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Recent Insights into the Mechanisms of Taste Transduction and Modulation*

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ABSTRACT

An amiloride-sensitive transport system is involved in the taste perception of sodium and lithium salts, as well as sweeteners. Taste can be modulated by purinergic compounds such as inosine monophosphate (IMP), as well as antagonists of adenosine, specifically, methyl xanthines. Kainic acid selectively reduced the taste responses to glutamic acid which suggests that the taste of glutamate is not mediated by the identical receptor population as the so-called 'primary tastes'.

INTRODUCTION

In the past several years, new insights into the mechanisms of taste transduction and modulation have been achieved by observing the psychophysical and neurophysiological changes that occur after application of pharmacological agents to the surface of the tongue. In this paper, the effects of four compounds on the taste system are discussed; they are amiloride, caffeine (and other methyl xanthines), inosine monophosphate and kainic acid.

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AMILORIDE: REDUCES TASTE INTENSITY OF Na^+ AND Li^+ SALTS AND SWEETENERS

Amiloride (*N*-amidino-3,5-diamino-6-chloropyrazine carboxamide) is a potassium sparing diuretic that has been used extensively as a specific inhibitor of sodium transport (see Benos, 1982). At low concentrations (1 μM), it has been shown to inhibit the apical sodium entry pathway of tight epithelia (Bentley, 1968; Benos, 1982); at higher concentrations, it blocks another pathway, that of Na^+–H^+ exchange (Kinsella & Aronson, 1981). Recently, amiloride has been found to reduce the perceived taste intensity of Na^+ and Li^+ and of sweeteners when applied to the human tongue (Schiffman *et al.*, 1983). In addition, it was found to inhibit electrophysiological responses to NaCl in single neurons recorded from the nucleus tractus solitarius of rat. These findings, described in detail below, suggest that an amiloride-sensitive sodium transporter is directly involved in taste perception for both humans and rats.

Human psychophysical studies

The subjects were university students who ranged in age from 18 to 35 years. All subjects were prescreened to ensure that they were able to make fine discriminations in concentrations of NaCl ranging from 0·05M to 0·60M.

The taste stimuli and concentrations that served as standards are illustrated by the solid black bars in Figs 1(a) to 1(e). The standard concentrations were selected to impart a moderately intense taste. Serial dilutions both higher and lower than the standard (e.g. 0·20M NaCl), that differed from one another by a factor of 2, were utilized as test stimuli (e.g. 0·05M, 0·10M, 0·20M and 0·40M NaCl). Intermediate concentrations between dilutions (e.g. 0·30M NaCl) were also included.

500 μM amiloride, impregnated in chromatography paper, was applied to half of the tongue for 4 min. Chromatography paper soaked in deionized water and placed on the other half of the tongue served as a control (Fig. 2(a)). The standard concentration of a taste stimulus was impregnated in 1·27-cm circles of chromatography paper and applied to the side of the tongue that was adapted to amiloride. Test stimuli were placed on the control side that was not treated with amiloride and the concentrations were adjusted to match the perceived intensity of the

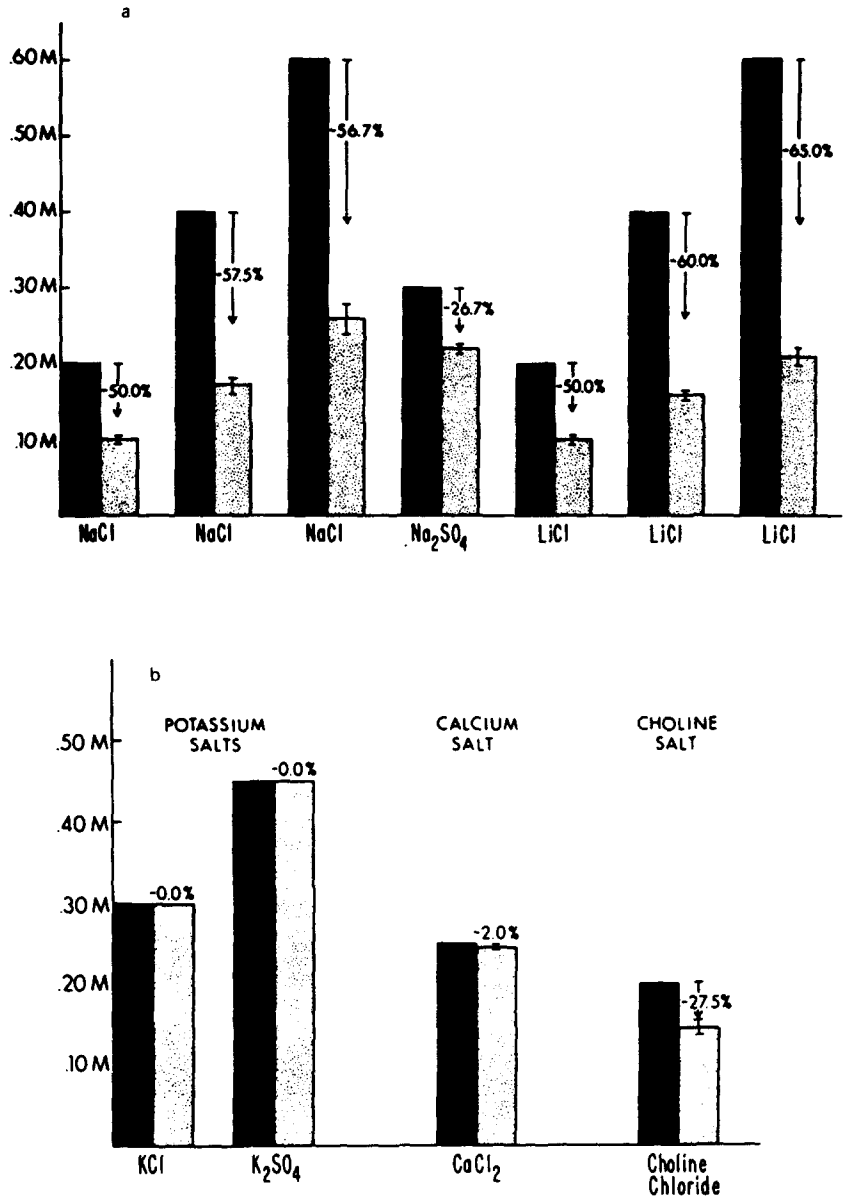


Fig. 1. Half of the tongue was adapted to 500 μM amiloride. The standard stimulus concentration applied to the amiloride side of the tongue is represented by the black bars. The mean concentration that matched the perceived taste intensity of the standard is given by the stippled bars. The per cent inhibition and standard errors are also given. (a) Sodium and lithium salts; (b) potassium, calcium and choline salts.

