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# Temporal Interactions between Oral Irritants: Piperine, Zingerone, and Capsaicin

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## Abstract

Sequential presentation of 2 irritants may produce cross-sensitization or cross-adaptation effects upon introduction of the second irritant. In Experiment 1, subjects were given either 34 min of stimulation with zingerone, capsaicin, or piperine or one of those irritants for 23 min followed by blanks for 23 min. In Experiment 2, subjects received one irritant for 23-min irritants, followed immediately by another for 23 min (piperine → zingerone, piperine → capsaicin, zingerone → piperine, or zingerone → capsaicin). Cross-sensitization was observed for the piperine → zingerone, zingerone → piperine, and piperine → capsaicin groups; cross-adaptation was observed for the zingerone → capsaicin group. Cross-adaptation and cross-sensitization were predicted by adding the independent time courses of the respective irritants, starting the second at the offset of the first. These responses were also predicted by a mathematical model of central processing of primary afferent responses.

**Key words:** adaptation, capsaicin, piperine, psychophysics, zingerone

## Introduction

Some sensory phenomena, including sensitization, desensitization/adaptation, are defined by their time course or by their relation to earlier stimulation. The purpose of this paper is to investigate whether differences in temporal properties of the response to single vanilloid irritants give insights into principles of central processing of irritant sensations. Prescott and Stevenson (1996b) found that the psychophysical response to zingerone peaks within about 20 s and then falls. This drop in subjective intensity is termed desensitization (Green 1993). Prescott and Stevenson (1996b) also noted that the capsaicin burn intensity peaks later than zingerone and persists for a considerably longer time. They further noted that capsaicin responses sensitize when the interstimulus interval is short and desensitize when it is longer. Prescott and Stevenson (1996a, 1996b) suggest that time course of the response is significant in predicting whether sensitization or desensitization will be found.

Applying the same considerations to interactions between different stimuli suggests that temporal properties of response to irritants may help to understand cross-sensitization and cross-desensitization/cross-adaptation. Cross-adaptation is believed to be an evidence that 2 stimuli activate the same sensory channels (Smith and McBurney 1969; Smith et al. 1983). Cross-sensitization suggests that the processing of the 2 stimuli is additive; the decaying response to the first stimulus adds to the rising response to the second stimulus (Green 1993).

The present report is the first of a 2-part study of the interactions between vanilloid irritants. In this paper, we report the time course of the burn produced by orally presented capsaicin, piperine, and zingerone. Then we consider the following pairs of irritants, presented sequentially: piperine → zingerone, piperine → capsaicin, zingerone → piperine, or zingerone → capsaicin. We first show that the interactions between pairs of irritants can be predicted by simply adding the psychophysical judgments of the second stimulus to the judgments of the first, starting the second at the offset of the first. This empirical addition tests the assumption that the 2 responses add linearly.

Next, we use a generalized form of a dynamic mathematical model to make explicit, quantitative predictions of the interactions between vanilloid irritants. The approach is well

established in engineering and physiology (cf., Fasol and Jorgl 1980). According to the model of McBurney and Balaban (McBurney et al. 1997), the stimulus activates a level detector, or tonic process, that rises slowly after stimulus onset to a plateau; a change detector, or phasic process, that rises quickly and returns to baseline; and a cumulative response, or double integrator, that rises for the duration of the stimulus. Each process has a time constant and a gain. The final output of the model is a linear combination of these separate processes. The response of each process to stimulus offset is the mirror image of its response to the onset.

The model predicts adaptation within and across daily sessions of oral capsaicin stimulation (McBurney et al. 1997), the results of repeated presentations of capsaicin (Balaban et al. 1999), the effects of concentration and individual differences (McBurney et al. 1999, 2001), and the effects of double-step increases or decreases in capsaicin concentration (Balaban et al. 2005). The modeling results from our study of the effects of repeated capsaicin stimuli showed that phenomena termed "sensitization" and "desensitization" are predicted by the model, with desensitization resulting from the summation of a negative-polarity off-response (inhibition) from the phasic component with the on-response to the next stimulus (Balaban et al. 1999). The purpose of the present study was to test the ability of this dynamic model to predict the interactions between irritants over time. Unlike previous studies, the model has been adapted so that the input is the temporal profile of trigeminal ganglion cells to vanilloid exposure (Liu and Simon 1996, 1998); the behavior of the tonic, phasic, and integrator components, however, are unaffected. Specifically, one may hypothesize that the contribution of the phasic component is critical for the appearance of cross-adaptation.

