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Research report

Acoustic frequency tuning of neurons in the basal forebrain of the waking guinea pig

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Abstract

The acoustic responses of cells in the basal forebrain were studied in the adult waking guinea pig. Frequency receptive fields were obtained across wide frequency (0.094–45.0 kHz) and intensity (0–90 dB) ranges. A total of 326 recordings were obtained in 26 electrode penetrations from five subjects; 205 from the globus pallidus (GP), 98 from the caudate–putamen (CPu) and 23 from the central nucleus of the amygdala (ACE). Twenty-nine recordings exhibited acoustic responses (GP = 20 (9.8%); CPu = 9 (9.2%); ACE = 0). Cells in the regions of the GP that project to the primary auditory cortex (ACx) exhibited frequency tuning that was dominantly suppressive. Responses in the CPu were excitatory, but poorly tuned. The spontaneous rate of discharge of GP cells that yielded complete tuning data was positively correlated with power in the beta bands (12–25 and 25–50 Hz) and negatively correlated with power in the delta band (1–4 Hz) of the EEG of the ACx. These findings suggest that acoustically tuned neurons in the GP that are inhibited by tones are involved in the regulation of auditory cortical state, possibly promoting deactivation to unimportant sounds, and may be cholinergic in nature.

Keywords: Auditory cortex; Caudate–putamen; Cholinergic; EEG; Globus pallidus; Receptive field; Response suppression

1. Introduction

The cerebral neocortex is universally believed to be involved in learning and memory. In contrast to the traditional view that learning and memory involve so-called 'association' cortex, it has been known for fifty years that the responses of primary sensory cortex to conditioned stimuli (CS) are altered by learning. Studied most extensively in primary auditory cortex (ACx), associative processes are known to alter responses to acoustic CSs, as revealed both by evoked field potentials (EP) and neuronal discharges (for review see Ref. [65]). More recently, the nature of such response plasticity has been clarified by determining responses, not simply to the frequency of the CS used during training trials, but rather by assessing complete frequency-receptive fields (RFs) before and at various retention periods following training.

These studies have revealed that learning modifies the processing of information to specifically emphasize the frequency of the CS, by facilitating responses to the CS frequency while depressing responses to other frequencies. These coordinated opposite changes are often large enough to produce a shift of tuning toward or even to the frequency of the CS, so that it often becomes the new best frequency of a cell. Such receptive-field plasticity has all of the major characteristics of forms of memory. Thus, it is (a) associative (requires pairing a tone with a reinforcer), (b) highly specific (facilitation can be limited to the CS frequency ± 0.05 octaves), (c) discriminative (facilitation of response to the reinforced CS + frequency with depression of response to the reinforced CS-frequency), (d) develops very rapidly (in as few as five trials) and (e) lasts indefinitely (present at the longest retention interval tested of eight weeks) [3,5,18,19,66]. (Also, habituation produces complementary frequency-specific decreases in response [11].) In addition to local tuning shifts, increased spatial representation of CS frequencies has been found by metabolic [24] and mapping studies [51] (for reviews see Refs. [23,58,63,64]).

The cholinergic system comprises a possible substrate of the induction of this learning-induced plasticity. It has long been known that blockade of the central cholinergic

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system impairs learning, particularly that involving the forebrain [38]. Further, release of ACh in the cerebral cortex by activation of the nucleus basalis of the basal forebrain appears to be necessary to shift the electroencephalogram (EEG) from the synchronized (high voltage slow waves) to the desynchronized (low voltage fast waves) pattern that characterizes the waking state [7,42] and is optimal for learning and learning-related plasticity in the ACx [1,13].

The basal forebrain, including the nucleus basalis (NB) and the globus pallidus (GP), are major sources of cortical acetylcholine (ACh) [29,30,36]. Neuronal responses in the basal forebrain are consistent with a prime role for ACh in cortical plasticity. Its cells respond to stimuli that signal a reinforcing stimulus [49,52,61,67,68] and can develop conditioned discharges to a tonal conditioned stimulus in fewer trials than does the ACx [37]. Also, iontophoretic application of muscarinic agonists [39] or anticholinesterases [2] within the ACx produces lasting modification of frequency tuning. Further, stimulation of the nucleus basalis produces atropine-sensitive long-duration modification of evoked responses in the auditory cortex, including facilitation of field potentials, cellular discharges and EPSPs [40,41] and facilitation of neuronal discharges to tones [16,17,28]. Muscarinic agonists acting in the ACx have been directly implicated in associatively-induced receptive field plasticity. Thus, pairing a tone with iontophoretic application of ACh produces pairing-specific, atropine sensitive, modification of RFs that include shifts of tuning to or toward the frequency of the paired tone [43] and pairing a tone with atropine-sensitive NB stimulation induces RF plasticity in the ACx similar to that found in behavioral learning [4]. Related effects occur in somatosensory cortex [31].

If cells in the basal forebrain promote RF plasticity in the ACx during learning trials (in addition to or instead of supporting a background state of cortical arousal), then they should receive some 'signal' to release ACh. While NB responses to conditioned stimuli have been documented (above), the sensory characteristics of input to this region have not been studied systematically. The purpose of this experiment was to determine if neurons in the basal forebrain exhibit specific responses to acoustic stimuli. We approached this problem by determining first if cells respond to pure tone stimulation and if so, whether they exhibit frequency specific tuning. We focused on the caudal globus pallidus because it contains cells that project to the auditory cortex and appear to use acetylcholine as a transmitter [36,45,57].

2. Methods

2.1. Animals and surgery

Adult male Hartley guinea pigs ($n = 5$) weighing 480–620 g were used as subjects. They were housed, three per cage, in a light- and temperature-controlled vivarium for at least 5 days before surgery. Surgery was conducted 2 to 3 days before the recording session. Subjects were premedicated with atropine (0.02 mg/kg i.p.) before being placed under general anesthesia (diazepam, 9.0 mg/kg i.p.) followed 15 min later by sodium pentobarbital, 25.0 mg/kg i.p.; the use of diazepam permits a lower dose of the barbiturate, reducing mortality while still achieving surgical levels of anesthesia [15,60]. Animals were placed into a stereotaxic apparatus and body temperature was controlled by a heating pad. Local anesthetic ointment (Xylocaine [Lidocaine]) was applied to the earbars. A 2 mm × 3 mm opening in the skull was made for access to the basal forebrain, centered at 4.5 mm lateral and 1 mm posterior to bregma, over the left hemisphere. Two silver ball electrodes for epidural EEG recording (0.5 mm in diameter) were inserted through holes drilled in the bone over the left auditory cortex, spaced 3 mm apart. Another silver ball was inserted over the posterior parietal cortex on the right side of the brain for use as a reference electrode. Electrodes were fixed with dental acrylic and two cylindrical threaded tubes were included in the pedestal to ensure atraumatic mounting into the stereotaxic apparatus for the recording session. A well of dental acrylic was formed around the opening in the skull. In order to prevent drying of the dura mater and to protect the brain, a layer of warm mixture of bone wax and mineral oil was put over the opening in the skull, followed by a layer of hard paraffin wax. A local antibiotic (Panalog [neomycin sulfate]) was applied to exposed skin surfaces. After surgery the animals were put in an incubator until recovery from anesthesia and then returned to their home cages.

