

A THEORY OF TASTE STIMULATION*

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INTRODUCTION

Many suggestions as to the mechanism of chemoreceptor stimulation have appeared in the literature during the past half century. They all lack, however, sufficient experimental data that can be treated quantitatively. Modern techniques of electrophysiology have recently been applied to the study of chemoreceptors so that there now exist quantitative data that may be mathematically analyzed (1, 2).

In a previous paper (1) the author presented properties of chemoreceptors which are important in the study of the mechanisms involved in the stimulation of these receptors. They are (1) The reactions involved in stimulation are in a time-independent state, very likely in thermodynamic equilibrium, since the response to 0.1 M NaCl was shown to remain constant during 10 minutes of continued salt stimulation. The magnitude of this response is the same no matter whether immediately preceded by higher or lower concentrations of the salt. (2) Stimulation is very rapid as shown by the fact that a response may be recorded within 50 msec. after 0.2 M NaCl is applied to the surface of the tongue. (3) The responses are completely reversible. (4) Both the cations and anions enter the reaction although the magnitude of response is primarily determined by the presence of the cation. (5) As the strength of the stimulus is increased, a level of response is reached at which a further increase in stimulus does not result in an appreciable increase in response. (6) The receptors of the tongue respond to a large number of different substances and over a wide range of concentrations.

Theoretical Treatment

The chemical stimuli react in some way with one or more substances of the chemoreceptor. Let us treat the reaction in a most general way by assuming that it obeys the mass action law. The interaction of the stimulus with a given substance of the receptor may then be mathematically expressed as

$$\frac{n}{S-n} = Kc \quad (1)$$

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in which

- n = total number of ions or molecules that react with the receptors at any given concentration, c , of the stimulus.
- S = maximum number of ions or molecules that can react.
- c = concentration of the applied chemical stimulus.
- K = equilibrium constant.

Assume that the magnitude of response is directly related to the number of ions or molecules that have reacted with the receptors. Therefore

$$R = an$$

in which

- R = magnitude of response.
- a = a constant.

For a maximum response to a given substance

$$R_m = aS$$

Substituting in Equation 1

$$Kc = \frac{R}{R_m - R}$$

or

$$\frac{c}{R} = \frac{c}{R_m} + \frac{1}{K R_m} \quad (2)$$

This is the fundamental equation relating the magnitude of response to the concentration of the applied chemical stimulus. If $\frac{c}{R}$ is plotted against c , a straight line should result with a slope equal to $\frac{1}{R_m}$ and a y intercept equal to $\frac{1}{K R_m}$. Equation 2 is similar to that of the well known adsorption isotherm of Langmuir. It is also similar to the equation used by Scatchard (3) and by Klotz (4) to express the binding of ions by proteins.

All the values of Equation 2 may be experimentally determined with the exception of the equilibrium constant, K , which, in turn, may be calculated from the y intercept. Both K and R_m are constants for any given substance used as the chemical stimulus. Note also that when $c = \frac{1}{K}$, then $R = \frac{R_m}{2}$.

Equation 2 is very useful since only the responses to two different strengths of stimuli need be experimentally determined in order to completely predict the responses to any other strengths of stimuli or to calculate the maximum level of response and the equilibrium constant. This is particularly important for those substances which at high concentrations may be harmful to the receptors.

One response of importance is that of threshold. This value may be defined as that response that is slightly greater than a given limiting value, usually that of inherent noise. At low concentrations Equation 2 reduces to

$$R = cKR_m$$

At threshold

$$R_T \geq N$$

or

$$N \leq c_T KR_m \quad (3)$$

in which

N = inherent noise or any other sensitivity—limiting factor.

c_T = threshold concentration of stimulus.

When thresholds are measured with electrophysiological techniques, N can be directly measured as the inherent noise of the recording system. However, human thresholds are behavioral in nature so that a direct measure of N cannot be determined. In this case the threshold to one sodium salt, let us say NaCl, must be experimentally determined and a value for N calculated from the above equation. Thus, thresholds to other sodium salts can then be calculated directly from the responses to superthreshold stimuli.

Application to Electrophysiological Data

The responses of chemoreceptors to sodium salt stimulation are very reproducible and do not initiate irreversible effects, even at high concentrations of stimuli. The response of a group of chemoreceptors of the tongue of the rat to various concentrations of a number of sodium salts has been quantitatively determined previously (1, 2). The mathematical analysis given above can therefore be simply tested for its validity by plotting $\frac{c}{R}$ versus c using the electrophysiological data. This plot should result in a straight line over large ranges of concentrations. Examples of such plots are given in Fig. 1.