## Experiment 1

### Subjects

One hundred and seventy one nonsmoking, undergraduate students participated in this study. Subjects were recruited from the Department of Psychology subject pool and participated for course credit. Subjects ranged in age from 18 to 30 years, and approximately equal numbers of males and females participated. The protocol was approved by the university's Institutional Review Board.

### Stimuli

All stimuli were delivered to subjects on 1.27-$cm^2$ filter paper disks onto which 25 μl of the respective irritant had been pipetted. Concentrations of irritants were chosen in pilot work to produce equal peak burn. Capsaicin (8-methyl-*n*-vanillyl-6-nonenamide; Sigma, St Louis, MO, 98%) was dissolved in 95% ethanol (50 mg capsaicin/25 ml ethanol) and brought up to 500 ml with distilled water to 100 ppm. Piperine (97%, Sigma) was dissolved in 95% ethanol (0.4 gm piperine/25 ml of ethanol) and brought up to 50 ml with distilled water to 8000 ppm. Zingerone (vanillyl-acetone; Sigma-Aldrich, 95%) was dissolved in ethanol (0.5 ml of zingerone/1 ml of ethanol) and brought up to 10 ml with distilled water to 5% solution. All irritants were stored at −10 °C. After application of 25 μl of the irritant solution, filter papers were dried and then rewetted with 50 μl of water just prior to delivery to the subject. In addition, 1 M NaCl was used as a standard stimulus. NaCl solution (25 μl) was pipetted onto the same-size filter paper.

### Design

Three separate groups of subjects participated in 3 conditions in both Experiments 1A and 1B, piperine, capsaicin, and zingerone. There were 27, 25, and 20 subjects in the respective groups in Experiment 1A, and 31, 34, and 34 in Experiment 1B.

### Procedure

Standard magnitude estimation instructions were read to each subject. Subjects received practice trials judging distances between the experimenter's hands. Subjects received the NaCl standard for 10 s and were told to consider the saltiness of the standard to be 10 (modulus). The stimuli that followed were to be judged in relation to the standard. This permitted us to determine the success of equating perceived burn of the 3 irritants.

After rating the standard, the filter paper containing the irritant stimulus was placed on the outstretched tongue and left for 1 min. Subjects held the filter paper on the tongue with a tongue depressor. During stimulation, subjects kept the tongue outstretched between the lips with the lips closed. At the end of 1 min, subjects rated the perceived magnitude of the irritant in relation to the standard. The filter paper was then removed with forceps, and a new filter paper containing the same irritant was immediately placed on the tongue for the next minute. Subjects were permitted to retract and rest the tongue between stimuli, if necessary. In Experiment 1A, subjects received a new filter paper every minute for 34 min. In Experiment 1B, subjects received a new filter paper every minute for 46 min. The first 23 filter papers contained the irritant, and the next 23 contained water only. Subjects rated the burn at the end of the first minute and every third minute throughout the session. A computer signaled the replacement of the filter paper at the end of each minute and when the subject was to rate the burn of the irritant.

### Data analysis

Data were normalized by dividing each rating of each subject by the average rating for that subject and then multiplying all those numbers by 100 so that each subject had an average rating of 100. This normalization allows each subject to provide an equal contribution to the overall data. Medians from

these normalized data were calculated for each time point within a group. Following McBurney et al. (1997), medians were used because they are less sensitive to outliers.

## Modeling

A dynamic mathematical model to make explicit, quantitative predictions of the interactions between vanilloid irritants is described in detail in the Appendix (Supplementary materials online). The model structure has been highly constrained because it serves as a proof-of-concept demonstration of a general central processing schema to explain psychophysical responses to oral irritants and interactions termed sensitization, adaptation, cross-sensitization, and cross-adaptation. The inputs to the model are based upon physiologic responses of trigeminal ganglion cells to irritant exposure (Liu and Simon 1996, 1998). This simple dynamic model is constrained to use the simplest possible filter configurations (first order) for the tonic, phasic, and double integrator components. It also has been constrained to be linear, with the absence of inhibitory (negative) outputs as the only permitted nonlinearity. Central processors with the same architecture and identical time constants are used for each of the 3 irritants. Hence, it should be viewed as a parsimonious representative of a family of potential solutions that can be refined by further studies.

