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Response properties of auditory activated cells in the occipital cortex of the blind mole rat: an electrophysiological study

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Abstract Previous studies have demonstrated that despite its blindness, the subterranean blind mole rat (*Spalax ehrenbergi*) possesses a noticeable lateral geniculate nucleus and a typical cyto-architectural occipital cortex that are reciprocally connected. These two areas, as revealed by the metabolic tracer 2-deoxyglucose, are activated by auditory stimuli. Using single unit recordings, we show that about 57% of 325 cells located within the occipital cortex of anesthetized mole rats responded to at least one of the following auditory stimuli — white noise, pure tones, clicks, and amplitude modulated tones — with the latter two being the most effective. About 85% of cells driven by either contralateral or ipsilateral stimulation also responded to binaural stimulation; about 13% responded only to binaural stimulation; and 2% were driven exclusively by contralateral stimulation. Comparing responsiveness and response strength to these three modes of stimulation revealed a contralateral predominance. Mean latency (±SD) of ipsilateral and contralateral responses were 48.5 ± 32.6 ms and 33.5 ± 9.4 ms, respectively. Characteristic frequencies could be divided into two distinct subgroups ranging between 80 and 125 Hz and between 2,500 and 4,400 Hz, corresponding to the most intensive spectral components of the vibratory intraspecific communication signals and airborne vocalizations.

Keywords Auditory responses · Mole rat, *Spalax ehrenbergi* · Occipital cortex

Abbreviations BMF: best modulation frequency · CF: characteristic frequency · 2-DG: 2-deoxyglucose · dLGN: dorsal lateral geniculate nucleus · IC: inferior colliculus · LGN: lateral geniculate nucleus · OC: occipital cortex · MTF: modulation transfer function · SAM: sinusoidally amplitude modulation · SC: superior colliculus

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Introduction

Recent years have revealed a growing interest in cross-modal neuroplasticity — the recruitment of brain areas normally used for the processing of one sensory modality, for the processing of another sensory modality. Compensatory neuronal reorganization and the diversion of one sensory modality to targets of another sensory modality have been demonstrated in various animal models deprived of a particular sensory input either congenitally or experimentally (e.g., Asanuma et al. 1988; Asanuma and Stanfield 1990; Schlaggar and O'Leary 1991; Bronchti et al. 1992; Toldi et al. 1994a, 1994b, 1996; Rauschecker and Korte 1993; Rauschecker and Kniepert 1994;Yaka et al. 1999, 2000; Izraeli et al. 2002).

Cross-modal reorganization in animal models has been induced, in most cases, by experimental procedures. For example, following removal of the lateral geniculate nucleus (LGN) and the superior colliculus (SC) in newborn Syrian hamsters and ferrets and the creation of an alternative target for the visual input by partial deafferentation of the somatosensory or auditory thalamic nuclei, visual fibers that had lost their original terminal space formed new connections in the 'abandoned' thalamic nuclei. It has been shown that neural responses evoked by visual stimuli in the somatosensory or auditory cortex of such neonatally operated hamsters and ferrets were similar to those of visual cortex cells in sighted hamsters and ferrets and that the surgically induced pathway could mediate visual pattern discrimination (e.g., Sur et al. 1988, 1990; Frost 1990; Pallas et al. 1990; Roe et al. 1990, 1992; Pallas and Sur 1994; Frost et al. 2000; von Melchner et al. 2000). The activation of primary visual areas

by other sensory modalities found in blind animal models is consistent with findings in early blind human subjects, as revealed electrophysiologically and by non-invasive brain imaging methods (e.g., Veraart et al. 1990; Uhl et al. 1991; Alho et al. 1993; Kujala et al. 1995, 2000; Sadato et al. 1996, 1998; De Volder et al. 1997; Roder et al. 2000).

In our current animal model, the subterranean blind mole rat (*Spalax ehrenbergi,* also known as *Nannospalax ehrenbergi*), we take advantage of blindness that is natural and congenital. Possession of a dorsal lateral geniculate nucleus (dLGN) and occipital cortex (OC) (Bronchti et al. 1989, 2002) render this rodent a good model system for studying cross-modal compensation. Indeed, earlier functional mapping using 2-deoxyglucose (2-DG) has revealed that in the blind mole rat these visual areas can be activated by auditory stimuli (Bronchti et al. 1989; Heil et al. 1991; Bronchti et al. 2002). The major source of this auditory input has been shown to be the inferior colliculus (IC), which in addition to all typical auditory targets, also projects to the dLGN (Doron and Wollberg 1994). Preliminary electrophysiological experiments also disclosed single unit responses to various auditory stimuli in the striate cortex (Heil et al. 1991). The present study describes and characterizes single unit responses to auditory stimuli in the blind mole rat's OC, expanding our previous functional mapping and projection tracing studies that indicated a takeover by auditory input of the OC in this naturally blind rodent.

Materials and methods

Animal preparation and surgical procedures

A total of 24 mole rats (*S. ehrenbergi*) of both sexes were captured in the northern part of the Negev desert in Israel. In the laboratory, animals were housed individually in separate cages under constant temperature (25 ± 2°C) and light/dark (14/10 h) illumination schedule, with food (vegetables and laboratory rat chow) provided ad libitum.

All surgical procedures and electrophysiological recordings were conducted under deep anesthesia. Because metabolic, respiratory and heart rates of the blind mole rat are normally very low (Arieli et al. 1977; Storier et al. 1981), attaining prolonged and stable anesthesia was problematic. Moreover, inter-individual differences in sensitivity to the anesthetic drugs were remarkable. We achieved a moderately stable and non-fatal anesthesia in most cases by an initial i.m. administration of a mixture of ketamin hydrochloride (27 mg kg^{-1} body mass) and xylazine hydrochloride 2% (0.3 ml kg^{-1} body mass). Recordings lasted several hours. Anesthesia was maintained throughout the experiment by subcutaneous administration of supplementary doses of the mixture as required by the different individuals (half of the initial dose, every 30–60 min). Anesthetized animals were restrained in a specially designed stereotaxic apparatus that left the ears unobstructed. The posterior skull was exposed by removing the overlying muscle, and a 5 mm diameter circular craniotomy was made unilaterally over the OC leaving the dura intact. To prevent desiccation of the exposed brain it was covered with paraffin oil. The animal was then placed in a suspended double-walled, sound-attenuation chamber (IAC 1203A) lined with sound-damping foam to reduce echo. All the electrophysiological recordings were conducted within this chamber.