2.2. Apparatus

Experiments were performed in an acoustically isolated chamber (IAC). The animals were tranquilized with diazepam (5 mg/kg i.p. initial dose; this dose was selected to be sufficient to promote sedation, as determined by previous pharmacological studies [25] and was half the dose employed by previous workers who studied basal forebrain physiology in waking subjects [54]); supplements were given throughout the recording session if the animal displayed any signs of anxiety or discomfort. Tranquilization was used in order to reduce spontaneous movements that would have precluded continual recordings from single neurons in the waking state. Animals were placed in a hammock, and the pedestal was fastened to a holder in order to immobilize the head for stereotaxic penetrations. Paws were allowed to rest on the table top and the head was maintained in a position in relation to the body that approximated the normal resting posture. Animals did not display any significant signs of discomfort during the experiment. However they were awake, as indicated by immediate reaction to, for example, a touch of the whiskers; moreover, the EEG was characteristic of waking, i.e.,

predominant low voltage fast activity. A speaker was fastened in a holder against the entrance to the right ear canal. Auditory stimuli were presented through a calibrated sound delivery system (BrainWave Systems). Sound pressure levels were previously calibrated at the entrance to the ear canal (because a closed system cannot be used in

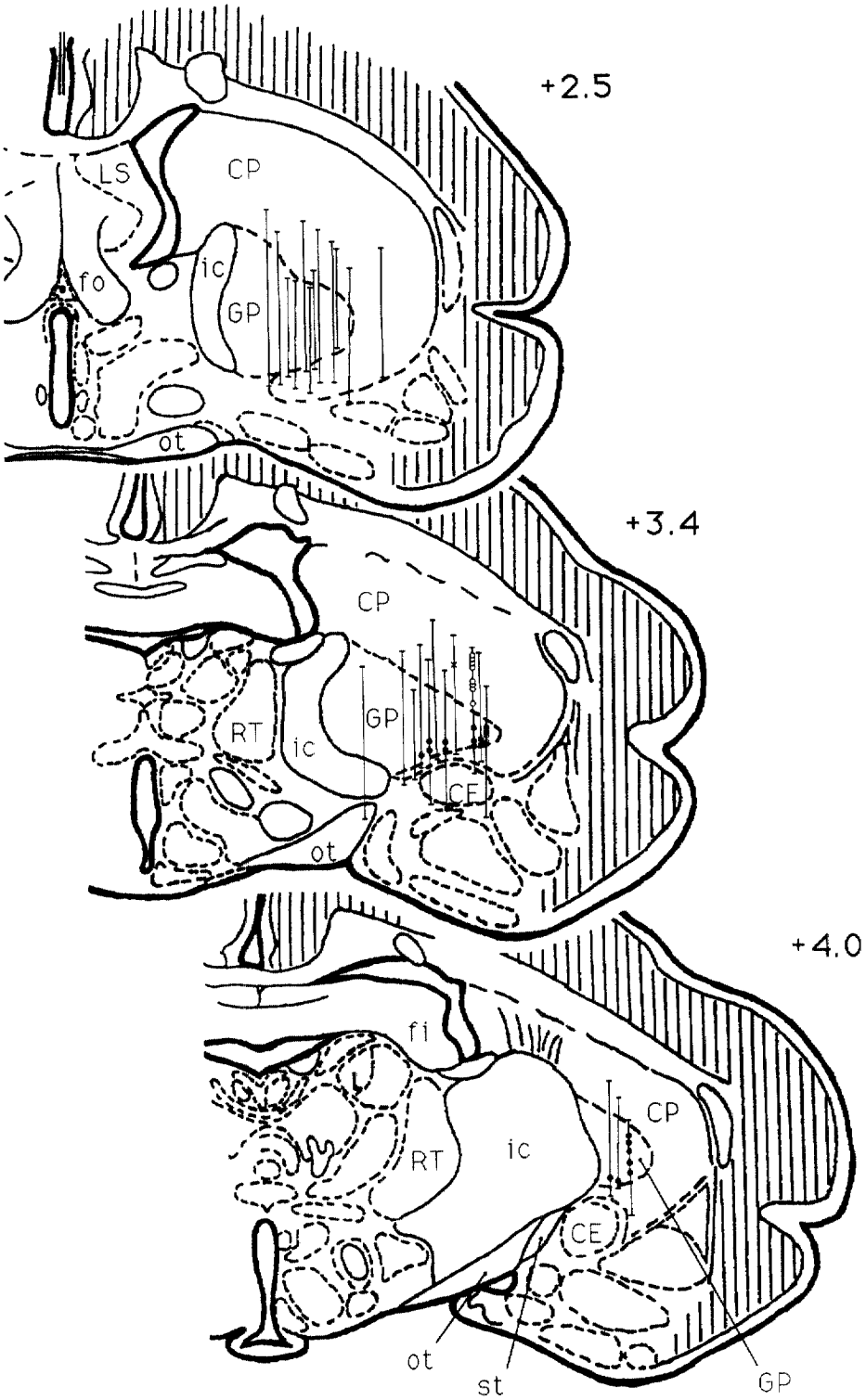


Fig. 1. Summary of recording sites. Each vertical line represents an electrode track. Closed circles denote sites of recording with response to tones having a clear suppression of response, often observed with an excitatory response. All of these sites are in the GP. Open circles denote recording sites with a pure excitatory response; all such responses were found only in the CPu. Crosses indicate two sites of unclassifiable responses. Nonacoustically responsive sites ($n = 297$) occurred along all electrode tracks, including the top and bottom of each track, and were too numerous to mark with symbols. Values for anterior–posterior planes are distances (mm) from bregma.