The structure of the model is shown in a block diagram in Figure 1. The main difference from our previous model is the time constant in the Laplace representation of the transfer function for the initial tonic process. This change was made because the model input was changed from the stimulus concentration (over time) to the afferent response to that concentration. The time constant of this tonic process pools the effects of kinetics of diffusion of the irritant to the receptors and the neural processing of that signal in the peripheral and central neurons. Hence, it is the first stage in the model. The time constants of the phasic and integrator processes represent the dynamic properties of signal processing (including adaptive changes such as tachyphylaxis) to produce a burning sensation. The lower panel in Figure 1 shows that the output of the tonic stage of the new model (input of which is afferent response) is identical to the output of the original model (input of which is capsaicin concentration). Thus, the new model is simply a generalization of a capsaicin concentration model for other oral irritants. As in the earlier model, responses are represented as a weighted sum of the 3 processes. The relative contribution of each is represented by its gain.

Briefly, responses were simulated with a program written in MATLAB, and gains were estimated by a Marquardt–Levenberg (lsqnonlin.m subroutine). As in previous studies, simulations were run using Laplace transforms and standard linear simulation routine (''lsim'' and ''step'') functions. For each irritant, the gains of the tonic, phasic, and integrator mechanisms were estimated to jointly minimize the deviation

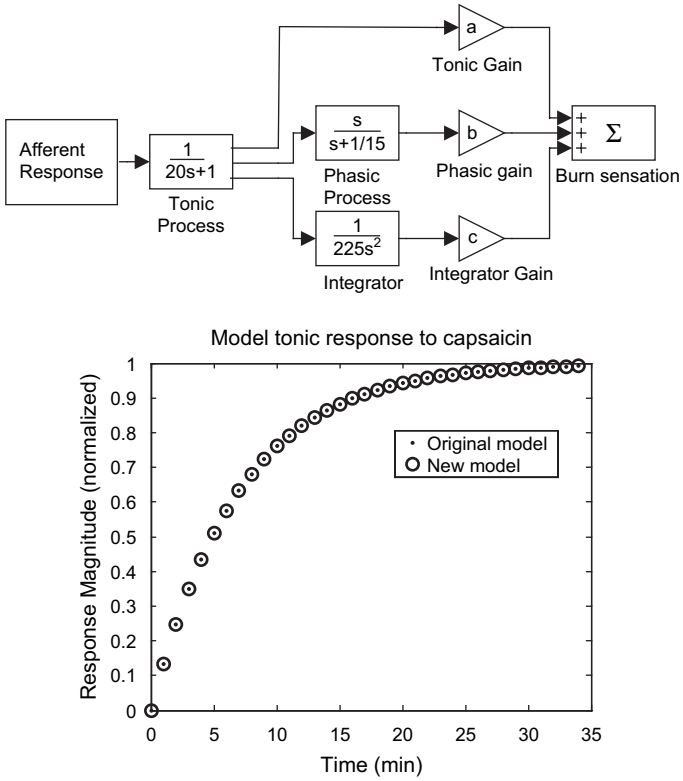


**Figure 1** The upper panel shows the transfer function for a model that used the afferent response to a constant capsaicin stimulus as an input and produces the same tonic, phasic, and integrator output profiles as our previous model (McBurney et al. 1997). The lower panel shows that the tonic response is identical to the response of the original model. Because the tonic response is the input to the phasic and the integrator components of the model, those responses are identical as well. The model is described in detail in the Appendix (Supplementary materials online).

of the fit to both the 34-min (Experiment 1A) and 23-min (Experiment 1B) stimulus presentations. The fits were also calculated for a final model that was optimized for a joint fit to all the data sets from Experiments 1A, 1B, and 2 using the same least squares algorithms.

## Results and discussion

Figure 2 shows the results from Experiments 1A and 1B. The left panels show the results of the 34-min presentations (Experiment 1A), and the right panels show the results of 23 min of irritation, followed by 23 min of water alone (Experiment 1B).

Each irritant yielded a distinctive profile of subjective burn over time. Piperine rose for the first 10 min and then remained steady; capsaicin rose more quickly than piperine and remained steady, whereas zingerone rose for the first 10 min and then declined.

