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Responses to Repeated Oral Irritation by Capsaicin, Cinnamaldehyde and Ethanol in PROP Tasters and Non-tasters

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Abstract

Both increases (sensitization) and decreases (desensitization) in oral irritation have been reported in response to repeated short-term stimulation by compounds such as capsaicin, zingerone and menthol. It is unclear why one irritant would show sensitization and another desensitization, and this is further complicated by substantial inter-individual variation in response patterns. These variations may be the result of individual differences such as that represented by sensitivity to 6-*n*-propylthiouracil (PROP), which has been associated with variation in the overall intensity of irritation. In addition, comparisons between irritants have almost always involved inter-study comparisons, entailing different subject groups and frequently different methods. In the studies reported here, responses to three irritants—capsaicin, cinnamaldehyde and ethanol—were examined as a function of PROP taster status. A common core of subjects also received all three irritants, allowing an assessment of the extent to which different response patterns between irritants seen previously were the result of different properties of the irritants themselves. Over a series of ten stimuli presented at 1 min intervals, PROP taster status differentiated subject responses on the basis of overall intensity, but not the pattern of responses over repeated stimulation. The group response to ethanol and cinnamaldehyde was desensitization, a pattern also shown by most of the individual subjects. In contrast, the group response to capsaicin was neither clear sensitization nor desensitization, reflecting much greater individual variability in response patterns. It is suggested that the time course to a single irritant stimulus largely determines between irritant response variations, while the inter-stimulus interval (ISI) used for a given irritant will have critical values for showing predominantly sensitization or desensitization.

Introduction

Recent research on human psychophysical responses to oral irritation has shown that, in contrast to the adaptation seen with tastes (Gent and McBurney, 1978), a series of irritant samples is able to produce sensitization (an increase in irritation intensity). Conversely, a pause in stimulation following such a series has been shown to produce a marked decrease in sensation intensity for a subsequent irritant stimulus (desensitization) (Stevens and Lawless, 1987; Green, 1989, 1991). However, while desensitization is the response observed with *in-vitro* preparations such as rat trigeminal ganglion cells (Liu and Simon, 1996), sensitization has been observed only as a human perceptual response. It is thus unclear whether these patterns of response to irritation reflect general properties of oral trigeminal physiology, or are a characteristic of the human perceptual response to irritation, which could reflect both cognitive factors and individual differences, in addition to the neural response. In order to determine the significance of sensitization, there is a need to explain two sources of variability observed in the responses to repeated oral irritation that are currently poorly understood. These are, firstly, variations in response which appear to be dependent on the irritant being studied and, secondly, the high degree of inter-individual variability observed in responses to a given irritant.

Although commonly observed in studies using capsaicin, the potent irritant in chilies (Green, 1989, 1991), sensitization does not appear to be produced by all oral irritants. Thus, while the irritation produced by sodium chloride (Green, 1989) sensitizes, this has not been evident for a number of other oral irritants, including menthol (Cliff and Green, 1994), ethanol (Green, 1990) and nicotine (Dessirier *et al.*, 1997). Studies on zingerone, the pungent compound present in ginger, predominantly showed desensitization, although some subjects did show sensitization (Prescott and Stevenson, 1996a,b). The reasons why irritants might respond differently include the activation of different excitatory mechanisms (Green and Lawless, 1991). The possibility that the method of stimulation might be important in determining response patterns was recently explored in a comparison of whole mouth rinses and filter papers as vehicles for capsaicin delivery (Prescott, 1999). There was little evidence from this study that the stimulus method *per*

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se was a significant influence. Amongst these studies, however, there has not been an examination of responses from the same group of subjects to repeated stimulation by a selection of different irritants. This is important to give some idea of the extent to which subject factors or stimulus factors determine response variability.

