Sensitivities of Single Nerve Fibers in the Hamster Chorda Tympani to Mixtures of Taste Stimuli

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ABSTRACT Responses of three groups of neural fibers from the chorda tympani of the hamster to binary mixtures of taste stimuli applied to the tongue were analyzed. The groups displayed different sensitivities to six chemicals at concentrations that had approximately equal effects on the whole nerve. Sucrose-best fibers responded strongly only to sucrose and D-phenylalanine. NaCl-best and HCl-best fibers responded to four electrolytes: equally to $CaCl_2$ and nearly equally to HCl, but the former responded more to NaCl, and the latter responded more to NH_4Cl. The groups of fibers dealt differently with binary mixtures. Sucrose-best fibers responded to a mixture of sucrose and D-phenylalanine as if one of the chemicals had been appropriately increased in concentration, but they responded to a mixture of either one and an electrolyte as if the concentration of sucrose or D-phenylalanine had been reduced. NaCl-best fibers responded to a mixture as if it were a "mixture" of two appropriate concentrations of one chemical, or somewhat less. But, responses of HCl-best fibers to mixtures were greater than that, approaching a sum of responses to components. These results explain effects on the whole nerve, suggest that the sensitivity of a mammalian taste receptor to one chemical can be affected by a second, which may or may not be a stimulus for that receptor, and suggest that some effects of taste mixtures in humans may be the result of peripheral processes.

INTRODUCTION

Neurophysiological study of the sensory effects of taste stimuli in mixtures is important in view of the prevalence of multicomponent stimuli in natural feeding situations. In the first systematic study of mixtures at any neural level in mammals, the responses of the whole chorda tympani of the hamster to binary stimuli were found not to be predictable from the responses to individual components (Hyman and Frank, 1980). Yet, the overlap in sensitivities to pairs of stimuli in individual afferent nerve fibers was the most useful predictor: the greater the overlap, the more closely a mixture of different chemicals has an effect indistinguishable from a "mixture" of two concentrations of one chemical. However, even this was not a satisfactory predictor of

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most effects of mixtures, and it was concluded that it was necessary to present the mixture itself to know its effect.

The chorda tympani, which innervates taste receptors on the anterior tongue in mammals, is composed of hundreds of nerve fibers with diverse sensitivities, which are summed in the recorded response. It is thought that taste quality is represented in relative amounts of activity in differentially sensitive neurons. If this is true, an understanding of effects on the intensity of a given taste quality requires knowledge of sensitivities of individual neurons to mixtures. The discovery that many effects of mixtures on the responses of the whole nerve could not be predicted from the sensitivities of single fibers to individual chemicals argues for a determination of their sensitivities to mixtures of chemicals; the effects of mixtures on single fibers must also not be predictable from sensitivities to individual components if the whole nerve response reflects the sum of single fiber responses. Knowledge of responses of single fibers to mixtures should explain, then, the responses of the whole nerve. More importantly, sensitivities of single taste fibers to mixtures are also necessary to understand the variables determining such mixture effects. Neurons innervate receptors that differ in their sensitivities to single-component stimuli; these receptors may also differ in the way they process two stimuli encountered simultaneously.

Chorda tympani nerve fibers of various mammals are differentially sensitive to chemicals that evoke different taste qualities in the human (for examples, see Pfaffmann [1955], Fishman [1957], and Erickson [1963]). Most fibers display one of a limited number of general sensitivity patterns (for examples, see Boudreau and Alev [1973], Frank [1973], Sato et al. [1975], and Pfaffmann et al. [1976]) that can be related to one of the four taste qualities described by humans, i.e., sweet, salty, sour, or bitter (Nowlis and Frank, 1977). In particular, the single fibers of the hamster chorda tympani can be divided into three groups (Frank, 1973). Fibers within a group have similar sensitivity profiles across a number of chemicals (Frank, 1975) and have been named sucrose-best, NaCl-best, and HCl-best because they respond more to a moderate intensity of the chemical indicated in their name than to others of four test stimuli. The test stimuli are single concentrations of sucrose, NaCl, HCl, and quinine hydrochloride and are prototypes of the human's taste qualities.

The response profiles of all nerve fibers within a group are certainly not identical. The variability within a category leads to some question as to the validity of the categorization (Erickson, 1977). However, the variability can, at least in part, be attributed to intraneuron changes, changes in sensitivities of fibers or taste cells that occur over time after the fibers are cut from their cell bodies (Berland et al., 1977), or to changes that occur with repeated stimulation of the taste receptors (Kruger and Boudreau, 1972). Both of these effects probably played a role in the variability reported for eight rat chorda tympani fibers (Ogawa et al., 1973); responses to six repetitions of a set of stimuli showed that some neurons displayed increased responsiveness, that others decreased, and that others both increased and decreased, depending upon the stimulus considered. With such changes occurring in sensitivities of a single fiber, diversity in the responsiveness of different fibers need not be attributed to systematic variation in sensitivity among neurons.

Although it is possible that gustatory neurons cannot be divided into such categories and that their inputs are not separately processed in the nervous system, it is likely that separate stimulation of the sucrose-best, the NaCl-best, or the HCl-best fibers will evoke very different taste qualities. In this regard, division of single nerve fibers into a few groups according to their relative sensitivity to four chemicals has been useful for the prediction of: (*a*) the responsiveness of afferent nerve fibers to stimuli other than the four prototypic stimuli in the hamster (Frank, 1974), rat (Frank, 1975), squirrel monkey (Pfaffmann, 1974; Pfaffmann et al., 1976) and macaque (Sato et al., 1975); (*b*) the squirrel monkey's preference for sugars (Pfaffmann, 1974; Pfaffmann et al., 1976; and (*c*) the behavioral classification of taste stimuli by hamsters and rats (Nowlis and Frank, 1977). Whether these three groups of fibers process mixtures in distinct ways is of considerable interest in view of the fact that sensations of different taste qualities are affected differentially in mixtures.

The literature of human taste psychophysics abounds with studies of mixtures of stimuli, but there are fewer studies on mixtures of stimuli that individually elicit the same taste quality than studies on mixtures of stimuli that individually elicit different qualities. Cameron (1943, 1944, 1945, and 1947) concluded in a classic set of studies of the relative sweetness of various sweet-tasting substances and their mixtures that the sweetness of a mixture could be predicted from the sum of the concentrations of a reference chemical, when the concentrations of the reference chemical correspond in taste intensity to the individual components of the mixture. In terms of more modern psychophysics (Stevens, 1957), the sum of subjectively equivalent concentrations is transformed into a sensation whose magnitude is given by the psychophysical function for taste intensity of the reference. One restriction on this formulation is that the psychophysical functions for the component stimuli and the reference must be similar for the prediction to be accurate. Moskowitz's determinations of sweetness (1973 and 1974 *a*) or sourness (1974 *b*) of mixtures of similar-tasting chemicals agree with Cameron's predictions; however, because the exponents of the power functions relating sensation to stimulus intensity are close to +1.00 for these data, it is also accurate to state that the taste intensity of these mixtures of similar-tasting substances is equal to the sum of the intensities of the components presented individually. Bartoshuk and Cleveland (1977) clarified the situation by manipulating exponents of psychophysical functions with changes in method of stimulus presentation. The magnitude of a sensation evoked by a mixture of similar-tasting substances could be predicted by the psychophysical functions for the component chemicals, as Cameron would have predicted.

Some generalizations formulated on the basis of the many studies of mixtures of chemicals that individually elicit different taste qualities and that may have relevance to neural recordings from the hamster chorda tympani follow. The effects of mixtures of salts, sugars, and acids on evoked sweetness, saltiness, and sourness will be considered since it is responses of sucrose-best, NaCl-best, and HCl-best units of the hamster chorda tympani to mixtures of these kinds of stimuli which will be reported here.

The sweetness of sucrose solutions is increased by the addition of subthreshold concentrations of NaCl (Fabian and Blum, 1943; Beebe-Center et al., 1959; Kamen et al., 1961; Pangborn, 1962; Indow, 1969), perhaps due to the reported sweetness of weak salt solutions (Richter and MacLean, 1939; Kahn, 1951; Bartoshuk et al., 1964; O'Mahoney et al., 1976; Cardello and Murphy, 1977). This may also be true of other sugars (Fabian and Blum, 1943). In contrast, moderate or intense concentrations of NaCl suppress the sweetness of sucrose (Beebe-Center et al., 1959; Kamen et al., 1961; Pangborn, 1962; Indow, 1969); glucose and fructose solutions are affected similarly (Moskowitz, 1972). Citric acid can reduce the sweetness of solutions of sucrose (Pangborn, 1960 and 1961), glucose, or fructose (Stone et al., 1969; Moskowitz, 1972). The suppression of sweetness by threshold and moderate concentrations of citric acid is much more marked than the effect of threshold or moderate concentrations of NaCl on the concentrations of sucrose (Pangborn, 1960, 1961, and 1962). Indeed, concentrations of citric acid sufficient to reduce the pH of sugar solutions from 5.8 to 2.7 cause a 50% reduction in sweetness (Stone et al., 1969). Corresponding concentrations of HCl have not been tested. However, weak solutions of HCl (Fabian and Blum, 1943) or the addition of citric acid sufficient to reduce the pH of sugar solutions to 4.0 (Stone et al., 1969) do not influence sweetness.

Sucrose suppresses the sourness of citric acid (Fabian and Blum, 1943; Pangborn, 1960; Kamen et al., 1961) and tartaric acid solutions (Fabian and Blum, 1943; Indow, 1969). Small amounts of NaCl, when added to citric acid solutions, reduce their sourness (Fabian and Blum, 1943; Pangborn, 1960; Kamen et al., 1961; Pangborn and Trabue, 1967), but there are conflicting reports as to whether the sourness of citric acid solutions is increased (Kamen et al., 1961) or decreased (Pangborn and Trabue, 1967) by the addition of larger quantities of NaCl.

Although Kamen et al., (1961) report that the addition of sucrose produces no effect on the saltiness of NaCl solutions, the more common finding is that saltiness is suppressed by a small amount of sucrose (Fabian and Blum, 1943; Beebe-Center et al., 1959; Pangborn, 1960 and 1962; Indow, 1969). Again, this may also be true of other sugars (Fabian and Blum, 1943). The saltiness of NaCl solutions is not affected by the addition of near-threshold concentrations of HCl (Fabian and Blum, 1943), but it is increased by the addition of citric acid at near-threshold concentrations (Fabian and Blum, 1943; Pangborn and Trabue, 1967) and decreased by the addition of citric acid at higher concentrations (Pangborn and Trabue, 1967).

In summary, the psychophysical reports state that (*a*) the sweetness of sugars is suppressed more by the addition of moderate amounts of citric acid than moderate amounts of NaCl and is enhanced by small amounts of NaCl, (*b*) that the addition of sucrose or small amounts of NaCl suppress the sourness of acids, and (*c*) that the saltiness of NaCl is typically suppressed by the addition of small amounts of sugars and large amounts of citric acid but is enhanced by small amounts of acid.

