Modulation of Parabrachial Taste Neurons by Electrical and Chemical Stimulation of the Lateral Hypothalamus and Amygdala

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The sensation of taste originating from receptors distributed on the tongue and oral cavity of rodents is first carried to the rostral portion of the nucleus of the solitary tract (NST) by parabrachial (PbN) and NST (Allen et al. 1991; Halsell 1998; van der Kooy et al. 1984).

The PbN processes taste information on its way to these forebrain gustatory areas (Norgren and Pfaffmann 1975; Van Buskirk and Smith 1981) and, along with the NST, also plays an important role in other visceral afferent modalities (Cechetto 1987; Fulwiler and Saper 1984). In neurons of the PbN, there is an increase in the degree of gustatory/mechanical and gustatory/visceral convergence compared with cells in the NST (Hermann and Rogers 1985; Hermann et al. 1983; Travers 1993). One might thus predict that physiological changes (e.g., fluctuations in blood glucose levels or salt balance), which are known to modulate taste responsiveness in the NST (Giza and Scott 1983; Jacobs et al. 1988), might also influence gustatory responses in the PbN. Conditioned taste aversion (CTA) requires multi-stage cooperation among gustatory and viscero- somory inputs and mechanisms of learning and memory in the CNS. The PbN plays an important role in the acquisition and retention of CTA (Grigson et al. 1997), and it is likely that descending inputs from forebrain gustatory targets are important in this processing (Hatfield et al. 1992; Schwartz and Teitelbaum 1974; Tokita et al. 2004).

The LH and CeA are involved in feeding and autonomic regulation (Bray 1985; Clark et al. 1991; Lenard and Hahn 1982; Murzi et al. 1986; Yan and Scott 1996). The LH is one of the forebrain targets of the PbN, and neurons in this area respond to gustatory stimulation (Norgren 1970; Yamamoto et al. 1982). Descending projections from the LH target both the PbN and NST (Moga et al. 1990; van der Kooy et al. 1984). There is physiological evidence that descending projections from the LH influence taste-responsive cells in the rat PbN (Lundy and Norgren 2004) and the hamster NST (Cho et al. 2002b, 2003). Another major forebrain target of the PbN is the CeA (Norgren 1976), which also sends centrifugal axons to the PbN and NST (Hopkins and Holstege 1978; Veening et al. 1984). There are electrophysiological studies demonstrating taste-responsive neurons in the CeA (Nishijo et al. 1998) and activation of Fos in the CeA by gustatory stimulation (Yamamoto et al. 1997). Stimulation of the CeA can modulate both rat PbN (Lundy and Norgren 2001, 2004) and hamster NST (Cho et al. 2003; Li et al. 2002) gustatory activity.

Even though there are reciprocal relationships between the PbN and both the LH and CeA, little is known about the details of this relationship. PbN cells in the rat have been shown to receive some convergent input from the LH and CeA (Lundy...
and Norgren 2004), but whether single PbN taste cells project to both the LH and CeA has not been investigated. Previous studies in hamsters have shown convergent modulation from LH and CeA of taste-responsive cells in the NST (Cho et al. 2003). There is also no information about the proportion of PbN neurons projecting to these areas relative to those sending centrifugal axons back to the PbN. For example, stimulation of the CeA antidromically activated 12 of 19 taste-responsive PbN neurons in the rat (Norgren 1976), although recent reports on orthodromic activation of the PbN by the CeA and LH (Lundy and Norgren 2001, 2004) do not report antidromically activated neurons. The present studies were designed to investigate the hypothesis that individual PbN taste cells can project to both the LH and CeA and that descending inputs from these areas modulate taste information processing in the hamster PbN.

A portion of these results was presented at the 2002 meeting of the Society for Neuroscience.

METHODS

Animal and surgery

The experimental procedures were conducted so as to minimize animal suffering and the number of animals used in accordance with the Institutional Animal Care and Use Committee and National Institutes of Health guidelines. Young adult male Syrian golden hamsters (Mesocricetus auratus), weighing between 125 and 178 g (n = 68), were deeply anesthetized with urethane (1.7 g/kg ip), and additional anesthetic (10% of original dose) was given as needed during the course of each experiment. The animal was tracheotomized and mounted in a stereotaxic instrument (Narishige SR-6N) using blunt earbars with the incisor bar at the same level as the interaural line. The tissue overlying the parietal bone was removed, and two holes were drilled on one side of the skull to access the LH and CeA. A concentric bipolar stimulating electrode, constructed from 26-gauge stainless steel tubing and 140-μm-thick stainless steel wire, was placed into the LH (1.8 mm lateral to the midline, 0.54 mm posterior to bregma, and 7 mm ventral to the surface of the brain) and CeA (3.9 mm lateral to the midline, 0.57 mm posterior to bregma, and 5.4 mm ventral to the brain surface) on one side of the brain and secured with dental cement. The electrodes, except for the tip area, were insulated with Epoxylite 6001 (Epoxytite, Irvine, CA).

After positioning the stimulating electrodes into the LH and CeA, the animal was mounted in a nontraumatic head holder (Erickson 1966) with the snout angled downward 27° from horizontal to straighten the brain stem and minimize brain movement associated with breathing (Van Buskirk and Smith 1981). An incision was made along the midline overlying the posterior skull and soft tissue, including muscles covering the occipital bone, was excised to expose the interparietal and occipital bones. A portion of the occipital bone and the underlying dura were removed to reveal the cerebellum. A portion of the cerebellum was aspirated for 5–6 mm anterior to the obex, allowing direct access to the PbN. Body temperature was monitored and maintained at 37 ± 1°C with an electric heating pad.

