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Modulators of the Adenylate Cyclase System Can Alter Electrophysiological Taste Responses in Gerbil

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SCHIFFMAN, S. S., L. A. GATLIN, M. S. SUGGS, S. A. HEIMAN, W. C. STAGNER AND R. P. ERICKSON. *Modulators of the adenylate cyclase system can alter electrophysiological taste responses in gerbil.* PHARMACOL BIOCHEM BEHAV 48(4) 983–990, 1994.—The adenylate cyclase system has been implicated in taste transduction. The purpose of this study was to determine whether application of modulators of the adenylate cyclase system to the tongue alter taste responses. Integrated chorda tympani (CT) recordings were made in gerbils to bitter, sweet, salty, sour, and glutamate tastants before and after a 4-min application of four types of modulators of the adenylate cyclase system. The four types of modulators tested were: a) NaF, a compound that promotes dissociation of GTP binding protein; b) forskolin, a powerful stimulant of adenylate cyclase; c) 8-bromoadenosine 3′ : 5′-cyclic monophosphate sodium salt (8BrcAMP) and N^6,2′-O-dibutyryladenosine 3′ : 5′-cyclic monophosphate sodium salt (DBcAMP), two membrane permeable forms of cAMP; and d) 1-(5-isoquinolinylsulfonyl)-2-methylpiperazine dihydrochloride (H-7) and *N*-(2-[methylamino]ethyl)-5-isoquinolinesulfonamide dihydrochloride) (H-8), which are protein kinase inhibitors. The taste compounds tested were: NaCl (30 mM), monosodium glutamate-MSG (50 mM), sucrose (30 mM), HCl (5 mM and 10 mM), KCl (300 mM), quinine HCl (30 mM), $MgCl_2$ (30 mM), erythromycin (0.7 mM and 1 mM), HCl (5 mM and 10 mM), and urea (2 M). The main findings were as follows. NaF (20 mM) significantly inhibited responses to bitter compounds up to 35% and enhanced the response to sucrose by 30%. NaCl (20 mM), used as a control for NaF, inhibited most responses up to 78% with no enhancement of sucrose as seen with NaF. 8BrcAMP (1.16 mM) reduced the responses to bitter-tasting quinine HCl, $MgCl_2$, and erythromycin but not to urea. It also blocked the responses to KCl and HCl which have bitter components. There was a slight enhancement of the sucrose response. It had no significant effect on NaCl or MSG. A similar trend was found for 5 mM DBcAMP. H-7 (300 μM) slightly altered responses to several stimuli. These data indicate that modulation of the adenylate cyclase system can affect the amplitude of neural responses of some bitter and sweet taste responses.

Adenylate cyclase Taste Electrophysiology Gerbils

RECENT data suggest that taste compounds activate a variety of transduction mechanisms in taste receptor cells including apically located channels and receptors (1,3,12,21,30,31). The current view is that salts, acids, and some bitter compounds interact with ion channels (13,20–22,32,33,38). Most sweet and bitter compounds are presumed to bind to cell-surface receptors and promote second-messenger cascades (17,40).

Two second-messenger systems have been implicated thus far in taste transduction, the adenylate cyclase system and the phosphatidylinositol system (2,6,7,17,19,24–26,28,37,39,40). The adenylate cyclase system appears to play a role in transduction of both sweet and bitter compounds; the phosphatidylinositol system is involved in bitter taste transduction. Evidence for the presence of these two second messenger systems in taste cells comes from biochemical experiments. GTP-binding proteins (6) as well as the second-messenger-generating enzymes adenylate cyclase (25,26,39) and phosphatidylinositol 4,5-bisphosphate phosphodiesterase (PIP2-PDE) have been identified in taste cells (19).

