257–266, 1997.

Introduction

Perception of the gustatory and somatosensory attributes of foods is not limited to the mouth. The taste, temperature, mechanical properties and irritancy of ingesta are also sensed in the pharynx and throat. As self-evident as this is, the study of human taste and oral somatosensation has focused almost exclusively on the sensitivity of the mouth. This parochial view undoubtedly owes largely to the greater accessibility of the rostral oral regions compared with the pharynx and throat, and to the tacit adoption of the anterior rinse, or 'sip-and-spit' procedure, as the standard method of stimulation. The sip-and-spit procedure is easy

to use and avoids potential complications from post-ingestional effects (e.g. satiety or nausea) and protective reflexes (e.g. gagging or coughing). However, because it restricts the stimulus to the front of the mouth, the procedure cultivates an over-simplified view of orosensory perception.

This over-simplification has been greater for somatosensation than for taste. Although there have been considerably fewer studies of gustation in the caudal than in the rostral oral cavity, the gustatory neurophysiology and sensitivity of the soft palate, posterior tongue and throat

have nevertheless received attention (e.g. Zotterman, 1935; Bradley *et al.*, 1986; Dickman and Smith, 1988; Frank, 1991; Grill *et al.*, 1992). The same is not true for somatosensation. The term 'trigeminal stimulus' is still used routinely to describe any and all stimuli that evoke sensations other than taste or smell (e.g. Silver, 1987; Carstens *et al.*, 1995; Prescott and Stevenson, 1995), even though the trigeminal nerve does not project to the oral pharynx or throat. Once stimuli pass the front two-thirds of the tongue they move into regions innervated by the glossopharyngeal (IX) and vagus (X) nerves, which contain somatosensory as well as gustatory fibers (Zotterman, 1935; Nail *et al.*, 1969; Sweazey and Bradley, 1989; Tsubone *et al.*, 1991). These two nerves innervate the posterior region off the tongue (IX), the soft palate (IX), the oral pharynx (IX and X) and the throat (X) (Brodal, 1972).

With the notable exception of the benchmark studies by Rozin and co-workers on the development of a preference for chili pepper (Rozin and Schiller, 1980; Rozin *et al.*, 1981, 1982), psychophysicists who have studied oral chemesthesis have consistently chosen methods (e.g. anterior rinses or flows, filter paper stimuli) that limit stimulation to the mouth. This is not to say that the sensitivity of the caudal regions has always been overlooked. Lawless (1984) included data on the frequency of occurrence of throat irritation caused by several chemical irritants, but because a sip-and-spit procedure was used the throat was stimulated only by the residual stimulus that leaked into posterior regions. Similarly, Cliff and Heymann (1992) asked subjects to rate sensations of irritation in the throat after sipping and expectorating capsaicin and a few other irritants, but throat irritation was not analyzed apart from overall irritation.

In the present study the perception of chemosensory irritation in the throat was studied directly. The first experiment, which required subjects to rate the irritation perceived at three oral sites and the throat after ingesting capsaicin, provided evidence that the throat is the primary site of chemosensory irritation when the stimulus is swallowed. The second experiment confirmed the pre-eminence of the caudal areas for perception of capsaicin, and showed that the sensory response to piperine was distributed more uniformly along the rostro-caudal axis.

Experiment 1

The objective of this experiment was to obtain information

about the spatial perception of sensory irritation from capsaicin when it is delivered in an aqueous solution and swallowed. A wide range of concentrations was used to discover whether regional responsiveness would vary with the strength of the stimulus.

Method

Subjects

Twenty subjects—10 men and 10 women (average age 24 years)—were paid to participate in the experiment. Half of the subjects were employees of the Monell Center and half were students of the University of Pennsylvania. All but two of the subjects had previously served in other studies of oral irritation in this laboratory.

Stimuli

The stimuli were 10 ml samples of a range of concentrations of natural capsaicin (98%; Sigma, St Louis, MO) prepared in an aqueous solution containing 4% ethanol as solvent, 1.0% Polysorbate 80 (Spectrum) to hold the capsaicin in solution, and 0.125 M sucrose (Spectrum, New Brunswick, NJ) as a sweetening agent to ameliorate the unpleasant flavor of the surfactant. The stimulus series included a blank (vehicle only) and eight capsaicin concentrations spaced in quarter-log steps: 0.32, 0.59, 0.98, 1.83, 3.2, 5.8, 9.8 and 18.3 μ M (0.1–5.6 p.p.m.). All stimuli were prepared weekly and stored in glass bottles.