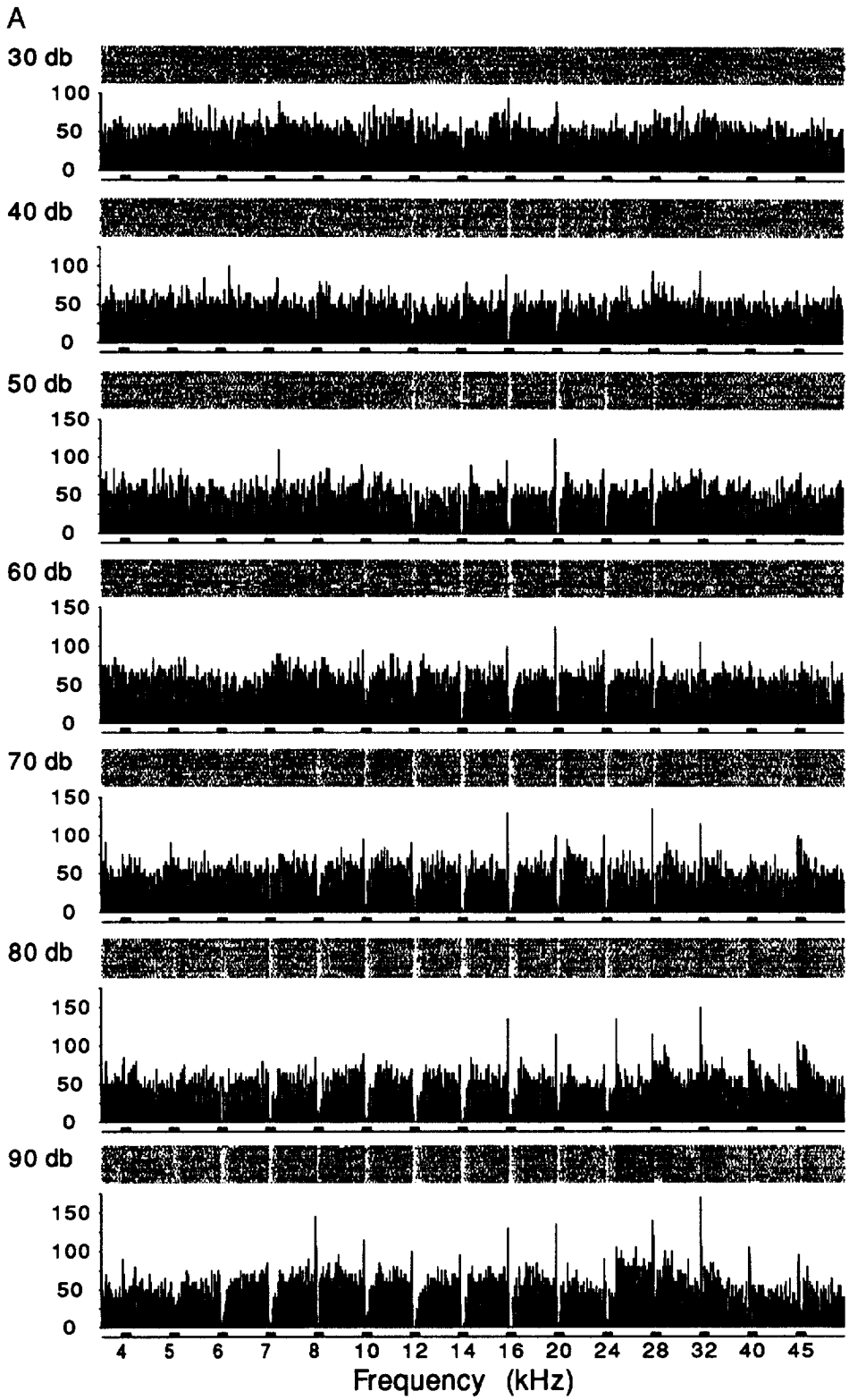


Fig. 2. (A) Rasters and PSTHs for a cell in the GP, across frequency (4.0–45.0 kHz) and intensity (30–90 dB). Note the high rate of background activity and the marked suppression, usually preceded by an excitatory onset response. In this figure and for all other figures showing PSTHs (Figs. 5, 6 and 8), tone presentations are denoted by solid bars below each PSTH which also provide a time calibration = 100 ms. (B) Corresponding tuning curves for onset and suppression responses. Note that onset responses are not as clearly tuned as suppressions. The solid arrow indicates the frequency of maximum suppression at threshold (16.0 kHz at 40 dB). The open arrow indicates the high frequency area that exhibited sideband excitation at comparable latencies (onset window = 11–20 ms; suppression window = 31–60 ms).

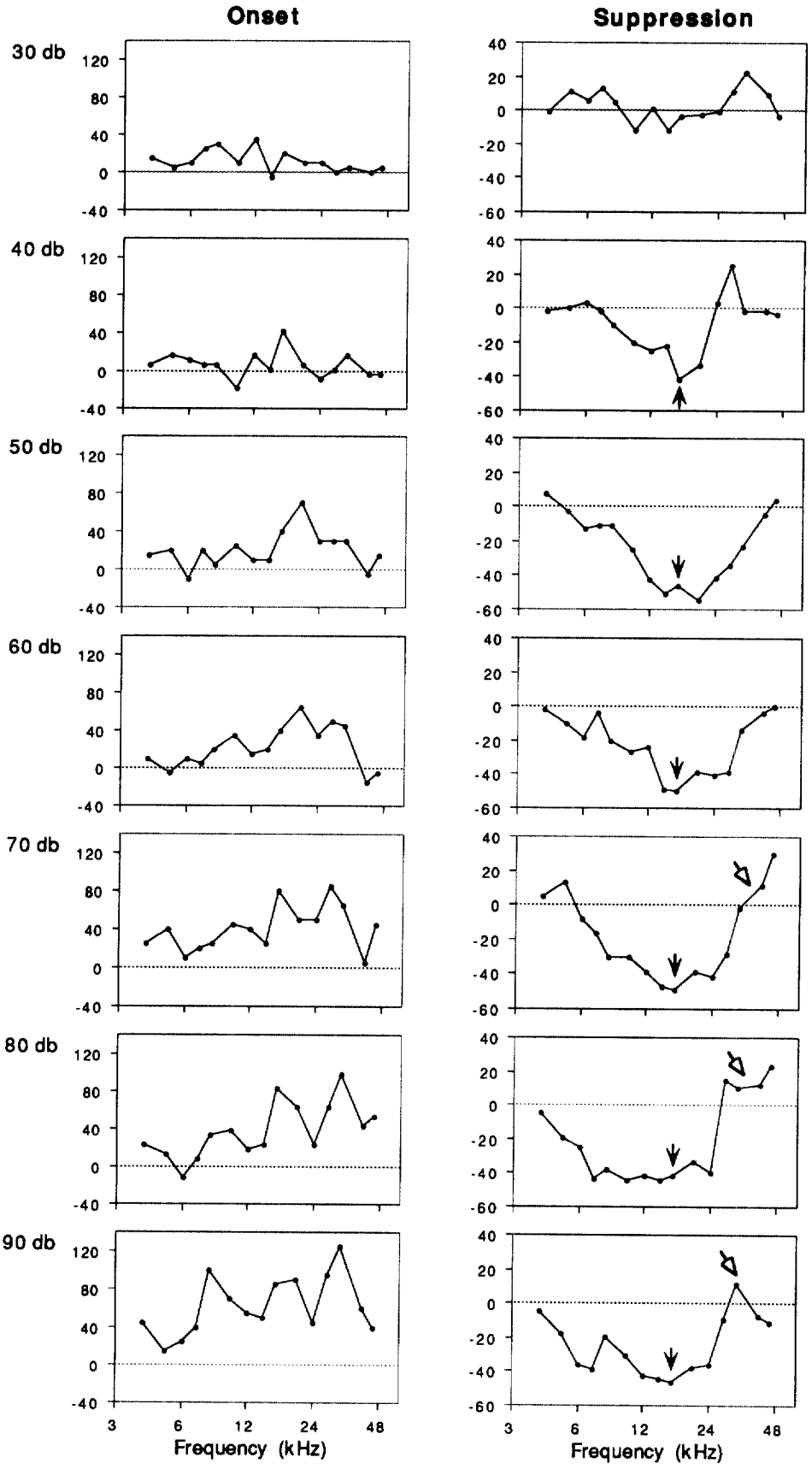
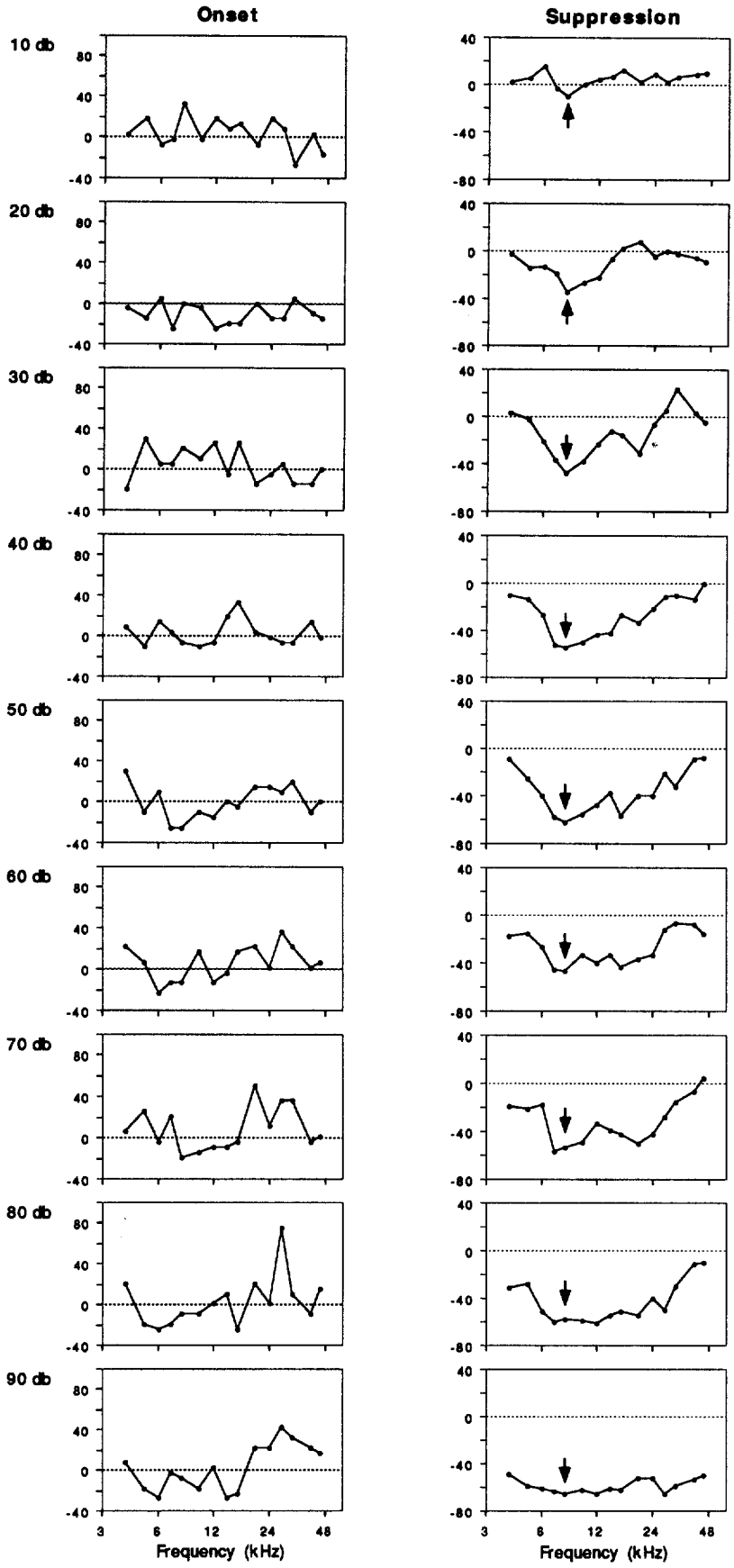