Unlike the psychophysics of taste stimuli in mixtures, the neurophysiology of taste stimuli in mixtures has not been studied systematically. However, in studies with major aims other than a description of effects of mixtures, both suppression and enhancement have been documented. Responses of some chorda tympani fibers of the rat to 0.1 M NaCl may be halved when 0.1 M potassium benzoate is added to the solution; whereas, responses of other fibers may not be affected at all by such an addition (Miller, 1971). Comparably, responses of acid-sensitive units (type I) in the geniculate ganglion (where cell bodies of chorda tympani fibers are located) of the cat to NaH_2PO_4 are halved when an equal concentration of NaCl is added to the solution. On the other hand, in units of the same ganglion that are sensitive to NaCl (type II), responses to mixtures of equimolar NaCl and NaH_2PO_4 are greater than the sum of the responses to the components presented individually (Kruger and Boudreau, 1972). This enhancement contrasts with the suppression of responses of type I units to this mixture. The responses of sucrose-sensitive chorda tympani fibers of rats to mixtures of 0.016 M monosodium glutamate and 0.00073 M inosine 5′-monophosphate (disodium salt) or other 5′-ribonucleotides (e.g., guanosine 5′-monophosphate) were also enhanced; responses to the same mixtures were not enhanced in fibers which were not sensitive to sucrose (Sato et al., 1970). These examples illustrate that the neurophysiological effects of taste stimuli in mixtures can differ for units which differ in their sensitivities to single-component stimuli. In fact, suppression and enhancement can be present to similar degrees in different groups of units (Kruger and Boudreau, 1972). A summation of these opposite effects would make them observable in recordings from the whole nerve.

In the present experiments, single nerve fibers of the hamster chorda tympani were divided into three groups according to their predominant sensitivities to single-component stimuli; the responses of the groups were analyzed separately. The effects of taste stimuli in mixtures proved to be considerably different for the three groups of nerve fibers.

METHODS

Recording Technique, Stimulation Scheme, and Response Measurement

Surgical and stimulating techniques were identical to those reported for whole nerve recordings (Hyman and Frank, 1980), with the following exceptions. For single-nerve-fiber recording, after the chorda tympani was dissected free and cut, the sheath surrounding the nerve was removed, and the nerve trunk was teased apart into small bundles of fibers. Each nerve bundle was in turn lifted onto the recording electrode. Action potentials were recorded differentially with respect to an indifferent electrode positioned on muscle close to the chorda tympani. Solutions of 0.01 M NaCl, 0.003 M HCl, and 0.1 M sucrose were flowed over the tongue, and their effect on the neural activity of each nerve bundle was observed. If the response of a single nerve fiber could be identified reliably, as judged by the amplitude and wave form of action potentials displayed on an oscilloscope and audiomonitor, stimulation proceeded according to a predesigned schedule.

In the following schedule of stimulation, the letters *A*, *B*, *C*, *D*, *E* and *F* refer to 0.01 M NaCl, 0.05 M NH_4Cl, 0.1 M sucrose, 0.01 M $CaCl_2$, 0.07 M D-phenylalanine, and

0.003 M HCl, respectively. A mixture of any two stimuli is designated by the appropriate two letters; e.g., *AB* refers to the mixture of 0.01 M NaCl and 0.05 M NH_4Cl. The concentration of a component in the mixture equals its concentration when presented alone. For any stimulus *X*, $+X$ is one-half log step higher, $-X$ is one-half log step lower, and $--X$ is one log step lower in concentration than that in the mixtures; e.g., $+A$ designates 0.03 M NaCl, $-A$ designates 0.003 M NaCl, and $--E$ designates 0.007 M D-phenylalanine.

In the first stage of stimulation, responses to the single-component stimuli were obtained (i.e., responses to *A*, *B*, *C*, *D*, *E*, and *F*, in random order). In the second stage of stimulation, stimulus-response functions (i.e., the variation of response with stimulus concentration) and responses to mixtures were obtained in the following order: (1) the *A* series: $-A$, $+A$, then *A*, *AB*, *AC*, *AD*, *AE*, and *AF* in random order: (2) the *B* series: $-B$, $+B$, then *B*, *BC*, *BD*, *BE*, and *BF* in random order; (3) the *C* series: $-C$, $+C$, then *C*, *CD*, *CE*, and *CF* in random order; (4) the *D* series: $-D$, $+D$, then *D*, *DE*, and *DF* in random order; (5) the *E* series: $--E$, $-E$, then *EF* and *E* in random order; and (6) the *F* series: $-F$, *F*, and $+F$. If a nerve fiber was lost before presentation of all six series, stage two of the experiment on the next fiber was begun with the series that was not completed in the previous experiment, and that series was rotated to (1). For example, if a nerve fiber were lost after completion of the *A* (NaCl), *B* (NH_4Cl), *C* (sucrose), and *D* ($CaCl_2$) series, the *E* (D-phenylalanine) series would be the first series to be presented to the next fiber; under these circumstances, the D-phenylalanine series would consist of eight stimuli: $--E$, $-E$, then *E*, *EA*, *EB*, *EC*, *ED*, and *EF* in random order.

There was an interval of at least 1 min between successive stimulations, and the tongue was rinsed with distilled water for at least 15 s before each stimulus presentation. The chemicals and their concentrations in mixtures were the same as those reported for whole-nerve experiments (Hyman and Frank, 1980). Only single nerve fibers for which responses to all of the single component stimuli were obtained are reported here. 44 single nerve fibers were functionally isolated from 20 hamster nerves. Responses of these fibers were recorded on analogue tape for future "off-line" processing.

Tape recordings were played back and oscilloscope displays were photographed. The number of action potentials occurring in the first 5 s of stimulation was determined from the photographs. Fig. 1 is a series of photographs of one fiber's responses to nine stimuli. Spontaneous response rate, measured as the mean response rate to distilled water in the 2-s periods preceding each stimulation, varied from 0.0 to 4.4 action potentials per second for different fibers and was not subtracted from responses to stimuli. The 5-s response measure was chosen because it had been used successfully in previous analyses of afferent taste nerve responses (Frank, 1973, 1974, and 1975; Pfaffmann, 1974; Pfaffmann et al., 1976; Sato et al., 1975).

Classification of Nerve Fibers

The single nerve fibers were divided into three groups on the basis of their responses to the single-component stimuli presented at the beginning of each experiment. The criteria are similar but not identical to those used by Frank (1973), who compared taste-fiber responses to four gustatory stimuli, each at one test concentration: 0.1 M sucrose, 0.003 M HCl, 0.03 M NaCl, and 0.001 M quinine hydrochloride. The term "best stimulus" refers to the test stimulus that elicits the largest number of action potentials in the first 5 s of stimulation. In the present study, six stimuli were used, only two of them the same as those used by Frank (i.e., the HCl and sucrose stimuli). The NaCl test stimulus used here is of lower intensity (i.e., 0.01 M) than that used by

Frank, and a quinine hydrochloride test stimulus was not used here because it had not been found useful in the classification of hamster chorda tympani nerve fibers (i.e., it is neither a very effective nor a selective stimulus).

17 single nerve fibers were classified as sucrose-best (S-best). In 15 of these fibers, the responses to 0.1 M sucrose and 0.07 M D-phenylalanine were at least twice the magnitude of the responses to 0.003 M HCl, 0.01 M NaCl, 0.05 M NH_4Cl, and 0.01 M $CaCl_2$; in two less sensitive fibers, the responses to the former stimuli were greater but not twice as great as responses to the other stimuli.

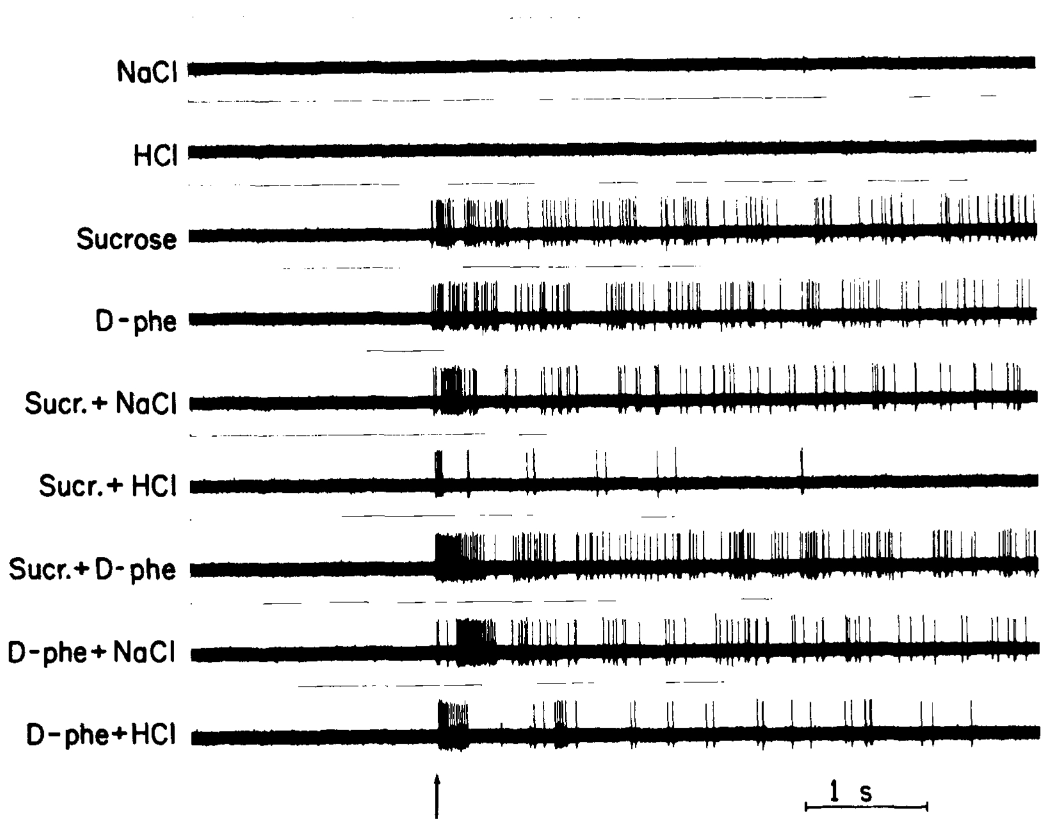

FIGURE 1. Photographs of oscillograph tracings of one hamster chorda tympani nerve fiber's responses to the indicated stimuli. Concentrations of stimuli, whether presented to the tongue individually or in a mixture (e.g., Sucr. + D-phe indicates a mixture of sucrose and D-phenylalanine), were 0.01 M NaCl, 0.003 M HCl, 0.1 M sucrose, and 0.07 M D-phenylalanine. 7 s of record are shown in each tracing: 2 s before and 5 s of the response. The arrow indicates the beginning of a response.

Twelve single nerve fibers were classified as acid-best, specifically HCl-best (H-best). In all of these fibers, the responses to 0.003 M HCl and 0.05 M NH_4Cl were at least five times the size of the responses to 0.1 M sucrose and 0.07 M D-phenylalanine. In 10 of these fibers, the responses to 0.003 M HCl and 0.05 M NH_4Cl were greater than twice the magnitude of the response to 0.01 M NaCl; in the other two fibers, the responses to HCl and NH_4Cl were much greater than, but not quite twice as great as, the response to NaCl. All fibers classified as HCl-best responded more, or nearly as much, to 0.05 M NH_4Cl as to 0.003 M HCl, and less to 0.01 M $CaCl_2$.