Procedure

In the first session sensory irritation was defined for subjects as any of the following qualities: burning, stinging/pricking, itching, tingling or numbness. These descriptors and their definitions (Cliff and Green, 1996) remained visible throughout the session. The Labeled Magnitude Scale (LMS) (Green *et al.*, 1993), which was used here to rate the intensity of sensations of irritation, was then presented on a computer screen and explained to the subject. Subjects who had experience with the LMS were reminded of its use, while those unfamiliar with the scale were given more detailed instructions. The latter instructions included asking subjects to rate the imagined intensities of a set of ten hypothetical oral stimuli that spanned a wide range of sensation intensities and qualities (e.g. the bitterness of celery, the coldness of an ice cube, the burning sensation from eating a whole chili pepper). Subjects were then presented with a 10 ml stimulus (vehicle only) to get

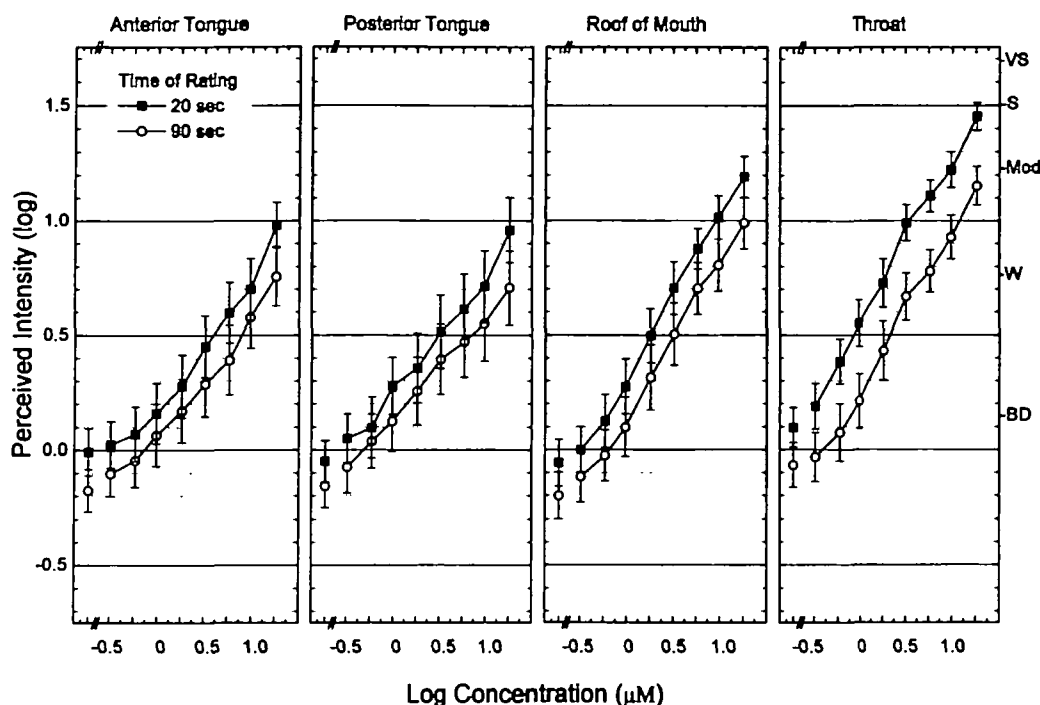


Figure 1 Log-means of the irritation ratings for capsaicin in Experiment 1 as a function of concentration for each of the four locations. The parameter in each graph is the time of rating. Note that irritation ratings tended to increase in the rostro-caudal direction and decrease between the 20 and 90 s observation times. The abbreviations on the right y-axis refer to descriptors on the LMS (BD = barely detectable, W = weak, M = moderate, S = strong, VS = very strong).

acquainted with the procedure and to help them distinguish between sensations caused merely by swallowing and those caused by capsaicin. The subject was instructed to sip the stimulus, to hold it in the mouth and agitate it slightly with the tongue, and after 3 s to swallow it.