A mediatory role for the adenylate cyclase system in bitter

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taste has been suggested by the work of Cagan (7), Kurihara (24), and Price (28). Cagan found that bitter-tasting caffeine, theophylline, and quinine stimulated the labeling of cAMP by up to twofold. He interpreted this increase in cAMP as due to inhibition of phosphodiesterase. Both inhibition and activation of phosphodiesterase have been reported in response to bitter compounds. Kurihara (24) found that all the bitter compounds that he tested (bactracin, papaverine HCl, naringin, gymnemic acid A, picric acid, quinine HCl, strychnine HNO_3, theophylline, caffeine, and theobromine) inhibited cyclic 3',5'-nucleotide phosphodiesterase. Price (28) found the opposite, i.e., that a bitter tastant activated phosphodiesterase; he suggested that a reduction of cAMP plays a role in bitter taste transduction. Certain bitter stimuli may also activate PIP2-PDE. The intensely bitter compound denatonium chloride increases intracellular Ca^{2+}, which appears to be released from intracellular stores (2). Denatonium, sucrose octaacetate, and strychnine, but not quinine, all elevate IP_3 levels in taste cells, suggesting that the PIP2-PDE system plays a role in transduction of these bitter tastes (17,37).

A role for the adenylate cyclase system in transduction of sweet taste has been suggested by Striem et al. (39). They found that sucrose significantly stimulated the activity of adenylate cyclase in membranes derived from the anterior-dorsal region of rat tongue. The enhancement of adenylate cyclase by sucrose was dose dependent, and the activation of adenylate cyclase was dependent on the presence of guanine nucleotides, which suggests the involvement of a GTP-binding protein. Sodium saccharin (which is sweet to the rat) activated the enzyme, although aspartame and neohesperidin dihydrochalcone (which are not sweet to the rat) did not. Depolarization of taste cells by sweet stimuli appears to result from cAMP-dependent closure of K^+ channels (5,11,44). Elevation of cAMP can be blocked by methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (40), which is an inhibitor of sweet taste (34).

The purpose of this paper is to determine if six different modulators of the adenylate cyclase system can alter electrophysiological taste signals. The adenylate cyclase system acts as a second-messenger system by altering intracellular cAMP (15) levels through activation or inhibition of the enzyme adenylate cyclase via a regulatory GTP-binding protein. The normal sequence of activation as well as the point of activity of the six modulators used in this study is as follows. First, a ligand (possibly a sweet or bitter-tasting compound) binds to a receptor on the cell membrane. Next, the ligand-receptor complex associates with a specific GTP binding protein (G protein) in the membrane. The G protein is a heterotrimer that consists of three subunits that are designated as the α, β, and γ subunits. When the G protein is inactive, the α unit is bound to the β and γ subunits, and GDP is bound to a high affinity site on the α subunit. Activation of the G protein results in displacement of GDP from the α subunit of G protein by GTP and the dissociation of the α subunit from a high-affinity complex of β and γ subunits. NaF (9,14,23) was used in the present study to promote this dissociation. When the G protein is activated, it also dissociates from the receptor. The α subunit of the G protein binds to the enzyme adenylate cyclase. Stimulation of the adenylate cyclase enhances the synthesis of cAMP from ATP and leads to the subsequent activation of cAMP-dependent protein kinase (protein kinase A). In this study, forskolin (4,8) was used to promote activation of adenylate cyclase. In addition, two membrane permeable derivatives of cyclic 3'-5' AMP (4,8,10,27) were used here to increase intracellular cAMP. The cAMP dependent protein kinase phosphorylates proteins that can result in depolarization of the cell. Two inhibitors of protein kinase, H-7 (29,41) and H-8 (42), were used in this study to determine their effects on taste. The G protein subunits then reassociate upon hydrolysis of GTP to GDP by an intrinsic GTPase, terminating the action of adenylate cyclase.

METHOD

Animals

Female Mongolian gerbils, *Meriones unguiculatus*, were obtained from Tumblebrook Farm, West Brookfield, MA. The gerbils were 10–12 weeks old and weighed from 45–60 g (mean = 50 g).