It is well known that human hedonic responses to irritants vary. Some individuals show high levels of dislike for foods that are pungent, while others develop preference for their daily consumption (Prescott and Stevenson, 1995a). The source of individual differences in preference is poorly understood, but may lie in different psychophysical responses. In studies of responses to repeated samples of the irritants zingerone (Prescott and Stevenson, 1996b), capsaicin (Cliff and Green, 1996; Prescott, 1999) or menthol (Cliff and Green, 1996), even when there was an overall group response pattern of sensitization or desensitization, a variety of individual response patterns was observed, including some individuals who show little or no change in rated intensity over successive samples. Previous studies have explored the role of frequency of hot (spicy) food consumption as a source of such variability. However, this factor was found to be relatively unimportant in predicting whether an individual sensitized or not over a series of zingerone stimuli (Prescott and Stevenson, 1996a). Nevertheless, low-frequency users of chili do rate the burn of capsaicin as more intense than frequent users (Prescott and Stevenson, 1995b). Explanations for this difference have been previously given in terms of either chronic desensitization (Karrer and Bartoshuk, 1991) or a context effect (Stevenson and Prescott, 1994). Another possibility, however, is that it represents pre-existing individual differences in sensitivity to irritation which, in turn, influence consumption frequency.

It has been shown that both thresholds and suprathreshold judgements for the bitterness of PROP show considerable variation within the population, and individuals have been classified as super-tasters, medium-tasters and non-tasters, according to their sensitivity to PROP bitterness (Bartoshuk *et al.*, 1994). These taste differences reflect underlying anatomical differences, in that the density of fungiform papillae and taste pores on the tongue increases with PROP sensitivity, with taste bud density doubling in each step from non-tasters to medium-tasters to super-tasters (Bartoshuk *et al.*, 1994). Other perceptual differences have been noted between these different responders to PROP, including differing degrees of sensitivity to the taste of other compounds (Bartoshuk *et al.*, 1988; Looy and Weingarten, 1992). PROP tasters have also been shown to rate the intensity of capsaicin as more intense than do non-tasters (Karrer and Bartoshuk, 1991). Trigeminal nerve fibres tend to be anatomically associated with fungiform papillae (Whitehead *et al.*, 1985), so the more papillae are present, the greater the number of trigeminal fibres and more intense the sensations of oral irritation. It would be expected, therefore, that other irritant compounds would also reveal differences between different taster groups, and there has been one report that PROP super-tasters also perceive the bitterness and irritation of ethanol as more intense than do non-tasters (Bartoshuk *et al.*, 1993).

Since variations in PROP sensitivity are associated with different responses to irritation intensity, it is possible that degree of PROP sensitivity may also predict different response patterns to repeated stimulation. If sensitization reflects additional recruitment of surrounding fibres during repeated stimulation, then PROP tasters (and especially super-tasters) with their greater density of fungiform papillae may be more likely to sensitize than non-tasters. Such a mechanism has been proposed to account for sensitization when using filter paper as the stimulus carrier (Karrer and Bartoshuk, 1991), but may be much less likely to occur when whole mouth rinses are used. Alternatively, and perhaps more likely, it has been argued that since temporal summation, reflected in the slow rates of both growth and decay of sensation, is a primary feature of irritation, this may be the mechanism behind sensitization (Green and Lawless, 1991). More intense irritant stimuli take longer to decay (Lawless, 1984), which should facilitate temporal summation. Thus, responses to individual irritant stimuli ought partly to predict the degree of sensitization that occurs. Hence, sensitization may be more likely to occur in PROP tasters, who perceive individual stimuli are as more intense, than in non-tasters.

The studies reported here examined responses to repeated stimulation by three oral irritants—capsaicin, cinnamaldehyde and ethanol—in groups of subjects who were divided according to their PROP taster status. Because a common core of subjects assessed all three irritants, this also allowed an examination of the extent to which differing response patterns were determined by the irritants themselves or were more strongly related to subject variability.

Materials and methods

Subjects

A group of 61 subjects (18–30 years of age; mean = 22.4 years; 14 males, 47 females), mainly students and staff from the University of Otago, participated. Subjects who consumed chili or other hot (spicy) food twice a week or more were excluded, as were non-consumers of hot foods. All subjects participated in an experiment in which they rated the intensity of capsaicin solutions. A subset of these subjects (n = 32; 23 females, nine males) also completed an experiment in which they rated the intensity of the cinnamaldehyde solutions, and those completing the ethanol experiment (n = 18; 14 females, four males) were, in turn, a subset of the cinnamaldehyde experiment subjects. Thus, a total of 18 subjects completed all three experiments.