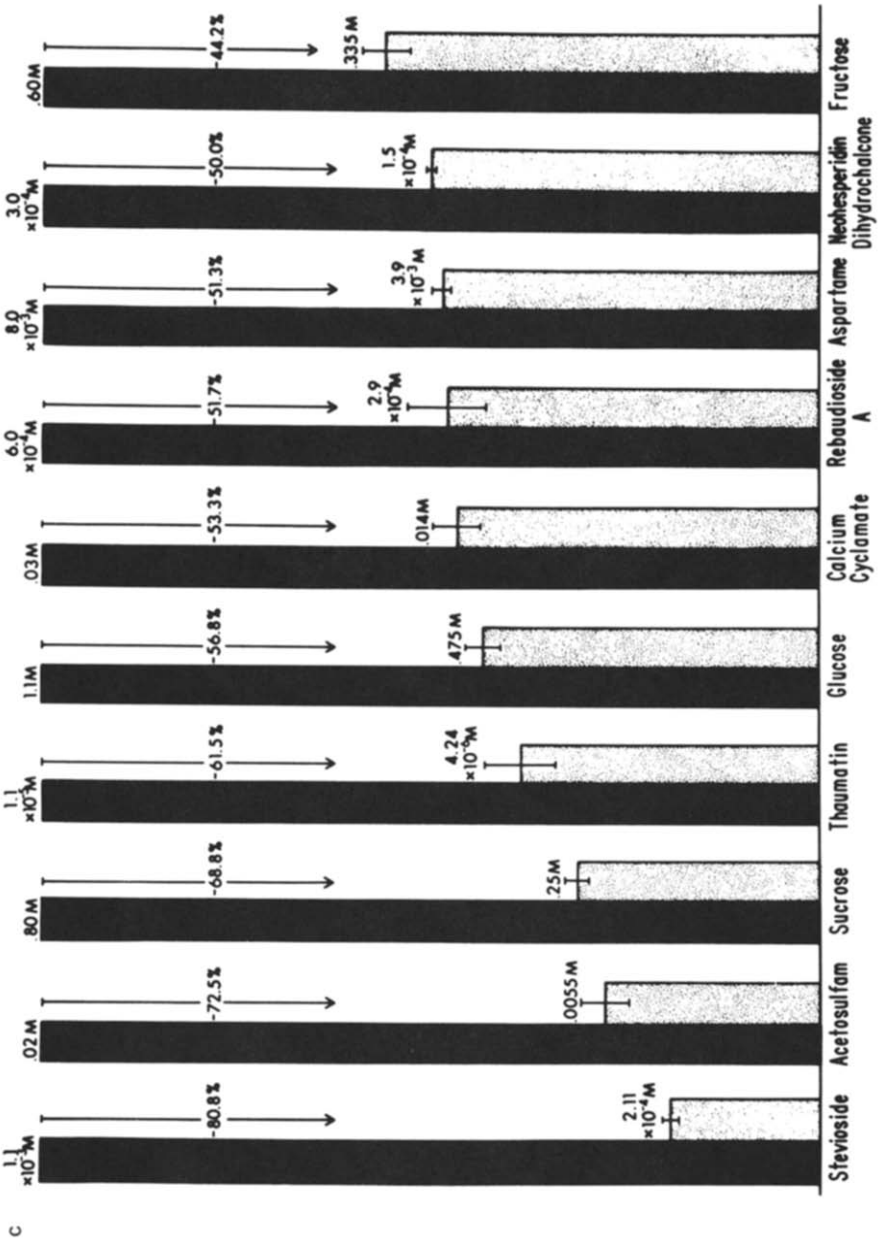


Fig. 1—*contd.* (c) Sweeteners.

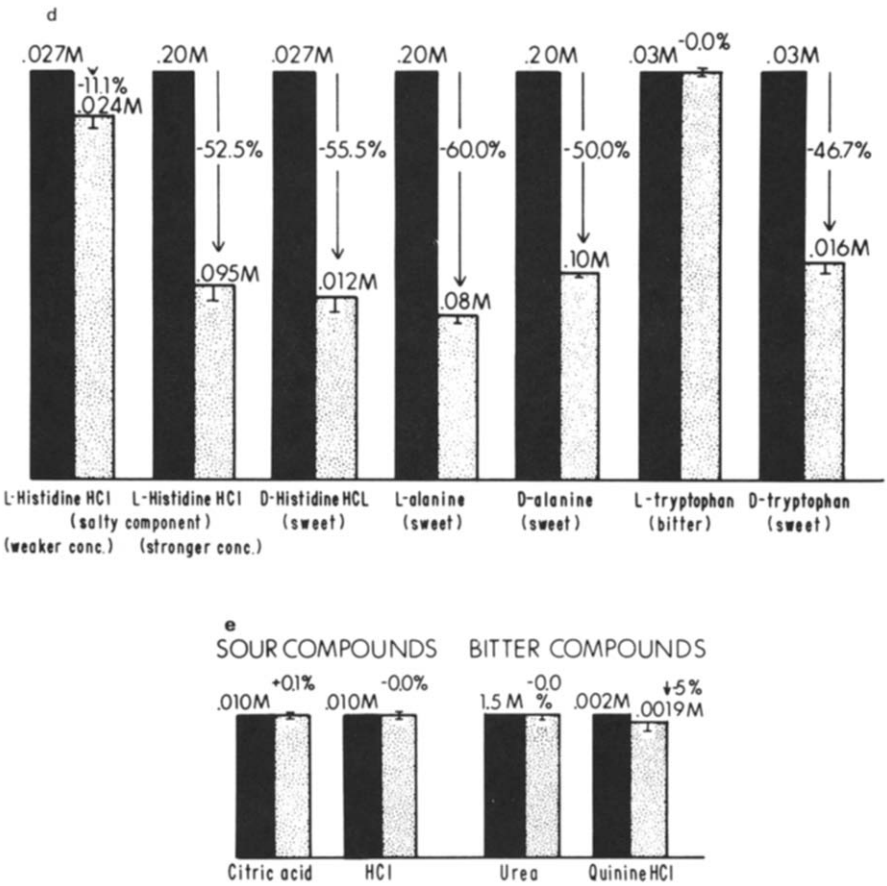


Fig. 1—*contd.* (d) Amino acids; (e) sour and bitter compounds.

standard (Fig. 2(b)). Details of the experimental procedure are given by Schiffman *et al.* (1983). Filter paper applications were used because whole mouth testing with a liquid rinsed the drug off the tongue.