Stimulation and recording procedures

Auditory stimuli consisted of 0.2 ms clicks (presented individually or in trains of four successive 0.2-ms clicks), broadband white noise (0.02–20 kHz) produced by a noise generator (Brüel and Kjaer type 1405; Naerum, Denmark) and pure tones generated by a voltage-controlled oscillator (Wavetek type 136, San Diego, USA). The latter were presented in linear ascending order in two separate series: 16 consecutive steps ranging from 100 to 1,300 Hz; and 64 consecutive steps ranging from 1,030 to 13,900 Hz. Noise and tones were shaped into 200-ms bursts with 20 ms rise and fall time, using a custom-made shaping unit. To simulate the pulsed periodic vibratory signals of the blind mole rat (Rado et al. 1987) we also used sinusoidally amplitude-modulated (SAM) tones shaped by a two-quadrant multiplier (responding to the positive voltages and chopping the negative voltages of the symmetrical sinusoidal modulating signal). The carrier frequency was 100 Hz, corresponding to the dominant frequency component in the natural seismic vibrations of the mole rat. Modulation frequencies varied between 2 and 64 Hz. Stimuli strength ranged between 80 and 90 dB SPL (unless indicated differently). Amplitudes were controlled by means of a custom-made power amplifier and a manually operated attenuator (HP350D Hewlett-Packard).

Stimuli were delivered at a repetition rate of 0.5 Hz through pre-calibrated earphones (Azden, New York, USA) coated and isolated from the animal's ears by vibration absorbing material. Signals were presented binaurally or monaurally, both contralateral and ipsilateral to the recording side. Sound pressure levels (in dB re. 20 μPa) were monitored by a calibrated condenser microphone (Brüel & Kjaer 4134) and a sound-level meter (Brüel & Kjaer 2209) serially connected to a 1/3-octave filter set (Brüel & Kjaer 1616). Frequency response of the entire sound-delivery system was fairly flat (± 4 dB) throughout the frequency range of 70 Hz to 20 kHz.

Single unit activity was extracellularly recorded using glass-coated platinum-iridium microelectrodes that were advanced through the dura by a calibrated and remotely controlled stepping motor (resolution: 4.5 μm/step; Sodeco-Saia, model AMA92, Switzerland). Of 55 penetrations, 51 were perpendicular to the brain surface. Most of the cells included in this study were detected through their spontaneous activity. However, we also occasionally used auditory 'search' stimuli. Neuronal activity was a.c. amplified, filtered (Digitimer Neurolog System; Digitimer Research Instrumentation, England), monitored for shape and size and discriminated from background activity by a window discriminator (WPI type 121; World Precision Instruments, USA). Discriminated spikes were digitized and displayed on-line as dot rasters. Field-evoked potentials used to delineate the occipital responsive area and to distinguish it from the auditory cortex were picked up by the same microelectrodes, a.c. amplified, filtered (bandwidth 0.05–5 kHz), averaged (RC Electronics, Ore., USA) and displayed on-line. Both cellular and field-evoked potentials were stored for off-line analyses on a personal computer. During the experiment, recording sites were stereotactically referred to the mid-line and the anterior border of the straight part of the transverse sinus.

At the end of the electrophysiological experiments, animals were anesthetized with fluothane and perfused transcardially with 0.9% saline solution followed by 10% neutral buffered formalin. The brains were then gently removed and deep frozen (−40°C). Assignment of electrode penetration tracks and recording sites was based on the calibrated microelectrode driver and coronal Nissl-stained frozen sections. The midline and the splenium of the corpus callosum served as internal references for orientation along the mediolateral and anteroposterior axes, respectively. In order to compare our results with earlier work on the auditory and somatosensory systems of this species, we adopted the schematic brain views and coordinate system of Necker et al. (1992) and

Bronchti et al. (2002). To compensate for inter-individual variability in size and weight (130–285 g) each individual map of penetration sites was scaled to fit a standard brain of a 200-g mole rat.

Results

General overview

A total of 325 single units were isolated along 55 electrode penetrations in the left occipital cortices of 24 blind mole rats. Figure 1A depicts the spatial distribution of all penetration sites superimposed over a normalized latero-dorsal view of the left hemisphere. Many of these penetrations were within areas identified previously as corresponding to cortical visual areas in sighted rodents, including area 17 (Bronchti et al. 2002). Parts of these areas have also been shown by 2-DG functional mapping to be activated by auditory stimuli (Heil et al. 1991; Bronchti et al. 2002). However, auditory driven cells were also found medial and rostral to these regions. Figure 1B illustrates the responses of several cells in the visual cortex to auditory clicks, noise bursts, tone bursts and SAM tone bursts (100-Hz carrier frequency, 30-Hz modulation frequency). Typically, responses to clicks consisted of a short excitation occasionally followed by some suppression of spontaneous activity. The most prevalent response (ca. 62%) elicited by noise and SAM tone bursts consisted of a short phasic excitatory component at the onset of the stimulus ('on excitation') or at its offset ('off excitation'). Onset responses were quite frequently followed by some suppression of spontaneous activity. Responses consisting of two or more discrete excitatory components were less common (about 19%) and sustained excitation or suppression throughout the stimulus or beyond it was scarce. Most of the responses elicited by pure tone bursts, throughout the entire effective frequency range, consisted of an onset excitation (70%) occasionally followed by some suppression of ongoing activity. A sustained excitation was rare (5%) and only in one case was an exclusive 'on-off' response discerned. All other response patterns (about 22%) were frequency dependent, altering from onset excitation at low frequencies to either 'off' or 'on-off' excitation at higher frequencies.