Stimuli

Six modulators of the adenylate cyclase system were tested for their effect on taste. Sodium fluoride (NaF) promotes dissociation of G proteins (9). [Note: the active agent is actually the aluminum tetrafluoride ion (AlF_4^-); aluminum is found naturally in the interstitial fluid surrounding the taste cells]. NaCl was tested as a control for the NaF experiment. Forskolin (7β-Acetoxy-8,13-epoxy-1μ,6β,9μ-trihydroxylabd-14-ene-11-one), an alkaloid extracted from an Indian herb *Coleus forskohlii,* is a powerful stimulant of adenylate cyclase and probably acts on the enzyme from the outside (8). Two membrane permeable derivatives of cyclic 3'-5' AMP were tested: 8-bromoadenosine 3':5'-cyclic monophosphate sodium salt (8BrcAMP, $C_{10}H_{10}BrN_5O_6PNa$) and N^6,2'-O-dibutyryladenosine 3':5'-cyclic monophosphate sodium salt (DBcAMP, $C_{18}H_{23}N_5O_8PNa$) (4,8,10,27). 1-(5-Isoquinolinylsulfonyl)-2 methylpiperazine dihydrochloride (H-7), inhibits protein kinase C and probably protein kinase A within 1–2 min (29). *N*-(2-[methyl amino]ethyl)-5-isoquinolinesulfonamide dihydrochloride (H-8, $C_{12}H_{15}N_3O_2S \cdot 2HCl$) is an isoquinolinesulfonamide compound (42). The concentrations used for each compound tested were: NaF, 20 mM; NaCl, 20 mM; forskolin, 0.12 mM; 8BrcAMP, 1.16 mM; DBcAMP, 5 mM; H-7, 300 μM; and H-8, 147 μM. These concentrations were selected because they have previously been found to be effective in other physiological systems. All of the compounds were dissolved in deionized water, with exception of forskolin, which was dissolved in 1% DMF (*N,N* dimethyl formamide). The pH of the solutions ranged from 6.0 to 7.0.

The effect of these modulators on 19 taste solutions was examined. The stimuli tested were: 30 mM NaCl, 300 mM KCl, 30 mM sucrose, 50 mM MSG, 5 mM and 10 mM HCl, 30 mM QHCl, 30 mM and 100 mM $MgCl_2$, 0.7 mM and 1 mM erythromycin, and 2 M urea. Not all of the taste solutions were tested at every concentration for every modulator due to the prohibitive cost of some of the modulators. All solutions were tested at room temperature (72°F).

Experimental Procedure

Gerbils were anesthetized with an intraperitoneal injection of ketamine HCl (Ketalar 50 mg/ml) at a dose of 330 mg/kg body weight. Ketalar was administered in two doses with 15 min in between each dose. Supplementary injections of sodium pentobarbital (Nembutal at 5 mg/ml) were delivered to maintain a surgical level of anesthesia. Integrated electrophysiological recordings from the chorda tympani nerve were made using the techniques described by Jakinovich and Oakley (18) and Schiffman et al. (35).

Recordings from a minimum of 5 and a maximum of 10 animals (with the exception of H-8 with only one trial) were obtained to evaluate the effect of a single concentration of