15 single nerve fibers were classified as salt-best, specifically NaCl-best (N-best). In all of these fibers, the response to 0.01 M NaCl was greater than twice the magnitude of the responses to 0.1 M sucrose and 0.07 M D-phenylalanine. In six of these fibers, the response to 0.01 M NaCl was greater than twice the magnitude of the responses to 0.003 M HCl, 0.05 M NH_4Cl, and 0.01 M $CaCl_2$; in four other fibers the response to NaCl was greater than, but not twice as great as, the responses to HCl, NH_4Cl, and $CaCl_2$. In yet five more fibers, the response to NaCl was slightly less than the response to HCl; these fibers were relatively nonspecific electrolyte-sensitive fibers, and were classified as NaCl-best rather than HCl-best because they (*a*) responded more to 0.01 M NaCl than any of the fibers classified as HCl-best and (*b*) because they responded more to 0.01 M $CaCl_2$ than to 0.05 M NH_4Cl, which was characteristic of NaCl-best and contrary to the response characteristics of all HCl-best fibers.

Although the criteria for classification differ slightly from those of Frank (1973), it was expected that the two methods would result in nearly identical grouping of the nerve fibers. With regard to sucrose-best fibers, 0.001 M quinine-HCl produced no effect in the earlier study; therefore, its omission here is not critical. The use of the stronger NaCl stimulus would not have affected classification, as is evidenced by the nearly equal responses to 0.03 M NaCl and 0.01 M NaCl in the 11 sucrose-best fibers that were so stimulated in the second stages of the experiments. With regard to HCl-best fibers, 0.001 M quinine-HCl was only weakly effective in the earlier study so that, again, its omission here is not critical; and in all but one of the nine HCl-best fibers stimulated with 0.03 M NaCl, that stimulus was less effective than the initial 0.003 M HCl application. With regard to the NaCl-best fibers, 0.001 M quinine-HCl was only weakly effective in the earlier study so that, again, its omission here is not critical; and in the five NaCl-best fibers that were stimulated with 0.03 M NaCl, it was more effective than the 0.01 M NaCl and 0.003 M HCl tested initially. Moreover, these five fibers include two fibers in which 0.01 M NaCl was less effective than 0.003 M HCl in the initial tests. Therefore, the five fibers that responded more to 0.003 M HCl than to 0.01 M NaCl would likely have been classified as NaCl-best on the basis of the Frank (1973) method as well.

Data from each group of nerve fibers were analyzed separately. Responses to the six single-component stimuli to variation in their concentrations and to each of the 15 two-component mixtures were considered separately for sucrose-best, NaCl-best, and HCl-best fibers. 13 of the 17 sucrose-best fibers, 10 of the 12 HCl-best fibers, and 9 of the 15 NaCl-best fibers contributed to at least one of the six sets of data on response vs. stimulus concentration of each fiber group. These stimulus-response functions were necessary to determine whether the response to a two-component mixture could be accounted for as a response to the sum of two concentrations, equal in intensity to the two stimuli in the mixture, of one chemical. 12 of the sucrose-best, nine of the HCl-best, and seven of the NaCl-best fibers contributed to the data from two-component mixtures. Responses to at least two complete mixture series were recorded from each of these fibers. Note that a smaller percentage of NaCl-best fibers survived long enough to be tested with mixtures. Only responses to mixture components of the fibers which contributed to the mixture data were used in the analysis of mixtures.

RESULTS

Effects of Single-component Stimuli on Single Nerve Fibers

Responses of single nerve fibers to the single-component stimuli presented at the beginning of each recording session are plotted in Fig. 2; response profiles

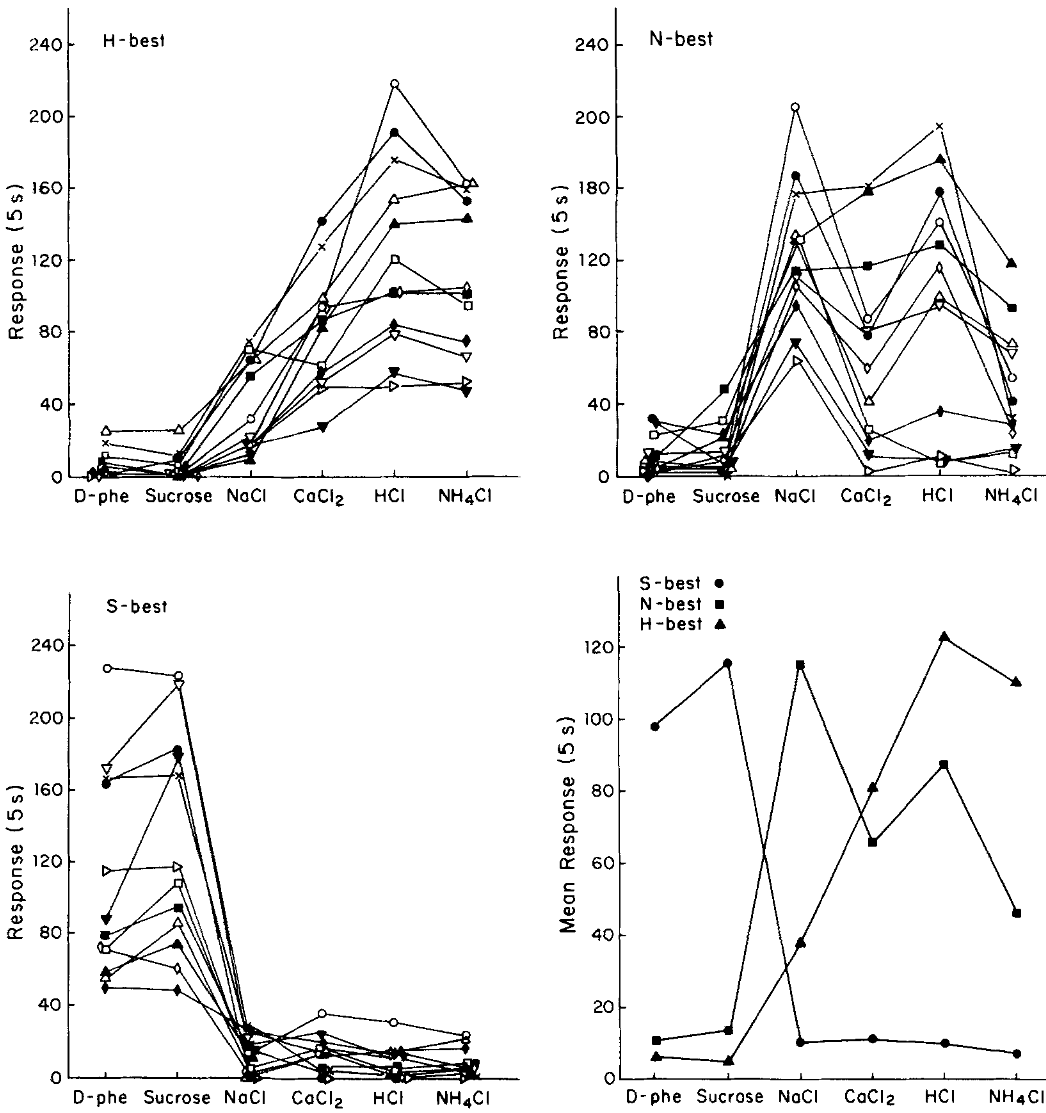

FIGURE 2. Response profiles of HCl(H)-best, NaCl(N)-best, and sucrose(S)-best hamster chorda tympani nerve fibers, as well as the mean profile for each group, to 0.07 M D-phenylalanine, 0.1 M sucrose, 0.01 M NaCl, 0.01 M $CaCl_2$, 0.003 M HCl, and 0.05 M NH_4Cl. Profiles for 12 fibers in each group are illustrated; 12 HCl-best, 15 NaCl-best and 17 sucrose-best fibers were sampled. Profiles in the latter two groups which showed the largest responses to their "best stimulus" (eight NaCl-best, six sucrose-best) and alternates of the less responsive are illustrated. All fibers' responses were included in the calculation of means. The response measure was the number of action potentials in the first 5 s of a response.

for the sucrose-best, HCl-best, and NaCl-best groups of fibers are plotted on separate sets of axes. In this and in similar figures in this paper, the discrete points along the abscissa indicate the chemicals presented, each at one test concentration. The order along the abscissa is arbitrary and does not imply a continuous scale or function; each line merely connects the points that represent the responses of a particular fiber to the indicated stimuli.

Responses to each stimulus vary in magnitude across fibers. At the test concentrations, NaCl, HCl, and sucrose are approximately equally good stimuli: 17 of the sampled single fibers respond best to sucrose; 15 fibers respond best to NaCl, and 12 fibers respond best to HCl. The number of single fibers responding with over 20 action potentials in the 5-s stimulation period is 22 for NaCl, 22 for HCl, and 17 for sucrose; over 100 action potentials in 5 s were elicited by NaCl in nine fibers, by HCl in eight fibers, and by sucrose in eight fibers; and within each group there are fibers whose best response was nearly 200 action potentials in 5 s.

All of the sucrose-best fibers are quite specific in their sensitivities, although the magnitude of the response to sucrose varies considerably across these fibers, ranging from 50 to 223 action potentials in 5 s. Responses to the electrolytes are small, if they occur; only two such responses exceed 30 action potentials in 5 s. In general, the fibers respond as much to D-phenylalanine as to sucrose.

All of the HCl-best fibers respond more to NH_4Cl than to $CaCl_2$ and NaCl. The order of responsiveness is $NH_4Cl > CaCl_2 > NaCl$ for every HCl-best fiber except one, whose response to NaCl slightly exceeds its response to $CaCl_2$. The response to HCl ranges from 50 to 218 action potentials/5 s in these fibers. The response to NH_4Cl approaches that to HCl and even exceeds it in several fibers. The response to NaCl is generally small. Responses to sucrose and D-phenylalanine, if they occur, are small; none exceeds 30 action potentials in 5 s.

The NaCl-best fibers whose best-response is among the lowest of the group respond little, if at all, to the other stimuli. However, with only one exception, fibers responding with at least 30 action potentials to either NH_4Cl or $CaCl_2$ respond more to $CaCl_2$ than to NH_4Cl. The response to NaCl ranges from 65 to 205 action potentials/5 s in the NaCl-best fibers. At these test concentrations, some NaCl-best fibers respond as much to HCl as to NaCl, or even more. These fibers are considered NaCl-best because of their large response to NaCl, their projected (or known) response to a stronger concentration of NaCl, and their greater sensitivity to $CaCl_2$ than NH_4Cl (see Methods). In the more sensitive NaCl-best fibers, responses to the other electrolytes are also high. Responses to sucrose and D-phenylalanine are very small; four exceed 30 action potentials in 5 s.