Single-unit recording and electrical stimulation

Single-barrel glass micropipettes (tip diameter = 2 μm, resistance = 7–10 MΩ) filled with 2% (wt/vol) solution of Chicago Sky Blue dye in 0.5 M sodium acetate were used for extracellular single-unit recording of action potentials from the gustatory PbN. The mean coordinates for the PbN recording were 4.0 ± 0.11 (SD) mm anterior to obex and 2.1 ± 0.07 mm lateral to the midline. Extracellular action potentials were amplified with a band-pass of 16–3,000 Hz (NeuroLog, Digitimer, Hertfordshire, UK), discriminated with a dual time-amplitude window discriminator (Bak DDIS-1, Bak Electronics, Germantown, MD), displayed on oscilloscopes, and monitored with an audio monitor. A Dell Pentium computer configured with a CED 1401-plus interface board and Spike2 software (Cambridge Electronic Design, Cambridge, UK) controlled taste stimulus delivery and online data acquisition and analysis. The taste responses of the PbN cells were initially identified by a change in neural activity associated with the application of anodal current pulses (50 μA, 0.5 s, 1/3 Hz) to the anterior tongue (Li and Smith 1997) and confirmed by responses to chemical stimulation of the tongue. Taste stimuli presented to the anterior tongue were: 0.032 M sucrose, 0.032 M sodium chloride (NaCl), 0.032 M quinine hydrochloride (QHCl), and 0.0032 M citric acid. These concentrations evoke approximately equal multiunit taste responses in the hamster NST (Duncan and Smith 1992). These tastants were delivered by a gravity-flow system composed of a two-way solenoid-operated valve connected via tubing to a distilled-water rinse reservoir and a stimulus funnel. The taste trial, during which the computer acquired data, was a continuous flow initiated by the delivery of 5 s of distilled water, followed by 10 s of stimulus, followed by 5 s of distilled-water rinse. The flow rate was 2 ml/s. After each taste trial, the tongue was rinsed with distilled water (>50 ml), and individual stimulations were separated by ≥2 min to avoid adaptation effects (Smith and Bealer 1976).

After each PbN neuron was characterized for its taste responsiveness, rectangular pulses (0.5 ms, ≤0.1 mA, 1/3 Hz) were delivered to the LH and CeA through each bipolar stimulating electrode from an isolated stimulator (Grass S88, Grass Instruments, Quincy, MA) to examine the effect of electrical stimulation of the forebrain on activity of the PbN cell. The criteria for antidromic activation were constant latency and the ability to follow a stimulus pulse pair at >200 Hz. For spontaneously active neurons, an additional collision test was applied between a spontaneous action potential and stimulus-evoked potential. For each PbN taste cell, a peristimulus time histogram (PSTH) was created from data acquired in response to 50–200 LH or CeA stimulus pulses.

To observe the influence of electrical stimulation of the LH and CeA on the responses of PbN cells to taste stimuli, taste responses of a subset of PbN neurons that were activated orthodromically from the LH and CeA were tested before and during trains of constant square pulses (100 Hz, 0.2 ms) to the LH and CeA. Typically, all four tastants were presented alone, and then the two most effective stimuli for each cell were repeated during stimulation of the LH and CeA. The electrical stimulation started at the beginning of each taste trial (i.e., 5 s prior to taste stimulus delivery) and lasted for 15 s. To prevent LH- or CeA-evoked spikes from contributing to the taste responses, the intensity of the forebrain stimulation was adjusted to 90% of the minimum intensity that would orthodromically activate the PbN cell using single pulses at 1/3 Hz. That is, train stimulation of the LH and CeA did not produce direct orthodromic action potentials in any PbN cell (see RESULTS). Stimulus artifacts during the pulse train were eliminated from the recorded data using the window discriminator.

Pharmacology and microinjections

To examine the effect of chemical stimulation of the LH and CeA on the spontaneous activity of taste-responsive PbN cells, ~50 nl of 10 mM dl-homocysteic acid (DLH; Aldrich Chemical, Milwaukee, WI) in buffered physiological saline (pH = 7.4) was microinjected into the LH and CeA. DLH is an excitatory amino acid analogue that presumably excites neuronal somata but not fibers of passage (Goodchild et al. 1982; Yang and Coote 1998). Microinjections were made using a double-barrel glass pipette glued to the stimulating electrode implanted in the LH and CeA (pipette tip = 35-μm diameter, 0.2 mm above the inner wire of the stimulating electrode). Pressure pulses (30 psi, 10 ms) from a Picospritzer II (General Valve, Fairfield, NJ) were used to trigger the microinjections.

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Histology

At the end of each experiment, the last recording site of the day was marked by passing a 10-μA cathodal current through the recording electrode for 10 min (5 s on-off) to deposit a spot of Chicago Blue dye. The stimulation sites in the LH and CeA were marked by passing 10-μA anodal current through the inner wire of the stimulating electrodes for 20–30 s to deposit a spot of iron. The hamster was then given an overdose of urethan and perfused through the heart with physiological saline followed by 4% formalin containing 3% potassium ferrocyanide and ferricyanide. The brain was removed and fixed; frozen sections (40 μm) were cut in the coronal plane and stained with Neutral Red. The recording and stimulating sites were located microscopically and plotted on standard hamster atlas sections (Morin and Wood 2001).

Data analysis

Action potentials in response to taste stimulation of the anterior tongue were accumulated over three consecutive time periods: 5 s of prestimulus water rinse, 10 s of stimulus flow, and 5 s of poststimulus water rinse. The net response was calculated as the mean number of action potentials (imp/s) during the first 5 s of chemical stimulation minus the number during the 5-s prestimulus water rinse (Vogt and Smith 1993). Responses are reported as means ± SE. For orthodromic responses of PbN cells to electrical stimulation of the LH and CeA, individual PSTHs were analyzed to determine excitatory or inhibitory epochs. A baseline period was defined as the 200 ms preceding stimulation; the mean ± SD of the number of spikes/1-ms bin during this baseline period was determined. An excitatory effect of forebrain stimulation was defined as an epoch of at least five consecutive bins with a mean value ≥2 SD above the baseline mean. Using a 5-ms window allowed us to clearly identify the very short-duration responses (see following text) as well as those of longer duration; a mean response ≥2 SD above background occurs with a probability <0.05. Inhibitory responses were defined as ≥20 consecutive bins with a mean <50% of baseline firing rate. Because of the slow rates of spontaneous firing of many PbN cells and their asynchronous discharge patterns, a criterion for inhibition based on variance is not practical; using 20 bins defines the inhibitory epoch as a relatively sustained decrease in firing rate. For statistical comparison of the effects of DLH on the responses of PbN cells, mean firing rates were compared over a 1-min period before and after DLH microinjection. For each PbN taste neuron that was antidromically activated after LH and/or CeA stimulation, the antidromic latency and threshold of antidromic activation were determined. The threshold of activation was defined as the lowest stimulus intensity that would produce antidromic action potentials on five consecutive trials.