Thirty seconds after the subject had sipped the practice stimulus he or she received the first of nine experimental stimuli. The same procedure was followed except that 20 and 90 s after sipping the stimulus the subject was prompted to rate the sensations of irritation felt at four locations in the oral cavity: the front of the tongue, the back of the tongue, the roof of the mouth and the throat. Half of the subjects rated the locations in rostral to caudal order, and half in caudal to rostral order. Rating all four areas took an average of ~15 s, and a new stimulus was presented every 2 min. Each subject participated in three sessions of ~20 min separated by at least 48 h in an effort to avoid desensitization across sessions.

Data analysis

Because ratings from the LMS tend to be distributed log-normally across subjects, the data were first transformed to logarithms. Zero intensity ratings were adjusted to 0.24,

the computer value associated with one pixel unit above 'no sensation' on the LMS. The data were then subjected to a repeated measures ANOVA with group (2) as a between-subject factor and session (3), concentration (9), time of rating (2) and location (4) as within-subject factors. Post hoc analyses were conducted using Tukey's HSD with the significance level set at $P < 0.05$.

Results and discussion

Figure 1 contains the mean irritation ratings as a function of concentration and time of rating for the four locations of interest. It is evident that the sensory irritation from capsaicin varied across locations, with sensations tending to be stronger in the more caudal regions. The decay of sensation as measured by the difference in intensity between the 20 and 90 s ratings also appeared to vary across locations. These visual impressions were confirmed by the ANOVA. There were significant main effects of concentration [$F(8,144) = 171.06$, $P < 0.0001$], time [$F(1,18) = 52.49$, $P < 0.0001$] and location [$F(3,54) = 7.20$, $P = 0.00038$]. The main effect of location reflected a continuous increase in mean irritation rating in the rostro-caudal direction. For example,

subjects' perception of the strongest stimulus of the concentration series at 20 s was just above 'weak' on the lingual locations, but was 'moderate' on the roof of the mouth and 'strong' in the throat. Tukey HSD tests revealed that when collapsed across concentrations the perceived intensity of irritation in the throat was significantly higher than the irritation perceived on the front or back of the tongue but not on the roof of the mouth.

The effect of concentration was also modified by location [$F(24,432) = 5.46$, $P < 0.0001$]. The best fitting power functions for the four areas indicate that increases in concentration produced more pronounced increases in irritation on the roof of the mouth and throat than on the two lingual sites. The exponents of the best-fitting power functions for the anterior and posterior tongue were 0.51 and 0.47, and for the roof of the mouth and throat 0.68 and 0.70 respectively (Pearson $r_s > 0.985$). The caudal regions therefore tended to be both more sensitive to capsaicin at a given concentration and to yield larger increments in irritation for a given increase in concentration.

The more rapid decay in irritation in the throat between the 20 and 90 s ratings was confirmed by an interaction between time of rating and location [$F(3,54) = 10.58$, $P < 0.0001$], and the effect of concentration also changed significantly with time [$F(8,144) = 2.17$, $P = 0.0328$] (the rate of growth in irritation was slightly lower at 90 s than at 20 s). The only other statistically significant effects were interactions between session and concentration [$F(16,288) = 3.29$, $P < 0.0001$] and between session and time [$F(2,36) = 3.30$, $P < 0.05$]. The former interaction was due to progressively lower ratings of irritation across sessions at the lowest but not the highest concentrations, and the latter interaction was due to a larger drop in irritation between the 20 and 90 s ratings in the third session compared with the first. These interactions are consistent with the development of slight desensitization across testing sessions (Karrer and Bartoshuk, 1991).

Because the blanks (vehicle) were not rated as producing even 'barely detectable' irritation, it is reasonable to use the concentration at which sensations were rated as more than 'barely detectable' as a rough estimate of the detection threshold at each site. Based on this assumption and looking at the ratings made at 20 s, the thresholds were 0.32 μM for the throat, 0.59 μM for the roof of the mouth and 0.98 μM for the anterior and posterior tongue. These values indicate a threefold difference in responsiveness across sites.