The agreement between the mathematical expression of Equation 2 and the actual data is seen to be excellent. This means that Equation 2 is found to be sufficient to completely describe the data, although it does not necessarily prove that the chosen theory of stimulation is a correct one.

The values of the maximum responses (sometimes referred to as the saturation levels) as calculated from the slopes of the curves in Fig. 1 are shown in Table I. These computed responses are seen to be within 10 to 12 per cent of the experimentally determined responses to 1.0 M stimulation.

Physical Interpretation

It was shown earlier that the taste stimulation process can be considered as at thermodynamic equilibrium. The change in free energies of the reactions may

therefore be computed from the measured equilibrium constants according to the expression

$$\Delta F = -RT \ln K$$

in which

- ΔF = change of free energy
 R = gas constant
 T = absolute temperature.

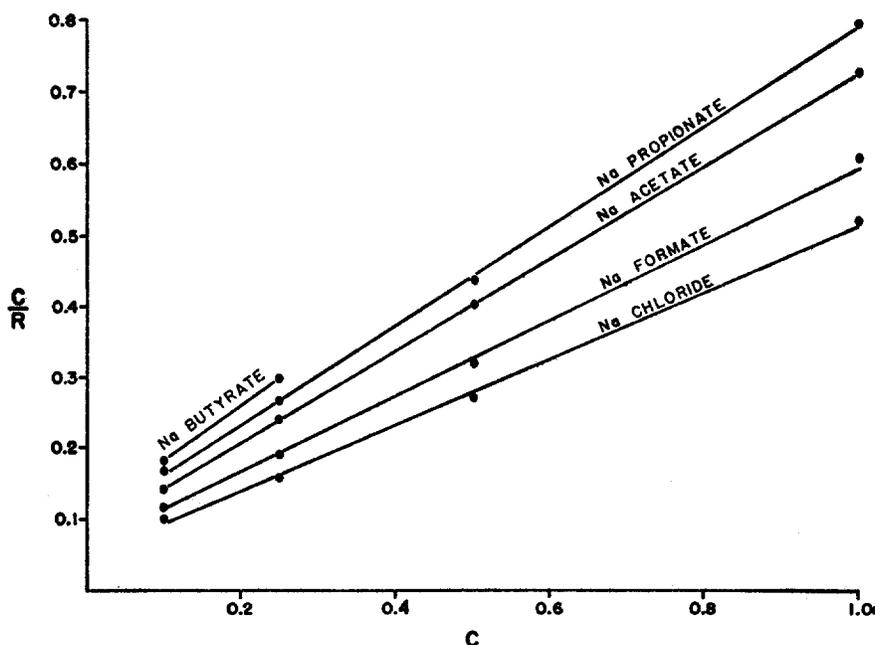


FIG. 1. The ratio of the molar concentration of the stimulus and the magnitude of the integrated response of the chemoreceptors is plotted against the molar concentration of the stimulus.

TABLE I

Sodium salts	Computed R_m	Response to 1.0 M salt	Equilibrium constant, K	ΔF
				<i>Cals./mole</i>
Sodium chloride	2.17	1.95	9.80	-1.37
Sodium formate	1.89	1.66	9.00	-1.32
Sodium acetate	1.55	1.38	8.55	-1.29
Sodium propionate	1.44	1.26	7.58	-1.22
Sodium butyrate	1.30	—	7.72	-1.23

The results of such computations are tabulated in Table I. The equilibrium constants are calculated from the slopes and y -intercepts of Fig. 1. Notice that the value for the change in free energy, ΔF , decreases slightly as the size of the anion increases. The low values for ΔF indicate that physical rather than chemical forces are involved in the interaction between the chemical stimulus and the receptors. These values are much smaller than those usually found for enzymatic reactions.