It can be seen in Fig. 1(a) that amiloride reduced the taste intensity of both sodium and lithium salts. The reductions for 0·20M, 0·40M and 0·60M NaCl were 50·0%, 57·5% and 56·7%, respectively. While amiloride had no effect on potassium or calcium salts, as shown in Fig. 1(b), choline chloride was moderately suppressed. This is noteworthy since choline salts are often used as salt substitutes. A surprising finding, shown in Fig. 1(c), was that the perceived intensity of all the sweet-tasting compounds was reduced. Amino acids, shown in Fig. 1(d), with

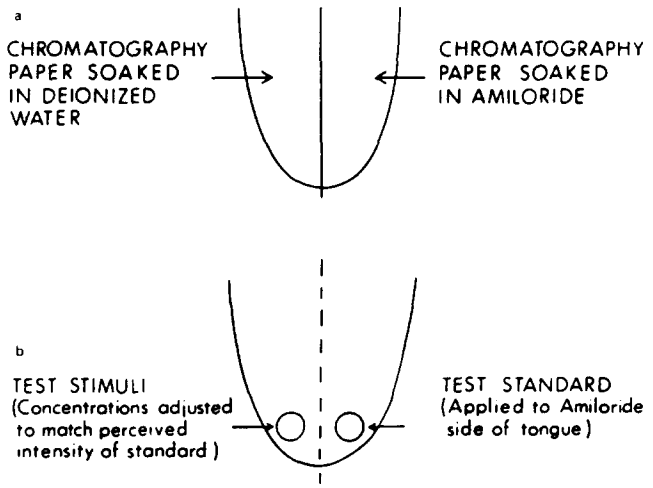


Fig. 2. (a) One half of the tongue was adapted to amiloride that was impregnated in filter paper. The other half of the tongue was adapted to deionized water which served as a control. (b) A standard concentration (represented by the black bars in Fig. 2) was impregnated in 1·27-cm circles of filter paper and placed on the side of the tongue to which amiloride had been applied. Concentrations of test stimuli applied to the non-amiloride side were adjusted to match the perceived intensity of the standard.

a sweet or salty component were also inhibited by amiloride. There was no taste reduction for bitter or sour stimuli, as shown in Fig. 1(e).

Similar results were found when the tongue was preadapted with 50 μM amiloride and when 500 μM amiloride was applied simultaneously with the taste standard without preadaption.

Neurophysiological studies

Extracellular recordings were made from eleven neurons in the nucleus tractus solitarius of rat (for details of these recording techniques, see Woolston & Erickson, 1979). Prior to amiloride treatment, a concentration series of NaCl was applied to the tongue to determine a moderate (half maximal) response for each neuron. KCl (0·25M) was used as a control. Stimuli were delivered for 5 s to the whole mouth with interstimulus rinses every 30 s. Next, the oral cavity was treated with amiloride (100 μM for 5 units, 500 μM for 6 units) for 5 min. The stimuli were reapplied with interstimulus rinses of amiloride. The number of spikes over the first 5 s of firing (corrected for background activity) was determined both prior to, and after, amiloride treatment.

It was found that amiloride reduced the activity in ten of the eleven neurons tested (see Schiffman *et al.*, 1983). For half of the units the response to NaCl was decreased less than 25% compared with the pretreatment control. For the other units, 60%–98% suppression was observed. In one unit the activity increased slightly. The response to KCl was relatively unaffected. The degree of suppression was not related to the concentration of amiloride used.

Discussion of amiloride studies

The psychophysical finding that the perceived intensity of sodium and lithium salts was reduced by amiloride is consistent with reports in other cellular and epithelial transport systems in which sodium and lithium fluxes are specifically blocked while those for other cations, such as potassium, are not (Herrera, 1972; Aceves & Cereijido, 1973; Candia & Chiarandini, 1973; Morel & Leblanc, 1975; Benos, 1982). It is interesting that choline was depressed in the human studies since amiloride and choline are known to share a transport pathway in proximal renal tubules (Rennick, 1981).

The finding that amiloride blocked all sweet-tasting compounds was surprising and may be due to one of several mechanisms. One possibility is that sweetness may be, in part, mediated by amiloride-sensitive sodium channels. Alternatively, amiloride may hydrogen bond to the same receptors as sweeteners. It has been suggested that intermolecular hydrogen bonding is a necessary condition for sweetness (Shallenberger & Acree, 1971). An AH–B configuration in the sweetener molecule is presumed to interact with an AH–B receptor site in the taste cell membrane. Amiloride, like sweeteners, has an AH–B unit capable of intermolecular hydrogen bonding.

The neurophysiological studies from rats are consistent with human data and indicate that amiloride suppresses responses to NaCl, leaving KCl relatively unaffected. Since this first report of neurophysiological decrements in the presence of amiloride (i.e. Schiffman *et al.*, 1983), subsequent studies (Heck *et al.*, 1984; Brand *et al.*, 1985) have confirmed these results. The psychophysical and neurophysiological data are also consistent with the recent finding of DeSimone *et al.* (1981) that amiloride substantially reduces the transport of sodium ions in epithelium isolated from dog tongue that is mounted between symmetrical Krebs–Henseleit

buffer solutions. Amiloride also reduces the inward current induced by sweeteners in the canine preparation (DeSimone *et al.*, 1984).

Thus, multidisciplinary data, including human psychophysical judgments, neurophysiological recordings from rat and transepithelial potential differences in isolated lingual epithelium of dog and rat, suggest that an amiloride-sensitive transport mechanism plays a rôle in taste transduction for sodium and lithium salts, as well as sweeteners.

CAFFEINE AND OTHER METHYL XANTHINES: ENHANCE SOME TASTES

The methyl xanthines (MX), caffeine, theophylline and theobromine, are potent antagonists of adenosine receptors (see Schiffman *et al.*, 1985, for a brief review of the literature). Adenosine is a purinergic compound that plays a significant rôle in the regulation and control of a variety of biological processes. It has profound effects on the cardiovascular system including slowed sinus rate, atrioventricular block, vasodilation and hypotension (Drury & Szent-Györgyi, 1929); adenosine also depresses neural activity (Snyder, 1984).

The two major types of cell surface adenosine receptors are illustrated in Figs 3(a); the A_1 high affinity receptor is inhibitory to adenylate cyclase and the A_2 low affinity receptor is stimulatory to adenylate cyclase (Van Calker *et al.*, 1978; Londos *et al.*, 1983). Caffeine (and other methyl xanthines) have the capacity to antagonize both types of adenosine receptor, as shown in Fig. 3(b).

In the experiments described below, it is shown that adaptation of the human tongue to caffeine (and other methyl xanthines) potentiates the taste of some compounds while leaving the intensity of others

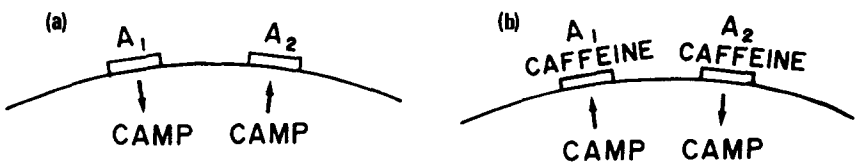


Fig. 3. (a) Two major types of cell surface adenosine receptor. The high affinity A_1 receptor is inhibitory to adenylate cyclase; the low affinity A_2 receptor is stimulatory to adenylate cyclase. (b) Caffeine and other methyl xanthines have the capacity to antagonize both types of adenosine receptor.

unchanged. Both human psychophysical data and neurophysiological data from rat will be described. Details of these studies are given in Schiffman *et al.* (1985, 1986).