Mean responses to the single-component stimuli for the sucrose-best, HCl-best and NaCl-best fibers are plotted on a fourth set of axes in Fig. 2. The mean best-responses (specifically, the mean responses to the three stimuli being used as markers to classify fibers) are nearly equal for the three groups. However, response profiles for the three groups of fibers are strikingly different. Fig. 3 presents mean relative response profiles (in which mean responses to the other stimuli are expressed as percentages of the mean best-response) for the more and less sensitive halves of each group, divided on the basis of the size of the response to the best-stimulus. In general, the same pattern of responsiveness is exhibited by the halves of each group, but there are a few trends that are noteworthy. Responses to other stimuli tend to be slightly larger percentages of the best response in less sensitive units; this is true for the means of all five other stimuli in sucrose-best units. On the other hand, mean responses to the other three electrolytes are larger percentages of the response to NaCl in more sensitive NaCl-best units. These trends can also be seen in the response profiles of individual nerve fibers. The increase in relative effect of less effective stimuli is expected if "noise" remained constant and "signal" decreased in the less responsive units; however, the relatively greater effect of

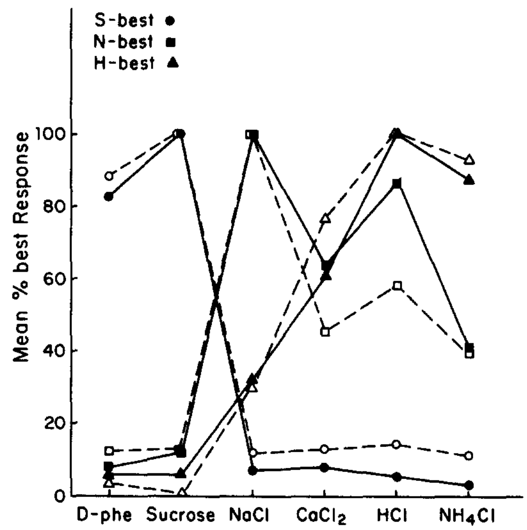

FIGURE 3. Mean relative response profiles of sucrose(S)-best, NaCl(N)-best, and HCl(H)-best hamster chorda tympani nerve fibers to 0.07 M D-phenylalanine, 0.1 M sucrose, 0.01 M NaCl, 0.01 M $CaCl_2$, 0.003 M HCl and 0.05 M NH_4Cl. Mean responses to the other stimuli were expressed as percentages of the mean response to the "best stimulus." Each of the three groups of fibers were divided into more and less sensitive halves, that is, into groups with the larger (solid lines) and smaller (broken lines) responses to the "best stimulus" of the group.

$CaCl_2$ and HCl in the more responsive NaCl-best units could not be the result of such a reduction in "signal".

The responses of single nerve fibers were recorded as the concentration of each single-component stimulus was varied over a limited range. The resulting stimulus-response functions for the mean responses calculated across the fibers of each group which had been so stimulated are presented in Fig. 4. Power functions were fitted to the data for each chemical with considerable effect for a given group of fibers. The exponents of the power functions (slopes of the straight lines fit to log stimulus concentration v. log mean response) are presented in Table I, with the correlation coefficients attesting to goodness of fit; all of the exponents are positive and less than +1.00.

Again, it is clear, as it was from the data on single concentrations of each stimulus, that the different groups of fibers exhibit different sensitivities, in this case to three concentrations spanning a log unit of molarity of a chemical's dynamic range of effect. Sucrose and D-phenylalanine are very effective stimuli for the sucrose-best fibers; the electrolytes hardly stimulate them at all. Of the electrolytes, NH_4Cl is the most selective in its effect on the other

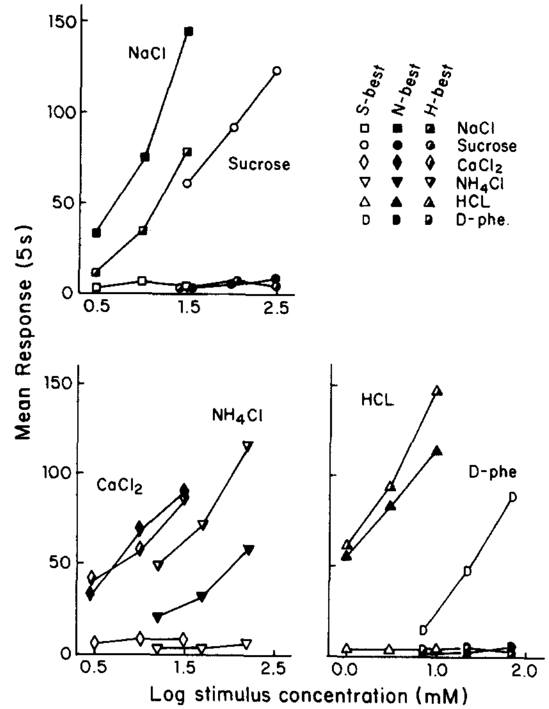

FIGURE 4. Mean responses of sucrose(S)-best, NaCl(N)-best, and HCl(H)-best nerve fibers of the hamster chorda tympani as a function of log concentration (millimoles per liter) of six chemicals. Lines connect points which represent the mean effect of each stimulus on one group of fibers. The response measure was the number of action potentials in the first 5 s of a response. Responses to electrolytes in N-best and H-best fibers, and responses to sucrose or D-phe in S-best fibers, are significantly greater (Wilcoxon test, $P \leq 0.05$) at the highest concentration than at the lowest concentration and are monotonically related to concentration; these properties do not hold for responses to sucrose or D-phe in N-best or H-best fibers, or for responses to electrolytes in S-best fibers. Responses of N-best and H-best units to NH_4Cl and NaCl differ significantly (Wilcoxon test, $P \leq 0.05$) in size.

two groups of fibers in that the HCl-best are much more responsive to it than the NaCl-best fibers. NaCl is also quite selective in effect, affecting the NaCl-best considerably more than the HCl-best fibers. HCl alone could not be used to separate the two fiber groups unless it were presented at a concentration of 10 mM, at which it tends to stimulate HCl-best fibers more than NaCl-best fibers. Finally, $CaCl_2$ is the least discriminating of the salts, affecting both NaCl-best and HCl-best fibers nearly equally at the three concentrations tested.

Exponents of the power functions fit to the responses to HCl, $CaCl_2$, and NH_4Cl are similar for the NaCl-best and HCl-best groups of fibers, varying from 0.32 to 0.42, and these values are similar to the exponent of the power function fit to the responses of sucrose-best fibers to sucrose (i.e., 0.31). The exponent for the responses to NaCl is higher than the exponents for the other electrolytes in both the NaCl-best and HCl-best groups of fibers, and the exponent for D-phenylalanine is higher than that for sucrose in the sucrose-best group of fibers. However, the range of concentrations tested is closer to threshold for NaCl and D-phenylalanine than for the other chemicals. Many NaCl-best and HCl-best fibers do not respond to 3 mM NaCl, and many

TABLE I

SLOPES OF STRAIGHT LINES FIT TO LOG STIMULUS CONCENTRATION VS. LOG MEAN 5-S RESPONSE PLOTS FOR SINGLE-COMPONENT STIMULI

Stimulus		Unit Group					
Chemical	Range of concentrations	Sucrose-best (n = 8–12)		NaCl-best (n = 5–6)		HCl-best (n = 8–9)	
	mM	*slope*	r*	*slope*	r*	*slope*	r*
NaCl	3–30	‡		0.63§	(0.9994)	0.82§	(0.9987)
HCl	1–10			0.32	(0.9949)	0.39	(1.0000)
$CaCl_2$	3–30			0.42	(0.9689)	0.33	(0.9976)
NH_4Cl	16–160			0.44	(0.9957)	0.37	(0.9987)
Sucrose	30–300	0.31	(0.9979)				
D-Phe	7–70	0.78§	(0.9850)				

* r is the Pearson product moment correlation coefficient between the three obtained and predicted points; it attests to relative goodness of fit.

‡ Straight lines were not fit to responses which did not exceed 10 impulses in 5 s to any of the three concentrations.

§ Slopes are significantly different (Wilcoxon test, $P \leq 0.05$) from the other slope(s) for the sucrose-best or HCl-best units, or for all units combined.

sucrose-best fibers do not respond to 7 mM D-phenylalanine. Therefore, differences in exponents presented here may be more characteristic of different portions of the stimulus-response function being represented than of the chemical itself.

Effects of Two-component Mixtures on Single Nerve Fibers

Mean responses of sucrose-best, NaCl-best, and HCl-best fibers to the single-component stimuli and their mixtures are represented in Fig. 5. The responses were obtained during the second part of each recording session from twelve sucrose-best, seven NaCl-best, and nine HCl-best fibers.

Only sucrose-best fibers responded well to sucrose, D-phenylalanine, and their mixture, and these fibers responded relatively little to the electrolytes presented individually or mixed with other electrolytes. Mixtures of sucrose or D-phenylalanine with each electrolyte did stimulate sucrose-best fibers, but generally less so than either sucrose or D-phenylalanine alone, the one exception being the mixture of D-phenylalanine and $CaCl_2$. Therefore, one of these electrolytes, although itself rather ineffective as a stimulus for sucrose-best fibers, reduces the effectiveness of sucrose and D-phenylalanine as stimuli for these fibers when presented in a mixture.

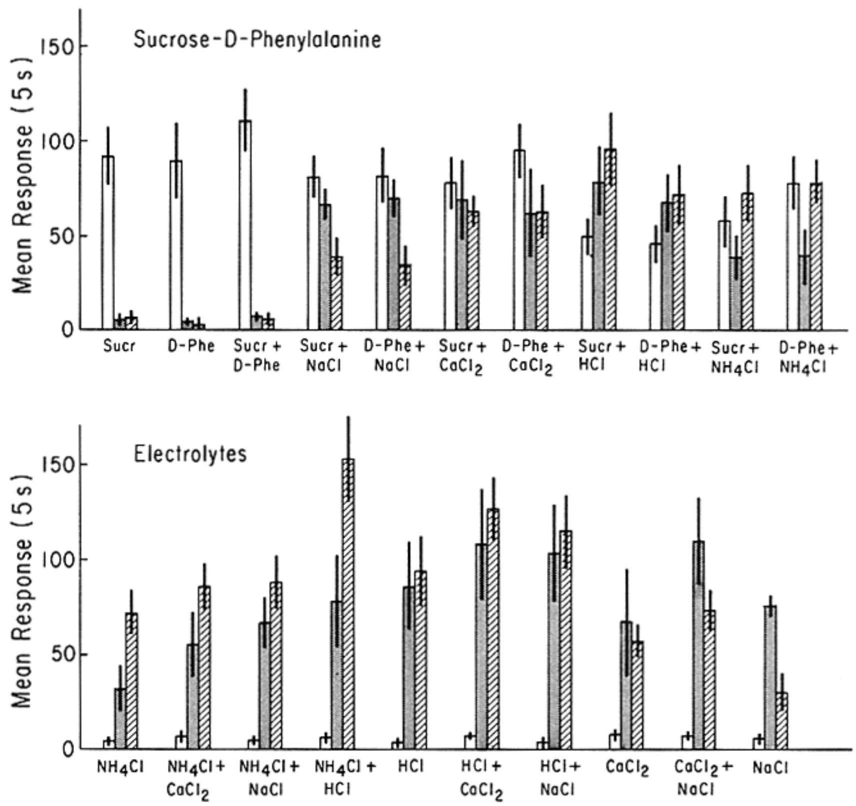

FIGURE 5. Mean responses of sucrose(S)-best, NaCl(N)-best, and HCl(H)-best nerve fibers of the hamster chorda tympani to 0.1 M sucrose, 0.07 M D-phenylalanine, 0.05 M NH_4Cl, 0.003 M HCl, 0.01 M $CaCl_2$, and 0.01 M NaCl presented individually and in binary mixtures. Each triplet of bars represents (from left to right) the mean responses of sucrose-best, NaCl-best, and HCl-best fibers, respectively, to the stimulus indicated directly below and shows the average pattern of activity across the three unit groups for each stimulus. The dark vertical line atop each bar indicates plus and minus one standard error of the mean and shows how much that average might vary in random samples of the same number. The response measured was the number of action potentials in the first 5 s of a response.

