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Effects of Moderately Intense Sound on Auditory Sensitivity in Rhesus Monkeys: Behavioral and Neural Observations

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SUMMARY AND CONCLUSIONS

1. Hearing threshold shifts in decibels and recovery time courses in minutes were monitored in rhesus monkeys exposed to short-lasting, moderately intense tones at one-half octave intervals throughout the major portion of their hearing range and compared to similar effects of identical stimuli on the response properties of single cells in auditory brain stem nuclei.

2. Both the magnitudes and time courses for recovery of the hearing losses were a function of the frequency of the exposure stimulus with less effective low-frequency stimuli averaging 3- to 8-dB losses that lasted from 3 to 7 min, while mid- and high-frequency stimulation produced up to 14-dB losses that lasted about 15 min.

3. Several features of the neural findings in unanesthetized monkeys were comparable to those observed in the behavioral studies whereby elevations in threshold for neurons in the ventral cochlear nucleus (CN) and central nucleus of the inferior colliculus (IC) revealed mean shifts that were greater and longer lasting for mid- and high-frequency characteristic frequency (CF) cells than for units with low-frequency CFs.

4. Sound exposure produced a simple reduction in the discharge rate of evoked activity at all signal levels tested for the majority of units. However, approximately one-third of our unit sample demonstrated more complex postexposure changes involving the customary decrease in firing for threshold and near-threshold test stimuli at the same time that discharge rates to more intense tone bursts were increased above control levels.

5. Spontaneous activity for some units with moderate to high discharge rates was momentarily increased, while for others, a temporary reduction in spontaneous firing occurred. For low-spontaneous-rate neurons (<2 spikes/s), spontaneous activity was generally unchanged.

6. Short-lasting alterations were also observed in intensity-dependent properties as reflected in discharge rate functions and in latency distributions for first spikes.

7. Finally, recovery was generally more rapid for spontaneous than for driven activity and for inferior colliculus than for cochlear nucleus units.

8. These results indicate that overstimulation with short-lasting, moderately intense tones reduced the sensitivity and altered the driven and spontaneous discharge rates of neurons in auditory brain stem structures in a manner that correlated with some of the behavioral symptoms of sound-induced temporary hearing loss. The magnitude and duration of changes in neuronal activity were frequently much greater and longer lasting than those indicated by corresponding pure-tone behavioral threshold measures.

INTRODUCTION

The threshold of detection for a tonal stimulus has long been the accepted procedure for assessing the integrity of the hearing apparatus and has formed the basis of modern auditory science. However, several recent studies employing loud sound as an ex-

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perimental agent have demonstrated poor correlations between residual pure-tone detection capability and the associated anatomical alterations to the receptor organ (4, 30, 55). For example, when chinchillas were exposed to an octave band of noise centered at 500 Hz at 95 dB for varying numbers of days, outer hair cell losses in the apex of less than 30% were not accompanied by permanent elevations in threshold for low-frequency tones (4). In addition, significant abnormalities in cochlear nerve fiber discharges have been found in the absence of as yet detectable alterations in hair cell morphology (15, 17, 23). Such findings pose serious questions concerning the nature of stimulus coding and detection in the auditory system as well as raise important issues regarding the mechanisms of damage in a sensory system easily altered by stimuli present in everyday experience.

In our own studies, we have been interested in describing alterations in single-unit activity that follow exposures to less intense sounds that result in relatively small, temporary elevations in hearing threshold. A major impetus for this work was our initial observations that following moderate, pure-tone exposures of 90 dB lasting 1 min, the average discharge rates of cochlear nerve fibers were severely depressed for as long as electrode contact could be satisfactorily maintained, in some cases for up to 33 min (25). These results suggested that during brief episodes of threshold shift, neuronal measures may detect the initial subtle effects of sound damage by demonstrating a dissociation between behavioral and neural responses similar to that observed in other anatomical-behavioral studies.

In order to test this notion, our goal in the present investigation was to determine the limits of behavioral change to a restricted range of short-lasting, moderately intense acoustic stimuli so that quantitative single-unit data could be collected using corresponding parameters of overstimulation. These studies formed a first step in bridging the gap between the transitory effects of sensory adaptation (50, 51) and the more permanent receptor alterations that inevitably follow the application of intense sound (53). The primary measure of behavioral hearing loss was a change in threshold sensitivity for pure-tone detection, often referred to in the behavioral literature as a temporary threshold shift (TTS). By keeping the duration and intensity aspects of our exposure stimuli constant, we have focused on documenting the sensitivity-reducing effects of moderate sound on the detection of low-intensity test signals that were systematically related to the frequency of the exposure stimulus. The first portion of the report describes the effects of such stimuli on the hearing of behaviorally trained monkeys, while the remaining part details the effects of identical loud sounds on the response properties of single auditory brain stem neurons in the unanesthetized monkey using an experimental protocol that permitted a direct comparison of pre- and postexposure measures within the same neuron. The data to be presented indicate that our moderately intense, short-lasting stimuli produced brief, restricted hearing losses that were significantly less in both magnitude and duration than corresponding alterations in the responses of single cells. A preliminary report of some of these results has been presented (24).

METHODS

Subjects

Subjects were eight Old World rhesus monkeys (*Macaca mulatta*), seven young adult males and one adult female, weighing 3–6 kg. Six monkeys with normal auditory sensitivity participated in the behavioral studies and two of these subjects were included in the group of four monkeys studied electrophysiologically. All animals were housed individually in a primate colony with behavioral subjects maintained on a mild, food-deprivation schedule. Monkeys were tested daily in a standard primate chair with their heads secured by pressure of circumaural ear cushions and adjustable Plexiglas guides.

Behavioral procedures

Behavioral threshold testing was based on an operantly shaped, reaction-time task employing positive reinforcement techniques and has been extensively described elsewhere (26, 28, 29, 56). Briefly, monkey subjects were trained to depress a telegraph key at the onset of a visual alerting stimulus, to hold down the key for a variable prestimulus period (1–4 s), and to release the key rapidly on monaural presentation of a tone burst. Intertrial intervals had a mean duration of approximately 1 s and latency of key release fol-

lowing stimulus onset defined reaction time. Key release within 1,000 ms of stimulus onset indicated a correct detection and resulted in bananasauce reinforcement. "Catch" trials in the absence of pure-tone stimuli were regularly presented to estimate "guessing" on the part of the subject. These trials comprised approximately 10% of the total number of trials needed to estimate a given threshold.