Fig. 2 (continued).


Onset
Suppression
10 db
20 db
30 db
40 db
50 db
60 db
70 db
80 db
90 db
80
40
0
-40
40
0
-40
-80
3
6
12
24
48
Frequency (kHz)

waking animals) by a B&K #4134 condenser microphone and preamplifier interfaced with a Hewlett–Packard sound-wave analyzer. Thus, stimulus levels were lower within the ear canal and so the levels specified in this experiment should not be considered absolute levels at the tympanic membrane. For determination of the RFs, sequences of 15 pure isointensity tones (100 ms in duration, 10 ms rise and fall times, 400 ms ISI) were presented in ascending order, with the distance between tones of 1/2, 1/4 or 1/8 of an octave in a particular sequence. All sequences used were confined to 0.094 Hz–45.0 kHz range. Each PSTH presented in this paper is based on 20 repetitions of the sequence.

For unit recording, custom-made stainless-steel microelectrodes were used (impedance 1.5–4 MΩ at 1 kHz AC). Recordings were made with an assembly of two identical microelectrodes spaced 1 mm in the anterior–posterior plane. Unit activity was amplified, filtered (0.5–3.0 kHz), displayed on oscilloscopes and sent to the Brain Wave acquisition system, based on a PC AT386 computer. The system allowed for voltage discrimination of the input signal and displayed and stored waveform (acquisition rate 24 kHz). The EEG was recorded differentially from the two auditory cortical epidural silver electrodes, amplified, filtered (1–100 Hz) and sent to BrainWave acquisition system (acquisition rate 205 Hz). During recording periods it was generally low voltage fast activity intermixed with some slower waves. Two spike channels and the EEG channel were recorded simultaneously.

2.3. Procedures

All layers of wax covering the opening in the skull were removed. Microelectrodes, attached to a stereotaxic holder, were slowly lowered into the brain through the dura. Then the opening was covered with a mixture of warm bone wax and mineral oil in order to stabilize the surface of the brain. To ensure stability of recording, the search for cells was not started for at least 10 min.

Recordings were made from the area 4.2–5.8 lateral to bregma, 0.3 mm anterior–2.1 mm posterior to bregma, and 5–8 mm below the surface of the brain. Electrodes were slowly lowered in small increments while the signal from the electrodes was monitored on the oscilloscope and through earphones. Whenever unit activity was found on one or both electrodes, the animal was presented with sequences of isointensity tones at 70 dB, covering a broad range of frequencies. On-line PSTHs were observed for the presence of any acoustic responses. If no response was found, then the search was continued. Otherwise, responses to sequences of isointensity tones of different intensities were recorded (within the range of 0 to 90 dB). If the cell was responsive to a narrow range of frequencies, then sequences of tones covering the appropriate range were used. If stable recording could be continued after acoustic responsiveness was recorded, then 30 to 60 discrete 5-s samples of spontaneous unit activity were recorded simultaneously with the EEG of the auditory cortex, for later analysis of the relationship between these two measures.

2.4. Histological verification

After completion of each penetration in which responsive cells were encountered, 2–4 lesions/iron deposits were made through the microelectrodes with anodal current (5 μA, 30 s), at the bottom of the penetration and 1–4 mm higher in the same track. After completion of the entire recording session, the animals were deeply anesthetized with an overdose of Nembutal and perfused with normal saline followed by 10% buffered formalin, containing 1% potassium ferricyanide for the Prussian blue reaction with deposited iron. The brains were removed, sectioned on a freezing microtome and mounted on slides. After drying, they were placed for 30 min in 1% hydrochloric acid, containing 1% ferrocyanide in order to enhance the Prussian blue staining. After that, sections were routinely stained with cresyl violet. Responsive tracks were reconstructed by microscopic examination of a number of consecutive sections through the recording area, and the localization of recorded cells was reconstructed relative to the sites stained with the Prussian blue reaction along the track. Unresponsive tracks also were reconstructed by microscopic examination of sections and verified by their known spatial relation to recorded tracks. Localization of epidural EEG electrodes was verified at the time the brains were removed from the skull after perfusion. Auditory cortex was determined by characteristic vasculature and in relation to major fissures (vasculature was made visible by application of a small amount of black ink onto the surface of the brain).

2.5. Data analysis

Data were processed with DataWave software (Longmont), which permitted continuous on-line monitoring of spike waveforms. In most cases, recordings were obtained from single neurons, in which the signal-to-noise ratio was ≥ 3:1 and the waveform was stable throughout the entire recording period. Rate measures are given in spikes per second (±S.D.). In some cases, more than one waveform was present; these are referred to as 'cluster' recordings.

Fig. 3. Tuning curves for a cell in the GP which exhibited clear tuning of suppression without comparable onset responses. The solid arrow indicates the threshold frequency of suppression (8.0 kHz). Note the increasing bandwidth of suppression with increasing intensity until there is virtually saturation of suppression at 90 dB (onset window = 11–20 ms; suppression window = 21–40 ms).

The files were then transferred to a Macintosh computer for histogram construction and quantitative analyses. For determination of the general nature of the response, 10 ms bin PSTHs were used; latencies of excitatory and inhibitory responses were determined from PSTHs with 2 ms bin resolution. The value on the time axis, corresponding to the middle of the first bin of the uninterrupted sequence of bins representing the response, was used as a latency of the response. Tuning curves were plotted by calculating the average unit activity in different time windows relative to the tone onset for all tones of a given sequence. Averaged unit activity over 200-ms periods preceding tone sequences was subtracted from those values to provide a measure of evoked rate of discharge that was independent of any changes in background activity.

The EEG record was subjected to fast Fourier transformation with DataWave software, and the total power for 1–50 Hz was determined, as well as percentage of the power for the following frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta 1 (12–25 Hz) and beta 2 (25–50 Hz), for each of the recorded 5-s samples. Correlation coefficients were determined to assess the relationship between the spontaneous spike rate of discharge and each band and total power of the EEG from the auditory cortex.

3. Results

We report here observations from a total of 326 recordings obtained in 26 electrode penetrations from five subjects. Of this total, 205 (63%) were from the GP, 98 (30%) were from the CPu and 23 (7%) were from the central nucleus of the amygdala (ACE). A total of 29 (9%) recordings exhibited acoustic responses: GP ($n = 20$ (9.8%), single units = 14, clusters = 6); CPu ($n = 9$ (9.2%), single units = 5, clusters = 4); ACE ($n = 0$).

Two basic types of response patterns were observed: (a), excitation only; (b), suppression, often with shorter latency excitation; (2 cells could not be classified). These response types were segregated anatomically. All cells with suppression were found in the GP; all cells with only excitation at CS onset were found in the CPu. Fig. 1 presents a summary of the histological analysis and the types of responses. Findings from each region will be presented in turn.