Experiment 2

The results of the first experiment confirmed that the sensory response to capsaicin was not uniform along the oro-pharyngeal axis. The primary aim of the second experiment was to discover if the same pattern of relative spatial sensitivity would be found if another irritant were tested. Piperine was selected as the second irritant because Lawless and Stevens (1988) had shown it produced a somewhat different pattern of irritation from capsaicin in the oral cavity. This raised the possibility that the throat might not be the most responsive site for piperine. In addition, we modified the testing procedure in a way we hoped would increase the ability to detect spatial differences. Instead of asking subjects to rate irritation in a fixed spatial sequence, the instructions were to rate the sites according to intensity of irritation, from strongest to weakest.

Method

Subjects

Sixteen subjects—eight females and eight males (average age 24 years)—were paid to participate. As in the first experiment, half of the subjects were employees of the Monell Center and half were students of the University of Pennsylvania. Nine of the subjects had participated in Experiment 1 but did not know its outcome.

Stimuli

The capsaicin (Sigma, 98%) concentration series was the same as in Experiment 1. The piperine (97%; Aldrich, Milwaukee, WI) stimuli were prepared from a 0.01 M stock solution, and the concentrations used were 24, 42, 75, 133, 240, 420, 750 and 1330 μM . Both stimuli were prepared by pipetting appropriate amounts of concentrated stock solutions (with ethanol as the solvent) into 10 ml of the vehicle (H_2O , Tween and sucrose in the same concentrations as before) moments before presentation to the subject. This was done because the highest concentration piperine stimulus, which had been determined in pilot testing to produce about the same level of irritation as the strongest capsaicin stimulus, tended to come out of solution when stored at room temperature. Increasing the amount of Tween or ethanol in the vehicle would have helped keep the piperine in solution, but would also have intensified the taste and irritancy of the vehicle to unacceptable levels. The

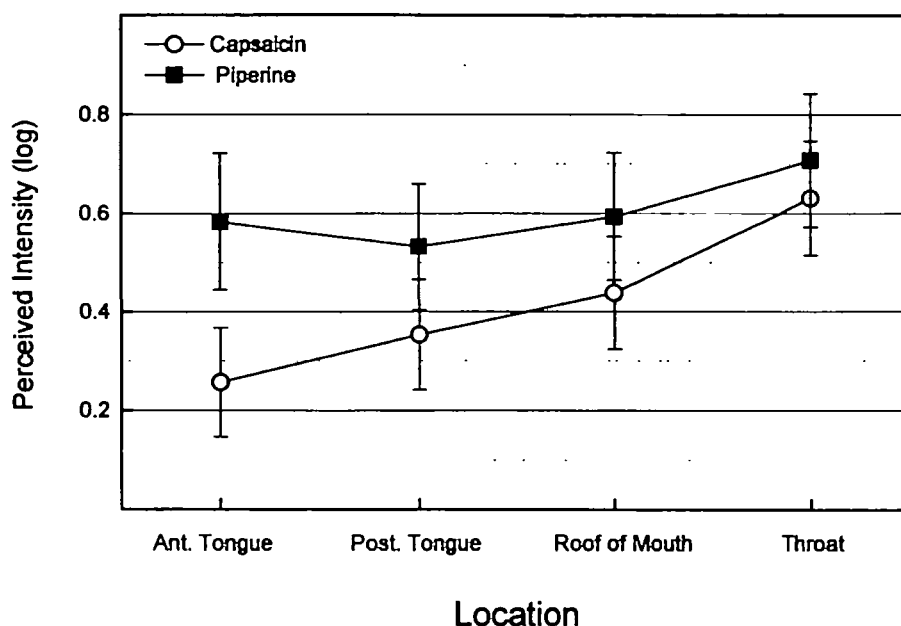


Figure 2 Log-means of irritation ratings for capsaicin and piperine as a function of perceived location. The data have been collapsed across concentration and time of rating. Note that subjects rated piperine as more irritating than capsaicin at the three oral locations, but not in the throat.

vehicle was prepared weekly and stored in airtight glass bottles.