The addition of sucrose or D-phenylalanine, comparably weak stimuli for NaCl-best and HCl-best fibers, does not have a dramatic effect on the response of these fibers to electrolytes. For example, the mean response of NaCl-best fibers to NaCl or HCl is but slightly changed in the presence of the two effective stimuli than D-phenylalanine alone. HCl reduces the stimulatory nonelectrolytes. However, there is a dramatic reduction in the response of HCl-best fibers to HCl when mixed with D-phenylalanine; but this effect is probably the result of the chemical interaction in the mixture.

The four electrolytes and the six two-component mixtures of electrolytes all strongly stimulate NaCl-best and HCl-best fibers. It is not as easy to interpret the responses to these mixtures as it is to interpret responses to mixtures of stimuli which differ so much in effect. However, a hint of the different ways in which the two groups of electrolyte-sensitive nerve fibers treat mixtures is given by two examples in Fig. 5. Consider the stimuli NH_4Cl, NaCl, and their mixture. NH_4Cl and NaCl are the most selective of the electrolytes tested: NH_4Cl stimulates HCl-best fibers more than twice as much as NaCl-best fibers; and NaCl stimulates NaCl-best fibers more than twice as much as HCl-best fibers. When these two salts are mixed, their effect on NaCl-best fibers is less than the effect of NaCl alone, but their effect on HCl-best fibers is more than the effect of NH_4Cl alone. Next, consider responses to NH_4Cl, HCl, and their mixture: the response of NaCl-best fibers to the mixture of NH_4Cl and HCl is less than their response to HCl alone; but the response of HCl-best fibers to this mixture is much larger than their response to HCl alone. These examples are a preview of more detailed analyses presented below, which show that responses of NaCl-best fibers to two-component mixtures approach a response predicted for a single-component "mixture" of one chemical, whereas responses of HCl-best fibers to mixtures approach the sum of the responses to the components presented individually.

Sucrose-best FIBERS: THE EFFECTS OF SUCROSE AND D-PHENYLALANINE ARE REDUCED BY ELECTROLYTES Mean responses of sucrose-best fibers to the single-component stimuli and their mixtures are plotted in Fig. 6. 12 of the 15 mixtures elicit mean responses smaller than the response to the more effective component of the mixture presented alone. One of the other three mixtures is sucrose mixed with D-phenylalanine; the response to this mixture is nearly equal to the response predicted from the stimulus-response function for sucrose for the sum of two concentrations of sucrose (100 mM and 110 mM) equal in intensity to the sucrose and D-phenylalanine stimuli. The sucrose-equivalence prediction (Sucr′) is plotted to the right of the bar representing the actual response of the mixture.

All of the mixtures of sucrose and an electrolyte are less effective than sucrose alone. Electrolytes have little positive effect by themselves, and the effect of their presence in a mixture can be considered negative (i.e., a reduction in the effect of the stimulating chemical). The reduction in the response to sucrose varies from 46% with HCl to 12% with NaCl. The great majority of nerve fibers (see Fig. 1 for a sample) showed this reduction; specifically, 10 of the 12 sucrose-best fibers so stimulated showed a reduced response to sucrose with HCl (or NaCl) added. The effect of the electrolytes in reducing the response to sucrose is ordered $HCl > NH_4Cl \gg CaCl_2 > NaCl$, with HCl and NH_4Cl more severely affecting the response to sucrose than $CaCl_2$ or NaCl.

Three of the four mixtures of D-phenylalanine with electrolytes are less effective stimuli than D-phenylalanine alone. HCl reduces the stimulatory effect of both sucrose and D-phenylalanine to about half. NH_4Cl reduces the mean response to D-phenylalanine only slightly in comparison with its effect on the response to sucrose. $CaCl_2$ does not reduce the effect of D-phenylalanine; indeed, the response to this mixture is slightly greater than predicted for sucrose-equivalence (Sucr′).

The electrolyte mixtures are without major effect on sucrose-best fibers, as are the component electrolytes when presented alone.

In summary, the sucrose-best fibers exhibit three characteristics in response

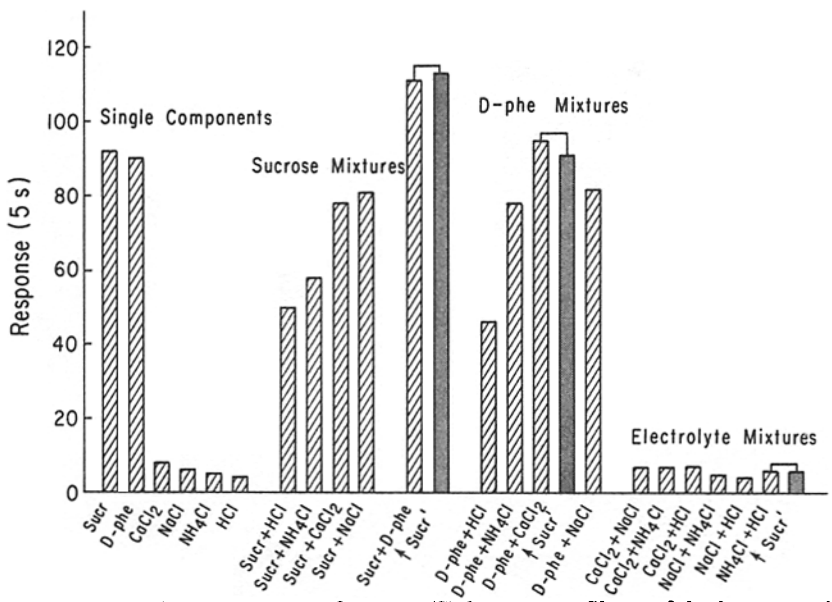

FIGURE 6. Mean responses of sucrose(S)-best nerve fibers of the hamster chorda tympani to 0.1 M sucrose, 0.07 M D-phenylalanine, 0.01 M $CaCl_2$, 0.01 M NaCl, 0.05 M NH_4Cl, and 0.003 M HCl; the binary mixtures of these six stimuli; and the response predicted for a "mixture" of two appropriate concentrations of sucrose (Sucr′), if the response to a mixture was greater than the response to the more effective component. Responses are represented by crosshatched bars and predictions by gray bars; the former are numbers of action potentials in the first 5 s of a response, and the latter were obtained from a power function fit to the data presented in Fig. 4.

to mixtures of taste stimuli: (*a*) in the presence of a second chemical that is itself a very effective stimulus, they respond as if confronted with a higher concentration of the first such stimulus; (*b*) the effectiveness of a stimulus is generally reduced by the presence of an electrolyte that itself is not a very effective stimulus; and (*c*) the effect of an electrolyte on responses to two different very effective stimuli can be similar but is not necessarily so. Statistical support for these descriptions of sucrose-best fibers' responses to mixtures is found in Table II.

NaCl-best FIBERS: ADDITION OF A SECOND ELECTROLYTE HAS AN EFFECT WHICH NEARLY EQUALS THE EFFECT OF INCREASING THE NaCl CONCENTRATION Mean responses of NaCl-best fibers to the single-component stimuli and their mixtures are represented in Fig. 7. 12 of the 15 mixtures elicit a response either smaller than the response to the more effective component presented alone or smaller than the response predicted from the NaCl stimulus-response function for the sum of two concentrations of NaCl equal in intensity to the components in the mixture.

NH_4Cl mixed with each of the other electrolytes elicits a mean response slightly smaller than that elicited by the other electrolyte presented alone; in contrast, the mean responses to NH_4Cl mixed with either sucrose or D-phenylalanine (i.e., two relatively ineffective stimuli for these fibers) are

TABLE II

STATISTICAL SUPPORT FOR DESCRIPTION OF RESPONSES TO MIXTURES: DIFFERENCES WITH A PROBABILITY OF OCCURRENCE OF <0.05 ARE LISTED*

Fiber Group	R_a vs. R_{ab}	R' vs. R_{ab}	R_{ab} vs. $\Sigma R_a, R_b$
Sucrose-best	Sucr < Sucr + D-Phe		Sucr + D-Phe < Sucr, D-Phe
	Sucr > Sucr + HCl		
	Sucr > Sucr + NH_4Cl		
	D-Phe > D-Phe + HCl		
NaCl-best	NH_4Cl < NH_4Cl + Sucr		NaCl + NH_4Cl < NaCl, NH_4Cl
HCl-best	HCl < HCl + NH_4Cl	HCl′ < HCl +NH_4Cl	
	HCl < HCl + $CaCl_2$		
	HCl < HCl + NaCl		
	NH_4Cl < NH_4Cl + $CaCl_2$		NH_4Cl + $CaCl_2$ < NH_4Cl, $CaCl_2$
	$CaCl_2$ < $CaCl_2$ + NaCl		
	HCl > HCl + D-Phe		
	NaCl < NaCl + Sucr	HCl′ < NaCl + Sucr	

Effect (R) of stimulus combination (a, b) in a mixture (R_{ab}) is compared with effect of the more effective of the two components, (R_a), an increase in concentration of one component (R'), and the effects of the two components, summed ($\Sigma R_a, R_b$).
* Friedman tests (analysis of variance by ranks) were applied to relevant data and, if a significant effect was observed, Wilcoxon tests (signed ranks) were applied to data for pairs of stimuli in which there were enough observations (at least six); a two-tailed probability was considered appropriate.

approximately equal to the sum of the responses to the components. NH_4Cl is the least effective of the electrolytes in stimulating NaCl-best fibers, and only for mixtures containing NH_4Cl were small reductions in the effect of the electrolytes or increases in the effect of nonelectrolyte stimuli observed.

The other three electrolyte mixtures (NaCl and HCl, $CaCl_2$ and HCl, and NaCl and $CaCl_2$) elicit mean responses somewhat greater than that elicited by the more effective component presented alone but a little less than the response predicted from the stimulus-response function for the sum of the two concentrations of NaCl equivalent in intensity to the components of the mixture.

Mean responses to mixtures of HCl or NaCl with sucrose or D-phenylalanine, or of $CaCl_2$ with D-phenylalanine were slightly smaller than the response to the electrolyte component presented alone. The addition of D-phenylalanine to HCl produced a larger reduction in the response of NaCl-best fibers to an electrolyte, but this effect most probably results from the chemical interaction in the mixture. The nonelectrolyte mixture of sucrose and D-phenylalanine had a slightly greater mean effect on NaCl-best fibers than did either of the components presented alone.