All 325 isolated neurons were tested binaurally with at least one of the four auditory stimuli routinely used: click, noise burst, tone bursts and sinusoidally amplitude modulated (SAM) tone. In this group, 187 neurons (57.5%) responded to at least one stimulus, with clicks and SAM tones being the most effective. A smaller group consisting of 78 neurons was subjected to all four stimuli. Of these, 52 cells (66.7%) responded to at least one stimulus, and clicks and SAM tones were the most effective stimuli (X^2-test: $P < 0.001$) (Fig. 2), with 51 neurons responding exclusively either to clicks or to SAM tone bursts, or to one of these two stimuli and at least one other stimulus.

Laterality, aural dominance and binaural interaction

Laterality

A total of 218 neurons isolated along 49 penetrations were tested with monaural (each ear) and binaural airborne clicks of about 90 dB SPL. The relatively high SPL was used because of the blind mole rat's low sensitivity to airborne sounds (Heffner and Heffner 1992; Rado et al. 1998). Of these 218 neurons, 141 (64.7%) responded to at least one of the three modes of stimulation. Figure 3A summarizes the distribution of cells according to the modes by which they could be

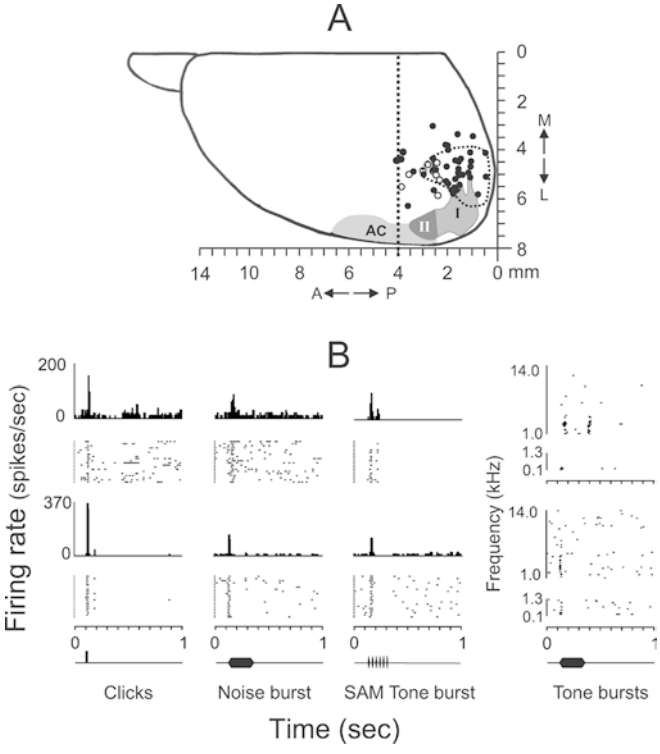

Fig. 1 Responses of single cells to auditory stimuli recorded at the occipital cortex of the blind mole-rat. **A** A schematic top view of the animal's left hemisphere of the brain indicating microelectrode penetration sites. *Filled and empty circles* specify, respectively, penetrations comprising responding and non-responding cells. *Gray areas* (*AC*, *I*, *II*) indicate auditory activated areas disclosed by 2-deoxyglucose (2-DG) functional mapping (Bronchti et al. 2002). Area 17 is delineated by a *dashed line*. *Vertical dashed line* designates the caudal border of the splenium of the corpus callosum. *A* anterior; *P* posterior; *M* medial; *L* lateral. Note that most responding cells were isolated within area 17. **B** Dot rasters and corresponding peri-stimulus time histograms (PSTHs; 5-ms bin duration) illustrating responses of 8 different cells elicited by clicks, noise bursts and sinusoidally amplitude modulation (SAM) tone bursts (carrier frequency 100 Hz; modulating frequency 30 Hz). Responses to pure tones are presented by two sets of dot rasters: (*lower set*) ranging between 0.1 and 1.3 kHz in 16 consecutive repetitions, the other (*upper set*) ranging between 1 and 14 kHz in 64 consecutive repetitions. *Left-most column of dots* in each raster represents onset of sweeps. All stimuli were presented at a constant intensity of 90 dB SPL. The timing of clicks and other stimuli is represented at the *bottom* of the dot rasters by the envelope of the stimulus

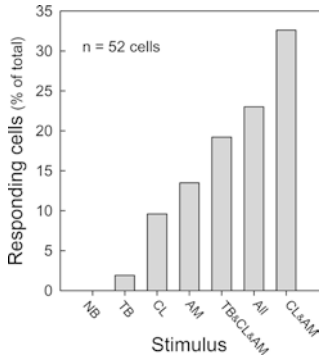

Fig. 2 Responsiveness to auditory stimuli. Responsiveness of cells that were subjected to all four auditory stimuli: *NB* noise burst, *TB* tone burst, *CL* click, *SAM* sinusoidal modulated tone

activated. It is apparent that all neurons but two (which were driven by contralateral stimulation only, 'C'), could be driven binaurally. About 12% could only be driven binaurally ('Bi'), while the others also responded to contralateral and/or ipsilateral stimulation ('C&Bi', 'C&Bi&I', 'I&Bi'). More neurons responded to contralateral than to ipsilateral stimulation.

Aural dominance and binaural interaction

Aural dominance and binaural interaction were determined by comparing the strength of excitatory responses of each neuron to clicks presented to the animal contralaterally, ipsilaterally and binaurally. Response strength was defined as the spike rate (mean ± SD) obtained from all 16–20 repetitions of the click within a time window, which was set individually for each cell on the basis of its response characteristics (such as latency and duration of excitatory and inhibitory response components) so that it captured the peak firing rate. For each cell the same time window was used for contralateral, ipsilateral and binaural stimulation. Aural dominance was estimated and compared statistically using a pairwise *t*-test. *P* values of 0.05 or less were taken as the criterion for a significant difference in response strength. The results (Fig. 3B) further emphasize the contralateral dominance in the auditory activated OC. Interestingly, some of the electrode penetrations showed a clear contralateral dominance whereas others revealed either ipsilateral or binaural dominance. These findings are probably indicative of some columnar organization, a possibility that requires further experimental corroboration.

