meter in 5 untreated terminals was 535 ± 11 Å, whereas in muscles treated with TPB for 30 min the mean vesicle diameter was 545 ± 4 Å ($n = 3$). In the TPB-treated preparations the remaining vesicles tended to be clustered at the presynaptic membrane and occasionally fusion vesicles were observed. Similar observations were made in longitudinal sections from the same muscle preparations.

This pattern of partial depletion, which probably indicates that vesicle recycling[10] is proceeding normally, has also been reported after procedures that greatly increase transmitter release e.g. rapid nerve stimulation[10,11] and lanthanum treatment[12]. However the pattern of vesicle depletion produced with this concentration of TPB differs from the total depletion produced by black widow spider venom[13,14], although higher concentrations of TPB may produce more drastic depletion. Greatly increased transmitter release has been shown recently to lead to a predominance of small amplitude MEPP[15,16]. Consequently, the marked increase of MEPP frequency in TPB may be a factor contributing to the reduction of quantal size noted. Other possible explanations for this reduction are that TPB may reduce the concentration of acetylcholine in the vesicles by precipitation or that TPB inhibits transmitter storage. A reduction of quantal size is seen after prolonged nerve stimulation in the presence of hemicholinium-3[17], although TPB itself appears to have no inhibitory action on choline uptake[4] or choline acetyltransferase[18]. In agreement with recent findings with hemicholinium in the frog[5,6] it was found that TPB produced no reduction of vesicle size, indicating that drug-induced reduction of quantal size is not accompanied by a reduction of vesicle diameter and that the vesicles observed after either TPB or hemicholinium treatment are either empty or only partially filled with acetylcholine.

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## Does an Initial Phasic Response Exist in the Receptor Potential of Taste Cells?

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*Summary.* The depolarizing receptor potentials to 0.5 *M* NaCl recorded from frog taste cells did not exhibit any phasic response, even when the rectangular waveform of stimulus onset was employed. The quickest depolarizations recorded reached the peak in 50 msec. On the other hand, the gustatory neural response showed initial overshoot of the impulse discharge even when 0.5 *M* NaCl was delivered at the slower rate of 0.06 ml/sec. It is concluded that the initial neural response may be associated with the rate of rise of the receptor potential before its plateau level is reached.

Depolarizing receptor potentials, which may be associated with the initiation of gustatory neural impulses, have been recorded intracellularly from vertebrate taste cells[2-8]. The depolarizations indicate a sustained response having no initial overshoot.

On the other hand, gustatory neural activities to NaCl, as well as other salts, usually consist of an initial phasic response followed by a smaller tonic response[9]. Because of lack of the initial phasic response in the taste receptor potentials, SATO and BEIDLER[8] have proposed that the initial phasic component of the gustatory neural responses may be related to the rate of rise of the receptor potentials or the following postsynaptic potentials. However, recently it has been suggested that since a very slow rate of taste stimulus onset was employed for the microelectrode study on taste cells, the initial phasic response in the taste receptor potential, which may be correlated with the phasic discharge in the gustatory nerve, could not have been found even if present[10,11].

Therefore, the purpose of the present experiments is to see whether or not the taste receptor potentials possess an initial overshoot component when using the rapid rate of rise of a taste stimulus. It will be shown that the taste receptor potentials having a 50 msec rise time still do not exhibit any overshoot component. Thus, it is suggested that the initial phasic burst of activity in the gustatory nerve may be related to the rate of rise of taste receptor potential.

*Materials and methods.* Tongues of bullfrogs (*Rana catesbeiana*) anesthetized with urethane were used in this experiment. The 3 *M* KCl-filled glass capillary microelectrodes of 15–45 MΩ were inserted into taste cells of the fungiform papillae. An indifferent electrode of chlorided silver wire was put into the musculature of a forelimb.