3.1. Globus pallidus

3.1.1. Characteristics of responses

The GP was examined from rostral levels to its caudal pole, throughout its dorsal–ventral extent and mainly in its

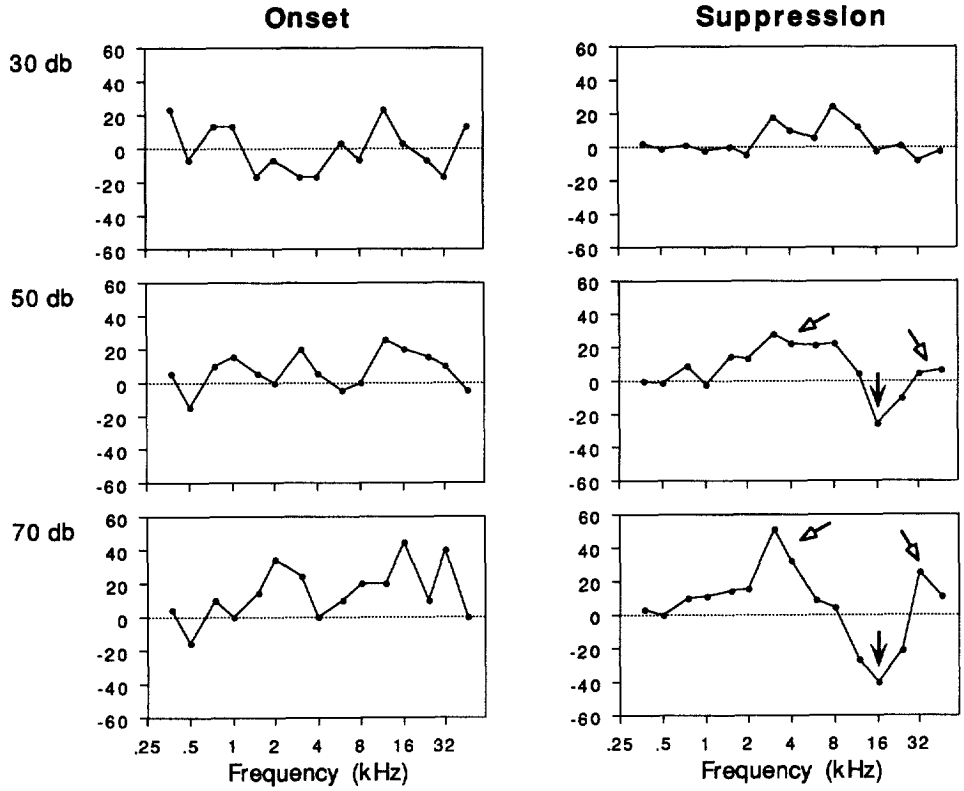


Fig. 4. Examples of tuning curves for a cell in the GP which exhibited tuned suppression and sideband excitation, without excitatory onset responses. The closed arrow indicates the threshold frequency of suppression (16.0 kHz) while the open arrows show the regions of both low and high frequency comparable latency sideband excitation (onset window = 11–20 ms; suppression window = 21–100 ms).

lateral two-thirds. No acoustic responsive cells were found rostrally. Most acoustic responses were obtained in the ventro–lateral–caudal GP (Fig. 1). All of the recordings exhibited high spontaneous rates (single units: mean 28.96 (±15.10), range 11.60–54.30).

Five response patterns could be discerned; the most common were brief onset excitation followed by suppression and suppression alone, which were observed in all cells. Less common were onset excitation alone, sustained excitation, and offset excitation. Usually, the same cell exhibited several patterns at one or more combinations of frequency and intensity. However, suppression predominated.

Fig. 2A, presents PSTHs and rasters for a single cell in the GP. Note the high spontaneous rate (~ 35–40 s/s). At its threshold intensity of response (30 db), slight onset excitation followed by clearly discernible suppression occurred at a few frequencies (mainly 16 and 20 kHz). As stimulus levels increased, the magnitude of excitatory onset responses increased and suppression became considerably stronger, in many cases causing a complete cessation of discharges for most of the tone duration (e.g., 50 dB, 20 kHz). As stimulus level increased, more frequencies exhibited responses; at 90 dB, these extended from 5 kHz (slight suppression only) through 45 kHz (excitation/suppression). Note that while suppression became more pronounced from 6–28 kHz, excitation alone appeared to develop at higher frequencies (60–90 dB).

Fig. 2B presents quantified tuning curves for this same cell. These reveal an increasing spread of frequencies (greater bandwidth), of both short latency excitatory responses and suppression, as stimulus level increased; the tuning of both initially centered on 14–16 kHz at 40 dB. The tuning curves also show that the suppression was accompanied by side-band excitation at the suppression latency. This is most clearly seen for higher frequencies, at 70–80 dB.

Tuned suppression also occurred without shorter-latency excitation. Fig. 3 presents an example. This cell exhibited no systematic excitatory responses, except perhaps for some responses at high frequencies (24–45 kHz) at 70–90 dB. In contrast, suppression was first evident at 10 dB, at 8 kHz). The magnitude and bandwidth of suppression centered on this frequency increased until saturation was attained. Note the suppression at all frequencies (4–45 kHz) at levels $\geq$ 40 dB.

Sideband excitation was also observed, both at frequencies lower and higher than the frequencies that elicited suppression, even in the absence of clearly tuned, shorter latency excitation (Fig. 4).

Suppression at higher stimulus levels could also 'replace' sustained excitation that was elicited at lower levels.

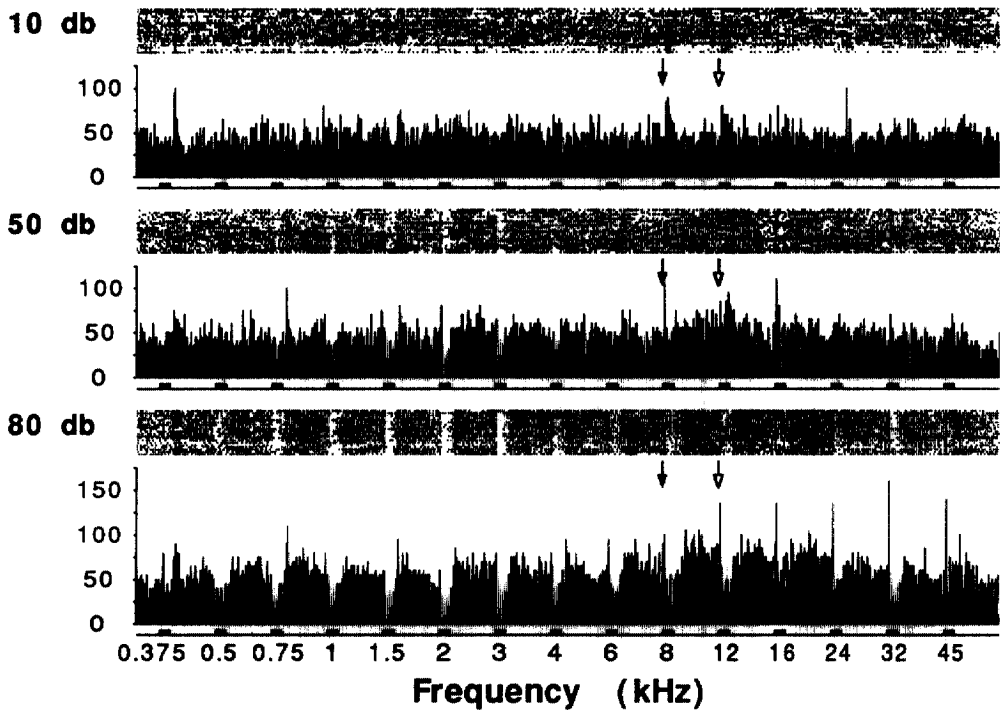


Fig. 5. Examples of rasters and PSTHs for a cell in the GP for which the pattern of response at threshold frequencies changed with increasing intensity. Sustained excitation was present at low intensity (closed and open arrows at 8.0 and 12.0 kHz, 10 dB), but seemed to be more phasic at moderate intensity (50 dB) where suppressions appeared at other frequencies; at high intensity (80 dB), the pattern was a phasic onset response followed by sustained suppression.

