Chem. Senses 30 (suppl 1): i176–i177, 2005 doi:10.1093/chemse/bjh171

Forebrain Modulation of Brainstem Gustatory Processing

David V. Smith[1], Cheng-Shu Li[1] and Young K. Cho[2]

[1]Department of Anatomy and Neurobiology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN 38163, USA and [2]Department of Physiology and Neuroscience, College of Dentistry, Kangnung National University, Kangwon-do, 210-702, Korea

Correspondence to be sent to:David V. Smith, e-mail: dvsmith@utmem.edu

Key words: bed nucleus of the stria terminalis, central nucleus of the amygdala, enkephalin, GABA, glutamate, insular cortex, lateral hypothalamus, nucleus of the solitary tract, taste

Introduction

Taste information in rodents is carried to the rostral portion of the nucleus of the solitary tract (NST) by axons of the VIIth, IXth and Xth cranial nerves (Beckstead and Norgren, 1979). From the NST, ascending gustatory fibers project to third-order cells within the parabrachial nuclei (PbN) of the pons (Norgren, 1978), and in turn to multiple forebrain nuclei, including the thalamus, insular cortex (IC), lateral hypothalamus (LH), central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BST) (Norgren, 1976; Saper and Loewy, 1980; Halsell, 1992). These forebrain targets send centrifugal axons to both the PbN and NST (van der Kooy *et al.*, 1984; Allen *et al.*, 1991; Halsell, 1998). The present manuscript summarizes recent work on the descending modulation of NST neuronal activity by these various forebrain targets of the gustatory system.

Forebrain stimulation and recording of NST activity

Previous research, involving either decerebration or electrical stimulation, suggested that descending pathways from the forebrain could modulate brainstem gustatory activity. In a series of experiments, we have examined systematically the centrifugal influence of various forebrain areas on taste-responsive neurons in the hamster NST. These experiments employed bilateral stimulating electrodes and drug-injection pipettes in forebrain nuclei and extracellular recording of neural activity from NST neurons. Brief electrical pulses (<0.1 mA, 0.5 ms) were applied repeatedly (1/3 Hz) to forebrain sites and peristimulus time histograms (PSTHs) were accumulated over 100–200 stimulus trials to reveal excitatory or inhibitory modulation of NST neuronal activity. Once such a connection was confirmed, electrical stimulus trains (100 Hz, 0.2 ms, at ×0.9 orthodromic threshold) were applied for 15 s before and during taste stimulation trials to determine the effects of descending modulation on taste-evoked activity. Stimulation of the forebrain was also done using DL-homocysteic acid (DLH) to limit stimulation to neuronal somata and not fibers of passage. Taste stimuli were 32 mM sucrose (S), 32 mM NaCl (N), 3.2 mM citric acid (C) and 32 mM quinine hydrochloride (Q), applied to the anterior tongue. Each NST cell was classified as S-, N-, C- or Q-best on the basis of its response to these stimuli.

Insular cortex

In an initial experiment (Smith and Li, 2000), we used multi-barrel glass micropipettes to record the activity of NST neurons extracellularly and to apply the $GABA_A$ antagonist bicuculline methiodide (BICM) into the vicinity of the cell. The ipsilateral IC was stimulated both electrically (0.5 mA, 100 Hz, 0.2 ms) and chemically (10 mM DLH) while the spontaneous activity of each NST cell was recorded. The baseline activity of 17 of 50 cells (34%) was modulated by cortical stimulation: eight cells were inhibited and nine were excited. BICM microinjected into the NST blocked the cortical-induced inhibition. Although the excitatory effects were distributed across S-, N- and C-best neurons, the inhibitory effects of cortical stimulation were significantly more common in N-best cells. These data suggest that corticofugal input to the NST may differentially inhibit gustatory afferent activity through GABAergic mechanisms. A more recent experiment, in which we implanted electrodes in the IC bilaterally, has demonstrated a slightly greater influence from the contralateral than the ipsilateral IC on NST taste cells: 16 of 50 cells (32%) were modulated ipsilaterally, whereas 20 of 50 (40%) responded to contralateral stimulation. Eleven of these neurons received converging modulation from both sides of the cortex: three were excited and eight inhibited bilaterally.

Lateral hypothalamus

Stimulation of the LH produces increases in food intake and alterations in taste preference behavior, whereas damage to this area has opposite effects. Bipolar stimulating electrodes were bilaterally implanted in the LH and the responses of 99 neurons in the NST, which were first characterized for their taste sensitivities, were tested for their response to both ipsilateral and contralateral LH stimulation (Cho *et al.*, 2002b). Half of the taste-responsive cells in the NST (49/99) were modulated by LH stimulation. Contralateral stimulation was more often effective (41 cells) than ipsilateral (13 cells) and always excitatory; 10 cells were excited bilaterally. Six cells were inhibited by ipsilateral stimulation. A subset of these cells (n = 13) was examined for the effects of microinjection of DLH into the LH. The effects of electrical stimulation were completely mimicked by DLH, indicating that cell somata in and around the LH are responsible for these effects. Other cells (n = 14) were tested for the effects of electrical stimulation of the LH on the responses to stimulation of the tongue with standard tastants (S, N, C and Q). Responses to taste stimuli were more than doubled by the excitatory influence of the LH, with no alteration of spontaneous activity. These effects would enhance taste discriminability by increasing the signal-to-noise ratio of taste-evoked activity. Thus, in addition to its role in feeding and metabolism, the LH exerts descending control over the processing of gustatory information through the brainstem. Specifically, when the LH is active, neurons of the NST may be capable of finer taste discriminations.