PROP status

Prior to the commencement of any of the experiments with irritants, all subjects evaluated the intensity of a filter paper saturated with 0.3 g/l PROP (Sigma). Subjects placed the filter paper on the anterior dorsal surface of the tongue, retracted the tongue and allowed the paper to become wet with saliva. Thirty seconds later, they removed the filter paper and rated the bitterness intensity using a labelled magnitude scale (LMS) (Green *et al.*, 1993). On the basis of these ratings (measured in millimetres from the base of the scale; range 0–165), the different taster groups were defined as follows: super-tasters (rating > 100); medium-tasters (ratings 20–100); and non-tasters (ratings < 20). These group definitions are based on the lower and upper 25% of values from the distribution from large data sets (L. Bartoshuk, personal communication). For the cinnamaldehyde and ethanol studies, because of fewer subjects, medium-tasters and super-tasters were grouped together into a single taster group for analysis.

Stimuli

The irritants used in each experiment, their concentrations and the number of subjects in each taster group are shown in Table 1. Capsaicin (8-methyl-*n*-vanillyl-6-nonenamide; Sigma, 98%) was dissolved in ethanol (0.1 g capsaicin/50 ml ethanol) which was then made up to 1 l using distilled water. This yielded a stock solution of 100 p.p.m., which was later diluted in distilled water to yield a concentration of 3 p.p.m. Solutions of 2 g/l of cinnamaldehyde (Sigma) were prepared by heating it in a mixture of polysorbate (Tween 80) and distilled water. The ethanol solution consisted of 47.5% ethanol (by wt) in distilled water. All irritant solutions were refrigerated during storage, but were evaluated at room temperature (~21°C) as 10 ml of solution presented in 40 ml plastic cups. The concentrations of cinnamaldehyde and ethanol were chosen to be approximately equal in intensity to that of 3 p.p.m. capsaicin solutions.

Procedure

The experiments on the different irritants were each separated by several weeks. Subjects were requested not to eat hot (spicy) foods for 24 h prior to each session. Prior to stimulus delivery, subjects were instructed in the use of the LMS and were briefed on the importance of keeping oral movements to a minimum during stimulus delivery. For each irritant, subjects assessed 11 samples. The initial series of ten samples was assessed at the rate of one sample per min. After placing each sample in the mouth, subjects waited for 25 s and then rated the intensity of the irritation using the LMS on a rating sheet which was then given to the experimenter. Subjects then expectorated. Thirty seconds later subjects received the next sample. Following the tenth sample, there was a 10 min break followed by the final sample. All timing was undertaken by the experimenter.

Table 1 Concentration of the irritants used and breakdown of the subjects in terms of super-tasters (STs), medium-tasters (MTs) and non-tasters (NTs)

Irritant	Conc. (%)	No. of subjects	STs	MTs	NTs
Capsaicin	0.0003%	61	17	14	30
Cinnamaldehyde	0.2%	32	17*		15
Ethanol	47.5%	18	9*		9

*For cinnamaldehyde and ethanol, STs and MTs were pooled into a 'taster' group.

Between samples, subjects were requested not to breathe through their mouth or to speak and no rinsing was allowed.

Analysis

LMS ratings were measured in millimetres from the base of the scale. These data were entered into group (super-, medium- and non-taster for capsaicin; taster and non-taster for cinnamaldehyde and ethanol) × samples (sample nos 1–11) repeated measures ANOVA for each irritant. The data from the subjects common to all three experiments were also analysed in an Irritant × Samples ANOVA to examine differences in pattern of response to the three irritants. *Post-hoc* analyses following significant ANOVA effects were conducted using the Scheffe test. A criterion of $\alpha = 0.05$ was used for all comparisons.

Results

Capsaicin

Analysis on ratings of capsaicin irritation was initially undertaken using three PROP taster groups. Despite apparently higher intensity ratings for PROP super-tasters, particularly when compared to non-tasters (see Figure 1), this ANOVA revealed no main effect for group [$F(2,58) = 2.34$, not significant]. When these data were re-analysed using groups based on tasters (super- and medium-tasters combined) and non-tasters, the group effect was marginally significant [$F(1,59) = 3.94$, $P = 0.052$]. In each case, the Samples effect was significant [$F(10,580) = 22.55$, $P = 0.0001$], and Figure 1 shows an initial decrease in intensity for each group, followed by a plateau. *Post hoc* tests revealed that sample 1 was rated as more intense than samples 2, 3, 5, 6, 7 and 11, and that there was a further decrease in rated intensity from sample 10 to sample 11 over the 10 min hiatus.