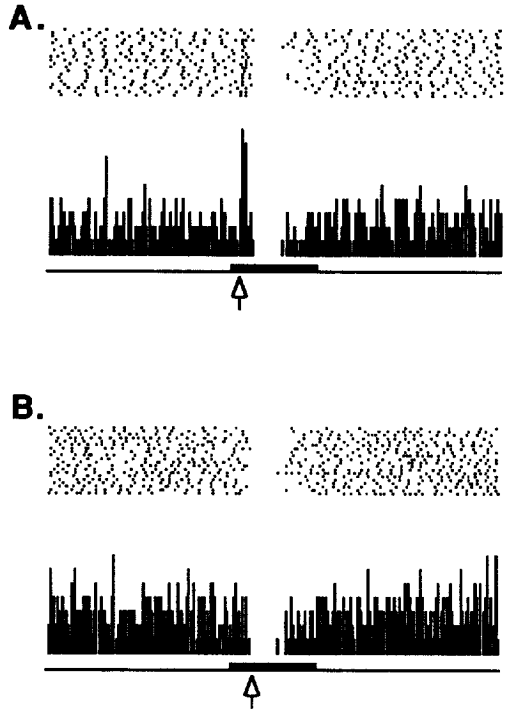


Fig. 6. Examples of PSTH types of responses in the GP used to determine the onset latency of (A) excitation and (B) suppression. The closed arrow points to the first bin of the respective responses.

The example presented in Fig. 5 shows excitation at 8 and 12 kHz at the threshold of 10 dB. This sustained excitation was weaker at moderate levels (e.g., 50 dB), and largely confined to onset excitatory responses. Finally, strong suppression developed at high levels (e.g., 80 dB).

Latency to response was determined generally at 70–80 dB, for the frequency that exhibited the largest onset excitation or suppression or both. Fig. 6 shows the types of PSTHs and rasters (2 ms bin size) that were used to determine response latency both for onset excitation and for suppression. Latency measures were pooled for available single unit and cluster recordings because the shortest latency of excitatory discharge within a cluster yields a valid measure of minimum response latency. (The shortest latency of suppression in theory might be masked by shorter latency excitation but measures of suppression latency could be accomplished all in cases that exhibited suppression only.) The mean latency to onset excitation was 11.44 ms (($\pm$2.01), range 9–17, median 11.0, $n = 18$). For the beginning of suppression, the mean latency was 30.0 ms (($\pm$14.28), range 19–71, median 25.0, $n = 18$). The latency of suppression was not significantly different as a function of whether or not it was preceded by shorter latency excitation.

3.1.2. Correlation with the electroencephalogram

The EEG of the auditory cortex was obtained simultaneously with background discharge (no acoustic stimulation) for 11 single cells in the GP. In eight of these cases (73%) correlational analyses showed a statistically significant relationship between the rate of discharge and the amount of power in one or more frequency bands. In all of these, the greater the discharge rate, the greater was the activated state of the cortex. This relationship was seen as both a direct correlation between discharge rate and power in the beta bands (18–25 and 26–50 Hz) and an inverse correlation between rate and power in the delta band (1–4 Hz) in 5/8 cells. Two additional cells exhibited only the significant positive correlation with beta while an eighth cell displayed only the negative correlation with delta. Fig. 7 presents an example of a cell for which there was a negative correlation for the delta and a positive correlation for the beta bands.

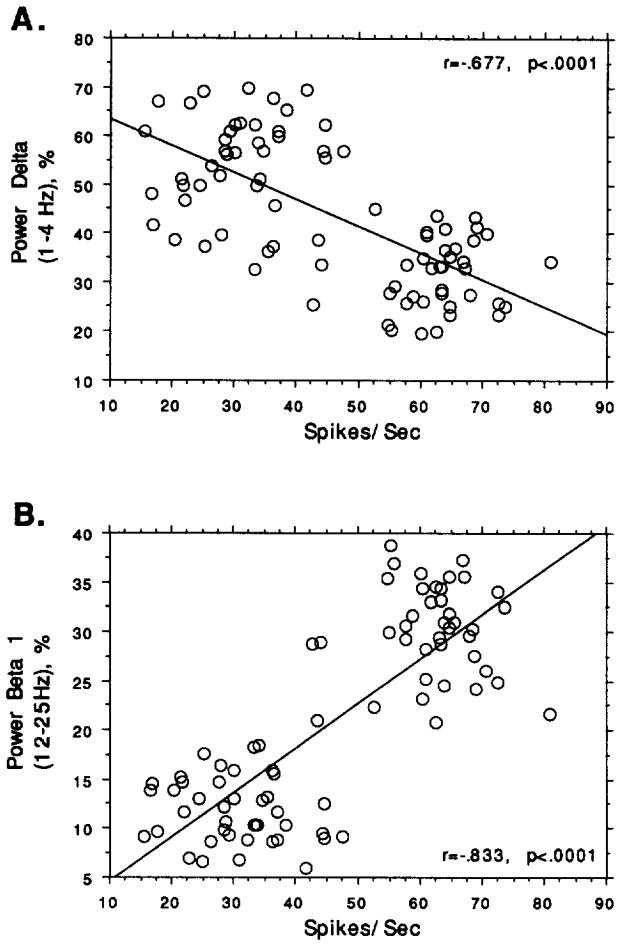


Fig. 7. An example of the relationship between the background rate of discharge of a cell in the GP and the spectrum of the EEG of the primary auditory cortex, which was recorded simultaneously. Scattergrams and correlation coefficients for (A) delta (1–4 Hz) and (B) beta (12–25 Hz). Note the significant negative correlation with delta and the significant positive correlation with beta. The general bimodal nature of the scattergrams reflects the fact that the multiple samples of neural and EEG activity were obtained when the subject was predominantly in a high voltage slow or low voltage fast state.