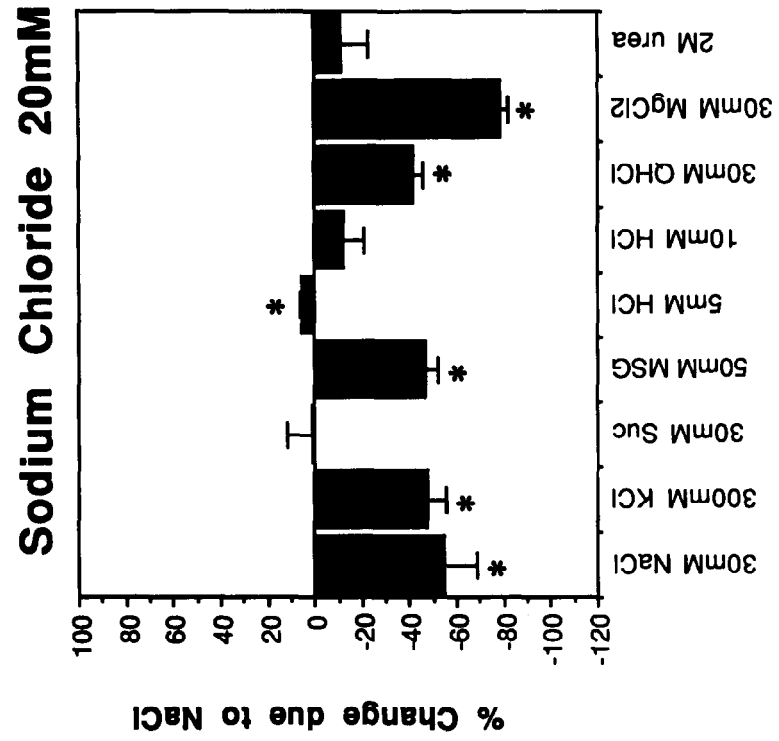

FIG. 2. Percent change in integrated chorda tympani responses after a 4-min application of 20 mM NaCl.

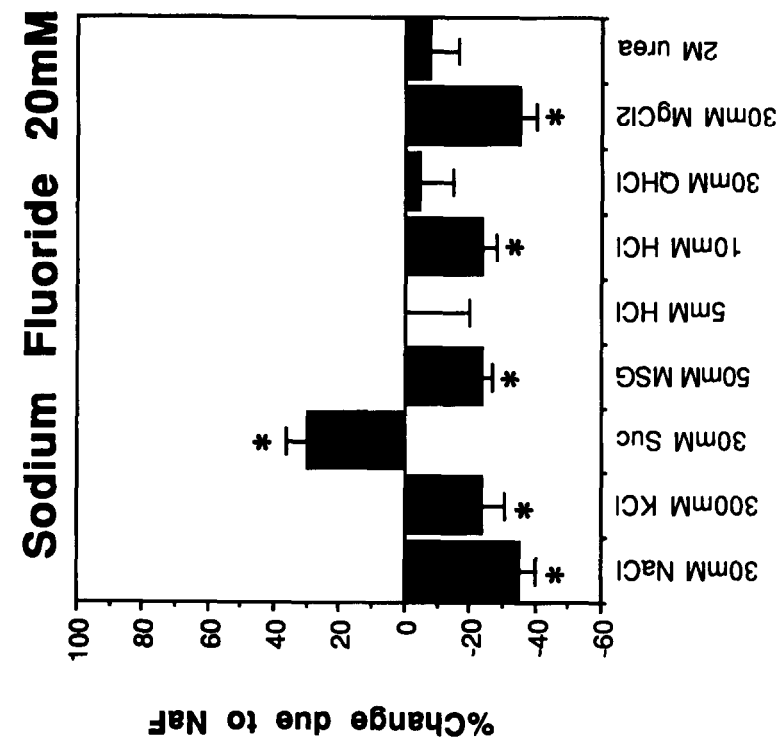

FIG. 1. Percent change in integrated chorda tympani responses after a 4-min application of 20 mM NaF. Abbreviations: NaCl, sodium chloride; KCl, potassium chloride; Suc, sucrose; MSG, monosodium glutamate; HCl, hydrochloric acid; QHCl, quinine hydrochloride; $MgCl_2$, magnesium chloride; urea, urea.