Behavioral stimuli were confined to 14 pure tones located at half-octave intervals from 0.354 to 32 kHz. Stimulus intensity was adjusted in 10-dB steps except near threshold where 2-dB intervals were used and randomly varied every trial following the psychophysical method of constant stimuli. The more closely spaced threshold intensities in combination with the catch trials permitted the collection of threshold responses simultaneously with suprathreshold measures (34, 35).

Threshold values were determined by plotting percent correct detections as a function of stimulus intensity to form perithreshold curves. Thresholds were then read as points on these functions halfway between the guess rate and the 100% correct point. For suprathreshold measures, median response latencies were plotted as a function of stimulus intensity to form latency-intensity or LI curves. The slopes and relative positions of the LI functions were used to infer the relation between the relative loudness of stimuli and the growth of loudness as a function of stimulus intensity (3, 28, 34, 54).

Stimulus generation and calibration

A solid-state, digital logic system was used for initiation and timing of stimuli and for control of behavioral contingencies. The logic instrumentation paced an on-line computer system (Prime 200) that controlled stimulus frequency and attenuation and tabulated behavioral responses. All stimulus generation and control instrumentation were located outside the double-walled, sound-attenuated experimental chamber. Pure-tone bursts, 200 ms in duration with 5-ms rise-fall times, were generated by a programmable frequency synthesizer, monitored by an electronic counter, and presented via an ear speaker (Beyer DT-48, 200 Ω) fitted with a circumaural ear cushion. Broadband noise bursts generated by a random-noise generator were used as search stimuli to identify auditory cells. Continuous pure-tone exposures were provided by a circuit that permitted switching of the amplified output of an audiooscillator to the ear speaker. Exposure-stimulus levels were controlled by manual attenuators and durations were timed electronically. Measured harmonic distortion components were at least 60 dB below primary tones at outputs below 70 dB sound pressure level (SPL) and 45 dB down at 100 dB SPL. Calibration measurements at test- and exposure-stimulus frequencies were made using a one-half-inch microphone fitted with a calibrated probe tube (Bruel & Kjaer) that was mounted in the ear cushion so that the microphone output just lateral to the tragus could be filtered and read in millivolts root mean square (rms) on a conventional wave analyzer. These rms values obtained by presenting brief, unattenuated, continuous pure tones were converted to decibels of sound pressure level (i.e., dB SPL) relative to 20 μPa, the reference for all stimulus intensities noted.

Neural recording procedures

Single-unit recordings were obtained from awake monkeys, using chronic recording techniques previously described (27, 36). Briefly, these procedures involved stereotaxically implanting a cylindrical, stainless steel chamber (13 mm ID), fitted with a Silastic-rubber diaphragm, on the skull over the ventral portion of the cochlear nucleus complex and perpendicular to the horizontal plane, using coordinates (AP−4 mm, ML7 mm) adapted from Smith et al. (49). Following fixation of the neural cylinder with stainless steel screws and dental acrylic, a head brace was attached in a similar manner, anteriorly and posteriorly to the chamber, so that the subject's head could be stabilized relative to the chair during neural recording sessions. For single-unit recordings, a hydraulic microdrive was locked onto the recording chamber with the aid of a dovetail coupler that permitted the microelectrode to be directed in 0.5-mm increments, at any desired brain stem site located within 5 mm of plug center. This 10-mm range allowed us to record from neurons in both the cochlear nucleus and ipsilateral inferior colliculus within the same animal. The precise movement of the coupler and subsequent electrode penetrations were recorded using a detailed map of the cylinder surface. Stimuli were presented to the ear ipsilateral to the recording site for cochlear nucleus neurons and contralateral for cells of the inferior colliculus.

Microelectrodes were etched tungsten insulated with a synthetic jacketing material and heavily coated at the tip with Epoxylite varnish. To satisfactorily isolate cochlear nucleus units, it was essential that the electrode be characterized by a long, slender taper with the tip diameter restricted to 1–2 μm. Stable recording conditions were facilitated by electroplating the tip with an iron solution to spherically increase its diameter to about 5–7 μm. Electrodes were protected by a beveled stainless steel cannula that was driven through the diaphragm and into the brain to terminate within approximately 5 mm of the nucleus.

The signal from the electrode was coupled through a unity-gain field effect transistor (FET) follower to a high-gain preamplifier. Neuronal activity was isolated on the basis of standard visual and auditory monitoring techniques (18) or with feedback available through use of a hard-wired, dot-raster system. All unit data, acoustic stimuli, synchronizing pulses, and voice commentary were recorded on analog tape for later off-line analyses. Spike discharge activity was recorded for as long as isolation remained adequate to ensure a constant waveform for individual unit potentials.

Experimental protocol

A standard experimental protocol was developed that permitted both behavioral and neural data collection under essentially identical conditions. Figure 1 shows the four separate stages of this paradigm, consisting of preexposure, control, exposure, and postexposure intervals. In behavioral experiments, the monkey was tested briefly at a selected test frequency to characterize threshold and suprathreshold hearing (preexposure) as well as to confirm that threshold showed no marked deviation from normative values. Visual stimuli (control) were then introduced as a substitution for tone bursts to assess the disruptive effects of loud sound on task performance. When performing reliably to light stimuli, the exposure period was begun in which a 100-dB, continuous pure tone either at the frequency of the test stimulus or a half-octave below it (−½ oct) was presented for 3 min. Preliminary studies indicated that these values produced replicable behavioral threshold shifts with reasonable recovery times of no more than 15–20 min on the average.

Immediately on termination of the exposure, pure-tone test signals were reinstated to track the sound-induced changes in hearing. The first estimate of threshold could routinely be made within 2 min postexposure. Hearing data were collected for postexposure periods typically ranging from 10–30 min to establish that behavioral threshold had returned to its preexposure value.