Cinnamaldehyde

As can be seen in Figure 2, PROP tasters rated the irritation of cinnamaldehyde as more intense overall than did non-tasters [$F(1,30) = 18.9$, $P = 0.0001$]. There was no groups × samples interaction, and both groups showed

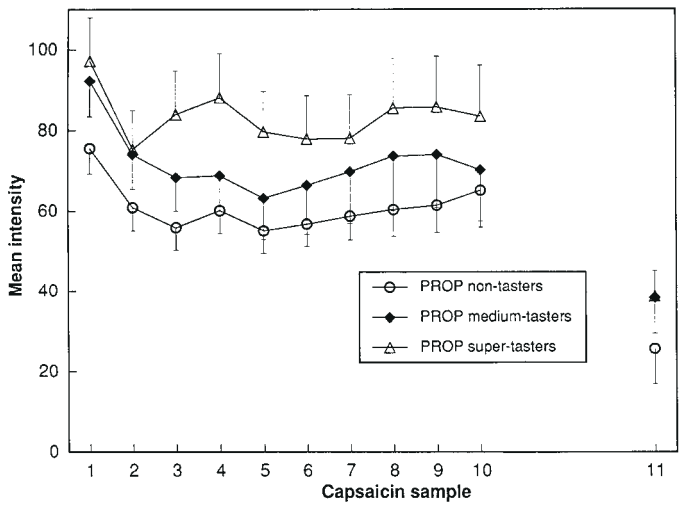

Figure 1 Mean ratings of irritation intensity in response to multiple samples of capsaicin by non-tasters, medium-tasters and super-tasters of PROP. The ISI is 1 min for samples 1–10 and 10 min between samples 10 and 11. Error bars are SEM.

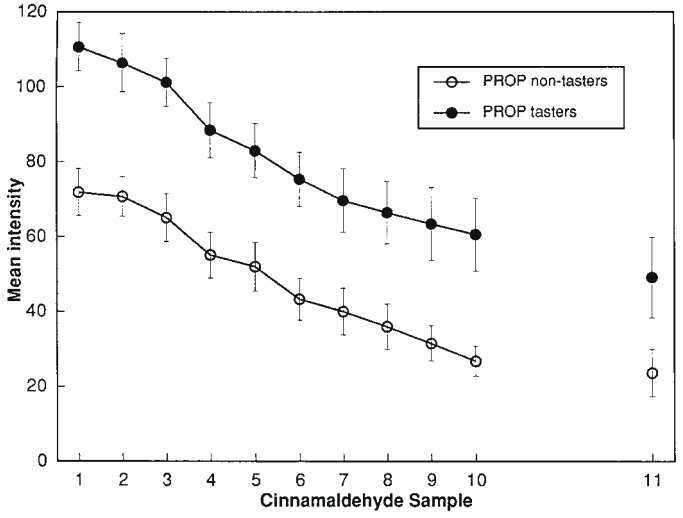

Figure 2 Mean ratings of irritation intensity in response to multiple samples of cinnamaldehyde by non-tasters and tasters of PROP. The ISI is 1 min for samples 1–10 and 10 min between samples 10 and 11. Error bars are SEM.

similar progressive decreases in ratings from sample 1 to sample 10 [main effect of samples: $F(10,300) = 26.01$, $P = 0.0001$]. Sample 1 was rated as more intense than samples 5–11. However, there was no change in intensity ratings over the hiatus (from sample 10 to sample 11).

Ethanol

The response to ethanol was very similar to that of cinnamaldehyde over the initial series of samples (see Figure 3). PROP tasters rated the irritation of ethanol as more intense overall than did non-tasters [$F(1,16) = 6.05$, $P = 0.026$], with both groups showing a progressive decrease in intensity ratings from sample 1 to sample 10 [main effect of samples: $F(10,160) = 12.67$, $P = 0.0001$]. Sample 1 was rated as more intense than samples 5–10. The response to ethanol over the hiatus from sample 10 to sample 11 differed from that to cinnamaldehyde, however. As can be seen in Figure 3, ratings of ethanol had recovered to their initial level over this period and there was no difference in mean ratings between samples 1 and 11.