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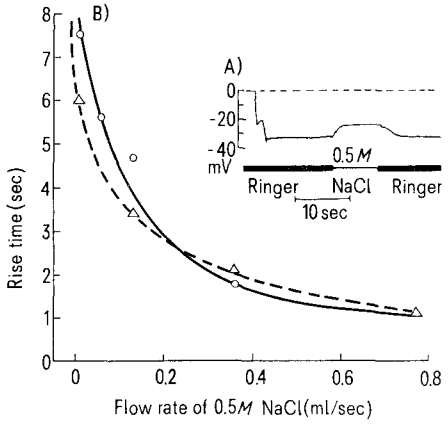


Fig. 1. A) Intracellularly recorded depolarizing receptor potential in response to 0.5 *M* NaCl, which was applied at the flow rate of 0.36 ml/sec. Sudden shift of potential shown at lefthand indicates the penetration of a taste cell through a supporting cell. Lower trace shows the application of adapting Ringer and stimulating 0.5 *M* NaCl solutions. B) Solid line shows the relation between rise times of depolarizing responses and flow rates of 0.5 *M* NaCl solution, and dashed line the relation between rise times of junction potentials which appeared at the microelectrode tip on the papilla and flow rates of 0.5 *M* NaCl solution. Each point is the mean from 6 to 17 taste cells (circles) and from 3 to 7 papillae (triangles).

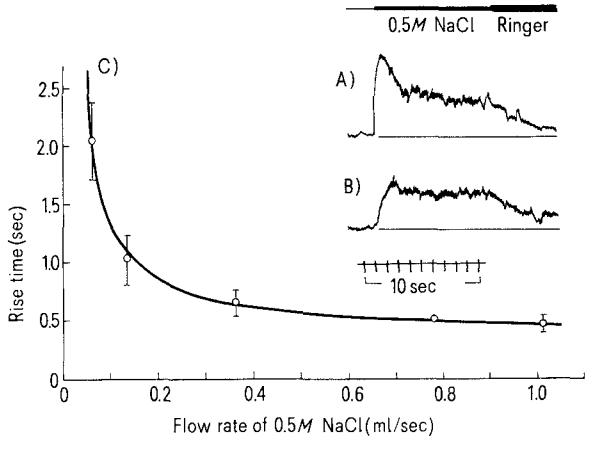


Fig. 2. A) and B) Integrated whole glossopharyngeal nerve responses to 0.5 *M* NaCl. The flow rate was 0.78 ml/sec in A) and 0.06 ml/sec in B). Integrator time constant was 0.1 sec. Upper trace denotes the duration of 0.5 *M* NaCl and rinsing Ringer applications. C) Relation between rise times of integrated gustatory neural responses and flow rates of 0.5 *M* NaCl stimuli. Each point is a mean ± (SE) of 5 measurements from 2 preparations.

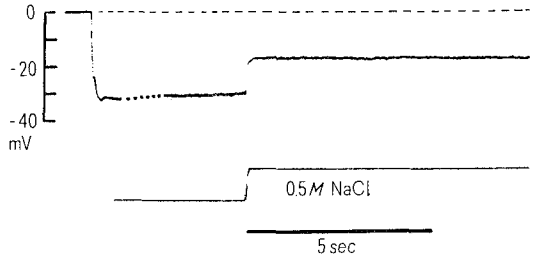


Fig. 3. Depolarizing response (upper trace) of a taste cell to 0.5 *M* NaCl which was flowed at 0.04 ml/sec. The nozzle of the gustatory stimulator was positioned about 300 µm away from the inserted microelectrode. Lower trace shows time course of physicochemical junction potential which occurred between the microelectrode tip on the papilla surface and 0.5 *M* NaCl flow.

The taste stimulus solution used was 0.5 *M* NaCl which was made up in pure water (Milli-Q reagent-grade water of Millipore Corp.). A semiautomatically controlled gustatory stimulator described previously[9] was employed to apply the taste solution to the tongue. The flow rate of taste solution was changed by changing the gauge number of injection needles that served as the stimulator nozzles.