Differences in mean firing rates between neurons responsive to LH and/or CeA stimulation and those that were nonresponsive to forebrain stimulation and differences in responses to the four taste stimuli were compared using ANOVA. The effect of DLH (or saline) on spontaneous activity, the effect of electrical stimulation on the mean firing rate to taste stimuli, and the differences in excitatory latency of LH and CeA stimulation were compared using t-tests. The numbers of LH- and CeA-responsive neurons following electrical stimulation and the distribution of excitatory and inhibitory responses across cell types were compared with the χ² test.

The entropy (H) of each neuron, which is a measure of its breadth of responsiveness across the four taste stimuli, was calculated by the following formula

\[ H = -1.661 \sum_i p_i \log_2 p_i \]

where \( H \) = breadth of responsiveness, 1.661 is a scaling constant, and \( p_i \) is the proportional response to each of the \( n \) compounds. \( H \) ranges from 0.0 for a cell that responds exclusively to one stimulus to 1.0 for a cell responding equally to all four (Smith and Travers 1979).

RESULTS

Histology

A total of 101 taste-responsive PbN cells were recorded from 68 hamsters; no cells were included that did not respond to taste stimulation. Sixty-eight recording sites and all stimulating sites were identified histologically and representative examples are shown in Fig. 1. Two iron deposits from the tips of the stimulating electrodes are located in this coronal section of the hamster brain (Fig. 1A). One is located in the LH, medial to the optic tract and lateral to the fornix (f) at the level of the ventromedial hypothalamic nucleus (VMH). The other iron deposit can be found in the center of the CeA, within the capsular portion (CeC) of the nucleus. A recording site in the PbN is shown in Fig. 1B. On this coronal section through the hamsterpons, a Chicago Blue dye mark is located in the medial PbN (MPB), medial to the superior cerebellar peduncle (scp), dorsal and lateral to the mesencephalic trigeminal nucleus (Me5) at the level where the locus coeruleus (LC) is most evident.

All recording and stimulating sites from 68 hamsters were reconstructed on standard atlas sections of the hamster brain (Morin and Wood 2001), shown in Fig. 2. The areas encompassing the effective stimulating sites in the LH and CeA are shown schematically in a midlevel section in Fig. 2A (same

FIG. 1. Photomicrographs of stimulating and recording sites in the hamster brain. A: coronal section through the ventral forebrain, stained with Neutral Red, showing the positions of the tips of the stimulating electrodes. Iron deposits and tissue damage indicate electrode placements within the central nucleus of the amygdala (CeA), specifically within its capsular portion (CeC), and in the lateral hypothalamus (LH). B: coronal section through the pons showing a recording site in the medial parabrachial nucleus (MPB), marked with Chicago Blue dye (arrow), BLA, basolateral amygdalar nucleus, anterior; CeM, central amygdalar nucleus, medial; f, fornix; ic, internal capsule; LC, locus coeruleus; Me5, mesencephalic 5 nucleus; MPB, medial parabrachial nucleus; ot, optic tract; scp, superior cerebellar peduncle; VMH, ventromedial hypothalamic nucleus. Calibration bar = 500 μm.
level as D), and individual electrode placements are depicted in Fig. 2, C–E, arranged from rostral (C) to caudal (E). Filled circles show placements that produced antidromic responses in PbN taste cells, half-filled circles indicate sites that induced excitatory responses, and open circles show electrode placements that produced inhibitory responses in gustatory cells of the PbN (cells that were both antidromically and orthodromically activated are indicated by filled circles). Open triangles indi-

FIG. 2. Standard atlas sections of the hamster brain (adapted from Morin and Wood 2001), showing the distribution of stimulating and recording sites for the 68 experimental animals. A: section through the diencephalon at the level of the anterior hypothalamus (same level as in D), showing the composite distribution of effective stimulating sites in the ipsilateral LH and CeA. B: distribution of 68 parabrachial nucleus (PbN) recording sites in the pons at the level of the motor trigeminal nucleus (Mo5), showing the location of the last PbN cell recorded from each animal. C–E: successive sections through the LH and CeA, from the most rostral electrode placements (C) to the most caudal (E). Sites producing antidromic, purely excitatory, purely inhibitory, or no effect on PbN neurons are indicated by different symbols; a subset of the antidromic sites also produced orthodromic activation (see text). 4V, fourth ventricle; 7n, facial nerve; ACo, anterior cortical amygdalar nucleus; AH, anterior hypothalamus; CeC, central amygdalar nucleus, capsular; CGPn, central gray of pons; DMTg, dorsomedial tegmental area; GP, globus pallidus; mt, mammillothalamic tract; LH, lateral hypothalamic area; LPBC, LPBE, LPBV, lateral parabrachial nucleus, central, external and ventral; mcp, middle cerebellar peduncle; MeAD and MeAV, medial amygdalar nucleus, anterodorsal and anteroventral; MGP, medial globus pallidus; ml, medial lemniscus; Mo5, motor trigeminal nucleus; MVe, medial vestibular nucleus; Pr5, principal sensory trigeminal nucleus; RMg, raphe magnus nucleus; s5, sensory root of trigeminal nerve; SCN, suprachiasmatic nucleus; SO, superior olive; ZIM, zona incerta, medial. Calibration bar = 1 mm in A, 500 μm in B–E.
cate stimulating sites that produced no effect on the recorded PbN neurons. It should be noted that these noneffective sites do not imply that these areas do not interact with the PbN but only that no PbN cells were recorded in these particular preparations that responded to forebrain stimulation. The tips of the stimulating electrodes in the 68 hamsters included in this study were confined to the LH or CeA. The stimulating sites in the LH were distributed in the area medial to the optic tract, lateral to the fornix and ventral and medial to the medial globus pallidus (MGP), from the level of the anterior hypothalamus rostrally to the appearance of the ventromedial hypothalamus (VMH) caudally. The CeA sites were concentrated in the more dorsal and middle regions of the CeC (Fig. 2), and they were distributed from the level of the first appearance of the medial amygdalar nucleus (MeAD) rostrally to the rostral tip of the VMH caudally. The location of the last PbN cell to be recorded in each animal was marked with Chicago Blue dye (as in Fig. 1B) and the positions of these cells (n = 68) are depicted in Fig. 2B on a standard atlas section of the pons at the level of the mesencephalic trigeminal nucleus (Me5). The recording sites are concentrated in the medial PbN (MPB) between the level at which LC is first apparent to the appearance of the accessory trigeminal nucleus.