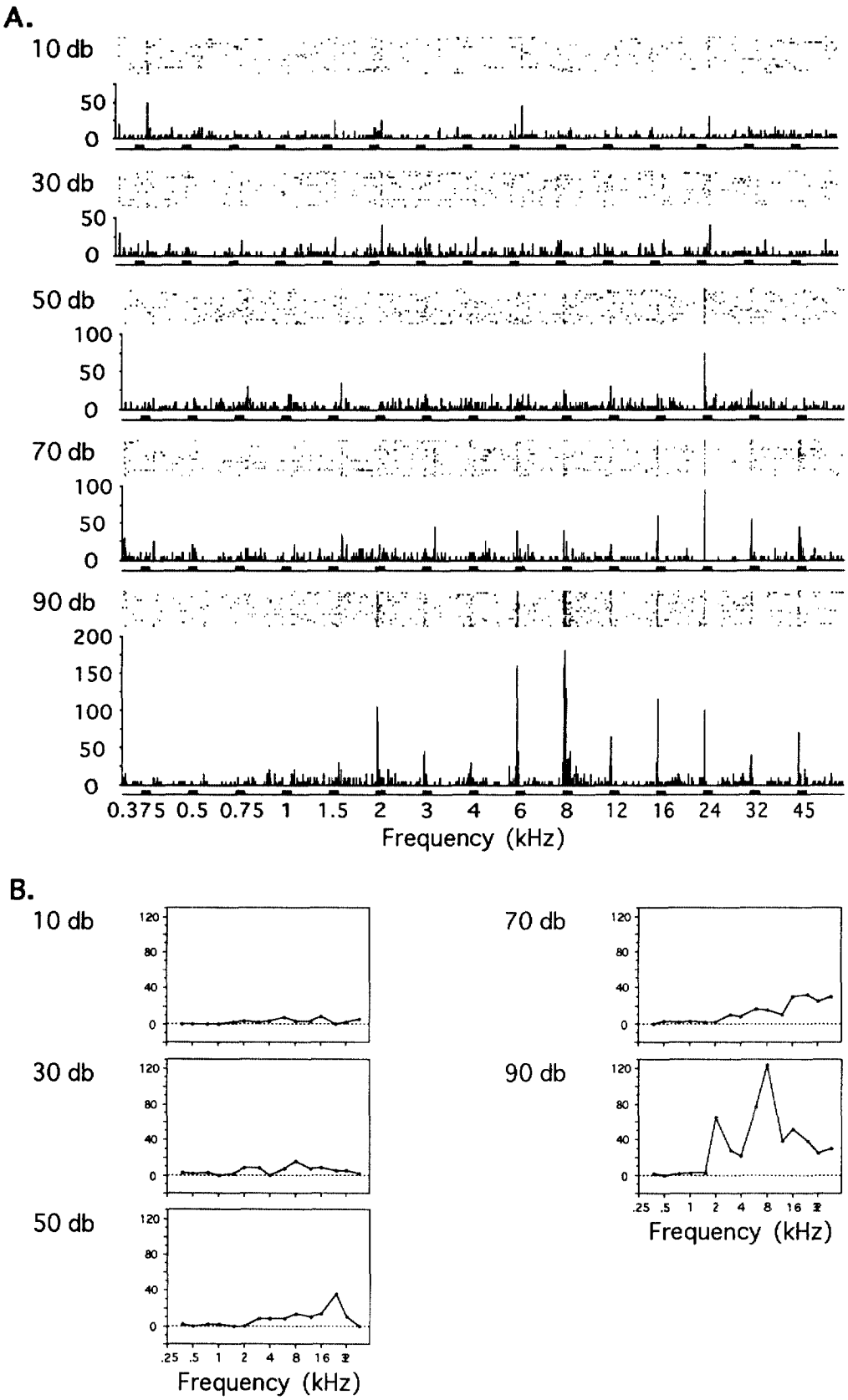


Fig. 8. An example of data for a cell in the CPu. (A) Examples of rasters and PSTHs, showing low rate of background activity and only offset responses at threshold (10 dB). Excitatory onset responses and their bandwidth increase with increasing intensity. (B) Corresponding tuning curves, showing some degree of tuning (onset window = 11–30 ms).

3.2. Caudate–putamen

3.2.1. Characteristics of responses

As the goal of this study was to determine response properties to tones in the GP, recordings in the overlying caudate–putamen (CPu) were obtained only in areas close to the GP. This included the rostral–caudal extent of GP recording sites, comprising mainly the ventro–medial CPu (Fig. 1). Responsive cells were obtained in two penetrations, one of which contained all eight cells whose responses could be classified; (one unclassified cell was in another penetration). CPu cells had low spontaneous rates of discharge, in contrast to GP neurons. The mean background rate for single units ($n = 5$) was 3.58 s/s ((± 5.52), range 0.33–13.80). The background rate for single units in the CPu was significantly less than in the GP (Student's unpaired t-test [df = 17] = 3.62, $p < 0.002$).

Fig. 8A presents PSTHs and rasters for a single cell in the CPu. At its threshold of 10 dB, the only responses were at tone offset, widely scattered from 0.375 kHz to 24 kHz. At 30 dB, the offsets were found at more frequencies at higher intensities together with a weak onset excitation at 8 kHz. At higher intensities, onset excitations became more prevalent and much stronger. Quantified tuning curves (Fig. 8B) for the period of onset excitation showed responses from 2.0 kHz to 45 kHz. As indicated in this example, and in contrast to cells in the GP, suppression during tones was not in evidence even when there was a sufficiently high rate of discharge to permit ready detection of suppression (e.g., Fig. 8A, 90 dB, response to 8 kHz).

The latency to onset of the excitatory response (measured at the same intensity range of 70–80 dB used for GP cells) was determined for all 9 CPu recordings. The mean latency was 8.78 ms ((± 1.20), range 7–11). This was significantly less than the mean GP excitatory latency of 11.44 ms ($t_{[25]} = 3.65$, $p < 0.001$).

3.2.2. Correlation with electroencephalogram

EEG recordings from the ACx were obtained for five single units. While four exhibited some significant correlation with the EEG, this relationship was inconsistent, in contrast to the findings for the GP. One cell in the CPu did have a positive correlation with beta and a negative correlation with power in the delta band, but another cell showed the reverse relationship. Two other cells showed negative correlations with beta activity while the fifth cell had no significant correlations.

4. Discussion

4.1. Summary of findings

We found that neurons in the basal forebrain of waking animals, specifically in the GP, exhibit acoustic response properties that have many characteristics of the responses of neurons within the auditory system proper. These cells have short latency excitatory onset responses, clear frequency tuning, a low threshold, an increasing range of responsive frequencies as stimulus level is increased, and responses to sideband frequencies that differed from those of the best frequencies (e.g., Figs. 2–5). However, they also exhibit some features that are not typical of responsive auditory system neurons; the acoustically-responsive GP cells from which we recorded have a very high spontaneous rate (~ 30 Hz) and, most notably, strong tuned suppression. The similarity of several response characteristics of cells in the GP to those found in the auditory system was unexpected and is without precedent to the best of our knowledge. Therefore, the validity of these findings must be considered.

One possibility is that the recordings were actually obtained from auditory system fibers of passage rather than from a nonauditory system of the brain. This seems unlikely because the only known nearby fibers of passage from the auditory system are from the auditory cortex to the medial geniculate nucleus; these cross the ventral CPu at levels posterior to the GP [55]. Physiologically, cells in the auditory cortex neither exhibit high background rates nor the types of responses obtained in the GP. Moreover, the waveforms we recorded were typical 1–2 ms soma-dendritic waveforms, the same cell could be recorded over ~ 25–50 microns of electrode displacement and recordings were routinely maintained for 45–60 min, all inconsistent with recordings from fibers.

The findings also support the conclusion that the frequency-tuned responses are from GP cells. The caudal GP contains neurons that project to the auditory cortex, participate in the control of the electroencephalogram of the auditory cortex and use acetylcholine as a transmitter in the cortex. The frequency tuned cells reported here have characteristics of such cholinergic projection neurons. First, they exhibited a statistically significant negative correlation with auditory cortical delta activity and a significant positive correlation with beta activity. Second, their location is consistent with the sites of cholinergic cells (i.e., acetylcholine containing neurons) that project to the auditory cortex (c.f., [36,45,57]). Third, such cells are known to be involved in control of the cortical EEG [7,42,48]. Fourth, the GP cells reported here have a high background rate of discharge; Detari and Vanderwolf [14] found that cells in the GP with similar background rates both increased their rates during cortical activation and projected to the neocortex. In any event, combined physiological and histochemical experiments are needed to definitively determine if these tuned cells are indeed corticopetal cholinergic neurons.

However, the basal forebrain also contains GABAergic cells that project to the neocortex [20]. It is possible that the acoustically-tuned cells reported here consist in whole or in part of such neurons. While it seems paradoxical that GABAergic cells would show a positive correlation with activation of the auditory cortex, at least some of these

neurons terminate on GABAergic cells in the neocortex [21]. This could produce inhibition of such cells, resulting in a disinhibitory cascade of their targets. The results might then be similar to those of basal forebrain–cortical cholinergic neurons, i.e., cortical activation.

Additionally, the caudal GP contains noncholinergic cells that project to several subcortical telencephalic regions, including the magnocellular medial geniculate nucleus, suggesting that the caudal GP is part of an auditory feedback loop [59]. This would not explain the high correlations obtained between discharge rate and the EEG of the primary auditory cortex. However, it was not possible to obtain correlational EEG data from all tuned cells, so that some of these neurons might contribute to this pallidofugal pathway.