All neural studies were based on a protocol that was essentially identical to that employed in the prior behavioral experiments. Following isolation of an acoustically responsive single unit, cell characteristic frequency (CF) and threshold were established using tone-burst stimuli in a nonperformance condition. During the preexposure period, the cell was tested at CF to systematically establish its threshold and suprathreshold response properties. Stimulus intensity was varied in 10-dB intervals with smaller 2-dB steps used near threshold. For each stimulus-intensity set, 10–15 tone bursts were presented at approximately 3-s intervals to completely describe dynamic range in terms of average discharge rate, latency to stimulus onset, and temporal response pattern. Stimulus sets typically tested five to six intensity levels that adequately described the control dynamic range properties. In the two behaviorally trained subjects, whenever possible, alterations in unit response characteristics and hearing measures were studied simultaneously.

Cells with CFs greater than 2 kHz were all exposed at the half-octave below the CF test stimuli while for low-frequency cells, the exposure stimulus was identical to the CF. These relationships of the exposure stimulus to CF have been shown to have the greatest effect in suppressing driven discharge rates of single fibers (25). Immediately on termination of the 3-min, 100-dB exposure period, pure-tone test stimuli at the various pretreatment levels were reinstated to determine the neural effects of overstimulation in terms of magnitude of threshold shift and duration of recovery time course.

Neural threshold shifts were calculated with

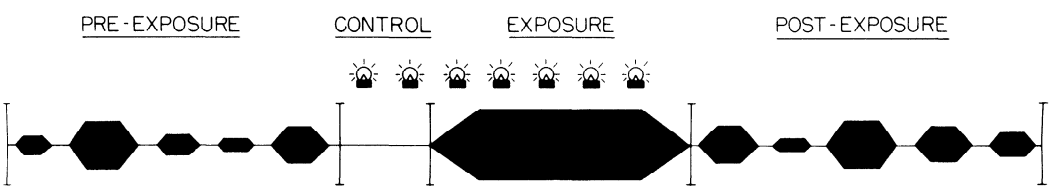

FIG. 1. Sequence of events in experimental protocol. In the preexposure stage, the pure-tone threshold for selected test stimuli was determined. Next, in behavioral experiments, to separate the purely disruptive effects of loud sound on task performance from those related to auditory system function, the animal was switched to a preexposure control period that required the performance of the reaction-time task to visual rather than auditory stimuli. When performing reliably to light stimuli for a 1-min period, the exposure period was begun in which a 100-dB, 3-min continuous tone systematically related to the frequency of test stimuli was presented. Immediately on termination of the exposure tone light stimuli were discontinued and test signals reinstated to track the magnitude and duration of the temporary elevation in threshold during the postexposure interval. In neural experiments, the paradigm was identical except that test stimuli were at cell CF and the preexposure control period involving light stimuli was omitted.

reference to rate-level functions by measuring the difference in decibels between pre- and postexposure signal intensities that resulted in the first consistent increase in discharge rate (>+1 SD) above spontaneous firing level. The recovery period was continued until either neural threshold returned to its control value or satisfactory electrode contact with the cell ended. When a cell was lost or injured during or immediately following exposure, sufficient time for complete behavioral recovery determined in the previous hearing studies was allowed. In addition, once a given CF region was stimulated, it was never reexposed within the same recording session. At the end of each successful electrode penetration, a microlesion was made by passing a 25-uA, anodal current (DC) for 15 s through the electrode tip.

Data analysis

On-line computer analyses provided trial-by-trial tabulations of the percent correct responses and median reaction times for each stimulus level. This capability permitted immediate updating of stimulus intensity in order to track the changing threshold efficiently. Loss in sensitivity was defined as the difference in decibels between the pre- and the first postexposure threshold. All performance data were stored on disks and following each experimental session, statistics that described threshold and suprathreshold hearing in the form of median reaction times and interquartile ranges were computed. Additionally, these statistics were automatically plotted as median response latency versus stimulus intensity or LI functions.

Neural-data analyses employed a series of standard programs to display unit response patterns in the form of dot-raster plots and peristimulus time (PST) histograms and compute descriptive statistics for average discharge rates and latencies within any desired peristimulus temporal period. Latency of spike discharge was computed from stimulus onset to the first evoked spike or any designated subsequent spike and was not corrected for acoustic or mechanical travel times. Categorization of temporal response patterns from PST histograms was based on 1-ms bin widths. Cochlear nucleus cell types were classified according to the electrophysiological categories originally distinguished by Pfeiffer (33) and later modified by Caspary (2). All PST histogram examples referred to in the text are displayed with 5-ms bin widths to increase resolution due to the restricted number of stimulus presentations per intensity.

Histological analysis

Following the completion of the 8- to 12-wk series of neural recording sessions, animals were perfused systemically under deep pentobarbital anesthesia and the brain removed and prepared for routine histological examination. A block of tissue containing the auditory brain stem was stereotaxically removed so that vertical cuts at predetermined anterior and posterior coordinates could be made parallel to the electrode tracks. Following fixation, the brain stem was frozen sectioned at 30-μm intervals, mounted, stained with cresyl violet, and microscopically examined to verify recording sites. Electrode locations were identified with reference to the cylinder maps and lesioned recording sites and documented with camera lucida drawings and/or photomicroscopy. Cochlear nucleus recording-site locations were specified in terms of their location within one of the three major identifiable subdivisions of the cochlear nucleus complex (42). Although it was not always possible to identify a particular electrode track for each cochlear nucleus unit, no lesioned site was ever located outside the region of the ventral cochlear nucleus. Lesioned inferior colliculus electrode sites were also identified with respect to its three major cytoarchitectonic subdivisions (39, 40), and all units recorded were located within the central nucleus.

Base-line measures of single-unit activity

All units recorded from the cochlear nucleus complex exhibited response properties in terms of discharge rate, latency, and temporal patterns previously described for antero- and posteroventral cochlear nucleus neurons in anesthetized preparations (2, 8, 13, 16, 33). Unit responses in awake monkey are briefly summarized here while a more detailed description will be presented elsewhere.