In summary, the response of NaCl-best fibers to mixtures is generally characterized by being somewhat smaller than or indistinguishable from the response to a single-component "mixture" of NaCl; none of the mixtures had

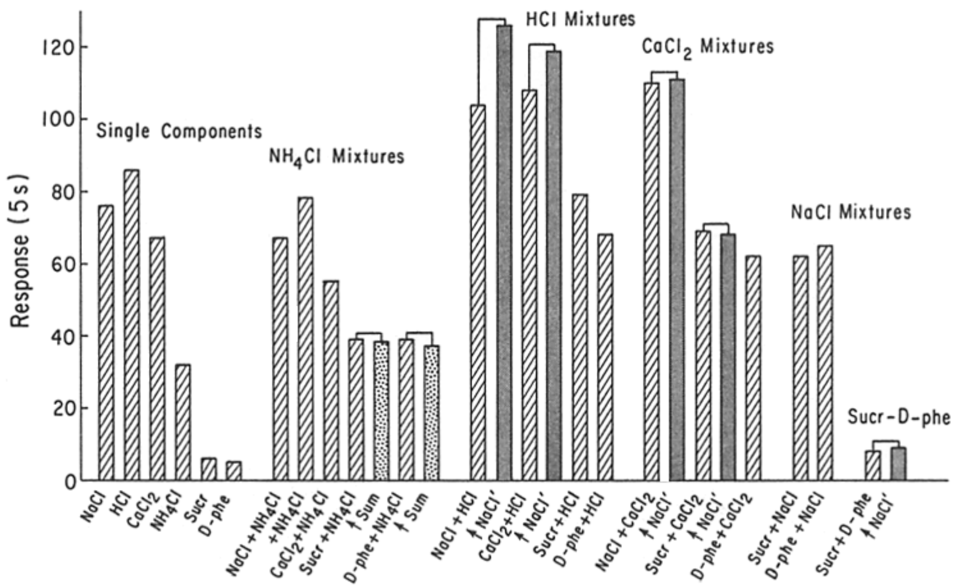

FIGURE 7. Mean responses of NaCl(N)-best nerve fibers of the hamster chorda tympani to 0.01 M NaCl, 0.003 M HCl, 0.01 M $CaCl_2$, 0.05 M NH_4Cl, 0.1 M sucrose, and 0.07 M D-phenylalanine; the binary mixtures of these six stimuli; the response predicted for a "mixture" of two appropriate concentrations of NaCl (NaCl′), if the response to a mixture was greater than the response to the more effective component; and the sum of the responses to the components (Sum), if the response to the mixture was greater than that sum. Obtained responses to a mixture are represented by crosshatched bars, predicted responses by gray bars, and summed component responses by dotted bars. Responses are numbers of action potentials in the first 5 s of a response, and predictions were obtained from a power function fit to the data presented in Fig. 4.

an effect very different from the effect an appropriate increase in NaCl would have produced.

HCl-best FIBERS: THE EFFECTS OF ELECTROLYTES IN MIXTURES ARE NEARLY EQUAL TO THEIR INDIVIDUAL EFFECTS Mean responses of HCl-best fibers to the single-component stimuli and their mixtures are represented in Fig. 8. 13 of the 15 mixtures elicit responses that exceed the response predicted from the stimulus-response function for a concentration of HCl equal to the sum of two concentrations equivalent in intensity to the components of the mixture. None of the mixtures of electrolytes elicit a mean response from these fibers less than that elicited by the more effective component. Indeed, the effect of each is greater than that of a single-component "mixture" of HCl and approaches to various degrees the sum of the effects of the components presented individually. For example, the mean response to the mixture of HCl and NH_4Cl is 92% of the sum of the responses to the components and 39% greater than the response predicted for a single-component "mixture" of equivalent concentra-

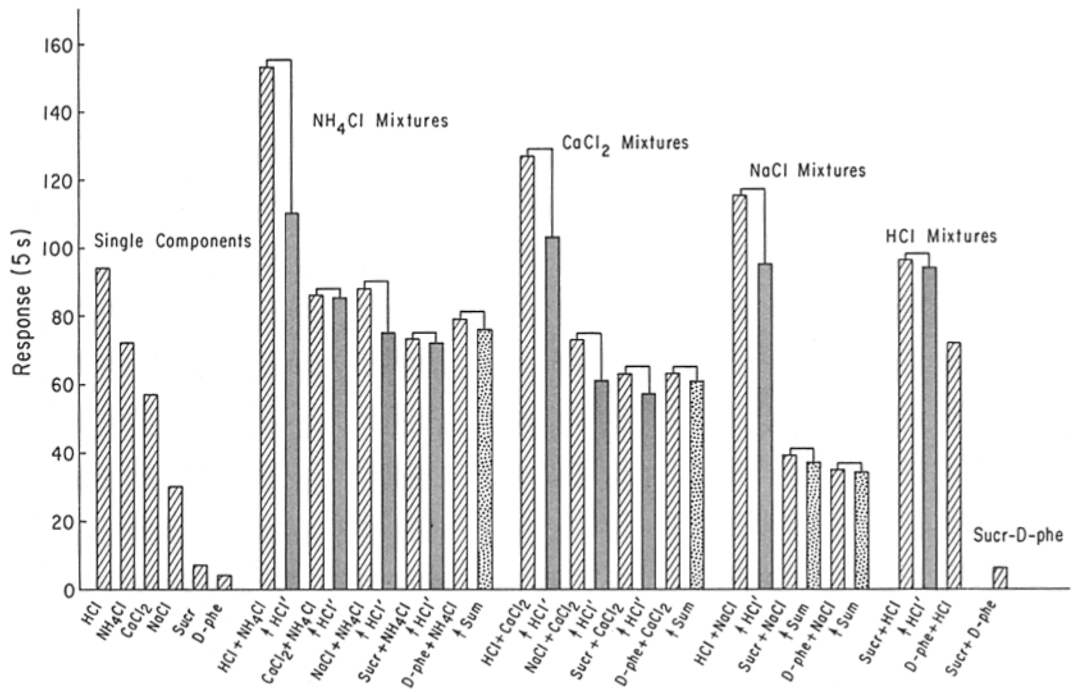

FIGURE 8. Mean responses of HCl(H)-best nerve fibers of the hamster chorda tympani to 0.003 M HCl, 0.05 M NH_4Cl, 0.01 M $CaCl_2$, 0.01 M NaCl, 0.1 M sucrose, and 0.07 M D-phenylalanine; the binary mixtures of these six stimuli; the response predicted for a "mixture" of two appropriate concentrations of HCl (HCl′), if the response to a mixture was greater than the response to the more effective component; and the sum of the responses to the components (Sum), if the response to the mixture was greater than that sum. Crosshatched bars represent obtained responses, dotted bars, the summed component responses, and gray bars, the predicted responses; the former two are numbers of action potentials in the first 5 s of a response; the latter were obtained from a power function fit to the data presented in Fig. 4.

tions of HCl (i.e., 3 mM and 1.5 mM HCl); but the mean response to the mixture of NH_4Cl and $CaCl_2$ is nearly equal to the response predicted for the sum of equivalent concentrations of HCl (i.e., 1.5 mM and 0.8 mM HCl). The mixture of NH_4Cl and $CaCl_2$ is the only electrolyte mixture whose effect closely approaches the response predicted for a single-component "mixture" of HCl. The mean effect of the HCl and NaCl mixture approaches the sum of the responses to the components more closely than the response to a "mixture" of two HCl concentrations; but the effects of the HCl and $CaCl_2$, the NaCl and NH_4Cl, and the NaCl and $CaCl_2$ mixtures fall about halfway between these two limits.

The mixture of sucrose and D-phenylalanine is as weak a stimulus for HCl-best fibers as either of its components. Mean responses to seven of the eight mixtures of sucrose and D-phenylalanine with an electrolyte exceed the response predicted for a single-component "mixture" of HCl and are nearly equal to the sum of the responses to the components, but these limits are similar due to small responses to nonelectrolytes. The one exception is the mixture of HCl and D-phenylalanine, which is about 75% as effective as HCl presented alone, which can be reasonably explained by the chemical interaction of the components in the mixture.

In summary, responses of HCl-best fibers to mixtures are generally characterized by their surpassing the responses to a single-component "mixture" of HCl and being nearly equal to the sum of responses to the components presented individually. In particular, mixtures of HCl and NaCl with each other or of either with NH_4Cl or $CaCl_2$ have effects which considerably exceed the effect of a concentration of HCl equal to the sum of two concentrations equivalent in intensity to the components in the mixture. On the other hand, one mixture of electrolytes (i.e., NH_4Cl and $CaCl_2$) elicits a response equal to that of a single-component "mixture" of HCl. As seen in Table II, the mixture of NH_4Cl and $CaCl_2$ is the only two-component mixture of electrolytes tested that elicits a response in HCl-best fibers which is statistically significantly smaller than the sum of the component responses.

DISCUSSION

Single-component Stimuli

CLASSIFICATION OF FIBERS Clearly, responsiveness differs for the three groups of nerve fibers, but response profiles also vary within each group of fibers. Some fibers are less responsive than others to the stimulus that elicits the largest response; sizes of responses to stimuli other than the most effective vary from fiber to fiber. This variation is comparable to that for fibers previously sampled from peripheral taste nerves (Fishman, 1957; Ogawa et al., 1968; Frank, 1973). Several recent observations argue for attributing such within-group variation to changes in responsiveness of individual fibers rather than to systematic variations in sensitivity from fiber to fiber (see Introduction).

Diversity in response profile is greatest for the NaCl-best group of fibers. In fact, responses to the less effective electrolytes tend to be larger percentages of the best response in the more sensitive of these fibers (Fig. 3). This result is opposite to that for the sucrose-best or HCl-best fibers and contradicts the notion of a proportional loss in sensitivity and specificity with deterioration of a preparation. However, Kruger and Boudreau (1972) found that after repeated stimulation some cat geniculate ganglion units (type I) decreased in sensitivity to H^+ and NaCl, whereas other units (type II) increased in sensitivity to both NaCl and H^+. If a change in sensitivity occurred in NaCl-best fibers of the hamster chorda tympani similar to that which occurred in the type II units, the result could be as reported here, i.e., the most sensitive NaCl-best fibers would be the least selective.

Moreover, the diversity of the NaCl-best group of fibers is exaggerated by the use of a weak NaCl stimulus. The NaCl stimulus used here, although only one-half log step lower in concentration than that used by Frank (1973), elicits a more specific response than the stronger concentration of NaCl. Sucrose-best fibers respond hardly, if at all, to 0.01 M NaCl and HCl-best fibers respond only weakly to it; in contrast, 0.03 M NaCl affects sucrose-best fibers somewhat and is half as effective as HCl for the HCl-best fibers (Frank, 1973). The effect on response profiles is to accentuate the specificity of HCl-best fibers while broadening the profiles of NaCl-best fibers. The effect on the correlations (see below) between response to pairs of stimuli is to sharpen the apparent distinctiveness of the three sensitivities. A weaker NaCl stimulus also affects the proportion of fibers sampled that are classified as being most sensitive to NaCl because it is apparently very close to threshold. Only a third of the fibers sampled here responded best to NaCl, in comparison with more than half in a previous sample (Frank, 1973).