Procedure

The procedure was changed from Experiment 1 to allow subjects to rate irritation at the four oropharyngeal sites in an order determined by the amount of irritation perceived at each site. Twenty seconds after sipping the solution the subject was presented with a list of the four locations on the computer screen with the instruction to select the area on which they felt the strongest irritation. After clicking on an area the LMS appeared on the screen and the subject rated the intensity of irritation for that site. Immediately after the rating was made a list of the remaining three locations appeared with the instruction to select the next most irritated location. This process continued until all four areas had been rated. A second set of ratings was made beginning 90 s after ingestion.

Capsaicin and piperine were presented in alternate sessions. Eight of the subjects received the capsaicin series in the first session (group I), and eight received piperine first (group II). Each subject participated in six ~20 min sessions with at least 48 h between sessions.

Data analysis

The data were transformed to logarithms (with zeros again

given the value of 0.24 before transformation), and the results for capsaicin and piperine were analyzed both together and individually. The overall analysis, which was run primarily to identify significant interactions involving irritant as a factor, was a five-way (irritant \times group \times location \times time \times concentration) repeated measures ANOVA, with group as a between-subjects factor. Session was not included as a factor because of limitations in the number of variables that could be accommodated by the statistical software. Session was included in the individual ANOVAs for the two chemicals. Tukey's HSD tests were carried out to investigate specific interactions among factors, with significance levels again set at $P < 0.05$.

Results and discussion

Capsaicin versus piperine

The overall analysis revealed several significant effects involving irritant as a factor. A main effect of irritant reflected somewhat higher ratings of irritation for piperine than for capsaicin [$F(1,14) = 23.58$, $P < 0.0001$]. However, this difference varied as a function of several factors, the most important one being the perceived location of irritation [irritant \times location, $F(3,42) = 5.95$, $P = 0.0018$]. This outcome can be seen graphically in Figure 2. Tukey tests showed that the piperine stimulus led to higher

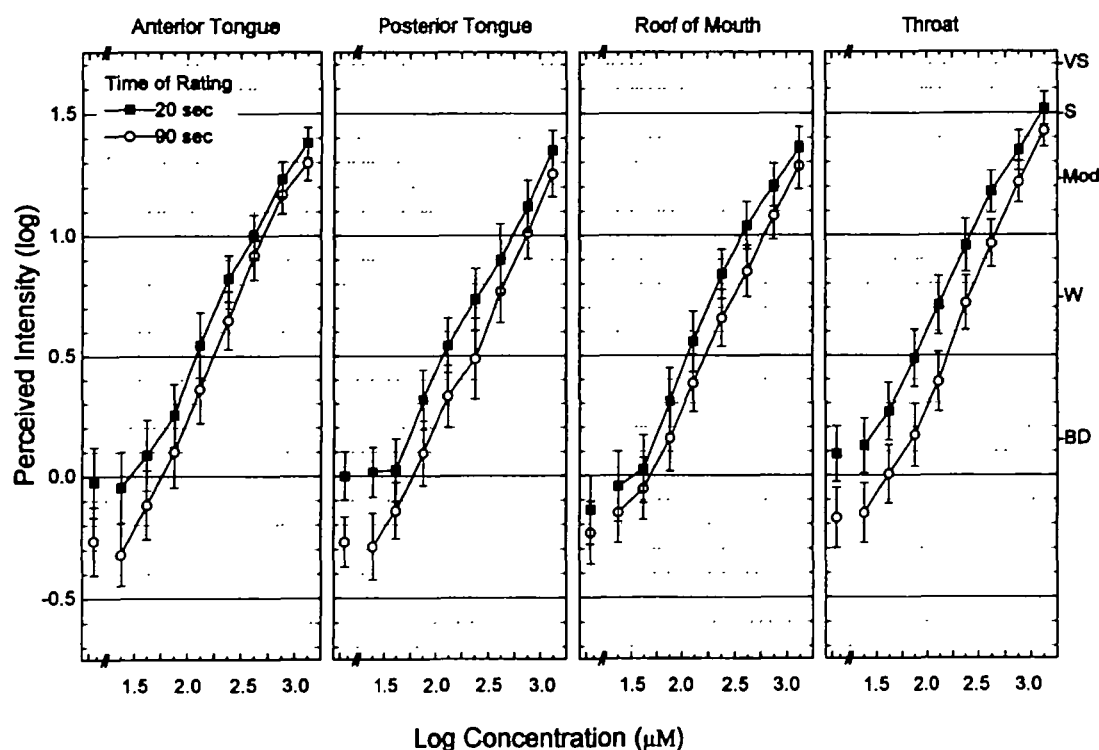


Figure 3 Log-means of irritation ratings for piperine in Experiment 2 as a function of concentration and time of rating for each of the four locations. Piperine did not yield a significant effect of perceived location (BD = barely detectable, W = weak, M = moderate, S = strong, VS = very strong).