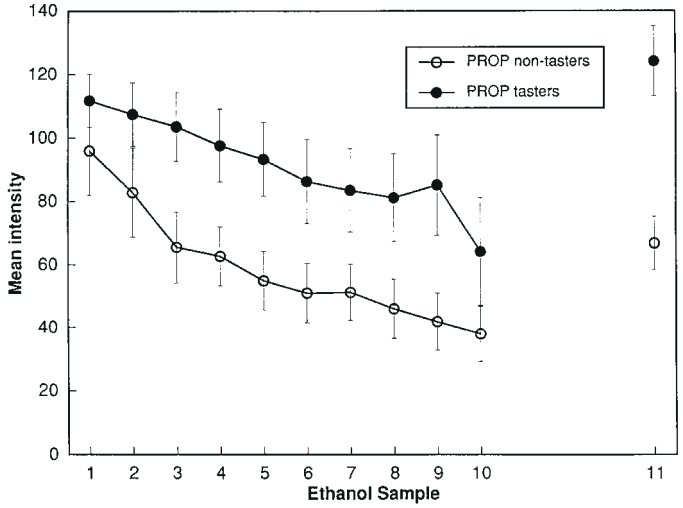

Figure 3 Mean ratings of irritation intensity in response to multiple samples of ethanol by non-tasters and tasters of PROP. The ISI is 1 min for samples 1–10 and 10 min between samples 10 and 11. Error bars are SEM.

Comparisons of ethanol, cinnamaldehyde and capsaicin

Since there were no interactions between PROP taster group and samples in any of the analyses for the individual irritants, the group data were pooled and the different irritants compared using the 18 subjects common to all three experiments. These data are shown in Figure 4.

Comparisons between responses to ethanol, cinnamaldehyde and capsaicin revealed no overall intensity difference between irritants [$F(2,51) = 1.004$]. However, the main effect for samples was significant [$F(10,510) = 19.96$, $P = 0.0001$], as was the irritants × samples interaction [$F(20,510) = 6.71$, $P = 0.0001$]. This interaction reflects the different patterns observed for capsaicin as compared to ethanol and cinnamaldehyde over both the initial ten samples, as well as changes from samples 10–11 which showed different response patterns depending on the irritant. Responses to capsaicin showed a marked decrease, indicative of desensitization, over the 10 min hiatus, whereas responses to cinnamaldehyde and ethanol showed no change, or complete recovery, respectively.

Individual differences

Except for an initial decrease, mean intensity ratings for the

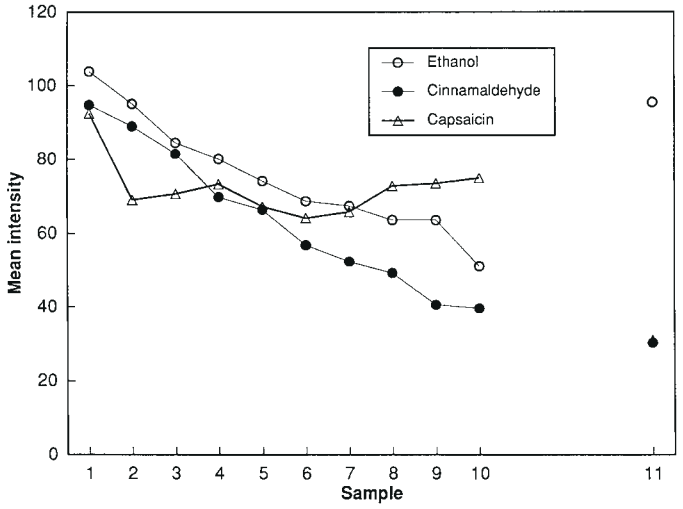

Figure 4 Mean ratings by the same group of subjects (n = 18) of irritation intensity in response to multiple samples of capsaicin, cinnamaldehyde and ethanol. The ISI is 1 min for samples 1–10 and 10 min between samples 10 and 11.

series of ten capsaicin samples showed neither clear sensitization nor desensitization. It has been previously found, under very similar stimulus conditions, that the mean response to multiple capsaicin solutions was an inaccurate reflection of the response patterns of the majority of individual subjects (Prescott, 1999). To examine this issue for all three irritants within the current data, the individual response patterns over the series of ten samples for each irritant were normalized by setting the value for the initial sample to the overall mean rating. These data are shown in Figure 5. For both cinnamaldehyde and ethanol, the majority of subjects (16/18) showed a decrease in intensity ratings over the ten samples (as indicated by a final response beneath the baseline), although there is clearly some variability in the rate and extent of the decrease. Interestingly, it was the same two subjects who showed an increase in ratings for both irritants. In contrast, responses to capsaicin show much more variability, including patterns reflecting rapid desensitization and moderate degrees of sensitization, while some subjects showed very little change in intensity ratings. These data show considerable similarity to the capsaicin rinse data of Cliff and Green (Cliff and Green, 1996), which were plotted in the same way.