Human psychophysical data

In the first of three studies described here, the human tongue was adapted to methyl xanthines (caffeine, theophylline or theobromine), at concentrations ranging from 10^{-5}M to 10^{-2}M, for 4 min. The methodology for adaptation and matching was similar to that used for amiloride

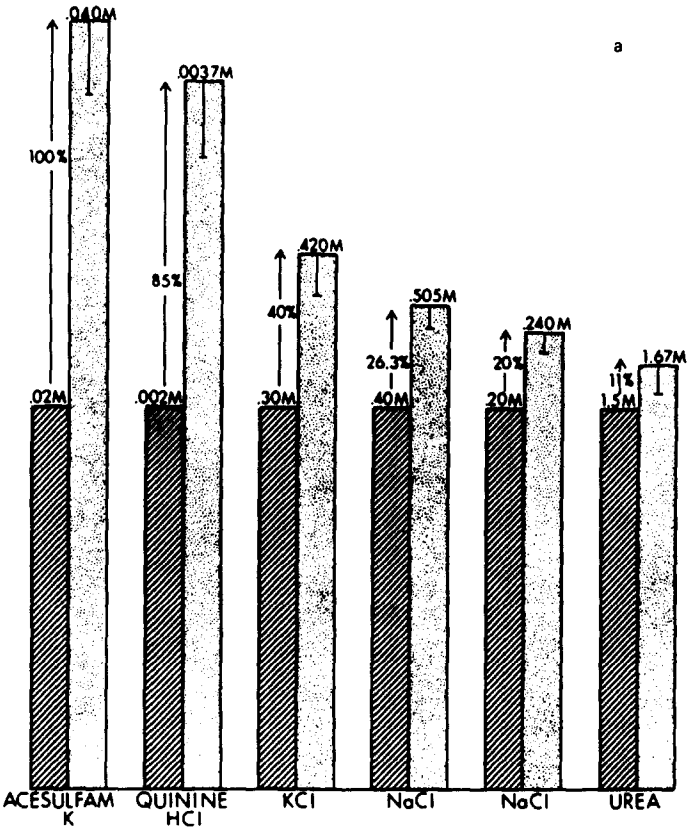


Fig. 4. Potentiation by caffeine. The striped bars indicate the standard concentration applied to the side of the tongue saturated with caffeine. The dotted bars represent the concentration of tastant perceived to match the standard. The per cent potentiation and standard errors are also given. Adaptation to (a) 10^{-5}M, (b) 10^{-3}M and (c) 10^{-2}M caffeine.

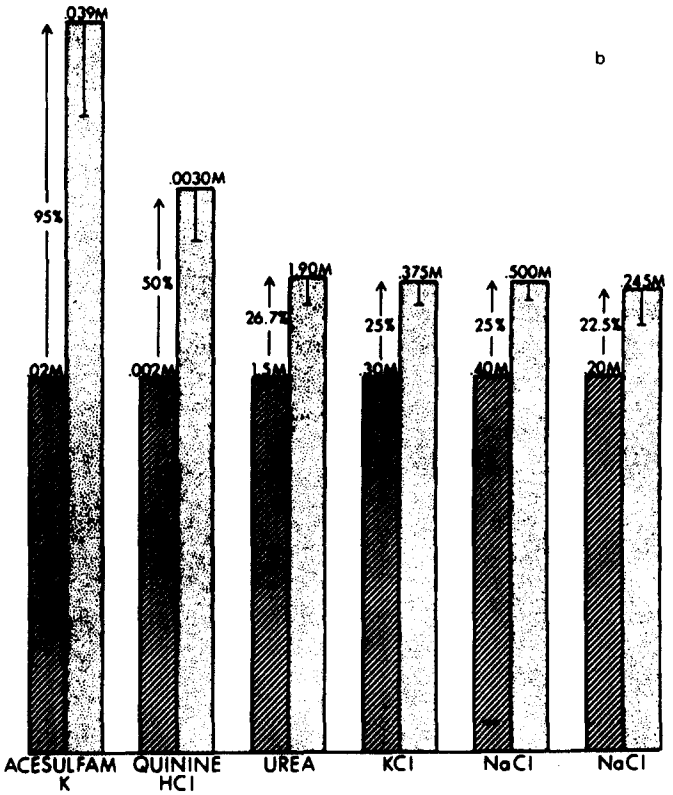


Fig. 4—*contd.*

and is described by Schiffman *et al.* (1985). Half of the tongue was adapted to a methyl xanthine and the other half to a water control. Of the six stimuli tested (0·20M and 0·40M NaCl, 0·30M KCl, 0·002M quinine HCl, 1·5M urea and 0·02M acesulfam-K), acesulfam-K, an artificial sweetener with a bitter component, was enhanced the most by methyl xanthines, as shown in Figs 4, 5 and 6. In Fig. 4(a) it can be seen that 10^{-5}M caffeine enhanced acesulfam-K by 100%. 10^{-5}M caffeine is a concentration known to inhibit adenosine receptors but below that required to inhibit phosphodiesterase (see Fredholm, 1980). Increasing the concentration of caffeine to 10^{-3}M and 10^{-2}M, levels known to inhibit phosphodiesterase, did not lead to further potentiation. Taste enhancement was also found for NaCl, quinine HCl and KCl. In Figs 5 and 6 it can be seen that adaptation of the tongue to 10^{-5}M

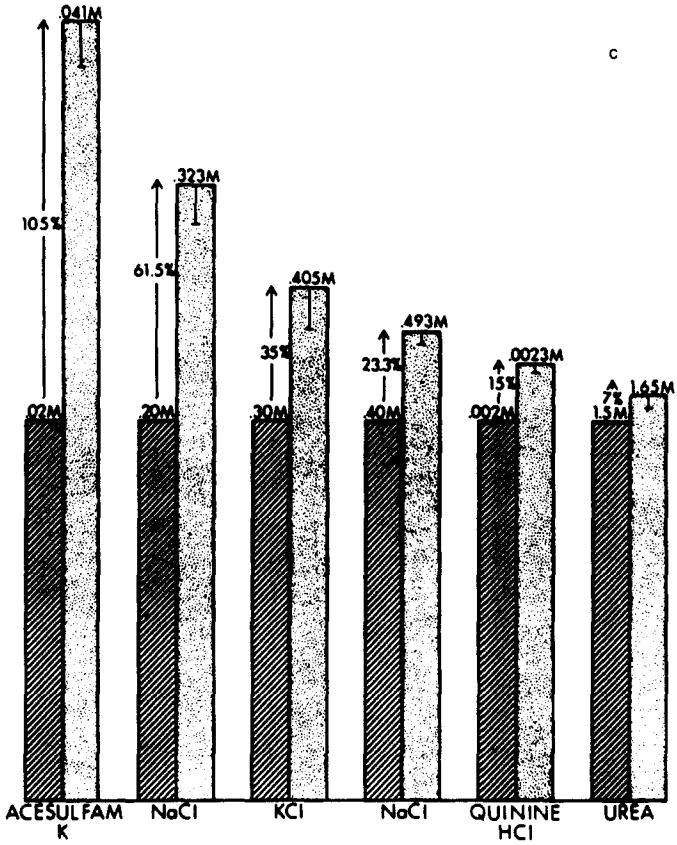


Fig. 4—*contd.*

theophylline, which is found in tea, and 10^{-5}M theobromine, that is found in chocolate, yields results similar to caffeine. Adenosine reversed the enhancement achieved by 10^{-5}M caffeine, as shown in Fig. 7.