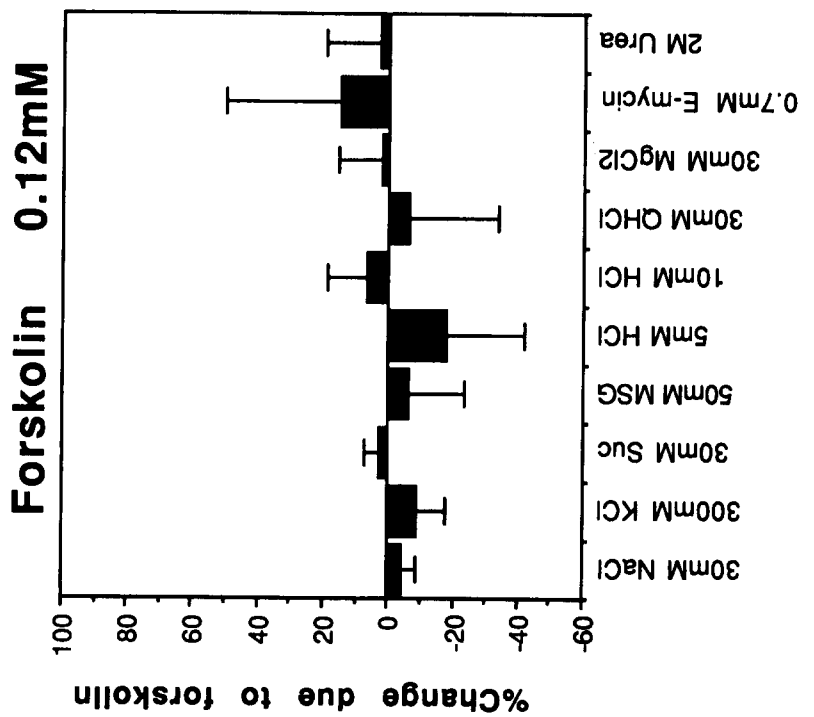

FIG. 3. Percent change in integrated chorda tympani responses after a 4-min application of 0.12 mM forskolin. Abbreviations: NaCl, sodium chloride; KCl, potassium chloride; Suc, sucrose; MSG, monosodium glutamate; HCl, hydrochloric acid; QHCl, quinine hydrochloride; $MgCl_2$, magnesium chloride; E-Mycin, erythromycin; urea, urea.

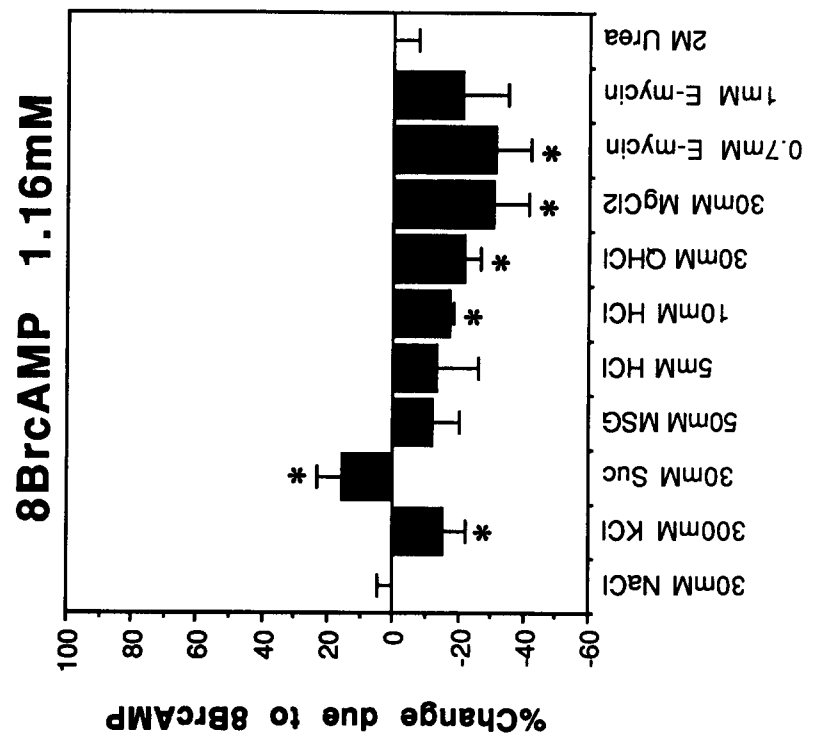

FIG. 4. Percent change in integrated chorda tympani responses after a 4-min application of 1.16 mM 8BrcAMP.