The results of a single model fit simultaneously to both stimulus durations are represented by a solid line. Note that a single model could explain at least 83% of the variance in

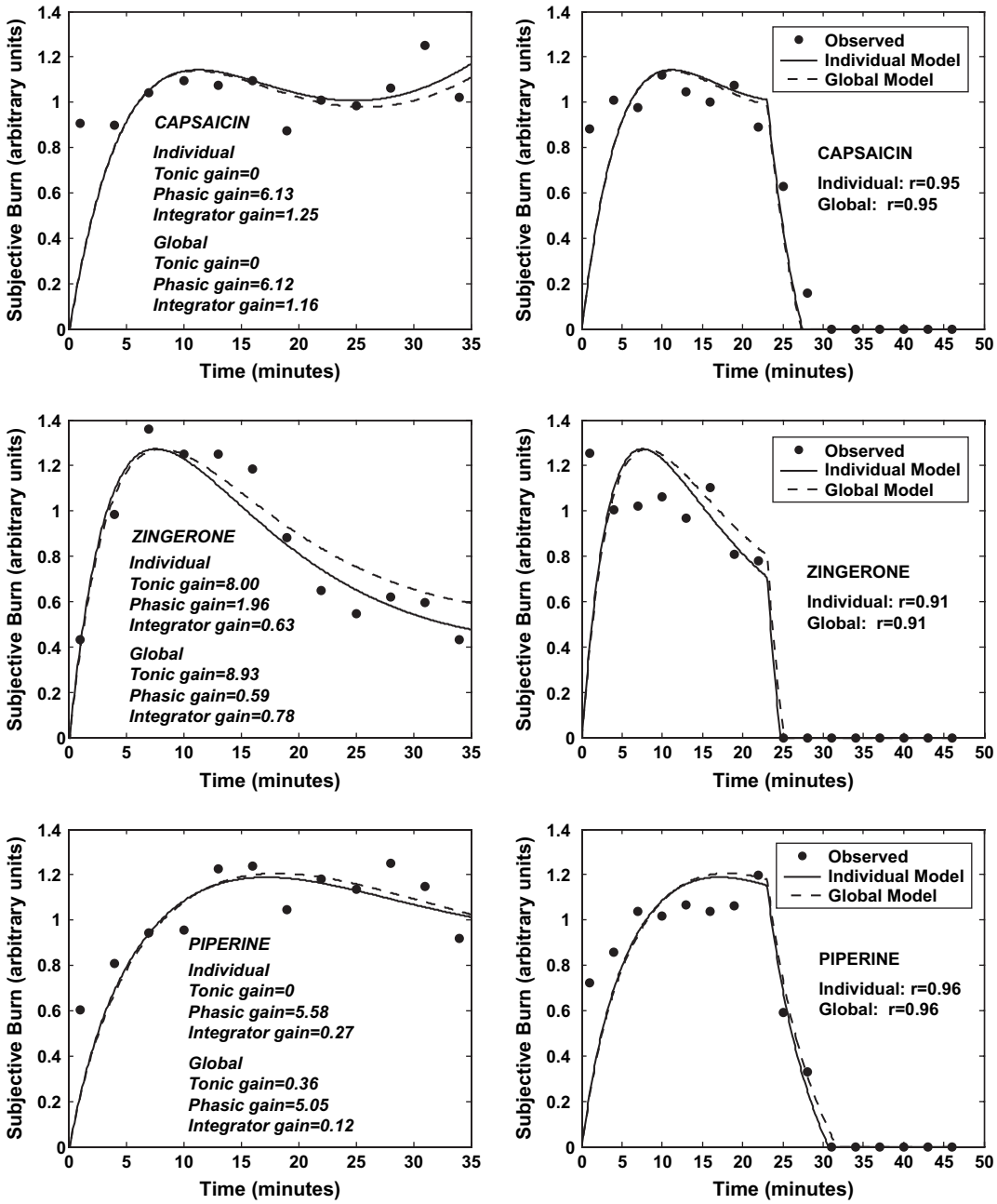


**Figure 2** Subjective burn as a function of time for 3 irritants. Left hand panels show the results of 34 min of stimulation (Experiment 1A). Right hand panels show the results of 23 min of stimulation, followed by 23 min of blanks (Experiment 1B). The curves indicate the model fit to the median data simultaneously for Experiments 1A and 1B for each irritant.

the data for each irritant. The burning sensations produced by piperine and capsaicin were fit by a major contribution of a phasic component with a small integrator component. The zingerone burning sensation, on the other hand, was fit by a predominantly tonic component responses, with small contributions from phasic and integrator components. These distinct profiles permitted us to use the model to make different predictions for the result of sequential presentation of different pairs of irritants.