irritation ratings than did the capsaicin stimulus on the anterior tongue, the posterior tongue and the roof of the mouth, but not in the throat. The effect of location was also influenced by time of rating and concentration [irritant \times time \times concentration, $F(8,112) = 4.03$, $P = 0.0003$]. The differences across sites were larger at the 20 s rating than at the 90 s rating, and at the higher concentrations than at the lower concentrations.

The order of testing, i.e. whether subjects received piperine first or capsaicin first, also significantly affected the results, but in a way that is difficult to interpret. A three-way interaction among group, irritant and concentration [$F(8,112) = 3.04$, $P < 0.0039$] was obtained because subjects who received piperine first rated it as more intense than capsaicin at all concentrations, whereas subjects who received capsaicin first rated piperine stronger only at the four highest concentrations.

Piperine analysis

The results obtained for piperine are graphed in Figure 3. The ANOVA on these data confirmed the obvious effect of concentration [$F(8,112) = 196.6$, $P < 0.0001$], as well as the effect of time of rating [$F(1,14) = 53.9$, $P < 0.0001$].

Consistent with the results of the overall ANOVA, the piperine analysis showed neither a significant main effect of location nor a significant interaction between location and concentration. Both of these effects had been found with capsaicin (see Experiment 1 and below). However, there was a significant interaction between location and time of rating [$F(3,42) = 7.43$, $P < 0.00042$], and Tukey tests revealed that it was attributable to changing patterns of significant differences across the two rating times. For example, at 20 s the throat was rated as significantly more irritated than all the other locations, whereas at 90 s there was no difference between the throat and the anterior tongue. On the other hand, at 90 s the posterior tongue and roof of the mouth differed significantly, whereas at 20 s they did not. Adding to the difficulty in interpreting these differences was a significant three-way interaction among group, time of rating and location [$F(3,42) = 3.09$, $P = 0.037$]. The apparent pattern of responsiveness depended to some degree on whether subjects were tested first with piperine or with capsaicin. This outcome provides further evidence that, compared with capsaicin, the spatial variations in responsiveness to piperine are smaller and less reliable.