In a second study, 10^{-5}M caffeine was found to potentiate the taste of other sweeteners with bitter components in addition to acesulfam-K (see Schiffman *et al.*, 1986). Caffeine statistically enhanced the taste of $3{\cdot}00 \times 10^{-4}$M neohesperidin dihydrochalcone, $1{\cdot}47 \times 10^{-2}$M D-tryptophan, $2{\cdot}78 \times 10^{-5}$M thaumatin, $1{\cdot}17 \times 10^{-3}$M stevioside and $1{\cdot}87 \times 10^{-3}$M sodium saccharin, as shown in Figs 8(a) and (b). When 10^{-5}M or 10^{-4}M adenosine was added to the caffeine, the potentiation was reversed. Four sweeteners without bitter components, aspartame, sucrose, fructose and calcium cyclamate, were not potentiated by

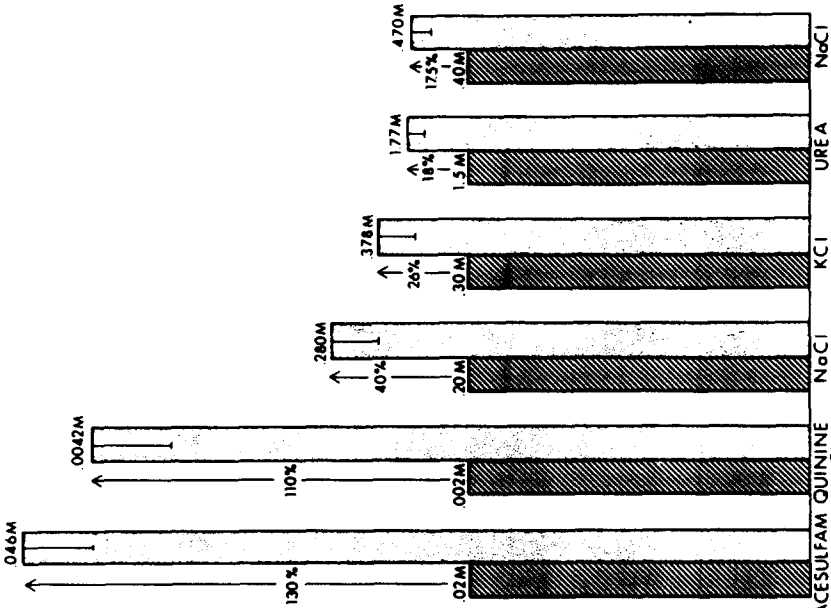


Fig. 6. Potentiation by 10^{-5}M theobromine.

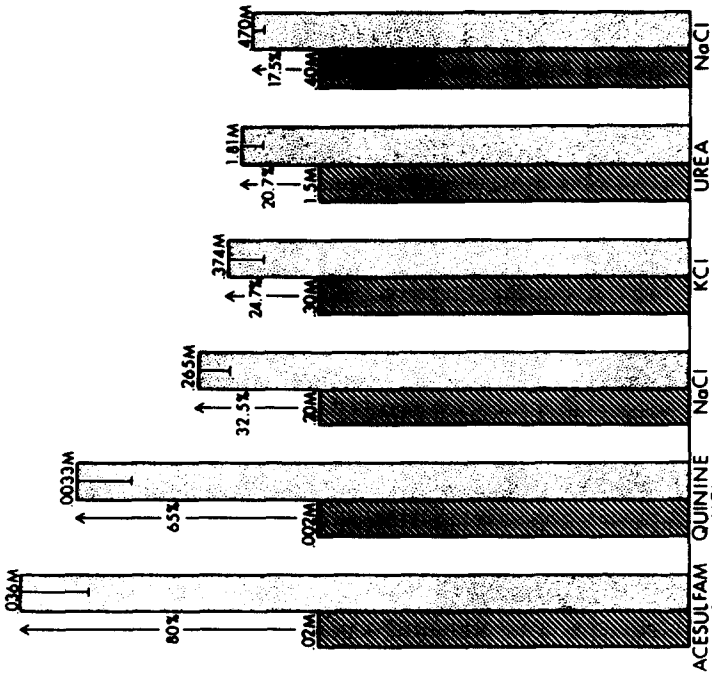


Fig. 5. Potentiation by 10^{-5}M theophylline.

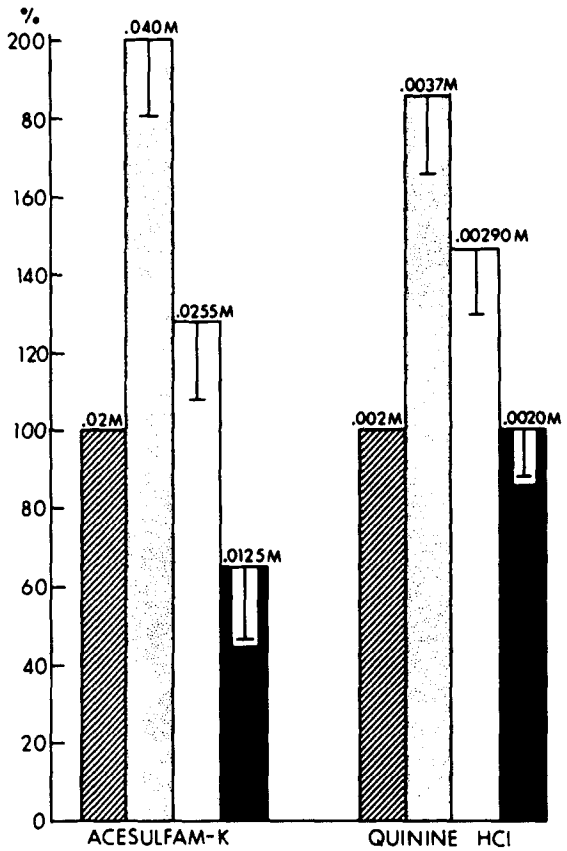


Fig. 7. The striped bars represent the standard concentrations of acesulfam-K and QHCl applied to the side of the tongue adapted to 10^{-5}M caffeine. The dotted bars indicate the concentrations perceived to match the standards after adaptation to 10^{-5}M caffeine. Acesulfam-K was enhanced by 100%, and QHCl by 85%, by 10^{-5}M caffeine. The blank bars represent the perceived intensity after application of 10^{-5}M caffeine and 10^{-5}M adenosine. This adaptation mixture resulted in less potentiation, 27·5% for acesulfam-K and 45·0% for QHCl, than 10^{-5}M caffeine by itself. A mixture of 10^{-5}M caffeine and 10^{-4}M adenosine actually depressed the response for acesulfam-K, leaving the response to QHCl unchanged, as shown in the solid bars. It can be concluded from these results that adenosine reverses the potentiation produced by caffeine. (From Schiffman *et al.*, 1985.)