In the cochlear nucleus, spontaneous discharge rate ranged from 0 to 91 spikes/s ($\bar{x}$ = 25 spikes/s while that for maximum driven discharge rate to CF stimuli within 50 dB of threshold varied from 37 to 410 spikes/s ($\bar{x}$ = 178 spikes/s). Seventy-one percent of the cells possessed monotonic dynamic-range properties while the remaining units demonstrated simple nonmonotonic functions. The CFs of cochlear nucleus neurons ranged from 0.398 to 39.960 kHz while threshold values varied from −2 to 54 dB, with units having CFs between 2 and 25 kHz being generally more sensitive than neurons best tuned to lower and higher frequencies. Onset latencies varied from 2.8 to 9.2 ms ($\bar{x} = 6 \pm 2.7$ ms), depending on CF, with high-frequency units generally demonstrating faster response latencies. The most common temporal response pattern (78%) for the ventrally located neurons was primarylike with sustained firing throughout stimulus duration which, depending on stimulus level, was sometimes followed by an inhibitory period for intervals lasting about 50–

150 ms (see example in Fig. 7*B*). A small number of these latter response types demonstrated a change from a classical primarylike response consisting of the phasic onset burst of spikes followed by a sustained, steady-state discharge rate that was about 60% of the dynamic firing level, to a tonic "flat," primarylike pattern at intense stimulus levels (2). The remainder of the cochlear nucleus units demonstrated some form of "on" pattern that was usually associated with posteroventral recording sites (8, 33). These neurons were the only cells that displayed distinct changes in the temporal portions of the response pattern associated with stimulus level in that some on-cells became "onset responders" (2) to low-intensity, near-threshold tone bursts (see example in Fig. 7*A*).

For inferior colliculus units, the majority of which were located in the posterior aspects of the central nucleus, spontaneous firing rates ranged from 0 to 38 spikes/s ($\bar{x}$ = 12 spikes/s) while the driven activity varied from 32 to 217 spikes/s ($\bar{x}$ = 100 spikes/s), both of which were somewhat less than that observed for cochlear nucleus neurons. Characteristic frequencies ranged from 0.504 to 36.020 kHz with 56% of the cells best tuned to frequencies below 2 kHz. Unit thresholds varied between 1 and 53 dB while dynamic-range functions were nonmonotonic for 55% of our sample. Temporal firing patterns resembled sustained, primarylike, notched, or pauserlike (using the terminology of Kiang and associates (8, 9, 16) for similar patterns observed for posteroventral and dorsal cochlear nucleus cells) and onsetlike types. Additionally, some tendency for notched-pauser units to become primarylike at low stimulus levels was noted. At high stimulus levels, initial spikes demonstrated latencies varying from 6.8 to 22 ms ($\bar{x}$ = 11.9 ± 3.8 ms).

As a test for the validity of our hearing measures, we compared single-unit and behavioral thresholds measured under identical conditions in the awake, unanesthetized monkey. Figure 2 shows the mean hearing-sensitivity curve for the behavioral subjects and thresholds for neurons recorded from cochlear nucleus and inferior colliculus. Our sample of unit thresholds spans a 50-dB range with 44% of either CN or IC cell thresholds lying within ±1 SD of the behavioral threshold. The finding that many unit thresholds overlapped our average hearing function suggests that the behavioral procedures provided an accurate measure of auditory sensitivity.

RESULTS

The primary purpose of our behavioral studies was to document systematically the temporary hearing loss resulting from exposure to short-duration, moderately intense stimuli so that these effects could be compared to similar changes in the responses of single brain stem neurons. Our routine tones produced little effect on hearing sensitivity at the lowest frequencies, but as frequency increased, threshold shift increased and was maximum at the highest test frequencies. Under identical conditions, the responses of 80 single brain stem neurons that satisfied the strict criterion of remaining well isolated for a minimum of 10 min following the exposure period were quantitatively studied. Of these units, 46 were known or judged on the basis of average latency to the first spike and temporal response characteristics to be located in the ventral cochlear nucleus, while the remaining 34 neurons were histologically verified to be located in the central nucleus of the inferior colliculus. Following the application of sustained stimuli, we observed effects on: *1*) evoked discharge rates, *2*) spontaneous firing, *3*) intensity-dependent rate and latency functions, and *4*) temporal patterns of activity. The effects of exposure stimuli on neural response properties were generally similar for both cochlear nucleus and inferior colliculus units, and only significant differences between these anatomical loci will be emphasized. Examples referred to in the text are limited to the ventral cochlear nucleus neurons as a logical first step in relating central changes to current studies of cochlear (e.g., Ref. 4) and eighth nerve (e.g., Ref. 23) alterations in sound-damaged ears.

Neurobehavioral comparisons

A primary goal of the present study was to determine the relationship between short-duration behavioral threshold shifts and corresponding neuronal measures. Figure 3 illustrates plots of median behavioral and neural threshold shifts in decibels as a function of the frequency of test stimuli. The behavioral curves (solid lines) show the effects of overstimulating either at the test frequency (open circles) or −½ oct below it (filled circles). Close inspection of the behavioral threshold shift functions reveals that our routine tones produced no effect on hearing at the lowest test frequency of 500 Hz, while between 707 Hz and 8 kHz, threshold shift ranged from 3 to 8 dB. As