Discussion

These studies are the first to examine responses to a range of oral irritants as a function of PROP taster status. They replicate the previous findings of overall differences in rated irritation intensity between PROP tasters and non-tasters demonstrated for capsaicin (Karrer and Bartoshuk, 1991) and also reported for ethanol (Bartoshuk *et al.*, 1993), and show that such differences also occurred with cinnamaldehyde irritation. These studies thus add to the growing

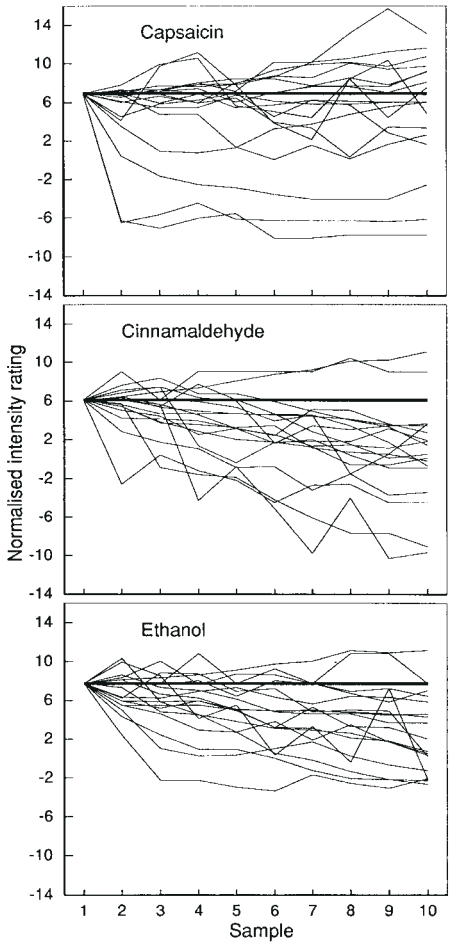

Figure 5 Normalized individual ratings by the same group of subjects (n = 18) of irritation intensity in response to multiple samples of capsaicin, cinnamaldehyde and ethanol. The ISI is 1 min. The bold line reflects the value of the initial intensity rating.

body of data revealing a variety of other differences in the psychophysical responses of individuals who vary in their response to PROP. The failure in the present study to find significant differences between the three different taster groups for capsaicin appears to be related to the high inter-individual variability in responses to this irritant, an interpretation suggested by the mean values, which are strongly indicative of underlying group differences, and also the fact that the group differences were more apparent when super- and medium-tasters were combined into a single group.

The different psychophysical responses of PROP tasters and non-tasters may underlie differences in the preference for, and consumption of, foods and beverages containing oral irritants. It is not known whether PROP tasters are less likely to consume hot (spicy) foods than non-tasters, although this would be predicted, particularly given evidence for a similar relationship between responses to PROP bitterness and consumption of foods that are bitter or 'sharp tasting' (Glanville and Kaplan, 1965; Drewnowski

and Rock, 1995). With respect to alcohol, the differences in responses to the irritation of ethanol between PROP tasters and non-tasters suggest the possibility that non-tasting might be associated with a more rapid and/or more frequent development of preferences for alcoholic beverages. In fact, a genetic link between PROP tasting and alcoholism has been proposed as a result of the finding that the adult children of alcoholics are more likely to be non-tasters than a control group of children of non-alcoholics (Pelchat and Danowski, 1992). It is quite possible that this is mediated by the differences in psychophysical, and subsequent hedonic, responses to the bitterness and/or irritation of the alcohol.

However, despite these overall differences between PROP taster groups in perceived irritation intensity, there was no evidence that PROP tasting is an important factor in explaining the individual variability that has been found in the responses to multiple samples of irritants, in particular capsaicin (Cliff and Green, 1996; Prescott, 1999), but also menthol (Cliff and Green, 1996) and zingerone (Prescott and Stevenson, 1996b). Thus, the different PROP taster groups showed very similar patterns of means over the initial series of stimuli for each of the three irritants, and there were no interactions between groups and samples. The overall intensity differences between PROP taster groups presumably relate to the summation of responses to stimulation of trigeminal fibres associated with greater (tasters) and lesser (non-tasters) numbers of fungiform papillae. The lack of group differences in response to repeated stimulation does not support the idea that sensitization results from increased spatial recruitment of such fibres, as has been suggested (Karrer and Bartoshuk, 1991). In particular, this is also unlikely given the use of whole mouth rinses, since the majority of responsive fibres are likely to be stimulated with each sample.