## Experiment 2

The data from Experiment 1 permit predictions of the time course of burn produced by sequential oral irritant exposure. More specifically, we can test the hypothesis that responses to sequentially presented oral irritants can be explained as a linear sum of the responses to the individual components. The following pairs were tested: piperine → zingerone, piperine → capsaicin, zingerone → piperine, and zingerone → capsaicin.

### Materials and methods

The methods in Experiment 2 were identical to those of Experiment 1, except as noted below.

### Subjects

One hundred and nineteen undergraduate students participated in this study, 30 in the piperine → zingerone group, 31 in the zingerone → piperine group, 28 in the piperine → capsaicin group, and 30 in the zingerone → capsaicin group.

### Procedure

The NaCl standard was employed as before, but no modulus was specified. For the remaining 4 groups, one irritant was presented for 23 min followed by a different irritant for 23 min. The following pairs of irritants were studied: piperine followed by zingerone, piperine followed by capsaicin, zingerone followed by piperine, or zingerone followed by capsaicin.

### Simulation

The time course of burn was predicted from the model using MATLAB, and $r^2$ values were calculated between the predicted and observed data. The structure is indicated in detail in the Appendix (Supplementary materials online). Briefly, the gains (weights) for the tonic, phasic, and integrator were fixed at the values estimated in the Experiment 1 data. The time constants remained fixed. As in Experiment 1, simulations were run using Laplace transforms and standard linear simulation routines. The data were fitted with the prediction from 2 model variants based upon the parameters obtained from the single irritant exposure data from Experiment 1. Both variants constrained the minimum value of the overall model output (subjective burn) to zero at all times to reflect the fact that subject responses are always a positive number. The first variant of the model is a form that explained adaptation to repeated capsaicin exposure (Balaban et al. 1999). This model is termed an inhibition model because it permits any negative values of the phasic and tonic components during an off-response to summate with positive values of the second response. Because this model permits an inhibitory off-response to participate in central summation, it is termed the "inhibition model." This inhibition results in a smaller second response or cross-adaptation. The second variant of the model excluded the possibility of a negative off-response to the first irritant, which is equivalent to limiting the central contribution of the sum of tonic, phasic, and integrator components of the response to a floor of zero. This is termed the "no-inhibition model." The resulting response will be a linear sum of (positive) responses to single stimuli or cross-sensitization.

### Results and discussion

Figure 3 shows the results of Experiment 2 together with the predictions based simply on adding the empirical data of Experiment 1B. The data points labeled "observed" show the data from Experiment 2, in which one irritant followed the other. The same figure also shows the results of adding the summed responses to the 2 independent stimulations from Experiment 1B, labeled "summed."

Consider first the observed data. The "piperine → zingerone," "zingerone → piperine," and "piperine → capsaicin" groups showed cross-sensitization; the "zingerone → capsaicin" group showed cross-adaptation. The summed data show considerable agreement with the observed data in 3 of the groups. The fourth group shows a combination of remarkable agreement for the first half of the data followed by marked deviation in the second half of the data.

Specifically, consider the upper left panel, which shows the data from the piperine → zingerone group. The data from the sequential presentation of zingerone followed by piperine closely match the data obtained by summing the responses to the 2 irritants alone.

The upper right panel shows the data for the zingerone → piperine group. The observed data closely fit the linear sum of the individual responses, which reproduced the 2 peaks in the sequential response and the slight drop from minutes 19 to 25.

The lower left panel shows the data from the piperine → capsaicin group. The linear summation of separate responses accounted for the data except for a short-duration dip around minute 25. Instead, the summed curve resulted in a short-duration spike at this interval followed by a rapid drop to the observed response.

The lower right figure illustrates the results for the zingerone → capsaicin group. The linear summation of separate responses accounted for the burn during zingerone exposure but not the sudden and sustained drop during capsaicin exposure. Thus, cross-desensitization cannot be explained as a linear sum of 2 independent responses.