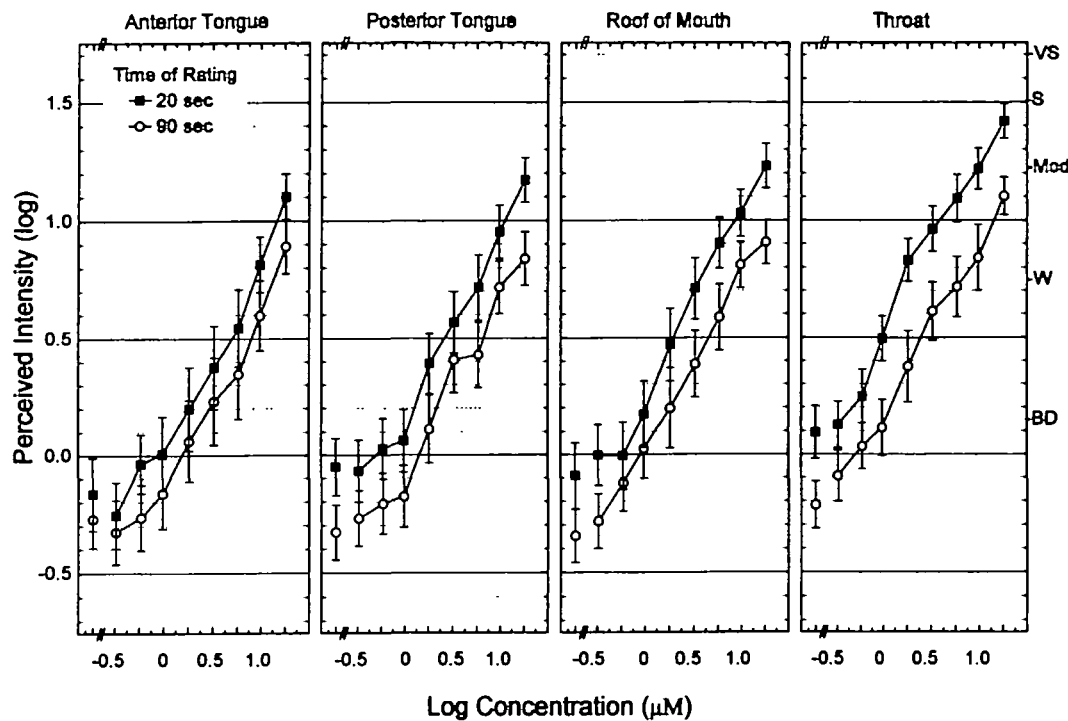


Figure 4 Same as Figure 1, but for capsaicin in Experiment 2.

The only other significant effects revealed by the ANOVA were a main effect of session, which reflected decreasing mean intensity ratings across the three sessions [$F(2,28) = 8.06$, $P = 0.0017$] that may be indicative of desensitization, and an interaction among group, concentration and time [$F(8,112) = 2.07$, $P = 0.044$], which reflected small differences in the psychophysical functions for the two groups at the two rating times.

Capsaicin analysis

The results for capsaicin, shown in Figure 4, were broadly consistent with the findings of Experiment 1. Most notably, in contrast to piperine, there was a main effect of location [$F(3,42) = 4.48$, $P = 0.0080$] and an interaction between location and concentration [$F(24,336) = 1.95$, $P = 0.0055$]. The latter interaction confirmed the trend found in Experiment 1 toward steeper psychophysical functions for the throat and roof of the mouth. Also as before, a significant time \times location effect was obtained [$F(3,42) = 7.51$, $P = 0.0004$] that was attributable to a more rapid decline in irritation for the throat than for the other areas, which had the effect of decreasing the spatial differences at 90 s. Time of rating also influenced the effect of

concentration [$F(8,112) = 2.88$, $P = 0.0059$], reducing it slightly at 90 s.

As with piperine, there was a main effect of session [$F(2,28) = 4.46$, $P = 0.0209$] that might be indicative of slight desensitization across days. Session also interacted with concentration [$F(16,224) = 4.03$, $P < 0.0001$], and with group and location [$F(6,84) = 2.34$, $P = 0.0384$]. Tukey tests showed that the interaction with concentration was attributable to significantly higher ratings at the three lowest concentrations during the first session. Whether these differences were the result of desensitization or a change in response criterion is difficult to say. The three-way interaction can be traced to the non-uniformity of the decline in irritation across locations, and to the occurrence of a larger decline for group 1 than for group 2.

General discussion

These results demonstrate that the throat is an important site of chemosensory irritation when solutions are ingested, and hence that 'oral' chemesthesis is not mediated exclusively by the trigeminal nerve. In fact, the branches of the glossopharyngeal and vagus nerves that innervate the pharynx, and perhaps the larynx, appear to respond more

strongly to ingested capsaicin than do the branches of the trigeminal nerve that innervate the oral mucosa. As described in the introduction, other workers have recognized that irritation occurs in caudal oral and pharyngeal areas, but the importance of these areas for perception of irritants during ingestion had not been established.

In the first experiment the level of irritation reported for capsaicin in the throat was as much as three times stronger than that reported for either lingual site. The second experiment confirmed the higher pharyngeal responsiveness to capsaicin, whereas the responsiveness to piperine was found to be more spatially uniform. It can be seen in Figure 2 that the difference between capsaicin and piperine derived chiefly from a lower responsiveness to capsaicin in the mouth than in the throat: the piperine stimulus produced stronger irritation overall than did the capsaicin stimulus, but the difference was not significant for the throat.