The gustatory neural activity was recorded from the whole glossopharyngeal nerve and integrated with an electronic integrator of 0.1 sec rise and fall time constant. All experiments were carried out at room temperature of between 23 °C and 26 °C.

*Results and discussion.* The tongue was adapted to a frog Ringer solution flowed over it at the rate of 0.04 ml/sec. Figure 1A shows the depolarizing receptor potential in response to 0.5 *M* NaCl applied to the tongue at the flow rate of 0.36 ml/sec immediately after the adapting Ringer flow was stopped. In this case, the distance between the recording microelectrode tip inserted into a papilla and the output needle of the gustatory stimulator was about 4.3 mm. It is seen that no phasic response appears in the initial portion of the depolarizing response and the time to peak after the onset of the depolarization is around 2 sec. Figure 1B (solid curve), which was obtained from the experiment as in Figure 1A, illustrates the relation between varying rates of 0.5 *M* NaCl flow and rise times of the depolarizing potentials, none of which overshot the tonic value. The rise time decreased exponentially as the flow rate was raised. The shortest time in response to the maximum flow rate used of 0.74 ml/sec was about 1 sec.

After recording intracellular responses from the taste cells, the time course of concentration change at the taste receptor membrane following the onset of 0.5 *M* NaCl application was estimated by measuring the change in the physicochemical junction potential that occurred at the microelectrode tip just withdrawn onto the papilla surface. The relation between varying flow rates and peak times of the junction potentials is shown in the dashed curve of Figure 1B. The mean rise times of junction potentials approximated those of receptor potentials. This indicates that the rise time of taste receptor potentials is strongly dependent on the initial time course of concentration change at the taste receptor surface after a taste stimulus is delivered.

On the other hand, Figure 2A and B illustrates an example of integrated glossopharyngeal nerve responses to 0.5 *M* NaCl delivered at 2 different flow rates of 0.78 ml/sec (A) and 0.06 ml/sec (B). Although one flow rate differed 13 times from the other, both integrated gustatory neural responses exhibited the initial phasic component followed by the tonic one. However, the amlitude of phasic response to the rate of 0.78 ml/sec was higher than that to 0.06 ml/sec, while the amplitudes of tonic responses were almost the same in both records. Figure 2C shows the relationship between the flow rate of 0.5 *M* NaCl solution and the rise time of the phasic neural responses. It is seen that the rise time of gustatory neural responses, like that of receptor potentials, decreased as the flow rate was raised. From comparison of Figures 1 and 2, it may be said that the initial dynamic burst of activity in the gustatory nerve is not caused by a phasic response of the taste cell.

It is known that the initial phasic response exists in the receptor or generator potentials of other sensory cells and is a function of the rate of rise of stimulus onset[12]. There-

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fore, it is important to examine further the taste receptor potential with an abrupt waveform of gustatory stimulation. To do this a nozzle of the gustatory stimulator was put 100–400 μm away from the microelectrode tip and 0.5 *M* NaCl was applied at the rate of 0.04 ml/sec. In successful cases, where intracellular recording was not disturbed, receptor potentials showing much shorter rise times were obtained. The upper trace of Figure 3 shows an example where the rise time was approximately 200 msec. In 17 investigated taste cells the rise time was in the range of 50–360 msec (mean ± SE, 160 ± 30 msec) and no phasic component was observed. In these experiments, an adapting Ringer solution was not flowed before the application of test 0.5 *M* NaCl solution. As shown in the lower trace of Figure 3, the concentration change of the onset of 0.5 *M* NaCl application was almost rectangular in form, which was measured as the junction potential between the microelectrode tip located on the papilla surface and the flowing 0.5 *M* NaCl.

It has been predicted that the taste receptor potential may possess an obvious initial phasic response when the rate of taste stimulus onset is steep and that the initial transient discharge in the gustatory nerve is caused by the phasic receptor potential[10,11]. This assumption probably must be discarded, however, because the present experiment done with the rapid rise of taste stimulus onset still could not exhibit any phasic component of receptor potential.