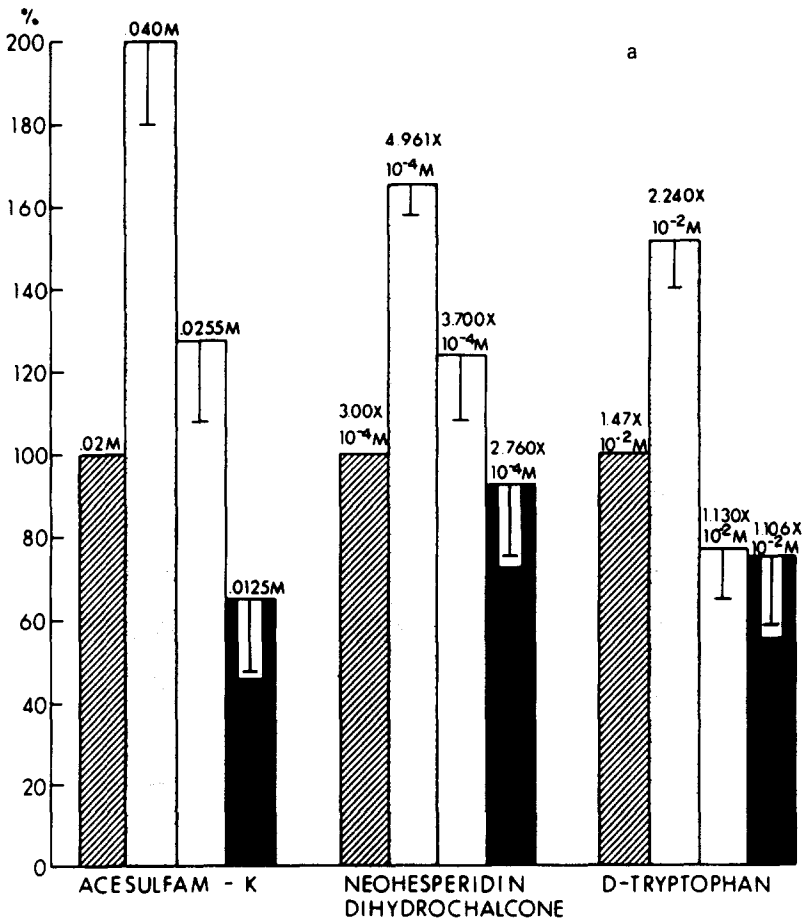


Fig. 8. The striped bars represent the standard concentration applied in the presence of 10^{-5}M caffeine. The dotted bars indicate the test concentration perceived to match the standard dissolved in caffeine. The blank bars indicate the perceived intensity after simultaneous application of 10^{-5}M caffeine and 10^{-5}M adenosine; the solid bars, after 10^{-5}M caffeine and 10^{-4}M adenosine. (a) and (b) Six sweeteners potentiated by 10^{-5}M caffeine. (c) Four sweeteners unaffected by 10^{-5}M caffeine.

caffeine, as shown in Fig. 8(c). These data lend support to the position that more than one receptor mechanism mediates sweetness. One sweet receptor type may be proximate to a bitter receptor (see Birch & Mylvaganam, 1976). Further evidence for multiple mechanisms will be given in the next section; IMP, inosine monophosphate, will be shown to enhance sucrose and aspartame but not other sweeteners.

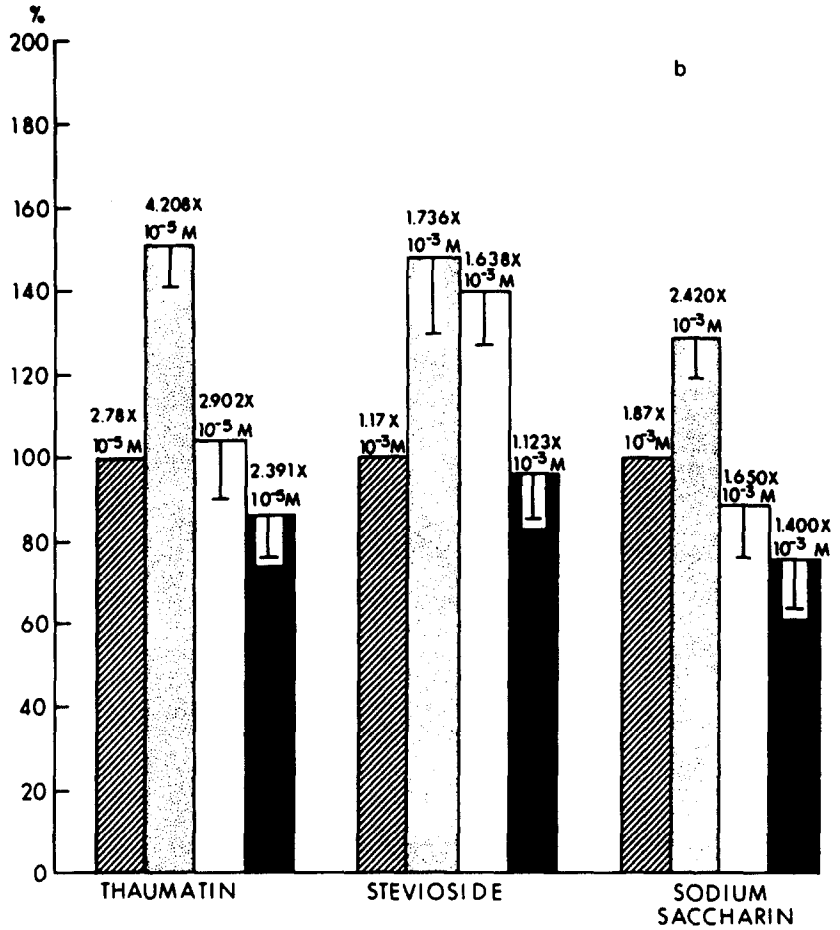


Fig. 8—*contd.*

In a third study the taste of amino acids was also found to be increased by 10^{-5}M caffeine, as shown in Figs 9(a) and (b). D-phenylalanine, L- and D-histidine, L-arginine, L-argenine HCl, L- and D-asparagine and L-alanine were statistically enhanced by 10^{-5}M caffeine. L- and D-glutamic acids were not affected (Fig. 9(c)).