Taste responsiveness of PbN neurons

The response characteristics of hamster PbN neurons has been previously described by this laboratory (Van Buskirk and Smith 1981), although in that experiment the stimulus concentrations were not equated for their overall effectiveness as in the present study. The spontaneous activity of the 101 taste-responsive PbN cells in the present experiment ranged from 0.05 to 17.2 imp/s with a mean of 3.92 ± 0.38 imp/s. This mean firing rate was significantly higher than that recorded in the NST in our previous experiments (e.g., 2.12 ± 0.27 imp/s) (Li et al. 2002) and slightly less than we reported previously for hamster PbN neurons (6.32 imp/s) (Van Buskirk and Smith 1981). Eighty-three of these neurons were antidromically activated from either the LH or CeA or both (see following text). There were no significant differences in spontaneous firing rate between cells that project to the LH and/or CeA (range = 0.15–6.7 imp/s, mean = 3.9 ± 0.38 imp/s) and nonprojection neurons (range = 0.05–17.2 imp/s, mean = 4.12 ± 1.18 imp/s; t = −0.238, df = 99, P = 0.812).

Each of the 101 PbN cells was tested for its responsiveness to the four basic taste stimuli and categorized as sucrose-, NaCl-, citric-acid-, or QHCl-best on the basis of its response profile. Taste responses are shown in Fig. 3, where the responses of the cells in each best-stimulus group are arranged along the abscissa in order of their response to the best stimulus for that group. The response to any one tantant is read across the pattern and that of any one neuron can be seen from top to bottom; responses to the stimuli are net responses (minus spontaneous activity; mean spontaneous activity of each cell is shown as distilled H2O at the bottom of the figure). Of the 101 neurons, 12 were sucrose-best (left), 35 were NaCl-best, 15 were citric acid-best, and 39 were QHCl-best (right). Ninety-six of these neurons were influenced by LH and/or CeA stimulation, either antidromically or orthodromically (see following text); the five neurons not influenced by the forebrain are shaded gray in Fig. 3. The responses of those cells excited by LH and/or CeA stimulation (see following text) are indicated in hatched fill in Fig. 3 and those inhibited by forebrain stimulation are shown in solid fill; some of these orthodromically activated neurons were also antidromically activated (see Table 1).

The breadth of responsiveness of each of these 101 neurons to four basic taste stimuli was calculated using the equation for entropy (Smith and Travers 1979). At these relatively equally effective stimulus concentrations, sucrose-best cells were the most narrowly tuned (H = 0.51 ± 0.09), followed by NaCl-best cells (H = 0.67 ± 0.04), and then by citric acid-best cells (H = 0.76 ± 0.03). QHCl-best cells were the most broadly tuned cell group (H = 0.78 ± 0.03). The differences in entropy among these groups were statistically significant [F(3,97) = 4.747, P < 0.05].

Antidromic activation of PbN cells

All 101 taste-responsive PbN cells were tested with electrical stimulation of the ipsilateral LH and CeA. Eighty-three of these neurons were activated antidromically by stimulation of the LH (n = 80) or CeA (n = 60); 57 of these were activated by both forebrain sites. The responses of two such neurons (A and B) are depicted in Fig. 4, which demonstrates fulfillment of the criteria for antidromic invasion from both the LH and the CeA. The superimposed oscilloscope traces (n > 3) show that evoked spikes occurred at constant latency after stimulation (†, top), followed closely paired stimulus pulses ( †, middle), and were cancelled (▲, bottom) by collision with spontaneously generated action potentials (*). For the cell in A, latencies for antidromic invasion were shorter after LH stimulation (2.0 ms) than after stimulation of the CeA (2.7 ms), whereas for the cell in B, the latencies were longer after LH (3.5 ms) than following CeA stimulation (2.4 ms). The taste responses for each cell to each of the four stimuli are shown below the oscilloscope traces.

The antidromic latencies after LH and CeA stimulation varied between 1.1–6.7 and 1.2–12.1 ms, and the mean latencies were 2.59 ± 0.13 (n = 80) and 4.73 ± 0.38 (SE) ms (n = 60), respectively. Antidromic latencies were significantly longer after CeA stimulation than after LH stimulation (Mann-Whitney U, U = 1,132, P < 0.001). Of the 57 PbN cells that were antidromically activated by both LH and CeA stimulation, the antidromic latencies of 47 cells were longer after CeA stimulation than those after LH stimulation. The remaining 10 cells showed longer latencies after LH stimulation. The thresholds for antidromic activation of PbN cells after LH and CeA stimulation ranged, respectively, from 11 to 98 and 12 to 100 μA, with mean thresholds of 50.4 ± 2.9 and 60.9 ± 3.2 μA.

Orthodromic activation of PbN cells

Orthodromic responses were seen in 34 PbN neurons after stimulation of the LH (n = 14) or the CeA (n = 26); 6 cells were orthodromically activated by both sites. PSTHs of the responses of several PbN cells after single-pulse LH and CeA stimulation are shown in Fig. 5, which depicts the temporal patterns of response observed. The responses of three cells after LH stimulation are shown in Fig. 5, A–C, and three others after CeA stimulation in D–F. Single-pulse stimulation produced short bursts of excitation (Fig. 5, A and B) or longer
duration excitation (Fig. 5D), sometimes followed by a period of inhibition (Fig. 5E). Electrical stimulation of the LH or CeA sometimes produced inhibition of PbN neuronal activity (Fig. 5, C and F). The distributions of evoked excitatory spikes after LH and CeA stimulation were spread over 4- to 10- and 4- to 34-ms periods, respectively. The spread of evoked excitatory spikes was narrower after LH stimulation than after CeA stimulation; the spikes were distributed over a 4- to 5-ms period in 4 of 5 cells after LH stimulation (as in Fig. 5, A and B), whereas the excitatory potentials were spread over more than a 10-ms period in 7 of 12 cells after CeA stimulation (as in Fig. 5D). As we reported in our previous study of NST taste cells (Li et al. 2002), some neurons show longer duration excitation, with duration ranges from 16 to 34 ms (Fig. 5D). Five PbN cells showed this more prolonged excitability (mean = 25.4 ± 2.9 ms), all after CeA stimulation. In three cells, short-duration excitatory responses were followed by a period of inhibition after CeA stimulation—one such cell is shown in Fig. 5E. Over all the cells, 15 were excited by forebrain stimulation—LH stimulation produced 5 excitatory responses and CeA stimulation 12; 2 cells were excited by both sites. The latencies of excitatory orthodromic responses after LH or CeA stimulation ranged from 6 to 37 and 7 to 20 ms, with mean latencies of 17.3 ± 4.2 and 13.3 ± 1.3 ms, respectively.