4.2. Relation to previous findings

Although frequency tuning has not been reported in the GP previously, a few studies have reported cellular responses to acoustic stimuli. The latencies reported vary widely: Richardson and Thompson [53], excitation at 'less than 60 ms'; Gardiner and Kitai [22], 45 ms for both excitation and suppression; Chudler et al. [9], 16 ms for excitation. (Bordi et al. [6] reported no cellular responses to tones.) We observed excitation at a mean of 11.44 ms and suppression at 30.00 ms for cells in the GP. The excitation is well within the limits of previous reports but the latency to suppression is considerably less than that reported by Gardiner and Kitai [22]. However these authors used 'low level' tones emanating from a remote speaker, compared to our use of 70–80 dB levels for latency measures and a speaker located at the ear canal; thus our shorter latencies might have been due in part to our use of louder tones at a shorter distance from the ear. Also, we determined the latencies at the best frequency whereas previous workers used a single frequency, which had only a remote chance of being optimal for any particular neuron. In any event, the present findings extend previous reports of acoustic responsiveness to the finding that GP cells have tuned frequency receptive fields.

The CPu exhibits excitatory responses to acoustic stimuli at latencies of 12–25 ms [6,9]. We observed excitatory responses having a mean onset response of 7–11 ms, slightly faster but probably not significantly different when differences in acoustic stimulus conditions are taken into account (e.g., free field vs. speaker fixed at the ear canal). Within the central nucleus of the amygdala, we found no cells that responded to acoustic stimuli. These findings replicate and extend the negative report of Bordi et al. [6].

4.3. Possible sources of frequency tuning in the globus pallidus

There are several possible sources of frequency tuning in the GP. It might originate in the subcortical auditory system via an unknown path; the auditory cortex appears to have no direct projections to the GP [50]. Or tuning might come from the peripeduncular area (PPA), which is considered to be closely related to the medial geniculate body [35,44]. Frequency tuning apparently has not been studied in this nucleus, but its involvement in auditory processing has been demonstrated by Fos-like immunoreactivity staining after tonal stimulation and after electrical stimulation of the cochlea [54,62]. The PPA makes direct synaptic contacts on cholinergic cells in the caudal basal forebrain [26] which gives rise to projections to the auditory cortex. These findings are in concert with our observation that auditory responses could be recorded in caudal but not rostral parts of the GP.

Frequency input might be relayed to the GP from the CPu, because the striatum receives projections from the auditory cortex [50], the medial geniculate body [34], and the PPA [34,46]. The CPu responds to electrical stimulation of the medial geniculate [10] and also to auditory stimulation (c.f., [32,69]). The PPA projections are restricted to the caudal CPu. Although recording from the CPu was not our primary goal, and only a small number of responsive cells were encountered, they were also located relatively caudally. Interestingly, Moriizumi and Hattori [46] found that terminals arising from the PPA were found in the caudal parts of both the GP and CPu, but EM data revealed marked differences in the morphology of synapses in the two structures. Labeled terminals in the GP mostly made symmetrical synapses on somata and major dendrites, whereas they made asymmetrical synapses on dendritic spines in the CPu. These findings suggest that PPA projections to the GP are predominantly inhibitory whereas those to the CPu are mainly excitatory (c.f., [56]). This could explain why all inhibitory responses in our study were observed in the GP while only purely excitatory responses were found in the CPu. Unfortunately, neither the involved transmitters nor the tuning properties of cells in the PPA are yet known. Understanding the tuned responses in the GP may also have to take into account direct or indirect connections between the GP and the PPA [27,33].

As the tuned suppression observed in the GP has not been reported in the auditory system, a source of the inhibition must be identified. The locus of putative inhibitory cells is unlikely to be within the GP (or adjacent CPu) for two reasons. First, we have not encountered any cells in the GP to which this inhibitory function may be ascribed; all responding cells in the GP seem to belong to the same homogeneous class of predominant tuned suppression. (Of course, recording methods may have been biased to miss such inhibitory cells.) Second, both minimum and median latencies of response suppression are much greater than those of the early excitatory response. Therefore, putative inhibitory cells are probably not all local. If the PPA is found to contain GABAergic cells that have an excitatory response and are tuned, they may be the source of the suppressive tuning in the GP.

4.4. Possible functional implications

The exploration of systematic sensory responses in nonsensory structures provides a way to determine the nature of sensory information that reaches such structures. Using this approach, Bordi et al. [6] discovered that the lateral nucleus of the amygdaloid complex and related striatum exhibit frequency tuning, for high frequencies and generally at thresholds considerably greater than found in the lemniscal auditory system. These findings allowed them to hypothesize that the amygdala receives acoustic information which is specifically related to the high-frequency spectrum of distress calls, so that calls from conspecifics would induce the organization of defensive behavior in the recipient, via the amygdala.

The present findings present a less clear scenario. Given the low thresholds and best frequencies across the acoustic spectrum, the GP cells appear to be tuned neither to particular species-specific vocalizations nor natural sounds. If one provisionally accepts the conclusion that they are cholinergic neurons involved in controlling the state of the auditory cortex, then they might provide a link between some auditory input and some regulation of the auditory cortex. We consider two possible functions, the first at the behavioral/psychological level, the second at the circuit level. But first it should be noted that only a small percentage (9.8%) of GP cells exhibited acoustic frequency tuning. Thus functional considerations must be tempered by the realization that frequency-specific processing of auditory stimuli does not constitute a predominant capability of the GP. (The same considerations hold for the CPu in which 9.2% of cells were acoustically responsive.) Nonetheless, ~ 10% of GP cells might be sufficient to produce effects of functional significance in the auditory cortex.

At the behavioral level, tuned suppression in the GP might be involved in a blocking of attention because blockade of the cholinergic system and lesions or temporary inactivation of the nucleus basalis are known to disrupt attention [8,47]. Cells in the basal forebrain habituate to repeated sensory stimulation [37,52,68] suggesting a decrease in attention. Our protocol of repeated presentation of behaviorally insignificant tones might have involved suppression of attention to the tones. A temporary suspension of the tonic activity in the cholinergic projection system to the auditory cortex may be part of such a process.

At the circuit level, there may be 'feedforward deactivation' of the auditory cortex from the basal forebrain. Pure tone stimulation generally produces phasic onset responses in the auditory cortex. This may be contrasted with more tonic responses in the ventral medial geniculate nucleus, the lemniscal thalamic source of projections to the primary auditory [12]. If ascending auditory input projects in parallel to the auditory cortex and to the nucleus basalis (directly or indirectly), then the result might be a phasic cortical response followed by a brief shift to a less activated cortical state due to acoustic inhibition of cholinergic cells that project to the auditory cortex. The effects might be quite subtle and not readily detectable at the level of the EEG. But the result could be a reduced capability of cortical cells to process information. Such effects need not be of short (e.g., ~ 200 ms) duration, as in the present case, that might be thought too brief for cholinergic effects. In preliminary experiments (in drug-free animals) when animals were presented with much longer tones (6-s duration), the inhibitory phase of the response lasted much longer, ~ 2–5 s. This scenario seems to be compatible with prior observations of cortical response decrement to repeated tones in the auditory cortex of the waking guinea pig [11]. However, as the latency of suppression in the GP is greater than the latency of onset responses in the ACx, such a process would be most effective on longer latency (i.e., sustained) discharges in the cortex.

Thus, quite independent of solely intracortical processes, such as recurrent inhibition, cortical processing might be gated to some extent by the globus pallidus and other related basal forebrain structures. However, other factors that could increase the tonic rate of discharge, e.g., high tonic arousal in response to physiological demands, could reduce this feedforward deactivation, thus permitting full processing.

This idea could be tested in a learning situation, particularly because learning is already known to alter cellular responses in the GP [22,67]. The hypothesis is that a tonal signal for reinforcement would not produce discharge suppression after learning, compared to other frequencies that have no such acquired behavioral significance. Extending standard conditioning paradigms to include determination of frequency receptive fields in the GP before and after learning should provide a critical test of this hypothesis.

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