CORRELATIONS BETWEEN RESPONSES TO PAIRS OF STIMULI The differential sensitivity of hamster chorda tympani nerve fibers, evident in the response profiles of individual fibers (fig. 2), is reflected in the correlation coefficients between responses to pairs of stimuli calculated across all fibers. Correlation coefficients were instituted as measures of the similarity of effects of two stimuli by Erickson (1963). The correlations indicated by the coefficients in Table III are consistent with the existence of fibers with three distinct sets of sensitivities in the hamster chorda tympani. One group of fibers is sensitive to sucrose and D-phenylalanine: responses to these stimuli are highly correlated (i.e., $r = +0.95$), indicating covariation in absolute sensitivities; strong responses to these stimuli and electrolytes do not occur in the same fibers, which is reflected by coefficients of ca. −0.5. At least two different sets of fibers must be sensitive to the electrolytes because the correlations between responses to some electrolyte pairs are quite low. The correlations between responses to NaCl and the other electrolytes are much lower (i.e., +0.24–+0.55) than those for HCl, NH_4Cl, and $CaCl_2$ (i.e., +0.81–+0.92). The sensitivities to HCl, NH_4Cl, and $CaCl_2$ are distributed similarly among hamster chorda tympani nerve fibers; in contrast, many fibers that respond to NaCl do not respond to other electrolytes, other fibers respond to both NaCl and other electrolytes, and many fibers that respond the most to the other electrolytes respond only weakly to NaCl. However, correlations between responses to NaCl and $CaCl_2$ or to NaCl and NH_4Cl, much lower than those for HCl and these two salts, do not indicate that all NaCl-best fibers are more specific in their sensitivities than HCl-best fibers. Rather, the NaCl stimulus is more specific in its effects than the other electrolytes, affecting predominantly NaCl-best and not HCl-best fibers.

The correlation coefficients between responses to pairs of stimuli are comparable to those reported earlier for hamster chorda tympani nerve fibers for sucrose, NaCl, and HCl by Ogawa et al. (1968) and Frank (1973). In the earlier reports, the same response measure was used, but some of the stimuli were tested at different concentrations. Yet, coefficients between responses to sucrose and electrolytes were negative, and coefficients between responses to electrolytes were positive, as they are here. The exact value of the correlation coefficient depends on the relative sensitivities of the fibers in the population to the test stimuli, and because changes in concentration affect the ratios of sensitivities of the various fibers, they consequently affect the coefficients generated.

RESPONSES PREDICTED TO SINGLE-COMPONENT "MIXTURES" The power functions, describing response as a function of stimulus concentration (see Results), serve perfectly well for predicting the responses to single-component "mixtures" providing the responses to the mixture components are within the range of responses used to develop the fitted function. Responses to the components of the electrolyte mixtures are within this range with one exception. The mean response of HCl-best fibers to NaCl (i.e., 30 action potentials/5 s) is below the range elicited in these fibers by HCl (i.e., 61–149 action potentials/5 s). If the exponent of the power function for HCl is higher at

TABLE III

PRODUCT-MOMENT CORRELATIONS BETWEEN RESPONSES TO TASTE STIMULI

$CaCl_2$	HCl	NH_4Cl	Sucrose	D-Phe	
+0.54	+0.55	+0.24	−0.48	−0.46	NaCl
	+0.92	+0.81	−0.50	−0.50	$CaCl_2$
		+0.85	−0.57	−0.54	HCl
			−0.52	−0.50	NH_4Cl
				+0.95	Sucrose

$n = 44$, $r \geq \pm 0.39$, $P \leq 0.01$, t test

concentrations lower than those tested, this small response might require a higher equivalent concentration of HCl than that estimated by extending the power function to the lower concentration. It is possible that the exponent in the range of concentrations of HCl which encircles the equivalent concentration of NaCl is 0.82 (as it is in these fibers for the NaCl stimulus-response function) instead of 0.39 (i.e., the exponent of the function fit to the range of HCl concentrations tested). Yet, even if such an extreme change in slope did occur, only relatively small changes in the predicted responses would result. In this case, the predicted response of HCl-best fibers to the mixture of NaCl and $CaCl_2$ would be most severely affected and would be increased by only 10%.

To predict the responses to single-component "mixtures," the power function fit to the stimulus-responses function of NaCl was used for NaCl-best fibers, HCl for HCl-best fibers, and sucrose for sucrose-best fibers. These functions were selected because: (*a*) the stimuli are the most effective for the respective fiber groups; (*b*) the range of responses elicited is appropriate (see above); (*c*) the goodness of fit of the functions are among the best.

Two-component Mixtures

SUPPRESSION OF RESPONSES OF sucrose-best FIBERS BY ELECTROLYTES The suppressive effects of electrolytes on the responses of sucrose-best fibers to sucrose are not correlated with concentration, activity, ionic strength, or the magnitude of the response to the electrolyte in these fibers. But the order of effectiveness of the electrolytes in reducing the response of sucrose-best fibers to sucrose in a mixture is the same as the order of their effectiveness in stimulating HCl-best fibers. Possible inhibitory interconnections between sucrose-best and HCl-best fibers and/or the cells they innervate could explain this. However, sucrose and D-phenylalanine are equally good stimuli for sucrose-best fibers; the response they elicit should then be suppressed to the same degree by each electrolyte. The suppression of the response to D-phenylalanine by HCl is as dramatic as that for sucrose. But NH_4Cl, which strongly suppresses the response to sucrose, does not suppress the response to D-phenylalanine very much. Similarly, the effects of $CaCl_2$ on the responses to sucrose and D-phenylalanine do not appear to be equivalent. The sensitivity of HCl-best fibers to these electrolyte stimuli does not predict their effect on a response to D-phenylalanine. Thus, their suppressive effects in mixtures cannot be due to inhibition of sucrose-best fibers by HCl-best fibers or the taste cells they innervate. The possibility of interaction between the taste cells innervated by HCl-best fibers and the cells sensitive to sucrose cannot be excluded, although these sucrose-sensitive cells could not be the cells which are sensitive to D-phenylalanine.

The electrolytes could interact chemically with, but not stimulate, receptors on the taste cells innervated by sucrose-best fibers. $CaCl_2$ and NH_4Cl might each affect the receptor(s) so as to reduce the effectiveness of the receptor's interaction with sucrose more than that with D-phenylalanine. In contrast, HCl could interfere with the receptor(s) interaction with sucrose and D-phenylalanine to the same degree. However, it is impossible to conclude from these data whether the receptors for sucrose and D-phenylalanine are the same. It is unlikely that there are distinct sucrose-sensitive and D-phenylalanine-sensitive taste cells because the response to the mixture of these stimuli very closely approximates the response to the sum of two equivalent concentrations of sucrose. If there were two types of taste cells innervated by each sucrose-best fiber, it would be necessary to postulate an inhibitory interaction for the response to the mixture to be so much less than the sum of the responses to the components presented individually. A more parsimonious explanation for the data is two receptors on the same taste cell or one receptor for both sucrose and D-phenylalanine, whose interaction with the two stimuli can be affected differentially.

The acid-base interaction of D-phenylalanine and HCl when mixed is too small to account for the suppression of the response to D-phenylalanine. The HCl in the mixture cannot reduce below 0.067 M the concentration of D-phenylalanine available for interaction with the taste receptors. The value predicted from the stimulus-response function for the response of sucrose-best fibers to 0.067 M D-phenylalanine is 97% of the response to D-phenylalanine at the 0.07 M test concentration; in contrast, the mixture of HCl and D-phenylalanine elicits a mean response that is 51% of the response to 0.07 M D-phenylalanine. However, because of the acid-base interaction, the pH of the D-phenylalanine and HCl mixture is higher than the pH of the sucrose and HCl mixture; since the suppressive effect of HCl on responses to sucrose and D-phenylalanine is the same, it cannot be attributed to the pH of the solution. An effect of hydrogen ions on the receptors of the taste cells innervated by the sucrose-best fibers might explain the suppression if the receptors are very strong bases capable of attracting hydrogen ions equally well from the two mixture solutions.

DIFFERENTIAL EFFECTS ON NaCl-best AND HCl-best FIBERS When an electrolyte is mixed with another in solution, its effective concentration is reduced by the presence of the other component. Activity is a measure of effective concentration and depends upon ionic strength and charge as well as concentration. The slight suppression observed in responses of NaCl-best fibers to electrolytes in mixtures could be partly a result of reductions in activity. The order of mean percent suppression (measured relative to the predicted response to a single-component "mixture" of two concentrations of NaCl equivalent in intensity to the components of the mixture) is $CaCl_2$ and NH_4Cl (31%) > NaCl and NH_4Cl (24%) > HCl and NH_4Cl (20%) > NaCl and HCl (17%) > $CaCl_2$ and HCl (9%) > NaCl and $CaCl_2$ (1%). The greatest percent suppression occurs with the $CaCl_2$-NH_4Cl pair and corresponds to the greatest percent reduction in activity (i.e., 19%)[1] of all the electrolytes in mixtures. Thus, 0.05 M NH_4Cl, a relatively ineffective stimulus for NaCl-best fibers, may effect a slight suppression by reducing the activity of the other component (e.g., NaCl, $CaCl_2$, or HCl) in a mixture. However, the small effects of the other electrolytes in mixtures on these fibers are not attributable to changes in activity; nor do they parallel changes in the ionic strength of the solution or the concentration of chloride ions present. The pH change when HCl is added may alter the effectiveness of stimuli but it cannot explain all effects.

The order of the small suppressive effects of the electrolytes in mixtures on NaCl-best fibers does not follow the order of their effectiveness as stimuli for either sucrose-best or HCl-best fibers. Therefore, interfiber interactions need not be considered. Indeed, the characteristic effect of electrolytes in mixtures on the responses of NaCl-best fibers may be due to several variables operating simultaneously, such as chemical effects of the electrolytes on each other (e.g., activity), on receptor processes, or, possibly, on the electrogenic abilities of the taste cell.

In contrast to their effects on NaCl-best fibers, the electrolytes do not

[1] The percent reduction in activity was estimated by taking the ratio of calculated activities of each component in mixture and alone, then weighting them by the relative size of the response elicited by each component. For example, $CaCl_2$ elicited a response of 67 action potentials/5 s, and NH_4Cl a response of 32; the activity of $CaCl_2$ alone is 0.0067 and 0.0051 when mixed with NH_4Cl; the activity of NH_4Cl alone is 0.0385 and 0.0359 when mixed with $CaCl_2$. 0.0051/0.0067 = 0.76, so the activity of $CaCl_2$ is reduced by 24%. The activity of NH_4Cl is reduced by 7%. (67 [0.76] + 32 [0.93])/99 = 0.81, so the effective reduction in activity is 19% for the $CaCl_2$-NH_4Cl mixture.

suppress the responses of HCl-best fibers. Mean responses of HCl-best fibers to mixtures of electrolytes are either equal to or greater than the response predicted in terms of equivalent concentrations of HCl. The order of measured increases (i.e., the percentage greater than the response predicted in terms of HCl equivalence) is HCl and NH_4Cl (39%) > HCl and $CaCl_2$ (23%) > HCl and NaCl (21%) > NaCl and $CaCl_2$ (20%) > NaCl and NH_4Cl (17%) > NH_4Cl and $CaCl_2$ (1%). This order does not follow reductions in activity upon mixing or chloride ion concentration. Beidler (1975) has noted that an acid may have increased effectiveness when the ionic strength of the solution is increased. The responses of HCl-best fibers follow this rule for HCl mixed with each of the salts; specifically, the addition of 0.05 M NH_4Cl to HCl increases the ionic strength and the response more than the addition of 0.02 M $CaCl_2$ or 0.01 M NaCl.

The degree of augmentation of the responses to mixtures above the values predicted for equivalent concentrations of HCl does not parallel the effects of the electrolytes as stimuli for sucrose-best or NaCl-best fibers or the suppressive effects of electrolytes on either of these groups of fibers. Therefore, the observed effects on HCl-best fibers could not be mediated via interneural interactions.