Inhibitory responses to forebrain stimulation (Fig. 5, E and F) were seen in 19 cells. LH stimulation produced 9 inhibitory responses, whereas stimulation of the CeA produced inhibition in 14 cells; 4 cells were inhibited by both LH and CeA stimulation. The duration of the silent period in spontaneous firing produced by electrical stimulation of the LH and CeA ranged from 69 to 102 and 61 to 135 ms, respectively. In these cells, no enhancement of excitability was ever observed.

Summary of electrical stimulation effects
The results of electrical stimulation of the LH and CeA on the 101 PbN neurons recorded in this study are summarized in...
Table 1. Numbers of PbN neurons that were antidromically and/or orthodromically activated by LH and CeA stimulation

<table>
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<th>Effect</th>
<th>No. of Cells</th>
<th>Total No. of Cells</th>
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<tr>
<td>Antidromic</td>
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<tr>
<td>Antidromic (LH and CeA)</td>
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<tr>
<td>Antidromic (LH), Inhibitory (CeA)</td>
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<td>Excitatory only</td>
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<td>Excitatory (LH), No effect (CeA)</td>
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<td>5</td>
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<tr>
<td>No effect (LH or CeA)</td>
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</table>

Total number of cells was 101. PbN, parabrachial nucleus; LH, lateral hypothalamus; CeA, central nucleus of the amygdala.

Table 1. In this table are indicated the numbers of cells antidromically activated, excited, inhibited or not affected by LH and/or CeA stimulation. Fifty-seven PbN neurons were antidromically activated by both the LH and CeA. Eighteen additional neurons that were antidromically activated by the LH were orthodromically driven by the CeA, whereas 3 cells that were antidromically driven by the CeA were orthodromically activated by the LH. Overall, 80 cells (79.2%) were activated antidromically by LH stimulation, whereas 14 cells (13.9%) exhibited orthodromic responses. After CeA stimulation, 60 cells (59.4%) were antidromically activated and 26 cells (25.8%) were driven orthodromically. Among the orthodromic responses, 5 cells (5.0%) were excited and 9 (8.9%) were inhibited by stimulation of the LH, whereas 12 cells (11.9%) were excited and 14 (13.9%) inhibited by CeA stimulation. Thirteen cells were either excited or inhibited, but not antidromically activated, by the LH and/or the CeA. Of the 34 neurons that were orthodromically activated, both the LH and CeA excited 2 and inhibited 4 (Table 1). There were no instances in which a cell was excited by one forebrain site and inhibited by another.

Effects of chemical stimulation of the LH and CeA on the activity of PbN neurons

The influence of DLH microinjection on spontaneous activity was tested in a subset of these taste-responsive PbN cells. DLH is known to act on receptors located on dendritic and somatic membranes and not on fibers of passage (Goodchild et al., 1987).
This experiment was designed to demonstrate that orthodromic activation of PbN cells by electrical stimulation of the LH and CeA is attributable to cells in and around these nuclei and that the descending pathway from the CeA is not activated by stimulation of the LH. The effect of DLH on the spontaneous activity of PbN cells is shown in Fig. 6. For 10 PbN cells that were orthodromically excited by electrical stimulation of the LH or the CeA, DLH and physiological saline were micrionjected into the LH (n = 5) and CeA (n = 5) through double-barrel glass pipettes attached to the stimulating electrodes. Microinjections of DLH into the LH and CeA increased the ongoing spontaneous activity of these cells over 1–2 min, whereas microinjections of saline were without effect (Fig. 6, A and B). Microinjection of DLH into the LH and CeA significantly increased the spontaneous activity of cells tested following both LH (Fig. 6C, t = 10.130, df = 4, P < 0.001) and CeA injection (Fig. 6D, t = 11.813, df = 4, P < 0.001). Saline injection was without effect (LH: t = 0.157, df = 4, P = 0.883; CeA: t = 1.169, df = 4, P = 0.307).

We also tested whether microinjection of DLH decreased the spontaneous activity of PbN cells that received inhibitory inputs from these forebrain nuclei. For 10 PbN cells that were inhibited by stimulation of the LH or the CeA, DLH and physiological saline were micrionjected into these sites using the protocol described in the preceding text. The spontaneous activity of the PbN cell shown in Fig. 6E was depressed by single-pulse electrical stimulation of both forebrain areas, and microinjection of DLH into both the LH and CeA depressed ongoing activity of this neuron over 2–3 min, whereas saline was without effect. The mean inhibitory effect of DLH on spontaneous activity of PbN cells is shown in Fig. 6, F and G. DLH injection into the LH (Fig. 6F) produced significant inhibition (t = 4.075, df = 4, P = 0.05), whereas physiological saline did not (t = 1.1514, df = 4, P = 0.313). Microinjection of DLH into the CeA (Fig. 6G) also significantly reduced ongoing spontaneous activity for those PbN cells inhibited by electrical stimulation of the CeA (t = 3.599, df = 4, P < 0.05), whereas physiological saline injection was without effect (t = 1.447, df = 4, P = 0.222).