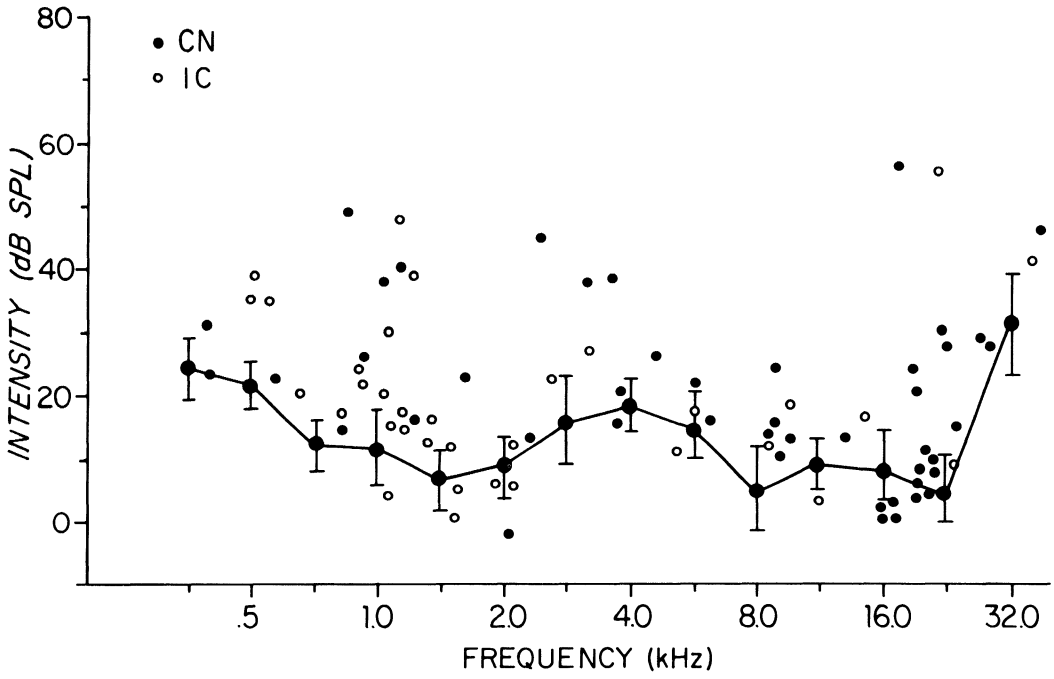

FIG. 2. Comparison of single-unit and behavioral thresholds under identical closed sound-field conditions. The solid line represents the mean sensitivity curve with variability indicated by standard deviations (vertical lines), for behavioral subjects at 14 selected test frequencies located at one-half-octave intervals between 354 Hz and 32 kHz. Thresholds for cochlear nucleus and inferior colliculus neurons from monkeys participating in the neural experiments are represented by the filled and opened circles, respectively.

frequency increased, threshold shift increased and was maximum at 14 dB for the highest test frequency of 22.6 kHz. It is important to note that above 5.6 kHz, exposure at the frequency of the test stimulus greatly reduced the amount of hearing loss measured at that frequency.

Not unexpectedly, recovery time was consistently found to be positively related to the severity of the hearing loss in that the greater the threshold shift, the longer the duration of the postexposure period. Thus, for low- and mid-frequency stimulation, recovery to control behavioral thresholds took, on the average, 3–7 min, while the more effective high-frequency exposures produced longer recovery times that were on the order of 12–15 min.

The dashed-line function above the behavioral curves illustrates the median amount of loss in sensitivity for neurons best tuned to CFs within the frequency ranges exposed and shows a good correspondence with respect to general pattern to that predicted by the contour of the hearing-loss function for the −½ oct condition. The principal finding was that both the magnitudes and durations of the elevated neural thresholds were much greater and lasted longer than those indicated by the pure-tone behavioral measures. For example, very-low-frequency exposures, which were behaviorally ineffective, commonly elevated neural thresholds an average of 5 dB, while for mid- and high-frequency exposures, median shifts ranged between 10 and 25 dB. Similarly, recovery periods were longer, ranging from 8 min for low-frequency stimuli to 56 min for high-frequency exposures. The great disparity between recovery times for unit and behavioral thresholds made it difficult to compare them quantitatively since many units were lost before recovery to control firing was complete.

Exposure activity

A reduction in driven activity was always observed for neurons during the exposure period. Briefly, discharge rate declined rapidly at first and then more slowly, after which firing asymptoted at a fairly constant

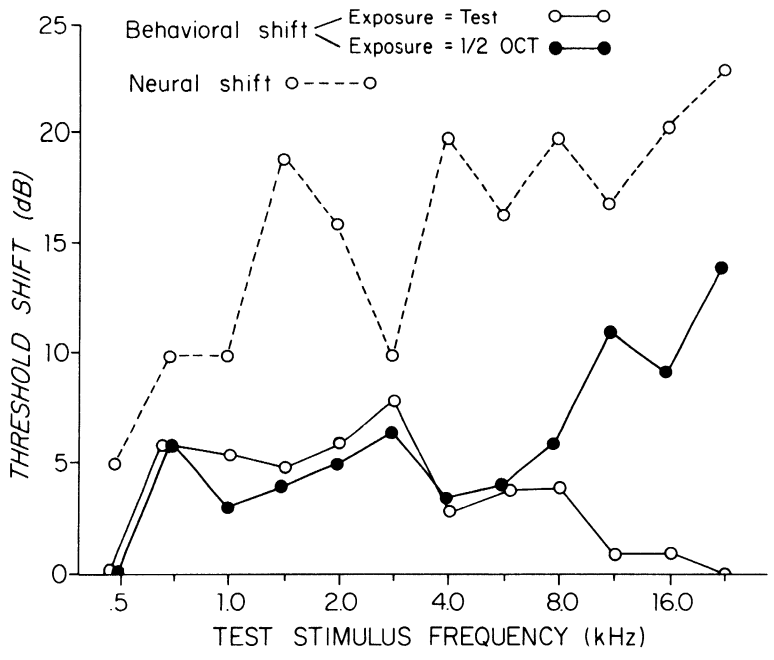

FIG. 3. Magnitude of behavioral versus neural threshold shifts. The solid curves illustrate elevations in behavioral threshold in median decibels (open circles: exposure, test stimulus; filled circles: exposure, $-\frac{1}{2}$ oct) as a function of frequency of test stimuli represented by 12 discrete frequencies between 500 Hz and 22.6 kHz. Each data point represents results of at least three experimental sessions (range, 3–20). These data were pooled from all six behaving monkeys to permit a measure of effects of moderately intense sound across the major portion of the monkey hearing range. The dashed line function above illustrates the median amount of loss in sensitivity for brain stem neurons best tuned to CFs within the frequency ranges exposed and shows a greater magnitude of threshold shift for single cells than for hearing.

rate within the first 30 s of the exposure interval. It is significant that similar to that observed for primary units (25, 59), the average discharge rate did not fall below spontaneous firing levels and that the amount of reduction in evoked firing by the end of the exposure failed to predict the magnitude of the resulting threshold shift ($r = 0.21$).