Typically, the response of HCl-best fibers to mixtures of electrolytes exceeds the response predicted for a single-component "mixture." The one exception is the response to NH_4Cl mixed with $CaCl_2$, which equals that predicted value. The notion of distinct and independent receptors for HCl, NH_4Cl, and NaCl (with NH_4Cl and $CaCl_2$ stimulating the same receptor), although attractive, cannot explain all of the results. The NaCl and NH_4Cl, HCl and $CaCl_2$, and NaCl and $CaCl_2$ mixtures do not show simple addition of their individual effects as this notion would predict; indeed, the response to each of these mixtures is between the value expected for independent receptors (i.e., the sum of the responses to the components) and the response predicted for a common receptor for the chemicals in the mixture (i.e., the response to a single-component "mixture" of two concentrations of one chemical). Another possibility is an enhancement of the effect of one electrolyte by the presence of another in the mixture produced by processes similar to those suggested to yield suppression of responses of NaCl-best fibers.

Fig. 9 graphically portrays differences in the mean effects of electrolytes in mixtures on the HCl-best and NaCl-best fibers of the hamster chorda tympani, showing HCl-best fibers diverging from predictions for "mixtures" of one chemical (i.e., HCl equivalence) in the positive direction (toward the sum of the responses to the components) but responses of the NaCl-best fibers diverging from the predicted value (i.e., NaCl equivalence) in the negative direction (with the components of the mixtures apparently reducing each other's stimulatory effects).

Explanation of the Whole-Nerve Responses to Mixtures

MIXTURES CONTAINING SUCROSE AND/OR D-PHENYLALANINE Sucrose and D-phenylalanine strongly stimulate the same group of fibers; the electrolytes stimulate those fibers minimally but strongly stimulate different fibers that, in turn, are stimulated minimally by sucrose and D-phenylalanine. On the basis of this small overlap in sensitivities to single-component stimuli, one would expect mixtures of sucrose or D-phenylalanine with an electrolyte to elicit whole-nerve responses that approach the sum of responses to the components. In fact, they are much smaller, with responses to mixtures of sucrose and the three salts falling further below this sum than responses of D-phenylalanine and the salts (Hyman and Frank, 1980). The greater suppression of responses to sucrose than responses to D-phenylalanine in sucrose-best fibers by the salts is the explanation.

Although HCl equally reduces the effectiveness of sucrose and D-phenylalanine as stimuli for sucrose-best fibers, sucrose and D-phenylalanine do not

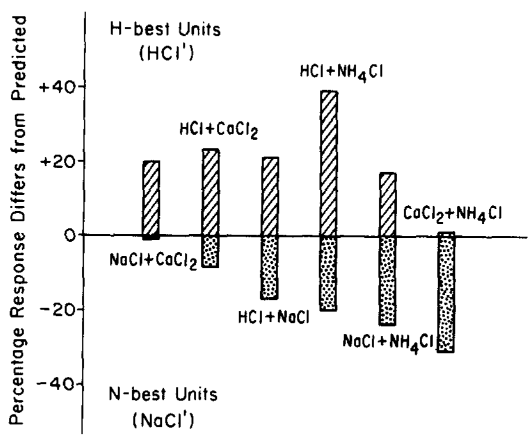

FIGURE 9. Percentages the responses to two-component mixtures differ from responses predicted for single-chemical "mixtures" for HCl-best and NaCl-best fibers of the hamster chorda tympani. Predictions for HCl-best fibers (represented by crosshatched bars) are based on the response function for HCl (HCl′) and predictions for NaCl-best fibers (represented by dotted bars) are based on the response function for NaCl (NaCl′) for the respective fiber groups. A positive value indicates that the response to the mixture was greater than a response to an increase in concentration; a negative value indicates it was smaller.

equally reduce the effectiveness of HCl as a stimulus for NaCl-best or HCl-best fibers. D-Phenylalanine especially reduces the responses of HCl-best fibers to HCl, whereas sucrose produces little change. This reduction in response magnitude is predictable from the acid-base interaction of D-phenylalanine and HCl. In the whole nerve, the reduction in response of sucrose-best fibers to D-phenylalanine by HCl adds to the reduction in effectiveness of HCl as a stimulus for HCl-best and NaCl-best fibers by D-phenylalanine. The result is a summed response to the mixture of HCl and D-phenylalanine that is less than the summed response to the mixture of HCl and sucrose.

The addition of 0.07 M D-phenylalanine to 0.003 M HCl considerably reduces the concentration of hydrogen ion available to stimulate the taste receptors, increasing the pH to 3.6. This concentration of hydrogen ion, if provided by a strong acid such as HCl, would hardly stimulate the NaCl-best and HCl-best fibers (c.f. Hyman and Frank, 1980). However, their responses are reduced by 15–20%, not 50–60%, as predicted on the basis of pH. Therefore, the free hydrogen ion concentration, although important, is not the sole determinant of response size in these fibers. Equal sourness measurements (Taylor et al., 1930) and whole-nerve recordings from the rat (Beidler, 1967) are in complete agreement with the finding that solutions of equal pH do not elicit responses of equal magnitude (Beidler, 1975).

Knowledge of the whole-nerve response to the stimuli presented individually and the overlap in the fiber groups stimulated by the mixture components permitted successful prediction of the whole-nerve response to just one mixture tested here: sucrose and D-phenylalanine. There is complete overlap of the sets of responding nerve fibers and the response of the whole nerve to their mixture was indistinguishable from the response predicted for a "mixture" of two concentrations of one stimulus (Hyman and Frank, 1980).

MIXTURES OF ELECTROLYTES Whole-nerve responses to mixtures of electrolytes (Hyman and Frank, 1980) can be explained by the suppressive effects of the electrolytes on the responses of NaCl-best fibers summed with their augmentative effects on the responses of HCl-best fibers; these opposite effects neutralize and yield a response indistinguishable from that predicted for a single-component "mixture." Neutralization is not complete when the opposite effects are of different magnitudes. For example, the mean response of NaCl-best fibers is suppressed the most by the $CaCl_2$ and NH_4Cl mixture, but the effects of these chemicals presented together are not augmented in terms of the responses of HCl-best fibers. Without an augmented effect to compensate for any suppressive effect on the activity of NaCl-best fibers, the whole-nerve response shows considerable suppression; on the other hand, the mixture of NaCl and $CaCl_2$ elicits a mean response in HCl-best fibers greater than that predicted by HCl equivalence, but produces no suppression in NaCl-best fibers; the augmented effects of the stimuli are not compensated for by opposing suppressive effects, allowing the balance to tilt in the additive direction, in the response summed across all fibers.

Comparison of Neural Recordings and Psychophysical Measurements

Although the neural records are from the chorda tympani of hamsters, comparison with taste intensity assessments by humans is not inappropriate. Recordings of summed responses of the human chorda tympani indicate an agreement between neurophysiological and psychophysical measures of thresholds for some stimuli and the relative effectiveness of various sugars (Diamant et al., 1963). Also, the taste of many single-component stimuli seems to be similar for the two species. Magnitude estimates by humans of the sweetness, saltiness, sourness, or bitterness of a large number of stimuli (McBurney and Shick, 1971) correspond well to the extent to which aversions learned to these chemicals are generalized to sucrose, NaCl, HCl, or quinine-HCl by hamsters (Nowlis and Frank, 1977); these four chemicals taste sweet, salty, sour, and bitter, respectively, to humans. Therefore, humans and hamsters similarly characterize the tastes of some stimuli. However, measurements of an animal's generalizations of gustatory stimuli and psychophysical measurements in humans could be influenced by more than the activity of the chorda tympani. There are other gustatory inputs (e.g., those transmitted via the glossopharyngeal nerve), nongustatory inputs (transmitted via the trigeminal nerve), and complex processes mediated centrally in the nervous system. Therefore, agreement between recordings from the chorda tympani and psychophysical assessments of taste intensity would indicate that this one gustatory input is not altered by other sensory inputs and that peripheral processes are preserved in the course of transmission to central structures.

Suppression of the sweetness of sucrose in humans by moderate intensities of NaCl or citric acid (see Introduction) corresponds to a suppression of the response to sucrose by salts and HCl in sucrose-best fibers of the hamster chorda tympani. For both perceived intensity and chorda tympani activity, the suppressive effect of acid on the response to sucrose is much more dramatic than the effect of NaCl. Sucrose-best fibers are the only ones that respond vigorously to the two chemicals which taste sweet to humans (i.e., sucrose and D-phenylalanine). These data suggest that sucrose-best fibers mediate the sensation of sweetness in hamsters. Moreover, making the analogy across species, the suppression of sweetness by acid or salt in humans may simply be a reduction in the peripheral effect of sucrose on the taste receptors when acid or NaCl is present.

The perceived intensity of saltiness evoked by NaCl in humans is reduced by moderate concentrations of sucrose or acid (see Introduction). Sucrose and D-phenylalanine slightly reduce the mean response of NaCl-best fibers of the hamster chorda tympani nerve to NaCl; however, they do not reduce the response of HCl-best fibers to NaCl. These data suggest that NaCl-best fibers mediate the sensation of saltiness in hamsters, and by correspondence, that this peripheral process is the mechanism of the suppression observed in humans. However, there is no reduction in the response of NaCl-best fibers to NaCl with the addition of HCl; in fact, HCl is a very effective stimulus for these fibers. But the psychophysical results in humans refer to citric acid suppressing saltiness, and the effects of this weaker acid on NaCl-best fibers may be different from the effects of HCl.

The suppression of sourness of an acid mixed with sucrose or NaCl (see Introduction) does not have a parallel in the responses of the hamster chorda tympani. The response of HCl-best fibers is increased very slightly when sucrose is added to HCl, as it is when NaCl is added. The neural activity evoked in NaCl-best fibers by HCl is slightly less with sucrose added, but NaCl increases the activity. However, many of the studies of the intensity of sourness in humans used citric acid, not HCl, and sensations evoked by citric acid and HCl may be affected differently. For example, the intensity of the sensation evoked by citric acid is enhanced after a human taste papilla is pretreated with sucrose (Kuznicki and McCutcheon, 1979), but the perceived intensity of HCl is not.

Conclusions

The effects of taste stimuli in mixtures on responses of the hamster chorda tympani are complex and require, at this stage, a stimulation of the taste receptors with the mixtures themselves for their appreciation. The effects are unpredictable because one chemical can affect the response of an afferent fiber to other stimuli; this cannot be observed by extracellular recording of responses to individual stimuli. However, fibers of one class (sucrose-best, NaCl-best, or HCl-best) tend to react in the same way to mixtures of chemicals of a given variety; fibers in different classes can react in an opposite way. These observed effects of mixtures on responses of afferent nerve fibers indicate that receptors innervated by distinct fiber populations process taste stimuli in mixtures differently, demonstrate that the sum of the several treatments of mixtures can account for the whole-nerve response to them, suggest that a quantitative study of effects of mixtures could lead to an understanding of the physical and chemical variables that affect different mechanisms of taste receptivity, and indicate that some effects of mixing on intensities of elicited taste qualities documented by studies of human taste psychophysics may be attributable to peripheral effects at the receptors.

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