**Effects of electrical stimulation of the forebrain on taste-evoked responses**

In another subset of PbN neurons, we examined the influence of electrical stimulation of the LH and/or CeA on re-
sponses to taste stimulation of the anterior tongue. This experiment was conducted on 8 taste trials in five PbN cells and 10 taste trials in another five cells that received excitatory input from the LH and CeA, respectively. After confirming a cell’s response to single pulse stimulation, as shown in Fig. 5, a 15-s train of rectangular pulses (100 Hz, 0.2-ms duration) was delivered to the LH and CeA during taste-stimulation trials. To avoid any contribution of orthodromically activated spikes, the intensity of the current delivered to the LH and CeA was adjusted to 90% of the minimum current intensity necessary to elicit a response in each PbN cell at 1/3 Hz. At this stimulus intensity, electrical stimulation produced no orthodromic responses in PbN neurons.

Examples of the excitatory effects of electrical stimulation on two of these cells are shown in Fig. 7, A (LH stimulation) and B (CeA stimulation). The cell in Fig. 7A was most responsive to sucrose and its activity (imp/s) during each taste stimulus is shown in 1-s bins for a 5-s prestimulus period (□), the 10-s stimulus period (■), and the 1st 5 s of the poststimulus rinse (□). This cell responded also to NaCl. When the cell was tested again with NaCl (N + ES) and sucrose (S + ES) during train stimulation of the LH, its response to taste stimulation was increased by 160 and 180%, respectively. There was no enhancement during the 5-s prestimulus rinse (prior to taste stimulation), during which time the electrical train stimulation was also present. The cell in Fig. 7B responded to both citric acid and QHCl. When taste trials were repeated during train stimulation of the CeA, its response to QHCl (Q + ES) and citric acid (C + ES) increased by 280 and 184%, respectively.

The mean taste responses recorded from five PbN cells before and during train stimulation of the LH and CeA are shown in Fig. 7, E and F, respectively. Application of electrical stimulation to the LH while repeating the same taste trials more than doubled the net response to the taste stimuli ($t = 9.295$, df = 7, $P < 0.001$), whereas the baseline activity (during the prestimulus rinse) was not significantly different before and during LH stimulation ($t = 0.812$, df = 7, $P = 0.443$; Fig. 7E). The mean net response of five cells to 10 taste trials was also
significantly doubled by stimulation of the CeA (t = 7.264, df = 9, P < 0.005), whereas baseline activity was not significantly different before and during CeA stimulation (t = 1.604, df = 9, P = 0.143; Fig. 7F). The enhancement of taste responses by stimulation of the LH and CeA occurred in all cell types tested; no cell that was shown to be excited by single-pulse stimulation failed to show enhanced taste responses during forebrain stimulation. In every instance, train stimulation of the LH and CeA enhanced taste responses of PbN neurons that were excited by single-pulse stimulation; all taste responses tested in each cell were enhanced.

Taste responses were more frequently inhibited than excited by stimulation of the LH and CeA. Thirteen and 14 taste trials were tested in five PbN cells each for the effects of electrical train stimulation of the LH and CeA on taste responsiveness (Fig. 7, C, D, G, and H). Examples of the responses of two cells that were tested before and during stimulation of the LH and CeA are shown in Fig. 7, C and D, respectively. The cell in Fig. 7C responded best to QHCl and also responded to NaCl and citric acid. When taste trials were repeated during stimulation of the LH, the responses to NaCl, citric acid, and QHCl were all decreased by >40%. Electrical stimulation did not alter the cell’s activity during the prestimulus water rinse. The effects of electrical stimulation of the CeA on the responses of another PbN cell to taste stimulation are shown in Fig. 7D. This cell also responded best to QHCl and to NaCl and citric acid. The responses to QHCl, citric acid, and NaCl were decreased when the taste trials were repeated during stimulation of the CeA.

The mean responses of these taste trials before and during train stimulation of the LH and CeA are shown in Fig. 7, G and H, respectively. The mean net response of five cells to 14 taste trials before stimulation of the LH was 13.34 ± 2.16 imp/s. Application of electrical stimulation to the LH while repeating the same taste trials significantly decreased the net response (t = 4.714, df = 13, P < 0.001), whereas the baseline activity of the cells was not significantly different before and during LH stimulation (t = 0.313, df = 13, P = 0.759; Fig. 7G). The mean net response of five cells to 13 taste trials without electrical train stimulation of the CeA was 12.58 ± 1.94 imp/s. Repeating the taste trials while stimulating the CeA signifi-
cantly decreased the net response \((t = 5.778, \text{ df} = 12, P < 0.001)\), whereas the baseline activity of the cells was not significantly different before and during CeA stimulation \((t = 0.567, \text{ df} = 12, P = 0.580; \text{ Fig. 7H})\). The inhibition of taste responses induced by electrical train stimulation of the LH and CeA occurred in all best-stimulus cell types tested. In all instances, train stimulation of the LH and CeA decreased taste responses of PbN cells that were inhibited by single-pulse stimulation of the forebrain.

**Taste characteristics of neurons targeted by the forebrain**

Among the 101 PbN neurons recorded in the present experiment, 34 were orthodromically activated by stimulation of the LH and/or CeA (see Table 1). Eighty-three neurons were antidromically activated by the LH or CeA, and 26 of these also received excitatory or inhibitory modulation. A small group of five cells was not connected to these forebrain targets, either antidromically or orthodromically. The mean responses to the four taste stimuli in the subsets of cells that were excited \((n = 15)\) and inhibited \((n = 19)\) by the forebrain are shown in Fig. 8. Between these two groups of cells, taste responses were different in magnitude: cells that were inhibited by forebrain stimulation showed the greatest responses; forebrain-excited cells were less responsive to taste stimuli \([F(3,128) = 10.725, P < 0.01]\). The mean responses to the four taste stimuli were also significantly different from one another \([F(3,128) = 3.138, P < 0.05]\). There was a significant interaction between excited and inhibited cells and the four basic taste stimuli \([F(3,128) = 3.172, P < 0.05]\). Individual one-way ANOVAs showed that the responses to citric acid \([F(1,32) = 4.906, P < 0.05]\) and to QHCl \([F(1,32) = 8.056, P < 0.01]\) were significantly greater in neurons that were inhibited by forebrain stimulation. There were no significant differences in the responses to sucrose or NaCl between these groups. In addition, within the sucrose-best category, instances of excitation \((n = 6; \text{ in 5 cells})\) were much more frequent than inhibition \((n = 1); \text{ whereas within the citric-acid- and QHCl-best groups of cells, inhibition \((n = 11); \text{ in 10 cells})\) was much more frequent than excitation \((n = 2)\). This difference in the distribution of excitatory and inhibitory effects was statistically significant \((\chi^2 = 9.377, \text{ df} = 3, P < 0.05)\). Within the NaCl-best cells, these effects were evenly distributed.