Binaural interaction was classified by comparing the strength of the response to binaural stimulation with that to stimulation of the dominant ear, using the same criteria as in the previous analysis. As in previous studies (e.g., Brugge and Merzenich 1973; Kelly and Sally 1988), we classified binaural interaction by a three-letter code: the first two letters designate, respectively, the responses to monaural stimulation of the contralateral and ipsilateral ears, where 'E' indicates an excitatory response and '0' no response. The third letter, separated from the first two by a '/', designates the kind of binaural interaction: 'F' is enhancement or facilitation of the dominant monaural excitation by binaural stimulation; 'S' is suppression of the dominant monaural excitation by

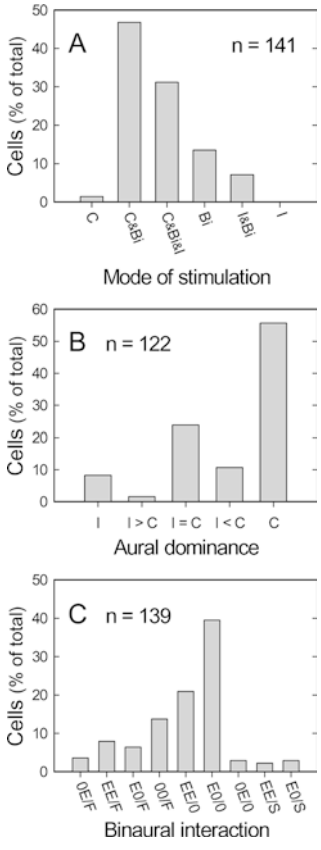

Fig. 3A–C Laterality, aural dominance and binaural interaction. **A** Laterality of cells revealed by their responsiveness to a click presented contralaterally, ipsilaterally (to the recording site) and binaurally. Note the dominance of a contralateral response as manifested by an exclusive response to contralateral stimulus (two cells), to contralateral and binaural stimulus or to all three modes of stimulation. *C* contralateral, *I* ipsilateral, *Bi* binaural. *n* total number of cells. **B** Distribution of aural dominance. Groups *I* and *C* indicate cells driven by one ear only (ipsilateral or contralateral, respectively). All other cells were driven by both ears. $I > C$ ipsilateral ear predominance; $I < C$ contralateral ear predominance; $I = C$ both ears elicit a similar response. Response strength (mean ± SD, spike s^{-1}) for each mode of stimulation was measured in 16–20 consecutive trains, using a time window that was set individually for each cell on the basis of response characteristics. The responses to ipsi and contralateral stimulation were compared statistically applying a pairwise *t*-test. Differences with *P* values of 0.05 or less were considered significant. **C** Binaural interaction. The first two letters designate, respectively, the responses to monaural stimulation of the contralateral and ipsilateral ears: '*E*' excitatory response, '*0*' no response. The *third letter* (separated from the first two by a '/') designates the kind of binaural interaction: '*F*' enhancement of the dominant monaural excitation by binaural stimulation; '*S*' suppression of the dominant monaural excitation by binaural stimulation; and '*0*' no effect of binaural stimulation on the dominant monaural excitation. Evaluation of response strength and statistical comparisons as in **B**. Note that in about 63% of the cells a binaural stimulus did not have any effect on the dominant monaural response (-/0)

binaural stimulation; and '0' no effect of binaural stimulation on the dominant monaural excitation. As a result of the relatively low spontaneous firing rates of the cells, we could reliably identify only two cells that showed a monaural suppression of the spontaneous firing rate. As our analysis was applied to binaural effects on excitatory monaural responses, these two cells were excluded from this analysis. However, a suppressive interaction could be detected in those cells in which a binaural stimulus significantly reduced monaural excitatory response.

Of 139 cells that were included in this sample (Fig. 3C), a binaural stimulus did not have any effect on the dominant monaural response (-/0) for 88 cells. More than half of these (55) were driven exclusively by contralateral stimulation. About 18% of the cells displayed enhancement of the monaural response (EE/F, E0/F 0E/F); about 14% could be driven exclusively by binaural stimulus (00/F); and only 5% showed a suppressive effect of binaural stimulation on the monaural response (EE/S and E0/S). Thus, in this regard the auditory activated visual cortex of the blind mole rat differs from the auditory cortex of albino rats, in which about 35% of the cells were shown to be of the EE/F type and about 42% of the E0/S type (Kelly and Sally 1988). Because of the relatively small number of cells that we sampled along each electrode track, we were unable to obtain a sufficiently reliable indication for a possible spatial or columnar organization as previously demonstrated in the primary auditory cortex of sighted species (e.g., Middlebrooks et al. 1980; Reale and Kettner 1986).

Response latencies

Latencies of neurons driven by ipsilaterally presented clicks ($n = 54$) ranged from 24 to 247 ms with a mean ± SD of 48.5 ± 32.6 ms and were significantly longer than latencies to contralateral stimulation ($n = 112$) which ranged from 18 to 86 ms with a mean ± SD of 33.5 ± 9.4 ms

Response latencies to binaural stimulation provided some information regarding the effect of binaural interaction on this parameter. For that purpose cells were divided into four sub-groups: cells that could be driven by all three modes of stimulation (binaural, ipsilateral and contralateral); by binaural and contralateral stimulation; by binaural and ipsilateral stimulation; only by binaural stimulation (Fig. 4). Latencies of neurons driven by binaural stimulation only and of those that responded to both binaural and ipsilateral stimulation were significantly longer than the latencies of neurons that were driven by both bilateral and contralateral stimulation or by all three modes of stimulation ($P < 0.001$; Bonferroni t-test). The significantly longer latencies of responses to ipsilateral, as compared to contralateral or binaural, stimulation is also apparent from the subset of 44 neurons that responded to all three modes of stimulation ($P < 0.001$) (inset in Fig. 4).