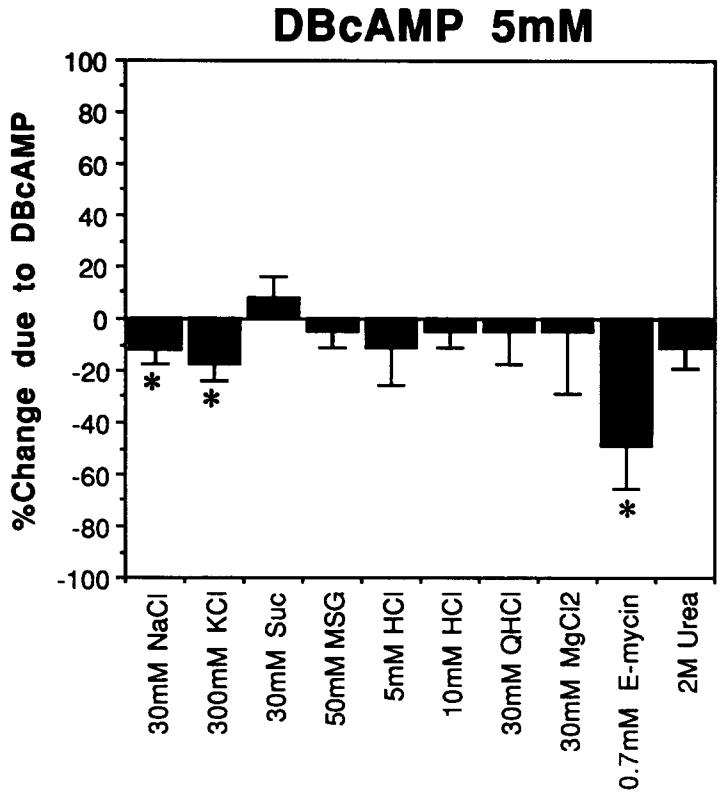

FIG. 5. Percent change in integrated chorda tympani responses after a 4-min application of 5 mM DBcAMP.

each adenylate cyclase system modulator on the taste stimuli. At each of the trials, NaCl, KCl, and sucrose were applied to the gerbil tongue followed by the remaining series of taste compounds with 1 min interstimulus rinses of deionized water (except for forskolin, in which 1% DMF was used). The stimuli were delivered in 2.0 ml samples by a gravity flow system at a rate of 0.20 ml per second. Next the tongue was adapted for 4 min with a modulator of the adenylate cyclase system followed by a reapplication of the taste solutions with interstimulus rinses of the modulator.

RESULTS

Several modulators of the adenylate cyclase system were found to modify taste.

NaF

Application of NaF (20 mM) to the gerbil tongue for 4 min resulted in significant changes in several of the taste responses. Sucrose (30 mM) was enhanced by 30.0% and several other responses were blocked. Reductions in responses were: 30 mM NaCl (35%), 300 mM KCl (24%), 50 mM MSG (24%), 10 mM HCl (24%), and 30 mM MgCl2 (35%) (see Fig. 1).

NaCl was also tested on the same stimuli at 20 mM and produced an inhibition for most of the taste compounds. The blockages were: 30 mM NaCl (54%), 300 mM KCl (48%), 50 mM MSG (46%), 30 mM QHCl (42%), and 30 mM $MgCl_2$ (78%). HCl (5 mM) was enhanced slightly by 6%. Sucrose (30 mM), 10 mM HCl, and 2 M urea were not significantly affected (see Fig. 2).

Forskolin

Application of 0.12 mM forskolin for 4 min to the tongue of the gerbil had no significant effects on any stimulus (see Fig. 3).

Membrane Permeable Forms of cAMP

Application of 1.16 mM 8BrcAMP for 4 min to the tongue significantly blocked responses to 300 mM KCl (15%), 10 mM HCl (17%), 30 mM quinine HCl (22%), 30 mM $MgCl_2$ (31%), and 0.7 mM erythromycin (31) (see Fig. 4). It slightly enhanced 30 mM sucrose by 16% but had no significant effect on 30 mM NaCl, 50 mM MSG, 5 mM HCl, 1 mM erythromycin, or 2 M urea.

When 5 mM DBcAMP was applied to the tongue for 4 min, the mean responses to three compounds were significantly suppressed. The reductions were: 30 mM NaCl (12%), 300 mM KCl (17%), and 0.7 mM erythromycin (49%) (see Fig. 5). The remaining stimuli were not significantly altered. Sample electrophysiological traces of taste responses before and after a 4-min application of 1.16 mM 8BrcAMP to the gerbil tongue are shown in Fig. 6.

Modulators of Protein Kinase

Application of H-7 (300 μM) for 4 min significantly depressed responses to: 50 mM MSG (26%), 5 mM HCl (23%), 30 mM $MgCl_2$ (38%), and 2 M urea (13%). Sucrose (30 mM) was enhanced by 21%. H-7 did not significantly effect any other stimuli (see Fig. 7). H-8, during one trial, yielded no consistent pattern of results.