Figure 4 shows model predictions for each cross-exposure paradigm. The dynamic subjective burn responses in the 3 conditions showing cross-sensitization, piperine → zingerone, zingerone → piperine, and piperine → capsaicin were consistent with predictions from the no-inhibition model. These models, based upon parameters from independent subject groups, accounted for more than 49% of the variance in each condition. For piperine → zingerone exposure, the no-inhibition model produced a reasonable approximation to the subject data, with a correlation coefficient of $r = 0.82$ (global $r = 0.83$). For the zingerone → piperine group, the no-inhibition model had a correlation of $r = 0.70$ (global $r = 0.70$). The no-inhibition model produced a fit with a higher correlation for the piperine → capsaicin group ($r = 0.92$).

By contrast, the no-inhibition model failed to account for the cross-adaptation response pattern of subjects in the zingerone → capsaicin group. The inhibition model provided the best reasonable fit to the data ($r = 0.78$, global model: $r = 0.79$), reproducing the cross-adaptation response pattern. The fit provided by this model indicates that

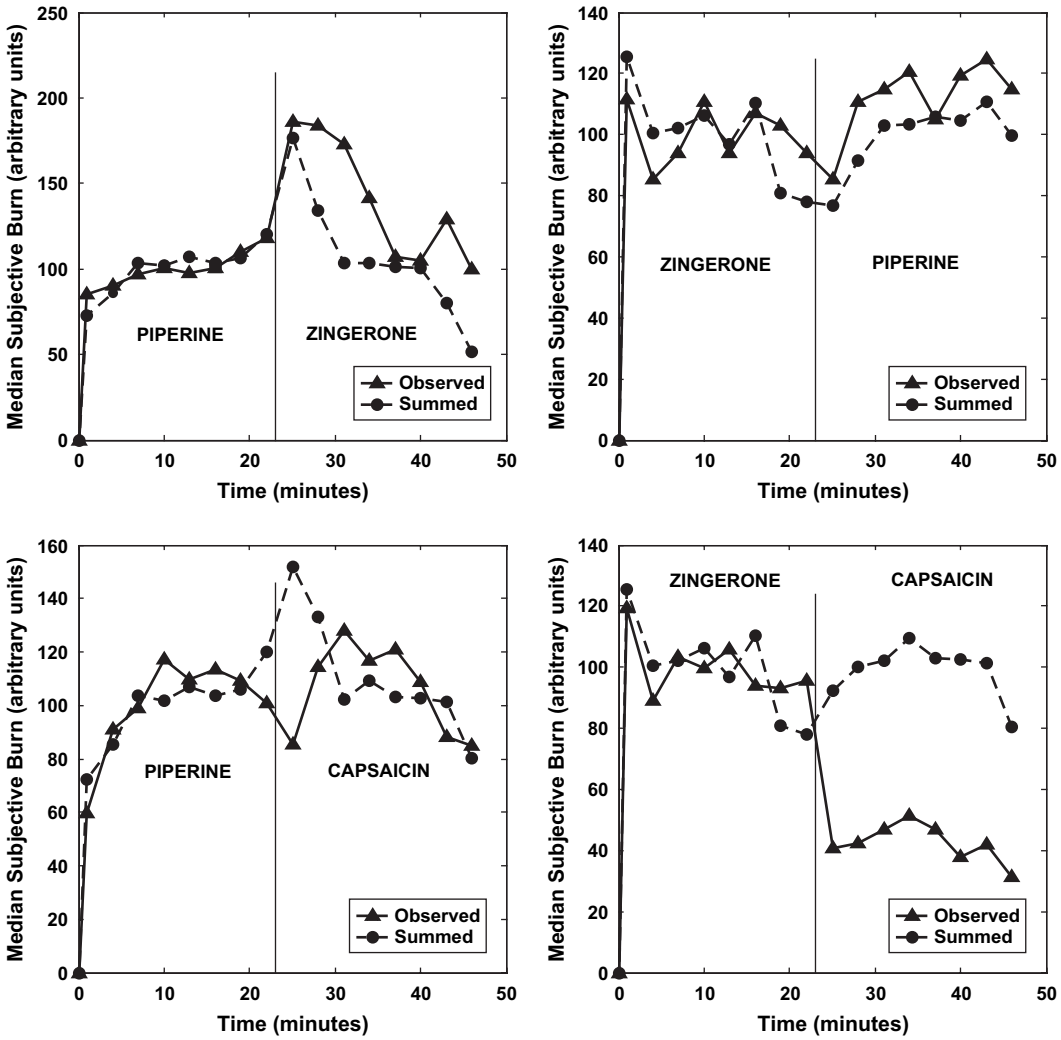


**Figure 3** Subjective burn to successive pairs of irritants. The triangles show the data obtained in Experiment 2 by presenting one irritant immediately after the other. The circles show the results of adding the independent responses to the second irritant to those to the first, starting the second at the end of stimulation by the first.

a temporal summation of negative off-responses to zingerone can explain the cross-adaptation response to the subsequent capsaicin exposure.