The present results also extend previous studies of responses to multiple irritant samples to show that the typical response to cinnamaldehyde is desensitization. However, this same finding of desensitization to repeated samples of ethanol is in contrast to previous research (Green, 1990) which showed that the intensity of ethanol irritation changed very little during repeated stimulation. Although sensitization has repeatedly been shown to be the dominant group pattern during responses to repeated presentation of capsaicin (Green, 1989, 1991; Prescott, 1999), the accumulated data on cinnamaldehyde and ethanol from the present studies, and from studies using zingerone (Prescott and Stevenson, 1996a,b), nicotine (Dessirier *et al.*, 1997) and menthol (Cliff and Green, 1994), point to sensitization being a relatively uncommon pattern for oral irritation *per se* (at least within the range of stimulus parameters studied). This raises the question of whether capsaicin is somehow unusual in its mode of action. This appears to be confirmed when comparisons were made of the responses of the same group of subjects to multiple samples of three different irritants. In contrast to the desensitization to ethanol and cinnamaldehyde seen over the initial ten samples, group responses to capsaicin showed an initial decrease followed by a plateau in response.

However, the response patterns to capsaicin in this study were, as in some previous studies, highly variable, and the means reflect a variety of different response patterns, including marked increases and decreases in rated intensity. Group response patterns may, in cases such as this, be of limited utility when attempting to interpret the phenomena of sensitization/desensitization over a series of capsaicin stimuli. In contrast, there was far less variability in the responses to ethanol and cinnamaldehyde, and examination of the data for individual subjects in response to both of these irritants indicated that the mean response patterns of desensitization shown in Figures 2 and 3 reflected the response patterns of most subjects.

The fact that the same group of subjects showed differing response patterns to capsaicin than they did to the other irritants therefore suggests that much of the variability must be a function of the irritants themselves. The three compounds studied, as well as being irritants, do differ in taste and odor qualities. It is unlikely that these differences can account for the present data since the irritation, on which the subjects were asked to focus, was considerably stronger than the other qualities. Moreover, pilot studies approxi- mately matched the three compounds for irritation intensity and this was reflected in the ratings of the initial samples. A much more likely contributing factor is variability in response to the temporal spacing of stimuli. Green (Green, 1991) demonstrated a relationship between the temporal properties of stimulation and the presence of sensitization. Using capsaicin filter papers, sensitization was apparent in the mean responses at ISIs of 0.5 and 1.5 min, but not at ISIs of 3.5 and 5.5 min. More recent research showed equivalently strong sensitization at several ISIs of less than 60 s, but not for 60 s (Green and Rentmeister-Bryant, 1998). Both studies suggest that some critical ISI value to show sensitization had been reached. Such critical values may differ between irritants, possibly as a function of the time course for an individual stimulus, which depends upon its affinity for the receptor and its binding strength, represented by the equilibrium constant, K_b (Cliff and Heymann, 1994). Cliff and Heymann (Cliff and Heymann, 1994) showed that cinnamaldehyde has a much lower K_b value than does capsaicin, indicating a lower affinity with the receptor. As a result of poorer binding, the time course of the irritation it produces is briefer. In support of this interpretation, in the present studies, for irritation of approximately equivalent initial intensity, desensitization occurred with the two relatively short acting irritants, but not for the longer-acting capsaicin (Cliff and Green, 1996). In this view, setting an ISI outside some critical period determined by this time course will probably result in desensitization, whereas within this period, sensitization will occur. Such variability has recently

been characterized by McBurney *et al.* (McBurney *et al.*, 1997) in terms of the time constant for a given irritant.