Postexposure evoked discharge rate

Many of the classic effects of exposure to loud sound are consistent with the notion of a simple reduction in sensitivity of peripheral auditory receptors. Consequently, one would expect brain stem neurons to reflect such a reduction by requiring higher sound pressure levels to obtain discharge rates identical to control firing. This effect was observed for approximately 64% of our unit sample and is illustrated in Fig. 4 which shows representative individual and group mean recovery functions at two typical stimulus levels, threshold (Fig. 4*A*) and 30 dB above threshold (Fig. 4*B*), as a percent of the preexposure control rate to the logarithm of recovery time. Although not apparent in these rate-recovery plots, on the average, postexposure threshold-test stimuli 20 dB more intense were needed to evoke the same discharge rate elicited by less intense signals during the pretreatment interval.

Both the individual recovery-time courses and their mean curves illustrate several additional findings typically observed for exposed brain stem neurons. For example, although all test-signal levels elicited decreased postexposure discharge rates, the activity evoked by threshold and near-threshold stimulus intensities demonstrated the largest reductions and took longest to approach recovery values, while driven activity to more intense suprathreshold stimuli was somewhat less affected and recovered more rapidly. Based on a number of observations during the first few minutes following cessation of the sustained tone, plots relating recovery

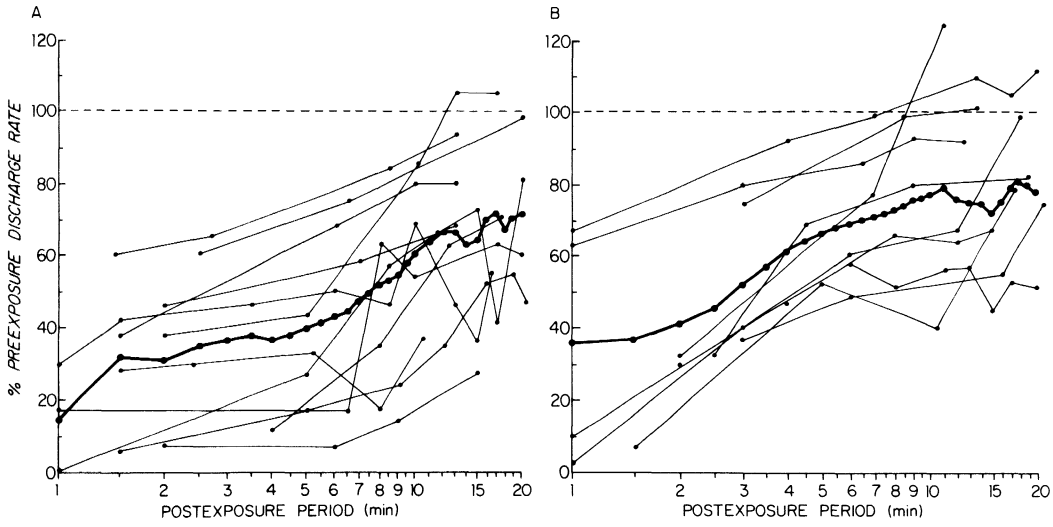

FIG. 4. Individual (small circles) and mean (large circles) recovery curves for cochlear nucleus neurons showing reduced postexposure discharge rates for threshold test stimuli (*A*) and tone bursts 30 dB above threshold (*B*) over the first 20 min of the recovery period. Although there was great variability in the course of recovery, neurons showing a decrement in driven rate often demonstrated only partial recovery to preexposure firing levels even if recording could be carried out over a reasonably long time interval. Note that even though the postexposure process reached a plateau at a similar precent level of recovery, recovery to 70% of the control rate to threshold-related tone bursts took about 9 min longer than for stimuli 30 dB above threshold. For these and all following recovery plots, driven discharge rate is expressed as a percentage of the average control rate for a specific signal level normalized by subtracting the corresponding spontaneous rate from the total firing rate. The dashed line parallel to the abscissa indicates the average evoked activity required to return to control firing levels.

of discharge rate to log time suggested that unlike that observed behaviorally, the neural recovery-time course demonstrated several distinct phases, both of which were approximately linear in log time. Thus, following an initial slow stage of recovery, the return to normal firing generally became more rapid before reaching a plateau at approximately 10–15 min postexposure. Additionally, a frequently observed finding for neurons demonstrating substantial decrements to all stimulus levels tested was the failure to return to control values even when the recovery period could be monitored for up to 60 min following overstimulation. Moreover, on occasion, slight reversals of the recovery process, 8–10 min postexposure, were observed when discharge rates showed transient small decreases as if more intense stimuli might be capable of contributing to the initial decrement.

Comparing the mean curves of Fig. 4*A* and *B*, it is apparent that for suprathreshold stimuli, the later rapidly recovering stage occurred earlier in the recovery process (3–5 min) than it did for threshold-related stimuli (7–12 min). These differential recovery rates tended to bring the initially parallel functions into closer approximation at the plateau stage. Extrapolation of these data to longer recovery times suggests that intensity-dependent processes would eventually become negligible.

A second general effect of moderately intense sound on evoked firing rate to be contrasted with an overall decrement in driven discharge rate to all levels of test stimulation was that for some units, postexposure firing to high-intensity test stimuli increased above pretreatment values, while those elicited by near-threshold signals decreased below control rates. This dissociative effect on driven discharge rate, documented in approximately 36% of our sample, is illustrated for a typical unit in Fig. 5 where increased firing to suprathreshold stimuli coexisted with decreased discharge rates to low-level stimuli that were below control values. Although for this particular neuron, the recovery time to control firing levels was similar for facili-

tated and reduced activity, it was not uncommon for supradischarge rates to return to within ±1 SD of pretreatment values somewhat sooner. Although not apparent in Fig. 5, for cells that demonstrated a decrement in spontaneous firing, resting activity frequently recovered more rapidly than did the corresponding decreased evoked discharge rate for near-threshold test stimuli.