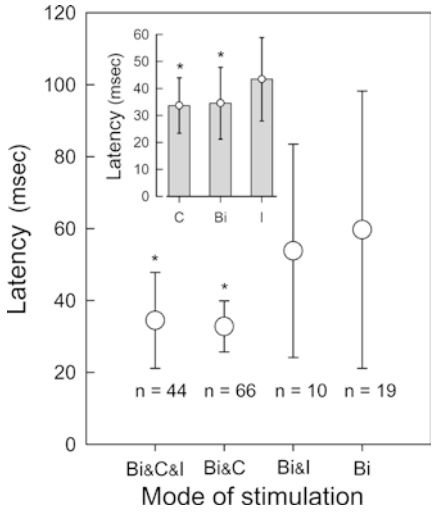

Fig. 4 Response latencies of single cells to clicks presented binaurally. Cells were divided into four sub-groups according to their responsiveness to the three modes of stimulation (see also Fig. 3A): cells that could be driven by all three modes of stimulation (*BiC&I*); by binaural and contralateral stimulation (*BiC*); by binaural and ipsilateral stimulation (*BiI*); only by binaural stimulation (*Bi*). Latencies to each mode of stimulation, of the BiC&I sub-set of cells are presented in the inset (*top*). Note the significantly shorter latencies to contralateral and binaural stimulation (one-way ANOVA, and a Bonferroni t-test for a pairwise multiple comparison, $P < 0.01$)

Responses to trains of clicks and SAM tones

Among the various behavioral, morphological and physiological adaptations of subterranean rodents (including the blind mole rat) to the underground life is the use of seismic vibrations for intraspecific communication (reviewed by Narins 2001). The blind mole rat generates these signals by short bursts of repeated head tappings on the roof of the tunnel, resulting in short periodic bursts (3–5 cycles) of vibrations (with most of the energy at frequencies ranging between 100 and 200 Hz) (Rado et al. 1987). The emitted vibrations are picked up from the soil by the receiver, through its lower jaw, and transmitted to its auditory system by means of bone conduction (Rado et al. 1989, 1998).

As an initial attempt to explore the possibility that the auditory-activated OC of the blind mole rat is somehow associated with the processing of these seismic communication signals, we used trains of clicks and of SAM tone bursts resembling the natural vibrations of the blind mole rat. The former consisted of four consecutive clicks with an inter-click interval of 150 ms and the latter of a 100-Hz carrier frequency and several sinusoidal modulating frequencies.

A sample of 50 cells that responded to a single click was subjected to trains of clicks, and all of these cells, as expected, responded to the leading click in the train (Fig. 5A). However, most of them (42 cells) responded only to the first click. The response pattern was similar to that elicited by a single click, consisting of a short excitation occasionally followed by some suppression of

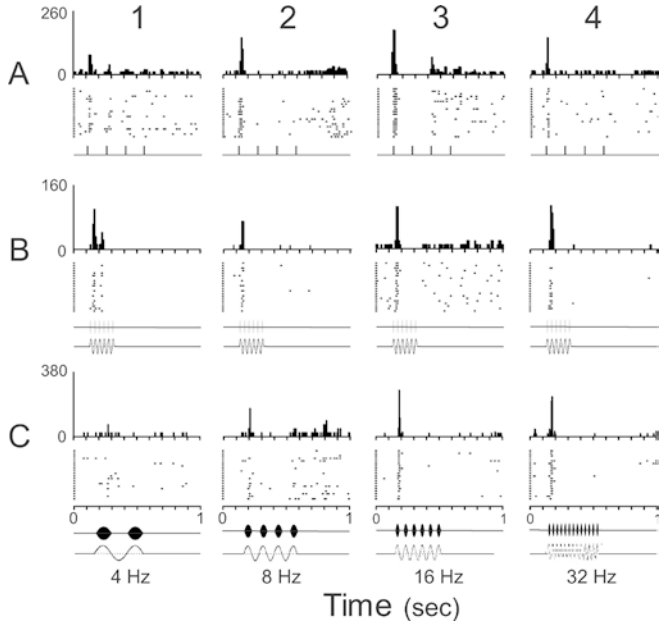

Fig. 5A–C Dot rasters and corresponding PSTHs illustrating responses of single cells to trains of short clicks and SAM tone bursts. **A** Responses of 4 cells (*1–4*) elicited by trains of 4 consecutive clicks (inter-stimulus interval: 150 ms). **B** Response of 4 different cells (*1–4*) to SAM tone bursts: carrier frequency — 100 Hz modulated by a 30-Hz sine wave. **C** Responses of a single cell to a carrier frequency of 100 Hz, sinusoidally amplitude modulated by four different frequencies (4, 8, 16 and 32 Hz). Ordinate of PSTHs: spikes s^{-1}. Timing of stimuli is designated by the envelopes of the stimuli at the bottom of each dot raster. SAM (**B** and **C**) stimuli are also represented by the sinusoidal waveform