Neurophysiological studies

The human psychophysical results were confirmed by animal studies (Schiffman *et al.*, 1985) in which single unit extracellular recordings

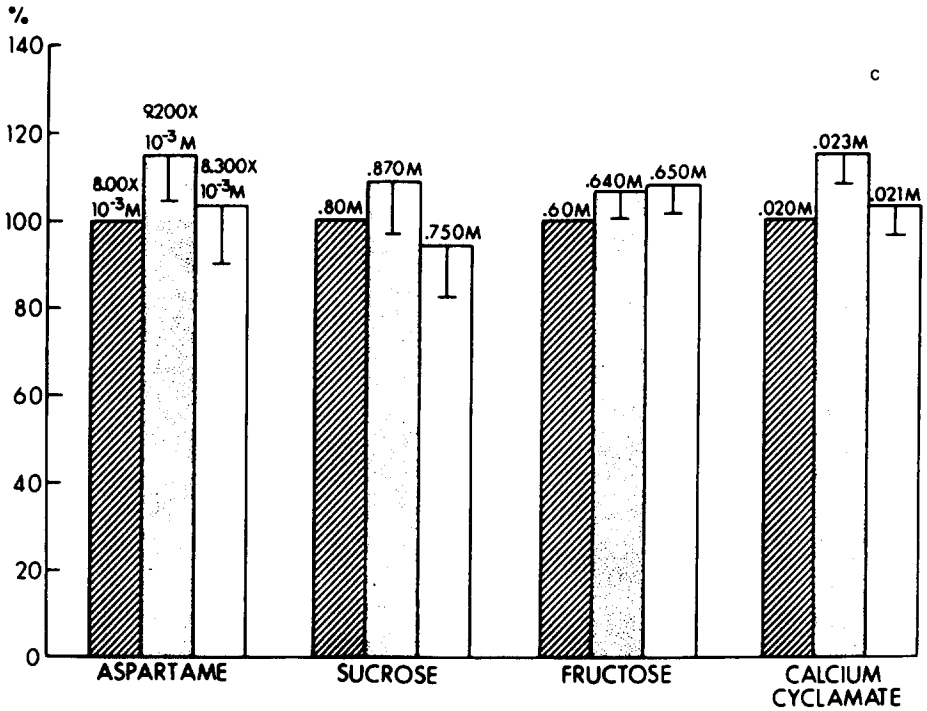


Fig. 8—*contd.*

were made from nucleus tractus solitarius in rat. Low levels of NaCl and the artificial sweetener, stevioside, were potentiated the most by 10^{-5}M caffeine.

Discussion of methyl xanthine studies

The data reported here indicate that adaptation of the anterior tongue to methyl xanthines can potentiate taste, and that adenosine reverses the potentiation. These findings suggest that the enhancement properties of methyl xanthines are due to inhibition of the A_1 adenosine receptor. The fact that prior adaptation of the tongue with methyl xanthines is required for perception of the increase in intensity may be due to the fact that a certain amount of time is required for cyclic AMP to build up inside the taste cell. Methyl xanthines probably antagonize the inhibitory effects of salivary adenosine that may well saturate the high affinity A_1 receptors on the tongue.

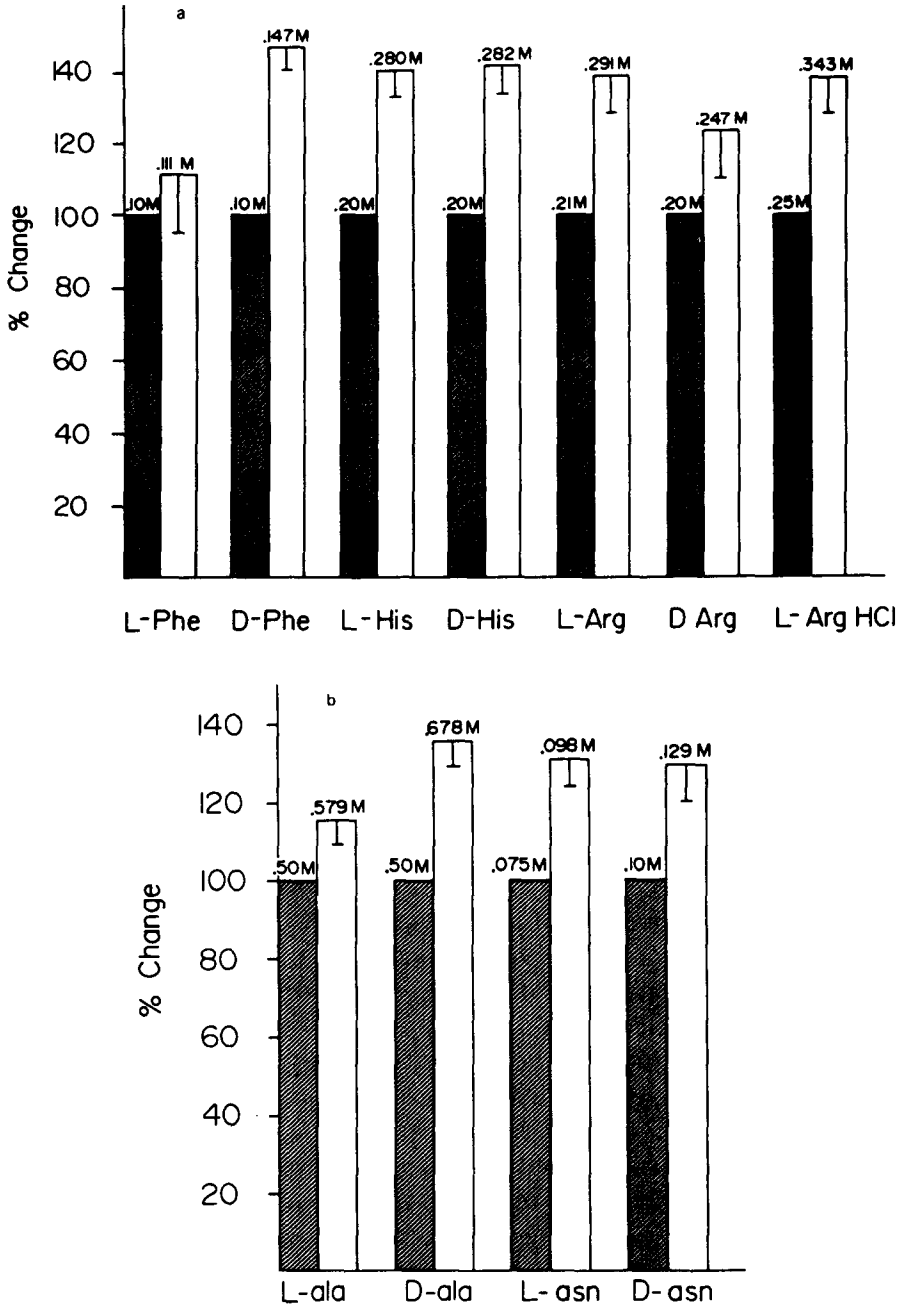


Fig. 9. The effect of 10^{-5}M caffeine on amino acids. The striped bars indicate the standard concentration applied to the caffeine-adapted side of the tongue. The blank bars represent the concentration perceived to match the standard. (a and b) Amino acids for which at least one enantiomer is enhanced.

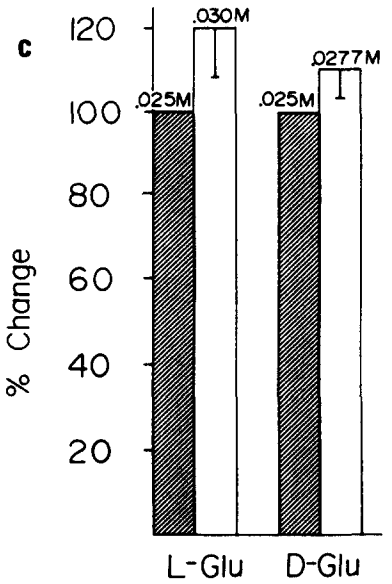


Fig. 9—*contd.* (c) D- and L-glutamic acid, neither of which is enhanced.