Central nucleus of the amygdala

The CeA contains neurons that respond differentially to hedonically positive and negative taste stimuli and both the CeA and basolateral amygdala are involved in conditioned taste aversion learning. Extracellular action potentials were recorded from 109 taste-responsive cells in the NST and analyzed for a change in excitability following electrical and chemical stimulation of the CeA (Li *et al.*, 2002). An

orthodromic excitatory response was observed in 33 of 109 taste-responsive cells (30.3%). An initial decrease in excitability, suggestive of post-synaptic inhibition, was observed in three of the 109 cells (2.7%). Many of these neurons were under the influence of the contralateral CeA (28/36 = 77.8%) as well as the ipsilateral (22/36 = 61.1%); 14 (38.9%) were excited bilaterally. Latencies for excitation were longer following ipsilateral than after contralateral CeA stimulation. Microinjection of DLH into the CeA mimicked the effect of electrical stimulation on each of the nine cells tested: DLH excited eight and inhibited one of these electrically activated NST cells. Application of subthreshold electrical stimulation to the CeA during taste trials enhanced the taste responses of every CeA-responsive NST cell tested with this protocol. NST cells modulated by the CeA were significantly less responsive to taste stimuli than cells that were not. Given that local-circuit neurons in the NST are less responsive to taste stimuli than cells that project to the PbN (Cho *et al.*, 2002a), this finding suggests that the CeA may preferentially target neurons involved in brainstem motor pathways, as may occur following taste aversion learning. In another study (Cho *et al.*, 2003), electrodes were implanted bilaterally in both the LH and CeA and 113/215 cells (52.6%) were modulated by either one or both of these forebrain sites. The LH and CeA both altered the responses of 52 of these cells, showing that these sites produce converging modulation of medullary taste neurons.

Bed nucleus of the stria terminalis

We examined the influence of electrical stimulation of the BST on NST taste cell activity. Stimulating electrodes were stereotaxically implanted into the BST bilaterally and extracellular single-unit activity was recorded from the NST. When a taste-responsive NST neuron was isolated, its gustatory response profile was determined and rectangular pulses (0.5 ms, 0.1 mA, 1/3 Hz) were delivered to the BST on each side. Electrical stimulation of the ipsilateral BST inhibited the activity of 29 of 121 NST taste cells (24.0%); two were excited. Stimulation of the contralateral BST inhibited 14 neurons and excited six. Seven cells were inhibited bilaterally and two were excited by contralateral stimulation and inhibited by ipsilateral. In all, 43 of 121 NST cells (35.5%) were modulated by stimulation of the BST. These results demonstrated that most of the BST influence on NST taste cells was inhibitory. This inhibition, like the excitation produced by LH and CeA stimulation, was distributed across all cell types in the NST (S-, N-, C- and Q-best).

Conclusions

This series of experiments demonstrates extensive centrifugal modulation of brainstem gustatory activity. Essentially every forebrain target of the gustatory system, including the IC, LH, CeA and BST, plays a descending modulatory role in the processing of taste information. The LH and CeA have predominantly an excitatory effect, whereas the IC and particularly the BST produce significant inhibiton of medullary taste responses. This extensive neural substrate no doubt underlies the modulation of taste activity by physiological and experiential factors. Further research should be directed toward determining how these pathways are engaged by alterations in blood glucose, gastric distension, conditioned taste aversion learning and other physiological conditions known to alter taste sensitivity.

References

Allen, G.V., Saper, C.B., Hurley, K.M. and **Cechetto, D.F.** (1991) *Organization of visceral and limbic connections in the insular cortex of the rat.* J. Comp. Neurol., 311, 1–23.

Beckstead, R.M. and **Norgren, R.** (1979) *An autoradiographic examination of the central distribution of the trigeminal, facial, glossopharyngeal, and vagal nerves in the monkey.* J. Comp. Neurol., 184, 455–472.

Cho, Y.K., Li, C.-S. and **Smith, D.V.** (2002a) *Gustatory projections from the nucleus of the solitary tract to the parabrachial nuclei in the hamster.* Chem. Senses, 27, 81–90.

Cho, Y.K., Li, C.-S. and **Smith, D.V.** (2002b) *Taste responses of neurons of the hamster solitary nucleus are enhanced by lateral hypothalamic stimulation.* J. Neurophysiol., 87, 1981–1992.

Cho, Y.K., Li, C.-S. and **Smith, D.V.** (2003) *Descending influences from the lateral hypothalamus and amygdala converge onto medullary taste neurons.* Chem. Senses, 28, 155–171.

Halsell, C.B. (1992) *Organization of parabrachial nucleus efferents to the thalamus and amygdala in the golden hamster.* J. Comp. Neurol., 317, 57–78.

Halsell, C.B. (1998) *Differential distribution of amygdaloid input across rostral solitary nucleus subdivisions in rat.* Ann. N. Y. Acad. Sci., 855, 482–485.

Li, C.-S., Cho, Y.K. and **Smith, D.V.** (2002) *Taste responses of neurons in the hamster solitary nucleus are modulated by the central nucleus of the amygdala.* J. Neurophysiol., 88, 2979–2992.

Norgren, R. (1976) *Taste pathways to hypothalamus and amygdala.* J. Comp. Neurol., 166, 17–30.

Norgren, R. (1978) *Projections from the nucleus of the solitary tract in the rat.* Neuroscience, 3, 207–218.

Saper, C.B. and **Loewy, A.D.** (1980) *Efferent connections of the parabrachial nucleus in the rat.* Brain Res., 197, 291–317.

Smith, D.V. and **Li, C.-S.** (2000) *GABA-mediated corticofugal inhibition of taste-responsive neurons in the nucleus of the solitary tract.* Brain Res., 858, 408–415.

van der Kooy, D., Koda, L.Y., McGinty, J.F., Gerfen, C.R. and **Bloom, F.E.** (1984) *The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in rat.* J. Comp. Neurol., 224, 1–24.