What was the reason for the discrepancy between the present data on ethanol and those of Green (Green, 1990) who showed effectively no change during repeated stimulation? The current study used a substantially greater concentration of ethanol than previously (47.5 versus 25%). In addition, whole mouth rinses effectively stimulate a much greater population of trigeminal fibres than do discrete filter papers, thereby increasing the stimulus intensity through spatial summation. While there is little evidence that increasing stimulus intensity significantly influences response patterns when sensitization is dominant, or there is a mixture of both sensitization and desensitization responses evident (Prescott and Stevenson, 1996b; Green and Rentmeister-Bryant, 1998), the same may not be true under ISI conditions which strongly favour desensitization. Green (Green, 1991) noted the greater likelihood of desensitization over a series of stimuli when the capsaicin concentration was increased from 3 to 30 p.p.m., and when the ISI was at least 9.5 min. Similar results were found with increases in the concentration of zingerone rinses, but only for the desensitization that occurred as a result of a hiatus in stimulation of at least 5 min (Prescott and Stevenson, 1996b). Thus, when the ISI strongly favours desensitization, as it did with ethanol, stimulus intensity may be influential.

The question arises as to why some subjects show sensitization and others desensitization, and yet others no change, given the same ISI. Although this was mainly apparent for capsaicin, a small minority of subjects showed anomalous responses to cinnamaldehyde and ethanol as well. Several lines of evidence, including sensitization occurring in the presence of significant desensitization—stimulus induced recovery (Green and Rentmeister-Bryant, 1998)—and the fact that desensitization does not require prior sensitization to occur (Green, 1989), have strongly suggested that these are distinct processes, and that repeatedly stimulating under temporal conditions that favour sensitization acts to delay the onset of desensitization. Green (Green, 1991) noted that there was increasing variability in subject responses to capsaicin as the ISI increased from 0.5 to 5.5 min. It is likely that the critical period for demonstrating one process rather than the other reflects an average of a range of values, which vary somewhat from person to person. At an ISI of 1 min, as used here, a certain percentage of subjects still showed desensitization and it appears that this ISI, at least when used with mouth rinses, does not act to favour one process or the other in a majority of subjects, despite the fact that it clearly does so for given individuals. Thus, use of this ISI may allow relatively greater influence of individual variability in responsiveness to capsaicin and, hence, also, of the particular study population. This may be the reason that, in the recent study noted above using filter paper for stimulus delivery, an ISI of 60 s did not lead to capsaicin sensitization (Green and Rentmeister-Bryant, 1998), despite that fact that this ISI has shown sensitization in other studies using the same methodology (Green, 1989 1991). Even with continuous capsaicin stimulation for 34 min, McBurney *et al.* (McBurney *et al.*, 1997) found that subjects' responses could still be classified in terms of risers, tonics and phasics, representing variations in growth of intensity during stimulation.

Individual variability in response patterns may reflect similar variability in responsiveness to individual irritant stimuli, consistent with the explanation of between irritant differences outlined above. Naswari and Pangborn (Naswari and Pangborn, 1990) studied responses over a series of capsaicin stimuli using an ISI that did not favour sensitization (2.5 min). They nevertheless found a number of individuals (who they termed 'enhancers') who showed sensitization. Moreover, they noted that, in response to a given stimulus, enhancers had a slower rate of mouth burn decay and took longer to reach maximum intensity than did 'depressors', suggesting the importance of the time course of responses to individual stimuli as an important predictor of whether sensitization took place. What would lie behind such individual differences in responsiveness? The present study appears to suggest that density of fungiform papillae, and associated trigeminal innervation, as indexed by PROP, is not important. Naswari and Pangborn examined another possible factor, salivary flow, but also found no link with enhancement. The role of other factors, including variations in the relative permeability of the oral mucosa to irritants, await investigation. In addition, however, given that an individual may sensitize on one occasion and desensitize on another (Prescott, 1999), the influence of cognitive factors (for example, attention) on the responsiveness of the individual to stimulation cannot be ruled out.

With respect to desensitization following an initial series of stimuli, the present results appear to confirm that, given a particular hiatus in stimulation, the recovery period differs markedly between these irritants. Previous research has shown that the recovery time of capsaicin from desensitization is in the order of hours to days, depending on the concentration (Green, 1989; Karrer and Bartoshuk, 1991), while that of a 1% zingerone solution, equivalent to a moderate degree of capsaicin irritation, was shown to be ~60 min (Prescott and Stevenson, 1996b). The present study shows that the recovery time for ethanol is within the 10 min ISI, but gives little indication of the recovery time for cinnamaldehyde, except that it is likely to be shorter than for capsaicin because of the indication that further decreases in intensity were not occurring during the 10 min hiatus. In addition, the present studies confirm previous findings that desensitization following a hiatus is a robust phenomenon, which is not influenced significantly by individual differences.

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