**DISCUSSION**

**Projection of PbN gustatory neurons to the LH and CeA**

The present investigation has demonstrated that taste-responsive PbN neurons project heavily to both the LH and CeA and, in turn, are subject to modulatory influences from both of these forebrain targets. A number of anatomical studies have demonstrated reciprocal connections between the PbN and the LH and CeA. Labeled fiber terminals were seen in the LH and CeA of rats after injection of tritiated proline into the pontine gustatory area (Norgren 1976). Similar injections into the LH demonstrated ascending fiber terminals distributed to the PbN taste area (Hosoya and Matsushita 1981). Injection of WGA-HRP into the PbN resulted in both retrograde and anterograde label in the LH and CeA in hamsters (Halsell 1992) and rats (Moga et al. 1990). The majority of rat PbN cells responding to rapid or thermal stimuli applied to the tongue was antidromically activated by stimulation of the amygdala (Norgren 1976). Cells responding to gustatory stimuli have been recorded in awake rats from both the LH (Norgren 1970; Yamamoto et al. 1989) and the CeA (Nishijo et al. 1998). These data suggest that taste-responsive cells of the PbN project to both the LH and the CeA. In the present experiment, we found that >82% of PbN taste cells in the hamster were antidromically activated by one or both of these forebrain sites. Eighty PbN cells projected to the LH (79%) and 60 to the CeA (59%) with 57 of these distributing axons to both areas.

Anatomical studies have shown that tracer injections into the PbN label fibers that travel rostrally from the injected site via the ipsilateral central tegmental tract through the posterior LH, the zona incerta, and the internal capsule to the CeA (Norgren 1995). Thus axons traveling from the PbN to the CeA do not pass through the more anterior portions of the LH that were stimulated in the present experiments (see Figs. 1 and 2). Results from microinjection of DLH support this contention. In every instance in which DLH was injected into the LH (see Fig. 6), the results mimicked the orthodromic effects of electrical stimulation, showing that fibers of passage were not the source of the descending modulation evoked by stimulation of the LH. In addition, although the latencies for antidromic invasion in 57 PbN cells that projected to both the LH and CeA were longer in 47 cells after CeA stimulation than after LH stimulation, 10 cells showed the opposite. That result would not occur if the stimulated axons were simply passing through the LH. These results suggest that a subpopulation of PbN taste cells branch and send bifurcating collaterals to both the LH and CeA. Other studies have shown that PbN taste cells send collaterals to the thalamus and substantia innominata (Norgren 1974) and to both the thalamic taste area and the CeA (Hayama
and Ogawa 1987). Taken together, these results indicate that individual PbN taste cells often target two or more forebrain areas. However, because only some (57 of 83) PbN cells project to both areas, the nature of the gustatory information provided to the LH and to the CeA would likely be different.

Excitatory and inhibitory modulation of PbN neurons by descending pathways

Results of the present experiment show that a subset of taste-responsive cells in the PbN is subject to descending modulation by the LH and/or the CeA. Electrical stimulation of the LH and CeA orthodromically activated 14 and 26 of the 101 PbN taste cells, respectively, indicating that small subsets of PbN taste cells are under the modulatory influence of these forebrain areas. These descending inputs were often inhibitory. Among the 34 cells showing orthodromic responses, 9 of 14 and 14 of 26 PbN neurons were inhibited by electrical stimulation of the LH and CeA, respectively. There was no significant difference in the excitatory and inhibitory influence of these two forebrain areas. Most (82%) PbN neurons in the hamster were antidromically activated from the LH and/or CeA. Of these, 18 cells were antidromically activated by the LH and orthodromically driven by the CeA; an additional 3 cells were activated antidromically by the CeA and orthodromically by the LH (see Table 1). Thirteen other cells were modulated orthodromically but were not antidromically activated by either site. Overall, many more PbN cells project to the LH and/or CeA than receive descending input from these areas. However, it is possible that we could have seen more descending influence using a more robust stimulation protocol, i.e., single-pulse stimulation may not have been synaptically effective for some cells.

Recent studies of forebrain influences on rat PbN neurons produced somewhat similar results, although the proportions of cells modulated were quite different (Lundy and Norgren 2001, 2004). Electrical stimulation of the CeA orthodromically modulated the activity of >76% of neurons recorded from the rat PbN, and this modulation was also predominantly inhibitory (Lundy and Norgren 2001). In a more recent experiment, stimulating electrodes in IC, CeA and LH produced converging modulation of PbN gustatory neurons (Lundy and Norgren 2004), similar to what we report here for the LH and CeA. The proportion of rat PbN cells modulated by these forebrain areas was much higher than that reported in the present study although there were no antidromic responses reported in the rat (Lundy and Norgren 2001, 2004). These investigators used a more prolonged stimulus train, which may have been more synaptically effective, but may also have masked the occurrence of antidromic spikes. In previous experiments (Norgren 1976, 1978), antidromic responses to stimulation of both the CeA and LH were seen in the majority of rat PbN taste neurons, so the relative distribution of antidromically and orthodromically activated PbN neurons in rats is not presently clear. The vast majority of hamster PbN cells projected axons to the forebrain, whereas only a small proportion of cells were orthodromically activated by the LH and/or CeA.