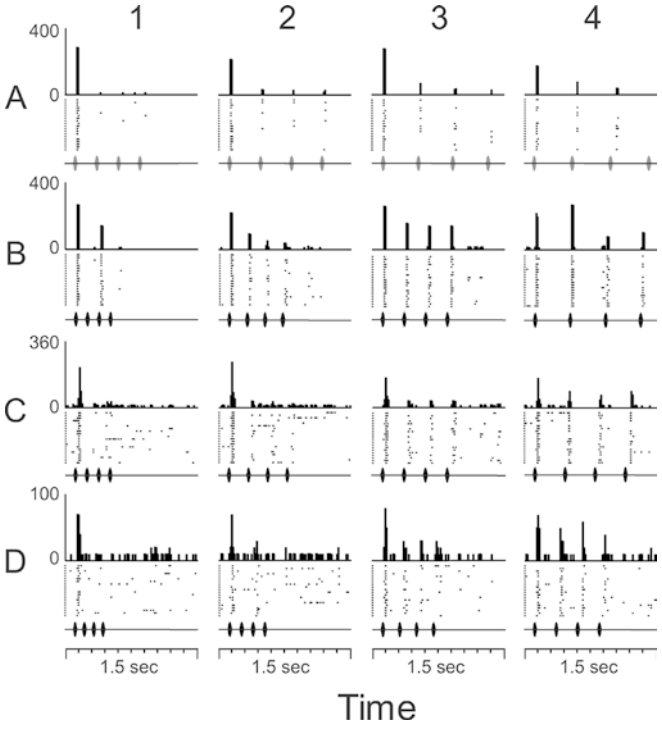

Fig. 6A–D Responses of cells to individual cycles of SAM tone. Dot rasters and corresponding PSTHs of four cells (**A**—**D**) to a burst of four sequential individual SAM tone pulses (carrier frequency 100 Hz, modulation frequency 30 Hz) with inter-pulse intervals systematically reduced (4−1). Timing and envelopes of stimuli are represented at the *bottom* of the dot rasters

spontaneous activity. In several cases this suppression was followed by a short rebound of spikes. Four cells responded to two clicks, one responded to three consecutive clicks and three cells were driven by all four clicks. In all cases where more than one click elicited a response, the response to the first click was stronger than those to the following clicks.

Of the 66 cells that responded to SAM tone bursts, 50 were tested with a modulation frequency of 30 Hz, and 16 with at least four modulating frequencies (4, 8, 16, and 32 Hz). In most cases only the first cycle elicited a response. This response consisted of a short excitation occasionally followed by some suppression of ongoing spontaneous activity. Figure 5B illustrates the responses of four different cells to 30-Hz SAM tone bursts, and Fig. 5C the responses of one cell to SAM tones of four different modulating frequencies. Four cells that were isolated along one penetration track were tested for their responsiveness to a sequence of four consecutive individual pulses of a SAM tone (100 Hz modulated by a 30-Hz sinusoidal wave) with the inter-pulse interval systematically reduced until the cell responded only to the first cycle (Fig. 6). It is apparent that the ability of a cell to follow sequential pulses is limited by the inter-pulse time interval and that this ability varies among the four tested cells. The minimum interval between consecutive pulses to which the cell clearly responded to all four cycles, though not necessarily at the same strength, ranged between 200 ms (Fig. 6B, panel 2) and 300 ms (Fig. 6A, panel 2).

Response to pure tones

Characteristic frequencies (CFs) and tuning curves, using audiovisual criteria, were determined for 24 single cells isolated along 16 penetrations in the left hemispheres of two mole rats. Of these, 17 had a single well-defined CF and the other 7 had distinctly double-peaked tuning curves. All CFs (except one) fell within two separate ranges, one extending from 80 to 125 Hz; and the other from 2,500 to 4,400 Hz (Fig. 7). Mean threshold SPLs in these ranges were 73.5 ± 7.6 dB SPL and 79.7 ± 8.0 dB SPL, respectively. The small number of CFs obtained precludes any conclusions regarding the frequency organization in this cortical area.

Discussion

General overview

Applying cyto- and myeloarchitectural procedures and using the metabolic marker 2-DG and the projection tracer HRP, we have previously shown that in the blind

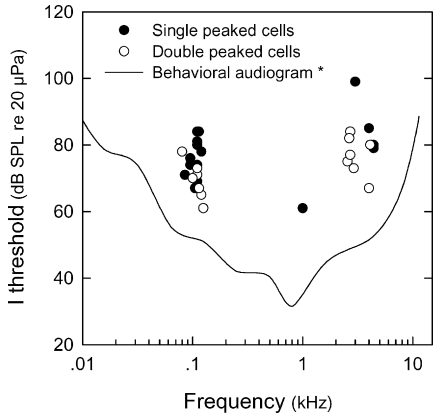

Fig. 7 Distribution of excitatory threshold intensities as a function of characteristic frequency (CF). *Solid line* is the mean behavioral audiogram of two blind mole rats (after Heffner and Heffner 1992). Note the two distinct subgroups of CFs corresponding to the most intensive spectral components of the vibratory intraspecific communication signals and the airborne vocalizations

mole rat (*S. ehrenbergi*) the dLGN as well as extensive areas of the OC can be activated by auditory stimuli (Bronchti et al. 1989, 2002; Heil et al. 1991). We have also shown that despite the almost total blindness of this fossorial rodent these cortical areas have retained the organization of a typical mammalian visual cortex; that they are reciprocally connected to the dLGN; and that the major origin of the auditory input to the visual system is the IC, which in addition to all its typical auditory targets, also projects to the dLGN (Doron and Wollberg 1994; Bronchti et al. 2002). Thus, it is apparent that the anatomically visual thalamo-cortical pathway, or at least a significant proportion of it, conveys and processes auditory information. In this study we described and characterized auditory responses of single cells in the OC of the blind mole rat, substantiating and extending our preliminary electrophysiological findings (Heil et al. 1991; Bronchti et al. 2002). These preliminary electrophysiological findings were challenged by Necker et al. (1992) who demonstrated somatosensory responses in the blind mole rat's OC, but failed to record auditory responses in this area. They suggested that the auditory responses demonstrated by us were in fact somatosensory responses resulting from our experimental procedures. In a recent paper (Bronchti et al. 2002) we provided evidence that refutes their criticisms. Moreover, we suggested that these investigators most probably missed the auditory responses in the mole rat's OC due to their experimental protocol. In that same study we looked for a possible somatosensory invasion into the mole rat's OC. Using the metabolic tracer 2-DG while stimulating the facial mystacial whiskers and reconstructing the cortical regions activated by these stimuli disclosed an area entirely compatible with the somatosensory cortex as defined by Necker et al. (1992) . Based on all our previous and present findings it is clear that extensive parts of the mole rat's OC are indeed activated by auditory stimuli. This, however, does not exclude the possibility that somatosensory input, other than from the facial mystacial whiskers, also invades the OC. Indeed, activation of visual areas by both auditory and/or somatosensory stimuli has been demonstrated in several congenitally blind or visually deprived animals (e.g., Asanuma and Stanfield 1990; Uhl et al. 1991; Alho et al. 1993; Kujala et al. 1995, 2000; Rauschecker 1995; Toldi et al. 1996; Kudo et al. 1997; Yaka et al. 1999; Izraeli et al. 2002) as well as in early blind humans (Sadato et al. 1996, 1998; Cohen et al. 1997, 1999; De Volder et al. 1997;Leclerc et al. 2000; Roder et al. 2000; Weeks et al. 2000).