## General discussion

This study confirms the suggestion of Prescott and Stevenson (1996a, 1996b) that temporal properties of the response to irritants and the temporal parameters of stimulation are key to understanding sensitization and desensitization. It also demonstrates that the central components of a dynamic model of the response to trigeminal afferents are sufficient to explain both the responses to other irritants (zingerone and piperine) and to account for both responses to individual irritants and cross-interactions between capsaicin, zingerone, and piperine. The inputs to the model are profiles of activity revealed in studies of trigeminal afferents, which show a rapid form of desensitization, which we term "peripheral desensitization." Specifically, whole-cell patch clamp studies of rat trigeminal ganglion cells have shown that capsaicin, zingerone, and piperine produce dose-dependent inward currents with relatively fast time courses (Liu and Simon 1996, 1998). Capsaicin produces an inward current that increases rapidly (phasic component) and then adapts with an exponential time course to a plateau response (tonic component). Zingerone, by contrast, has a highly phasic type of ganglion cell response that increases rapidly and then declines with an exponential time course to a small outward current plateau. Piperine responses appear to be similar to capsaicin responses, but the peripheral desensitization of these responses, which serves as inputs to our model, cannot explain the prolonged time course of subjective burning sensations. Rather, the prolonged time course of subjective burn responses must necessarily reflect central neural transformations