Why the throat was equally responsive to both stimuli while the mouth was less responsive to the capsaicin stimulus is unclear. The most likely explanations have to do with possible regional differences in the permeability of the mucosa to the two chemicals, and possible differences in the spatial distribution of the afferent fibers they stimulate. Although the two chemicals share several basic molecular characteristics (e.g. an aromatic ring and an alkyl side-chain), they also differ in ways that could influence their abilities to penetrate the epithelium (Govindarajan, 1980). Unfortunately we could find no published data on the absorption of capsaicin and piperine by mucosal tissue. On the other hand, the possibility that the two chemicals stimulate different populations of receptors receives indirect support from several sources. Piperine was reported to resist significant cross-desensitization by capsaicin in a behavioral study in rats (Szolcsanyi and Jancso-Gabor, 1976), but to exhibit cross-desensitization to a high concentration of capsaicin in a urinary bladder preparation (Patacchini *et al.*, 1990). In our own laboratory we have observed asymmetrical cross-desensitization between capsaicin and piperine on lingual tissue (Green, 1996) and cross-sensitization between capsaicin and piperine (unpublished data). The latter finding is consistent with earlier reports of 'enhancement' of irritation when the two chemicals were presented either sequentially or in mixture (Stevens and Lawless, 1987; Lawless and Stevens, 1990). Lawless and Stevens (1990) hypothesized that enhancement resulted from varying degrees of overlap in the receptor populations stimulated by capsaicin and piperine.

It should be emphasized that exposing the entire oropharyngeal area to these irritants and asking subjects to rate the sensations at specified sites may have led to an underestimation of the actual differences in responsiveness among the sites. Sipping and swallowing the stimulus creates a 'stream' of sensation through the throat and mouth that crosses all anatomical boundaries. The subject must attempt to segment his or her oropharyngeal region into the areas requested by the experimenter, and to assign intensity ratings to sensations within those areas. It is arguable that it would be difficult enough to attend to individual anatomical regions in the absence of widespread irritation. When irritation occurs throughout much of the region simultaneously the subject is confronted with the chemesthetic equivalent of visual glare: the irritation in the throat seems to radiate into the oral cavity. This situation may have led to an overestimation of irritation on the posterior tongue and palate, and thus to an underestimation of the spatial variation in sensitivity. However, the naturalistic method of stimulus presentation also invited the occurrence of counterirritation, an inhibitory phenomenon within the nociceptive and thermal systems in which stronger stimuli attenuate the perceived intensity of weaker ones (Duncker, 1937; Gammon and Starr, 1941; Macarthur and Alstead, 1953; Wand-Tetley, 1956). Spatial suppression of this sort would be expected to counteract 'glare' by increasing the 'contrast' between areas of high and low stimulation. In addition, it is possible that reciprocal inhibitory mechanisms are intrinsic to somatosensory processing along the oropharyngeal axis just as they appear to be between the gustatory elements of the chorda tympani and glossopharyngeal nerves (Halpern and Nelson, 1965; Lehman *et al.*, 1995).

With these complexities and limitations of the 'sip-and-swallow' method in mind, the present results nevertheless demonstrate that the throat is an important area for the perception of chemical irritation and that its contribution relative to more rostral areas depends upon the irritant that is ingested. To discover the absolute sensitivity of the various oropharyngeal areas will require an approach similar to that used by Lawless and Stevens (1988) in their study of the oral cavity. However, the pharynx and throat present difficulties for access and stimulus control that will require the development of new methods of stimulus delivery or, alternatively, the use of topical anesthesia to deaden one area while stimulating others. Once appropriate techniques have been developed they can be used to obtain a

more complete picture of how the oral and pharyngeal areas differ in sensitivity to different types of irritants (e.g. acids versus salts) and to explore spatial interactions (e.g. counterirritation) between the trigeminal system and the vagal and glossopharyngeal systems that affect perception during normal consumption. With regard to the latter, it will also be informative to investigate the perception of irritants

during consumption of solids. In contrast to liquids, solids dwell in the oral cavity for several seconds as they are masticated or dissolved. Because the solutions in the present experiment were held in the mouth for only 3 s before being swallowed, the longer oral exposures that occur during mastication may increase perceived irritation in the mouth to levels that equal or exceed those in the throat.

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