Postexposure spontaneous discharge rate

Approximately one-third of the units sampled showed no difference between mean pre- and postexposure spontaneous firing during the 500-ms period preceding stimulus onset. The majority of these cells with unaffected spontaneous discharge had extremely low resting rates, typically under 2 spikes/s. The remainder of our sample showed either a transitory decrease or increase in spontaneous discharge rate following overstimulation. Examples of temporary decrements in spontaneous activity are illustrated in Fig. 6*A* for a number of cochlear nucleus units. For these neurons, evoked discharge to near-threshold stimuli was also reduced at the same time that firing levels to high-intensity, suprathreshold stimuli could be either decreased or elevated. Reduced spontaneous activity generally recovered over a longer postexposure interval than elevated spontaneous firing, but routinely returned to within ±1 SD of control rates more rapidly than did corresponding decremented activity evoked by low-intensity test stimuli.

Several examples of the facilitatory effect, which was usually associated with a relatively high pretreatment spontaneous firing level, are illustrated in Fig. 6*B* for other cochlear nucleus neurons. It is evident from this plot that increases in spontaneous firing always recovered within the first few minutes of the recovery period.

Postexposure spatiotemporal response properties

Postexposure temporal firing patterns at a given sound pressure level were most often attenuated versions of the same basic pretreatment responses. For other more complex neurons, which demonstrated intensity-dependent alterations in control response patterns, the exposure treatment, at first inspection, appeared to alter the firing pattern of these units. For example, the histogram at the left of Fig. 7*A* illustrates the preexposure temporal discharge pattern of a cochlear nucleus neuron to high-level CF tone bursts that can be described as displaying the familiar burst in firing rate associated with stimulus onset followed by sustained activity at a lower level for the duration of the stimulus. However, as indicated by the middle histogram, less intense test stimuli elicited an onsetlike respnse pattern during the preexposure interval. It is clearly evident in the last histogram (DUO11C-0110) that immediately following exposure, moderately intense test signals evoked an onset activity pattern formerly associated with much less intense, near-threshold tone bursts. Thus, when loss in sensitivity was compensated for by increasing tone-burst intensity, apparent changes in the temporal activity pattern disappeared.

Another alteration in temporal response properties is demonstrated below in Fig. 7*B*, showing in the plot on the left the pretreatment histogram for a cochlear nucleus neuron that was characterized by a long-lasting inhibitory period in which spontaneous firing was suppressed following the cessation of moderately intense test stimuli. However, the adjacent preexposure histogram indicates that less intense stimuli evoked a significantly shorter poststimulus decrement in spontaneous activity. Following exposure, as depicted in the histogram at the right of Fig. 7*B*, the poststimulus inhibitory period was considerably reduced so that high-level stimuli evoked approximately the same poststimulus response pattern that much less intense signals did during the control period. Again, these apparent alterations in the unitary firing pattern associated with tone-burst stimulation appeared to simply reflect a projected loss in peripheral sensitivity rather than a change in inherent temporal response characteristics.

Finally, since the temporal portions of the response patterns for cochlear nucleus neurons in the ventral region commonly exhibited both a dynamic and a steady-state component, it was of interest to determine if differential effects of sound exposure on these responses could be demonstrated. Since alterations in the control response sometimes occurred as a function of stimulus level, a