INOSINE MONOPHOSPHATE (IMP): ENHANCES SOME TASTES INCLUDING ASPARTAME

It has been well recognized that 5′ ribonucleotides not only have a unique taste of their own but can potentiate the taste of monosodium glutamate (Kuninaka *et al.*, 1964; Yamaguchi & Kimizuka, 1979). The nucleotides best known for their taste-enhancing properties are those having a purine nucleus with a hydroxy group in the 6- position and a ribose moiety esterified in the 5′ position with phosphoric acid (see Fig. 10). Examples include IMP (inosine monophosphate) and GMP (guanosine monophosphate). In a series of experiments that have just been completed in our laboratory, it was found that 10^{-3}M IMP applied to the tongue for 4 min prior to application of sucrose or aspartame led to potentiation of sweetness. The taste of sucrose was reliably potentiated by 38·2% in 60% of 20 subjects. The sweetness of aspartame was enhanced by 36·4% in the same subjects for whom sucrose was also enhanced. Woskow (1969) has previously reported that IMP potentiated the taste of sucrose.

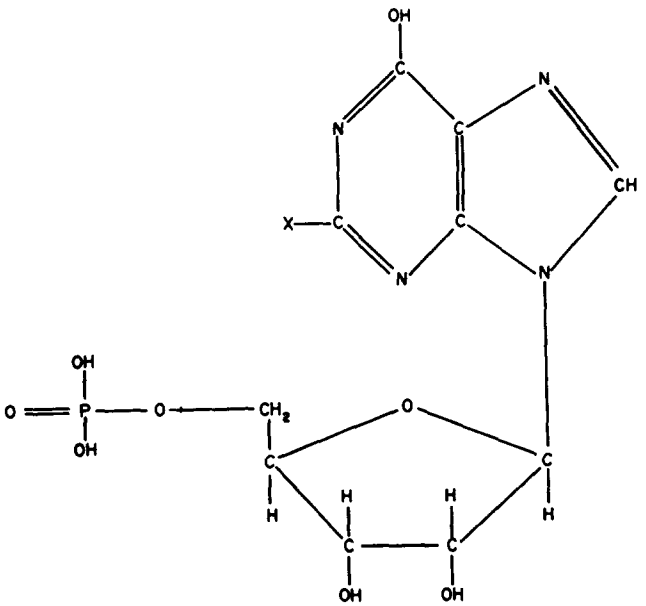


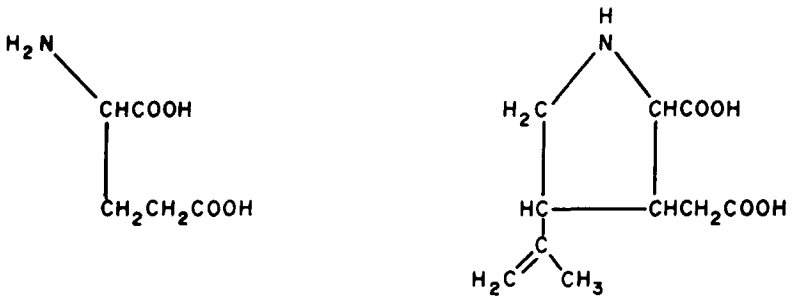
Fig. 10. Structure of 5′ ribonucleotide.

Discussion of IMP studies

It is noteworthy that sucrose, aspartame and glutamic acid, which were not enhanced by caffeine, an antagonist of the inhibitory adenosine receptor, are enhanced by IMP. This enhancement may result from an increase in cyclic nucleotides within the cell that occurs when IMP binds to a cell surface excitatory purinergic (5′ ribonucleotide) receptor. The cyclic nucleotides could, in turn, lead to modification of an allosteric protein located in the plasma membrane from the intracellular side, leading to an increase in the available glutamate or sweetener receptor sites (see Cagan *et al.*, 1979).

KAINIC ACID: REDUCES TASTE RESPONSES TO GLUTAMIC ACID

Kainic acid, shown in Fig. 11, is a glutamate agonist that has been reported to be 50 times more potent with respect to binding than glutamic acid (Peck, 1980). In a neurophysiological experiment recently



GLUTAMIC ACID KAINIC ACID

Fig. 11. Structures of glutamic acid and kainic acid.

completed in our laboratory, kainic acid, a rigid analog of glutamic acid, was found to selectively depress integrated neural firing to glutamic acid in rat but had no significant effect on the other stimuli tested. These results suggest that the taste system has selective receptor mechanisms for glutamic acid.

Recordings were made as follows. Multiunit activity was recorded from the nucleus tractus solitarius in ten Sprague Dawley rats using low impedance electrodes. Taste stimuli were delivered to the entire dorsal tongue via gravity flow to a flow chamber that held the tongue loosely but did not exclude saliva. The stimuli were 0·1M NaCl, 0·5M sucrose, 0·01M HCl, 0·05M monosodium glutamate (MSG), 0·05M monopotassium glutamate (MKG), 0·01M aspartic acid and 0·1M glutamic acid. Each stimulus was presented twice for approximately 5 s interspersed with interstimulus rinses of deionized water. Then, 5×10^{-3}M kainic acid was applied to the tongue for 4 min. Finally, the stimuli were presented again with interstimulus rinses of kainic acid.

The maximum deflection that occurred during the 5-s stimulus presentation was determined and expressed as a percentage of the NaCl response to allow comparisons between animals. The per cent suppression resulting from the application of kainic acid is given in Fig. 12 along with the standard errors. The responses to glutamic acid were significantly suppressed. Aspartic acid and HCl also tended to be reduced, but not significantly. Although this suppression could be due to a pH change induced by kainic acid, this is unlikely since there was no significant correlation between the degree of suppression induced and by the pH values measured for the stimuli.

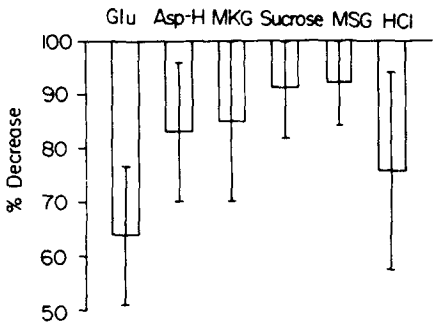


Fig. 12. Per cent suppression after exposure of the tongue to 5×10^{-3}M kainic acid. The stimuli were: 0·1M glutamic acid, 0·01M aspartic acid, 0·05M MSG, 0·05M MKG, 0·5M sucrose and 0·01M HCl. Standard errors are also given.

A more likely explanation is that kainic acid preferentially binds to the glutamate receptor, reducing the amount of bound glutamic acid. MSG and MKG are only slightly reduced, probably because sodium and potassium account for the major part of the neural response. In addition, the molarity of MSG and MKG was only half that used for glutamic acid.

Discussion of kainic acid studies

The selectivity of kainic acid suggests that glutamic acid is not mediated by the identical receptor populations as so-called 'primary tastes' and lends support to the position that there are more taste qualities than 'sweet', 'sour', 'salty' and 'bitter'.

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