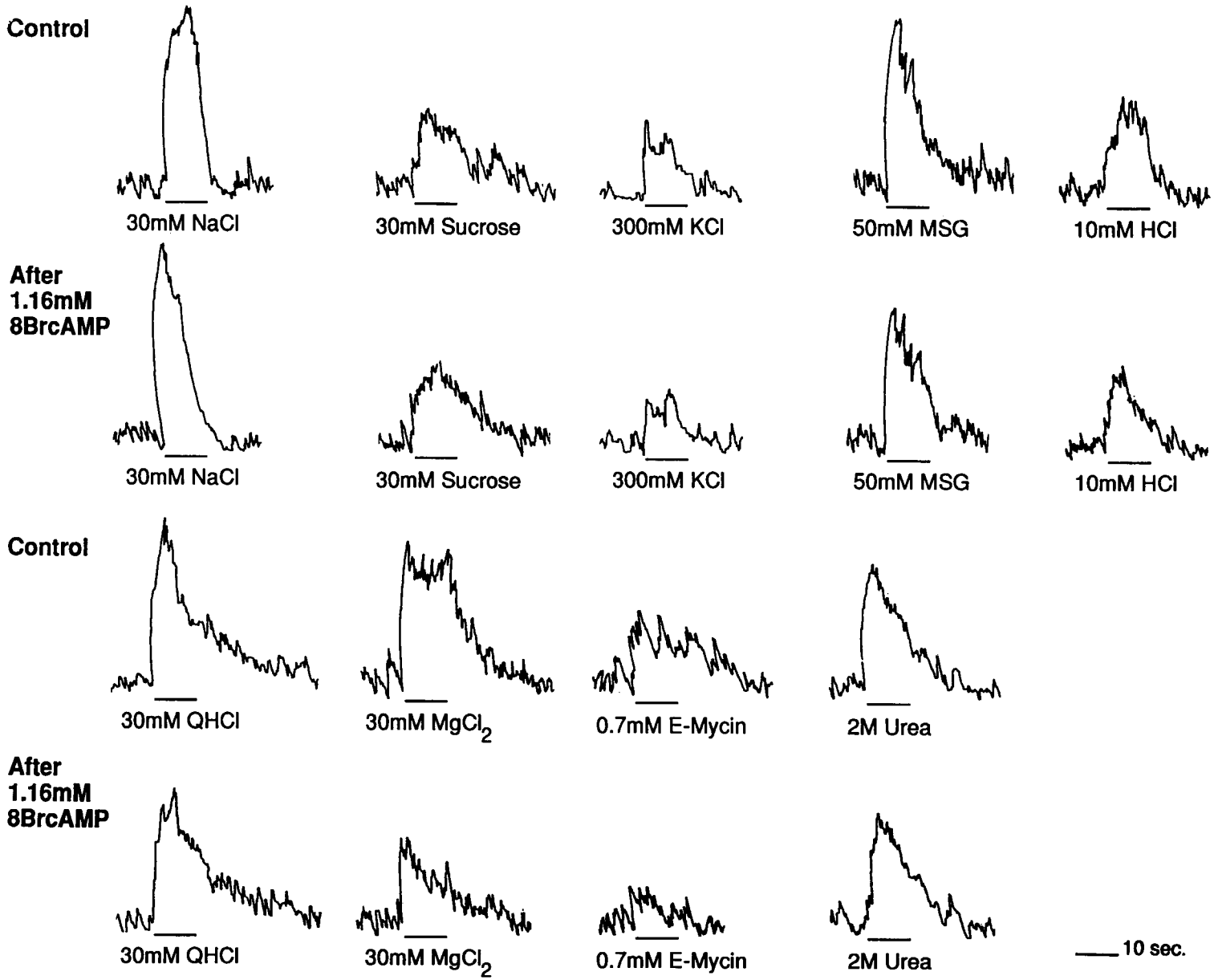

FIG. 6. Representative traces before and after a 4-min application of 1.16 mM 8BrcAMP.