Taste characteristics of PbN neurons

In the present study, we recorded the activity of 101 taste-responsive cells in the PbN, and these cells were relatively evenly divided into four groups based on their responses to sucrose, NaCl, citric acid, and QHCl. The smallest and most narrowly tuned group was the sucrose-best neurons (12 cells), which had an entropy value of 0.51. This group of cells responded predominantly to sucrose with most cells showing some response to NaCl. The largest and most broadly tuned group of cells was the QHCl-best neurons (39 cells), which had an entropy value of 0.78. These cells responded to most of the stimuli, including sucrose. The NaCl-best cells and the citric-acid-best cells were intermediate in their numbers and their breadth of responsiveness (see Fig. 3). Stimulus concentrations used in the present experiment are those that produce roughly equal responses in the hamster NST (Duncan and Smith 1992). As a consequence, there are many more QHCl-best neurons evident than when half-maximal stimulus concentrations are used (cf. Van Buskirk and Smith 1981). A lower QHCl concentration (i.e., 1 mM) would result in many of these QHCl-best neurons being classified as citric-acid-best or as NaCl-best. However, in our earlier study of hamster NST neurons, this stronger concentration of QHCl identified a subset of NST neurons with substantially and uniformly slower conduction velocities than all other neuron types (Cho et al. 2002a), suggesting a physiologically relevant classification based on this stronger concentration. Therefore using these equally effective stimulus concentrations appears to effectively identify four functional groups of both NST and PbN taste cells.

Forebrain modulation of taste responses

To investigate a direct influence of the LH and CeA on the gustatory activity of individual PbN neurons, we first confirmed which PbN cells received excitatory or inhibitory input using single-pulse stimulation of the LH and CeA and then applied electrical train stimulation before and during taste stimulation for subsets of these neurons. This approach demonstrated that in every instance taste responses of PbN neurons were modulated as predicted by the single-pulse effects on spontaneous activity. That is, the responses to taste stimulation of PbN cells that received excitatory input were increased, whereas when stimulation of the LH and CeA induced an inhibition of spontaneous activity, the responses to taste stimulation were decreased (Fig. 7). Train stimulation did not produce effects on baseline activity because its intensity was adjusted to 0.9 times orthodromic threshold. Although the excitatory or inhibitory effects within a single neuron were not restricted to a particular stimulus, there was a significant difference in the responsiveness of the cells that were excited and inhibited by the forebrain. Those cells that were inhibited were significantly more responsive to citric acid and QHCl than those that were excited by forebrain stimulation (Fig. 8). In addition, inhibition was more frequent than excitation in citric-acid- and QHCl-best neurons, whereas excitation was seen more frequently than inhibition in sucrose-best cells (Fig. 3). These data suggest that responses to aversive stimuli are likely to be inhibited by forebrain activity, whereas the neural response to sucrose is likely to be enhanced.

Modulation of taste responses of NST cells by electrical stimulation of the LH and CeA has been previously reported (Cho et al. 2002b, 2003; Li et al. 2002). The enhancement or decrement of taste responses of NST cells induced by electrical
train stimulation of the LH and CeA did not appear to be selective for specific taste responses. However, both the LH and the CeA have predominantly an excitatory effect on NST neurons. Among 113 NST neurons that were modulated by either the LH or CeA or both, 102 of these were excited and only 11 inhibited by forebrain stimulation (Cho et al. 2003). These data suggest that the overall effect of LH and CeA activity on NST neurons is to increase their excitability to gustatory stimuli. This would have the effect of making the gustatory system more capable of discriminating among gustatory stimuli, stemming directly from an increased signal-to-noise ratio. On the other hand, the effects of forebrain activation on taste responses in the PbN seem to have more targeted effects, enhancing responses to preferred stimuli such as sucrose and decreasing responses to aversive substances such as acids and bitter-tasting compounds or narrowing the breadth of tuning of the cells (see Lundy and Norgren 2001, 2004). Such conclusions must be interpreted with caution, however, in that electrical stimulation of the forebrain does not in any way mimic natural neuronal patterns of firing that may well produce much more specific effects on brain stem activity.

Understanding the relationship between activity in the LH and CeA and the processing of gustatory information is a complicated goal. There has been only limited work on the role of the LH in guiding responses to taste stimuli. Global stimulation of the LH leads to increases in food intake (Shiraishi 1991; Sweet et al. 1999) and increased consumption of taste solutions, even aversive ones (Vasudev et al. 1985). Damage to this area of the hypothalamus results in disruptions in feeding behavior (Grossman and Grossman 1982) and has been shown to alter taste preference for saccharin (Touzani and Velley 1990). However, because LH stimulation and disruption affect the motivation to feed, the specific effects of LH manipulations on behavioral responses to taste stimuli are difficult to interpret in a straightforward manner.

Several subnuclei of the amygdala are important for conditioned taste aversion (CTA) learning, including the acquisition of taste information, hedonic evaluation of that information and integration, retention and expression of a CTA (Yamamoto et al. 1994, 1997). Both the CeA and the basolateral amygdala (BLA) are heavily involved in associative processes underlying appetitive and aversive emotional behavior (Everitt et al. 2000). The CeA contains neurons that respond differentially to hedonically positive and negative stimuli (Nishijo et al. 1998), and both the BLA and the CeA appear to be involved in acquisition and/or retention of a CTA (Lampecht et al. 1997; Yamamoto et al. 1994). Therefore it is possible that the altered gustatory activity in the NST that results from CTA (Chang and Scott 1984) could be mediated through descending pathways from the amygdala (see also Tokita et al. 2004). In addition to its effects on ingestion, CTA alters dramatically the reflexive responses to gustatory stimuli (Grill 1985), which undoubtedly depend on connections between the forebrain and brain stem oromotor nuclei (Travers and Norgren 1983), probably through descending connections with the PbN and NST.

Taken together, these data on PbN gustatory neurons and our earlier work on the modulation of taste responses in the NST by forebrain stimulation demonstrate that activity in brain stem taste neurons is not simply the result of afferent input. This series of experiments demonstrates extensive centrifugal modulation of brain stem gustatory activity. Each of the forebrain targets of the gustatory system that have so far been examined, including the IC, LH, and CeA, plays a descending modulatory role in the processing of taste information. The LH and CeA have predominantly an excitatory effect on the NST, whereas their influence on PbN taste neurons is at least equally inhibitory. Stimulation of the LH and/or CeA also differentially affects responses to appetitive and aversive stimuli. 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 (Giza and Scott 1983), gastric distension (Glenn and Erickson 1976), intraduodenal lipids (Hajnal et al. 1999), CTA learning (Chang and Scott 1984), and other physiological conditions known to alter taste sensitivity.

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