## Histamine-Induced Hypotension Modified by $H_1$ and $H_2$ Antagonists in the Monkey (*Macaca mulatta*)

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*Summary.* Blocking $H_2$ receptors with burimamide in the dose used (20 mg/kg) approximately doubles the amount of histamine needed to produce the same effect as seen when $H_1$ antagonists (chlorpheniramine or mepyramine) are used alone. The $K_z$ ratios for chlorpheniramine-chlorpheniramine plus burimamide are 117–204 and for mepyramine-mepyramine phus burimamide are 200–478. $H_1$ and $H_2$ receptors, in the monkey, when stimulated, both cause cardiovascular responses in the same direction.

There are two types of histamine receptors[2], the $H_1$ receptors which are blocked by the classical 'mepyramine-like' antihistamines and the $H_2$ receptors which are insensitive to this group of antihistamines. Even large doses of $H_1$ antagonists do not completely block the hypotensive effects of histamine.

In the cat, $H_1$ and $H_2$ receptors both act in the same direction to lower blood pressure[3]. However, in the calf, some of the $H_2$ receptors modulate the depressor effect of $H_1$ receptor stimulation, the two receptors acting in opposite directions[4].

Burimamide, a thiourea analogue of histamine, which seems to be a specific antagonist of the $H_2$ receptors, was introduced in 1972[3]. The present study was undertaken to determine the hypotensive response of monkeys to histamine and the extent and direction to which the $H_1$ antagonists chlorpheniramine and mepyramine and the $H_2$ antagonist burimamide affect this response.

*Materials and methods.* The animals used in this study were young, healthy *Macaca mulatta*, weighing 3.0–3.5 kg. Injections were made through a femoral venous catheter, and blood pressure measurements were made with a catheter inserted into the femoral artery. Prior to each test, each animal was anesthetized with an i.v. injection of sodium Nembutal (35 mg/kg). Each animal was then given a series of histamine injections of gradually increasing concentration from 0.025 to 100 μg/kg. After each dose of histamine, changes in blood pressure were measured as the maximum decrease of mean arterial pressure. Each animal's blood pressure was allowed to recover to normal between doses which were given at least 10 min apart.

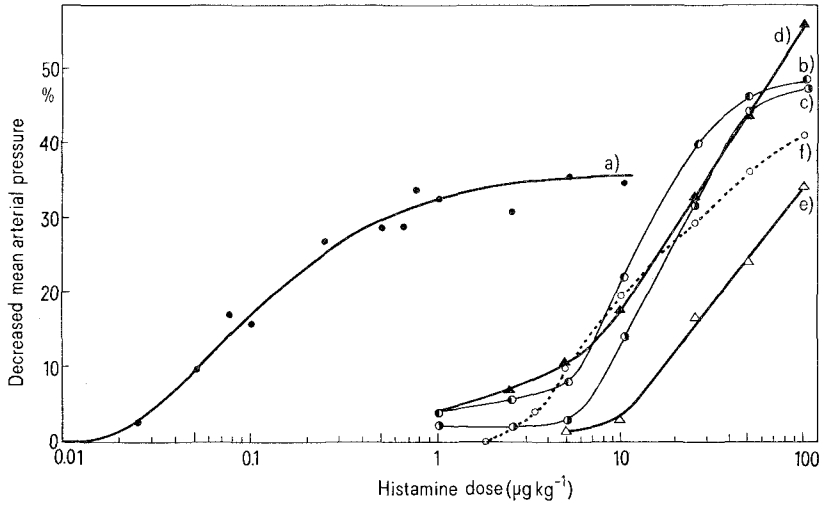


Fig. 1. Effect of histamine antagonists on histamine-induced vasodilation in the monkey. a) Histamine alone; b) after chlorpheniramine; c) after chlorpheniramine and burimamide; d) after mepyramine; e) after mepyramine and burimamide; f) after phenoxybenzamine.