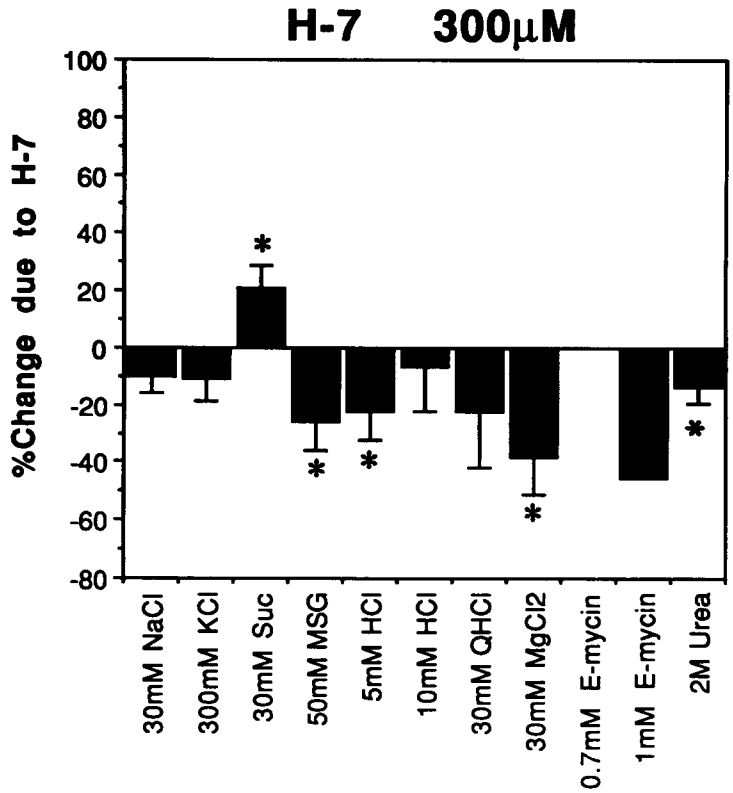

FIG. 7. Percent change in integrated chorda tympani responses after a 4-min application of 300 μM H-7.

DISCUSSION

The main finding was that activation of G proteins with NaF and application of membrane permeable forms of cAMP enhanced the response to sucrose and suppressed responses to some bitter tastants. NaF may produce these effects by making it easier for a subunits to dissociate and, thus, become active when stimulated by a receptor-agonist complex (45). Another possibility is that activation of a G protein by NaF has a separate action to modify the channel or receptor that transduces a sweet or bitter taste (36). Inhibition of taste responses of all the salt stimuli by NaF and NaCl is partially due to adaptation caused by repeated exposure to the Na^+ ion (31). The membrane permeable forms of cAMP may increase the effective levels of cAMP within the cell and, thus, produce effects consistent with those resulting from activation of the G protein.

The failure of forskolin to mimick the effects of membrane permeable forms of cAMP suggests an alternative interpretation of the data. The inhibition of bitter taste induced by cAMP derivatives might be related to: a) nucleotide receptors on the outside of the cell or b) breakdown products of cAMP such as adenosine. More likely, however, forskolin may fail to act because it does not stimulate adenylate cyclase in an in vivo preparation at the concentration used.

The finding that H-7 enhanced the sucrose response and suppressed bitter taste responses is unexpected, given the actions of NaF and membrane-permeable forms of cAMP. However, H-7 has numerous actions and inhibits protein kinase C as well as protein kinase A. Protein kinase C plays a role in the phophoinositide system, another second-messenger system active in cells (29). Thus, H-7 may produce its activity through the phosphoinositide system system rather that the adenylate cyclase system. Crosstalk between the adenylate cyclase system and phosphatidylinositol system is known to occur (16). For example, the intracellular messenger cAMP may modulate taste by interacting with the phosphoinositide system, i.e., elevation of cAMP may lead to release of Ca^{2+} from intracellular stores (2,43).

The ultimate test of biochemical theories about taste must be verified electrophysiologically or psychophysically. Comparison of biochemical results with electrophysiological data can give insight into mechanisms of transduction and modulation.

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