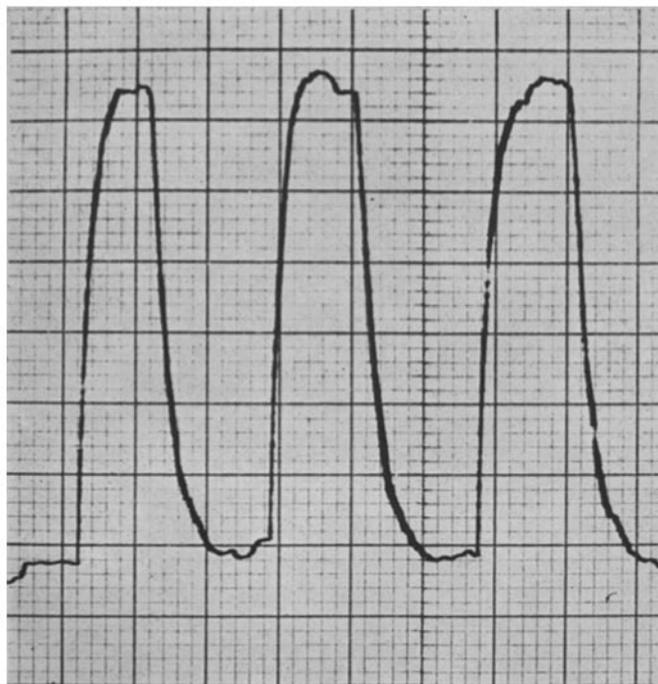


FIG. 2. Response of chemoreceptors of rat to 0.5 M NaCl at 25°C., 30°C., and 20°C. Ordinate, integrated response. Abscissa, 1 large unit = 20 seconds.

The magnitude of response to a salt stimulation has been found to vary little with change in temperature (see Fig. 2). Therefore, since $\Delta H = 0$, most of the ΔF is attributable to changes in entropy of the system. The temperature independence is evidence that enzymatic reactions are probably not directly involved in the initial steps of taste receptor stimulation by sodium salts.

The small temperature dependence and the low values for ΔF suggest a reaction similar to those that occur with ion binding by proteins or natural polyelectrolytes. A direct quantitative comparison between the ΔF values of this paper and those found for other reactions must be made with caution. Each

ΔF is dependent upon the choice of standard state of each reactant and the state of the reacting component of the chemoreceptor is not known.

Additional properties of the reacting groups of the molecules that bind the sodium can be determined by their dependence upon pH. Experiments were performed with 0.5 M NaCl and it was found that little or no change in magnitude of response was observed over a pH range of 3.0 to 11.0 (see Fig. 3). This is evidence that the reacting anionic groups of the molecules of the chemoreceptors are strong acidic radicals. The relatively weak carboxyl radical of a protein, for example, cannot be considered as the reacting group. The phosphate and sulfate radicals of such natural polyelectrolytes as nucleic acids and certain



FIG. 3. Response of chemoreceptors of rat to 0.5 M NaCl, pH = 6.0; 0.5 M NaCl, pH = 3.0; 0.5 M NaCl, pH = 11.0; 0.5 M NaCl, pH = 6.0 (pH adjusted with HCl or NaOH). Ordinate, integrated response. Abscissa, 1 large unit = 20 seconds.

polysaccharides are able to bind cations in a manner consistent with the properties of taste receptors as described above.

Recent evidence indicates that nucleic acid may be found in cellular membranes (5). It has also been demonstrated that calf thymus deoxyribose nucleic acid binds cations predominantly over anions and that the extent of binding does not change with depolymerization (6).

Although the cation is most effective in the stimulation process, the anion still helps to determine the magnitude of the response. This is clearly seen in Fig. 1. Since adsorption increases with chain length, it may be assumed that the number of anions bound to the receptors also increases with chain length within an homologous series. However, the response is seen to decrease with chain length so that the bound anion appears to produce an effect opposite to that of a cation. Whether such is the case or whether the binding of the anions merely limits the number of sites available for cations cannot be determined from present data.

The ability of the taste receptors to respond to cations other than sodium would vary not only with the nature of the reacting radical primarily involved, but also with the proximity of other possible reacting groups of the same or neighboring molecules. Differences in responses of taste receptors among various species of animals can be anticipated since the detailed configuration of the reacting molecules of the receptor surface may differ from one species to another. However, low values of ΔF should be expected for all species of mammals if the mechanism of taste stimulation as outlined in this paper is a general one.

CONCLUSIONS

The treatment in this paper of available quantitative data on the response of taste receptors to sodium salt stimulation clearly indicates that the ions of the chemical stimulus are loosely bound to some substance of the taste receptor. This can be thought of as an initial reaction which ultimately leads to stimulation of the receptor and an eventual depolarization of the associated sensory neuron. The speed of the total reaction suggests that the receptor substance is located on or near the surface of the receptor.

The recently proposed (7) enzymatic reactions for chemoreceptors do not appear plausible for sodium salt stimulation of the taste receptors of the rat.

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