Response properties

Lacking comparable data from the auditory cortex of the blind mole rat we compared the neuronal auditory responses in the OC with data from the auditory cortex of other mammals, especially rodents such as rats and hamsters. Some of the response properties that we examined resembled those typical of auditory cortex cells in various anesthetized mammals. This holds true with regard to temporal response patterns, some aspects of binaural interaction and the limited ability of the neurons to follow periodic stimuli such as trains of consecutive clicks and SAM tone bursts (e.g., Orman and Phillips 1984; Muller-Preuss et al. 1986; Schreiner and Urbas 1986; Phillips et al. 1988; Kelly and Phillips 1991; Langner 1992; Izraeli et al. 2002). These similarities are not surprising. A comparison of response properties of auditory cortex and brainstem cells, in sighted animals, indicates that the auditory cortex preserves some properties determined in the brainstem (Phillips et al. 1991). In the blind mole rat and in neonatally enucleated hamsters, and probably in other blind mammals too, it is the LGN that receives direct auditory input from the IC, the main mesencephalic auditory nucleus (Doron and Wollberg 1994; Izraeli et al. 2002) . Hence, the auditory information that reaches the dLGN and from there to the OC in these animals reflects, at least partially, processing up to and including the inferior colliculus.

Other response properties of auditory activated cells in the OC of the blind mole rat differed somewhat from those of a typical auditory cortex. About 67% of the cells that were tested with all the auditory stimuli that we used responded to at least one of them. This value is significantly lower than the values from auditory cortices of either normal or neonatally enucleated hamsters ($>90\%$) determined under the same experimental conditions and procedures (Izraeli et al. 2002) as well as from the auditory cortex of rats (e.g., Doron et al. 2002), but is similar to that (63%) found in the visual cortex of neonatally enucleated hamsters. It is possible that those cells in the OC of congenitally blind mole rats and neonatally enucleated hamsters that did not respond to auditory stimuli might be activated by other sensory modalities, most probably the somatosensory one. This

possibility is supported by earlier findings demonstrating the induction of somatosensory input into the LGN in congenitally blind mice (e.g. Asanuma and Stanfield, 1990) and the expansion of the somatic barrel field into the visual cortex in neonatally enucleated mice (Bronchti et al. 1992).

Response latencies to auditory stimuli, of neurons at all levels of the auditory pathway, vary with stimulus parameters such as rise time, rise function, SPL and spectral composition (e.g., Heil 1997a, 1997b). Hence, comparing latencies determined by different auditory stimuli and/or under different experimental procedures is not straightforward. The most relevant comparison, in our case, would be with data from normal and neonatally enucleated hamsters obtained in our laboratory under the same experimental procedures. We have shown that latencies of typical auditory cortex cells of normal hamsters do not differ from those of auditory cortical cells in enucleated hamsters, but are significantly shorter than those of auditory activated cells in the visual cortex of these enucleated animals (Izraeli et al. 2002). A statistical comparison (*t*-test) between latencies in the OC of enucleated hamsters and blind mole rats, revealed that in the latter the latencies are even significantly longer (mean ± SD: 24.9 ± 11.9 ms and 33.5 ± 9.4 ms, respectively; $P < 0.001$). Considering the relatively low sensitivity of this subterranean rodent to airborne sounds this is not too surprising. For the same reason it is very likely that latencies in the mole rat's auditory cortex are longer than those in the hamster's auditory cortex. This, however, remains to be corroborated experimentally.

The relatively high thresholds of the auditory activated cells in the OC are in accordance with behavioral data (Bronchti et al. 1989; Heffner and Heffner 1992), apparently reflecting the low efficiency of the mole rat's middle ear in transmitting airborne sounds (Rado et al. 1989, 1998). As shown previously, blind mole rats possess two parallel auditory communication systems, one for long distance and the other for short distance (Heth et al. 1987, 1988; Rado et al. 1987). The former, based on seismic vibrations that are picked up by bone conduction, enables intraspecific communication between individuals inhabiting remote tunnel systems. The latter, based on airborne vocalizations is used for communication between adults incidentally encountering each other in the same tunnel system, and between mother and pups. Considering that the airborne vocalizations are used only for short-distance communication, and taking into account the stethoscopic effect in the tunnels, the relatively low sensitivity of the blind mole rat to airborne sounds does not appear to be a degeneration but rather an adaptation to fossorial life. This low sensitivity was also manifested by the relatively high sound levels required to elicit responses in the OC. In some cases it was essentially impossible to construct reliable tuning curves and to determine the characteristic frequencies.

Intriguingly, however, unlike the behavioral audiogram of the mole rat, which has a single sensitivity maximum at about 1 kHz (see Fig. 7 and Heffner and Heffner 1992), the CFs that we observed fell into two distinct clusters (with one exception): one centered around 100 Hz, matching the most prominent spectral component of the vibratory signals used by the mole rat for long-distance communication, and the other ranging from 2,500 to 4,400 Hz, corresponding to the main spectral components of its airborne vocalizations. Neuronal threshold SPLs in these frequency ranges varied and the lowest thresholds were higher than the behavioral threshold. This difference results, most likely, from the different procedures and conditions under which these two types of experiments were conducted. However, the existence of two discrete groups of cellular CFs could also be a manifestation of some functional organization, a possibility that will be discussed later on.