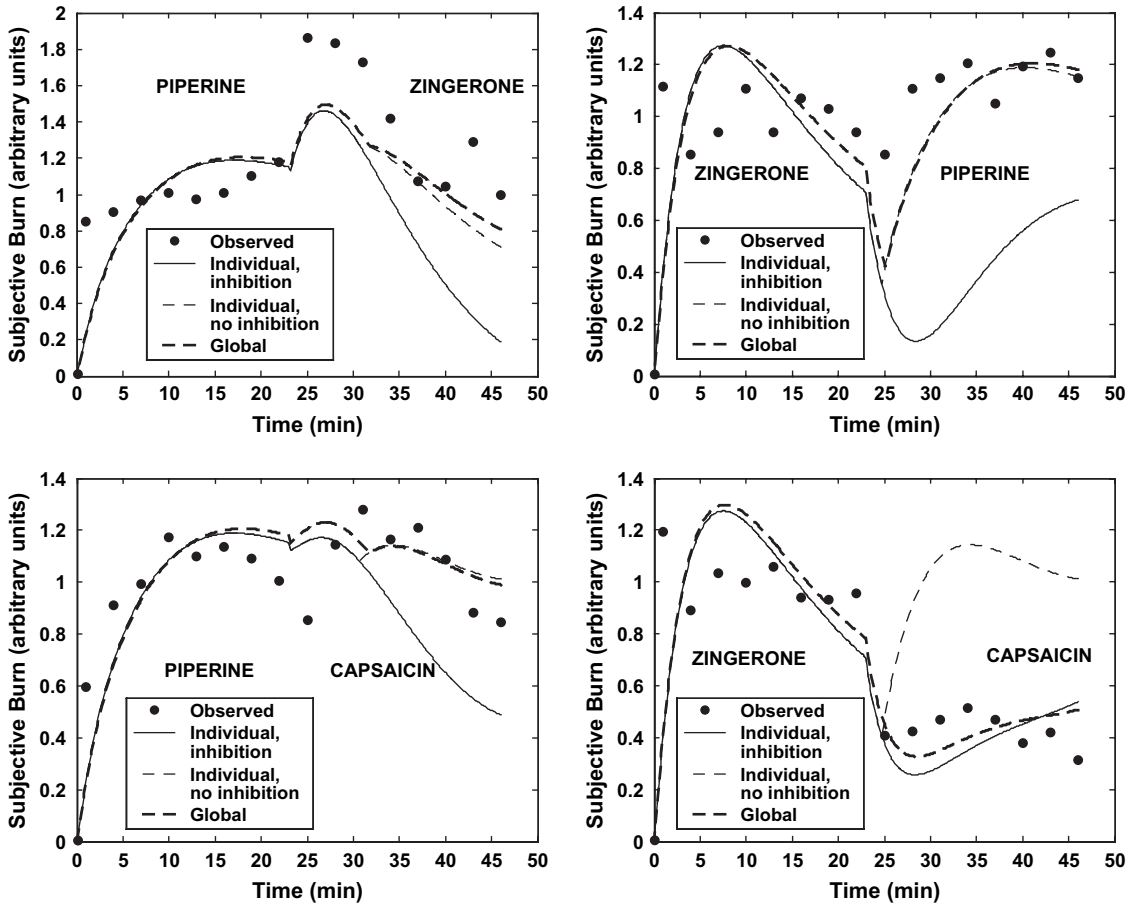


**Figure 4** Modeling of responses to sequential presentation of oral irritants. Subject responses from the accompanying appendix (see Supplementary materials) are shown for each combination of stimuli. The solid and light dashed lines show model predictions based upon the parameters estimated for the individual models in Figure 2. The solid line shows the predication when negative-going off-responses of the tonic and phasic model components behave as inhibitory signals in the central processor model. The light dashed line shows the prediction when the off-responses are not permitted to be less than zero (i.e., no inhibition). Note that the no-inhibition model provides a reasonable estimation of the behavior of the conditions showing cross-sensitization, whereas the inhibition model explains the condition showing cross-desensitization. The bold dashed line shows the global optimized fit of the final model (Appendix, Supplementary materials online) for all data conditions in Figures 2 and 3.

of the signals, such that irritant sensation persists after the peripheral neurons have ceased to respond to a persistent stimulus.

The modeling results (see Appendix, Supplementary materials online) demonstrate that a processing schema using a weighted sum of tonic, phasic, and integrator channels is a useful heuristic device for understanding how a relatively rapidly adapting peripheral neural responses can produce the slower psychophysical phenomena termed cross-sensitization and cross-adaptation. Capsaicin, piperine, and zingerone are all agonists at transient receptor potential vanilloid type 1 channels on primary afferents, and each irritant produces responses that desensitize to repeated exposures (e.g., Liu et al. 2000; McNamara et al. 2005). These fast processes were modeled as inputs to distinct processing channels because they elicit distinct psychophysical responses (see also Liu [2000] for the question of how the same receptor in the same neuron can elicit different burning responses). The model of sensory processes generates these slower psychophysical phenomena as a temporal summation of the underlying tonic, phasic, and integrator components (see Appendix Figure 5, Supplementary materials online). The model processes each represent lumped effects of synaptic integration and adaptive changes (e.g., desensitization or tachyphylaxis) in peripheral and central components of pathways that produce the burning sensation. Cross-sensitization occurs when there are no inhibitory interactions between the irritants, which is equivalent conceptually to a temporal summation of an on-response with an off-response that lacks inhibition. We have modeled this cross-sensitizing phenomenon as an interaction between 2 independent channels. Cross-adaptation, on the other hand, is produced by the temporal summation of an on-response of the second irritant (capsaicin) with an inhibitory off-response to the first irritant (zingerone); we have modeled this cross-adaptation as an inhibitory interaction in a common processing channel.

We have reported previously that this form of inhibitory temporal summation is sufficient to explain adaptation to a second transient presentation of capsaicin (Balaban et al. 1999).

The present study considered responses only within the context of a single session. It has been known for some time that capsaicin desensitization has long-term effects, from 6 days (Karrer and Bartoshuk 1991) to more than a week (McBurney et al. 2001). Long-term desensitization is handled within our model by reduction in the gains primarily of the tonic and integrator processes (McBurney 1997).

The model approach discussed in this study demonstrates that sensitization, cross-sensitization, desensitization/adaptation, and cross-desensitization/cross-adaptation to oral irritants can be explained by temporal summation of inputs that display the behavior of primary afferent responses. These primary afferents show the effects of receptor sensitization and desensitization, which have a much faster time course than the corresponding psychophysical effects. Therefore, we propose that processes similar to our model framework are responsible for prolonging the time course of the responses.

## Supplementary materials

Supplementary materials as Appendix can be found at http://www.chemse.oxfordjournals.org.

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