In about 37% of the occipital cells that responded to sound — a binaural stimulus had an effect on the dominant monaural response — well below the typical values for the auditory cortex, such as 77% for rats (Kelly and Sally 1988). If these values are representative of the auditory system as a whole, they may reflect the poor sound-localization ability of this subterranean species (Heffner and Heffner 1992). Another plausible basis for the limited binaural interaction is that it is associated with the unique 'jaw hearing' of the blind mole rat. The vibrational signals that are used for long-distance communication by this species are picked up from the soil by the animal firmly pressing one side of its lower jaw, left or right, against the tunnel wall, and are transmitted thereafter by bone conduction (Rado et al. 1989, 1998). Hence, it is mainly one of the ears that is affected by these signals.

Periodicity

Intraspecific communication signals, used by various animals, often comprise periodic components. The use of such signals may be associated with the fact that the ability of the ear to detect weak periodic signals is enhanced in the presence of a wide dynamic range of background noise, a phenomenon referring to a nonlinear dynamic process known as 'stochastic resonance' (e.g., Ehrenberger et al. 1999; Henry 1999; Zeng et al. 2000). This is probably also pertinent for blind mole rats, which often inhabit noisy environments near or even under roads or railway tracks and whose periodic vibratory signals are the only means for long-distance communication. Indeed, amplitude-modulated tones that resemble the natural amplitude-modulated vibrations used by this subterranean species for intraspecific communication, were one of the two most effective stimuli that we used.

The consecutive vibratory cycles within each burst of the periodic modulated vibrations that blind mole rats use for long-distance communication are punctuated by silent periods of similar duration. The frequency of these cycles ranges between about 8 and 20 Hz with an aver-

age of about 13 Hz (Rado et al. 1987). As a first attempt to disclose possible coding of these specific modulation frequencies in the auditory activated visual cortex of this fossorial rodent, cells were examined for their responses to SAM tone bursts that simulate the natural vibratory signals of the blind mole rat. Within the range of modulation frequencies that we used, most cells responded only to the first cycle in the burst. Therefore, although we have some indication for the existence of cells that are sensitive to modulation frequency (as indicated in Fig. 6C), modulation transfer functions (rate-MTF and synchronization-MTF) and best modulation frequency (BMF) which have been used to describe periodicity coding of SAM tones in the auditory cortex of several mammalian species (e.g., Schreiner and Urbas 1986; Gaese and Ostwald 1995; Bieser and Müller-Preuss 1996; Schulze and Langner 1997), could not effectively been obtained. Moreover, considering the possibility that anesthesia might have had an effect on the response properties of these cells, a more definite answer to the question of how neurons in the blind mole rat brain encode auditory signals, particularly periodic signals, requires experiments with awake animals. Unfortunately, however, we did not manage to record reliably single cell responses from the brain of awake and not paralyzed mole rats. This animal is very strong, very aggressive and it is practically impossible neither to restrain it without seriously hurting it, nor having it moving free with implanted electrodes. All our attempts to do it, so far, failed. Hence, broadening our knowledge regarding the question of how different messages that are embedded in the periodic temporal patterns of the seismic signals that the blind mole rat uses for intraspecific communication requires further behavioral and electrophysiological investigation.

Presumptive function

Two questions are frequently raised regarding activation of the OC by somatosensory and/or auditory input in blind animals and humans. One question is whether this area represents an expansion of the typical auditory cortex and/or somatosensory fields into occipital regions at the expense of the original classical visual cortex; or is it, rather, that the preserved visual cortex has been taken over by the somatosensory and/or auditory input? The second question is whether this auditory or somatosensory recruited area has any behavioral function. Concerning the first question, we have shown that auditory input to the visual cortex results from a rerouting of auditory projections into the thalamo-cortical visual system rather than an expansion of the auditory system (Bronchti et al. 1989; Doron and Wollberg 1994) This also appears to be true with regard to neonatally enucleated hamsters (Izraeli et al. 2002), and probably other blind animals as well.

Regarding the second question, based on behavioral and some electrophysiological experiments it has been suggested that cross-modal neuronal reorganization in the blind might account for certain superior tactile and/or hearing capabilities (Rauschecker and Kniepert 1994; Lessard et al. 1998; Roder et al. 1999). This assumption, however, is not unequivocally supported by experimental evidence. Attempts to find a causal relationship between electrophysiological response properties in deprived visual areas and superior hearing or somatosensory abilities are scarce, and the results are not conclusive and remain debatable (for a detailed discussion on this issue see Izraeli et al. 2002).

As mentioned above, the existence of two distinct groups of cellular CFs in the OC of the blind mole rat, corresponding to the most intensive spectral components of the vibratory intraspecific communication signals and the airborne vocalizations could be associated with certain specific function(s). It is possible that the OC that has been recruited during evolution by the auditory system is dedicated, primarily or even exclusively, to enhancing processing of the two types of communication signals, while the overall hearing capability of the blind mole rat is represented by its behavioral audiogram. However, it should be stressed that there is no evidence that there is any enhancement of either hearing or seismic communication compared to non-blind animals like kangaroo rats and gerbils which also communicate by drumming.

Specialization of auditory sub-regions for the processing of specific auditory signals that have high survival value, in sub-primate mammals, is not without precedent. One such extensively studied case is that of echolocating bats, in which sub-regions of the auditory cortex are dedicated to the processing of their own emitted sounds and echoes used for echolocation (e.g., Suga 1984; Suga et al. 1998). To further explore these very intriguing issues, more combined behavioral, structural and electrophysiological experiments, using various auditory stimuli including the mole rat's own communication signals, should be conducted.

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