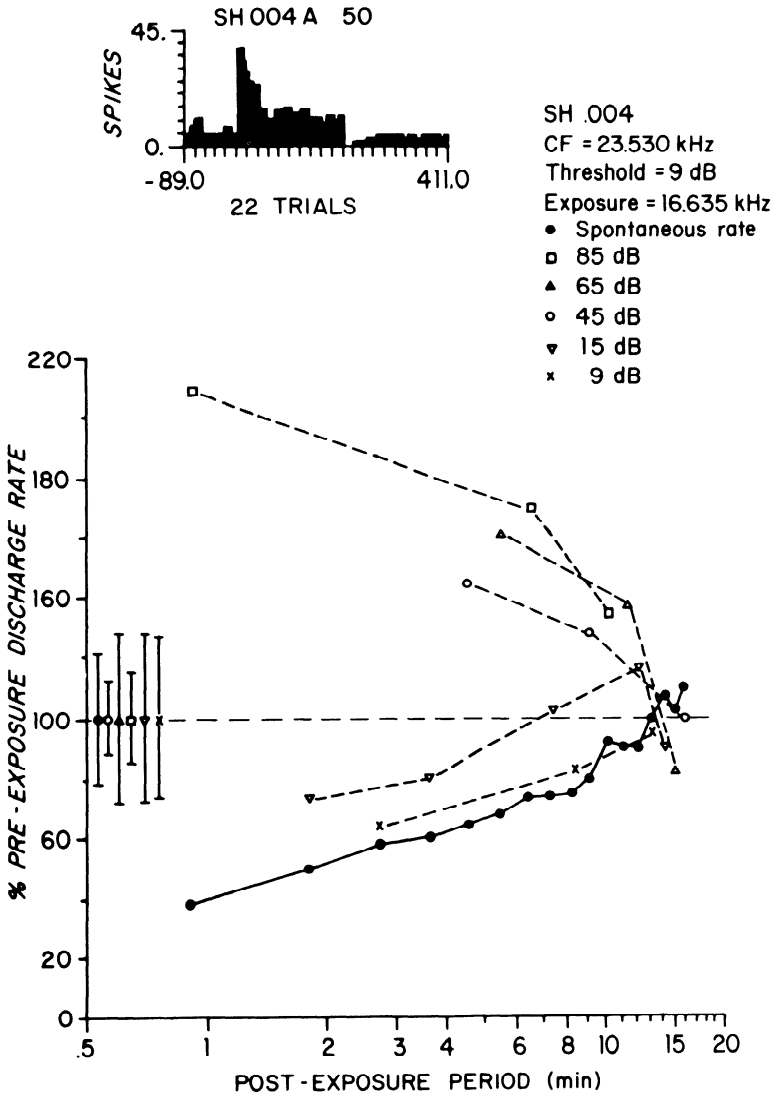

FIG. 5. Rate-recovery functions for a representative cochlear nucleus neuron (SH004) following sustained overstimulation, one-half octave below CF, that displayed facilitated discharge rates to suprathreshold stimuli, while evoked firing to low-intensity, near-threshold stimuli were below control values. Note the clearly visible increased postexposure response to the 85-dB tone bursts and the concomitant reduced postexposure response to the lower intensity tone bursts at 9 and 15 dB. Not apparent in this plot is a 14-dB shift in unit threshold at the same time that the corresponding behavioral threshold was elevated only 2 dB. The standard deviations for the mean discharge rates elicited by each test stimulus level in the preexposure period are indicated by the vertical bars on the appropriate unconnected symbols in the upper left portion of the plot. The PST histogram inset illustrates the primarylike temporal response pattern for this unit drawn from an actual computer printout. For this and all subsequent histograms presented, the label indicating animal and unit number is at the top of each plot. The ending letter A indicates that the histogram was averaged from data collected during the preexposure period while a C signifies data collected during the postexposure recovery interval. The two numbers following the unit label indicate the amount of attenuation in decibels applied to the maximum output of the system at CF. In the poststimulatory C periods of subsequent figures, the signal attenuation values are represented by the last two of a four-digit number with time postexposure coded by the first two numbers. The abscissa begins 89 ms before the tone switch on-pulse (origin) and includes 411 ms following this event. The time base is calibrated in 20-ms intervals and all tone-burst stimuli lasted 200 ms. Values of the indication marks along the ordinate vary between two and four spikes, depending on the maximum value of the y axis. The number of stimulus presentations the unit histogram was based on is indicated under the abscissa and was constant within a neuron for each signal level.

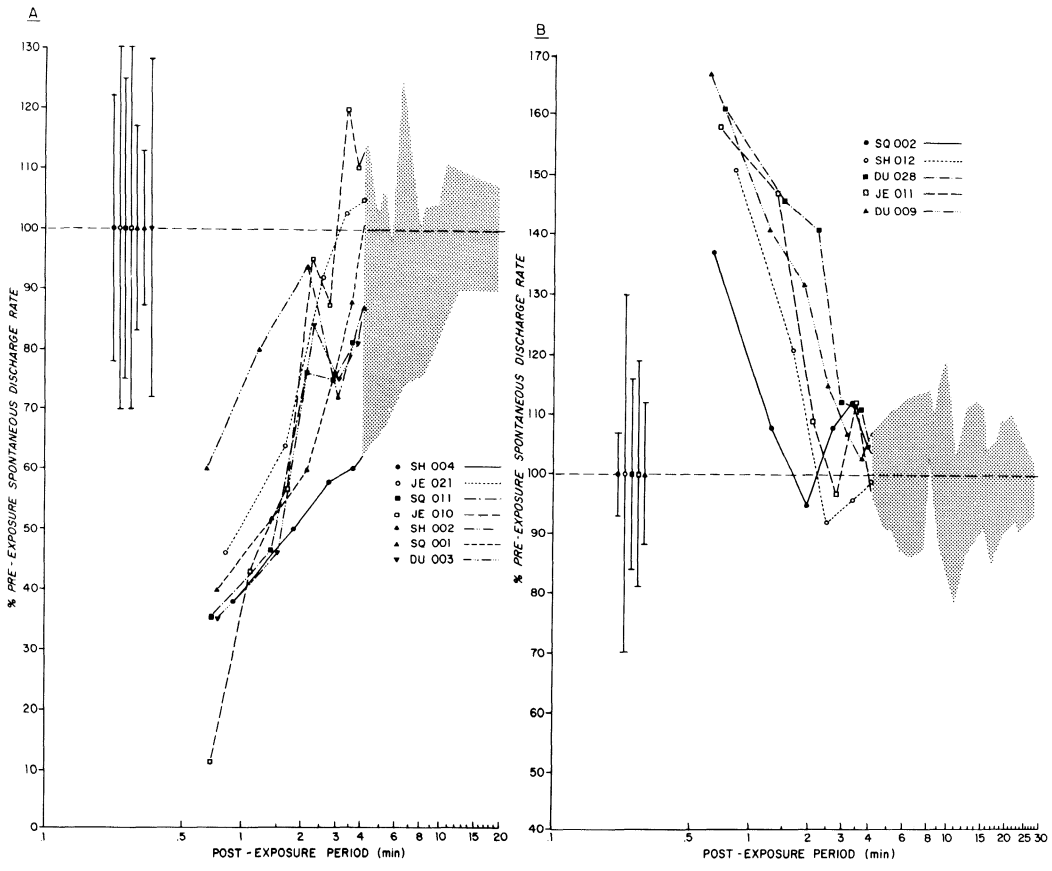

FIG. 6. Postexposure time course recovery for spontaneous activity for cochlear nucleus units showing either a reduction (*A*) or facilitation (*B*) in discharge rate. Neurons showing a decrease in spontaneous firing level tended to recover slightly slower than those demonstrating an increased response rate, even though the magnitude of the initial change in either direction was similar. The stippled regions represent times postexposure when the range of discharge rates for individual units became indistinguishable as they approached the preexposure distribution of firing levels shown at the left.

comparison of onset versus sustained components was not meaningful in every case. However, Fig. 8 illustrates a representative analysis for a unit that demonstrated an overall decrement in poststimulatory discharge rate to both threshold and suprathreshold stimuli using measures that compared firing rate during the first 10 ms of the onset response to a similar interval during the sustained portion, 50 ms following stimulus onset. For this and similarly analyzed cells, the static component during the reduced firing state demonstrated a greater decrement in response rate than did the phasic portion in terms of percent reduction, but the slopes of their respective recovery curves were roughly equivalent. Thus, similar to that observed for adaptive properties in primary nerve fibers (50, 51), onset and steady-state postexposure responses recovered in parallel.

Postexposure dynamic range

In instances where relatively complete postexposure rate-intensity functions were obtained, changes in the slopes of these functions could be consistently related to observed alterations in average discharge rate in that slopes tended to: *1*) decrease for units displaying depressed discharge rates to all stimulus intensities tested, and *2*) increase for neurons showing an elevation in firing to suprathreshold stimuli concomitant with a reduced discharge rate to near-threshold

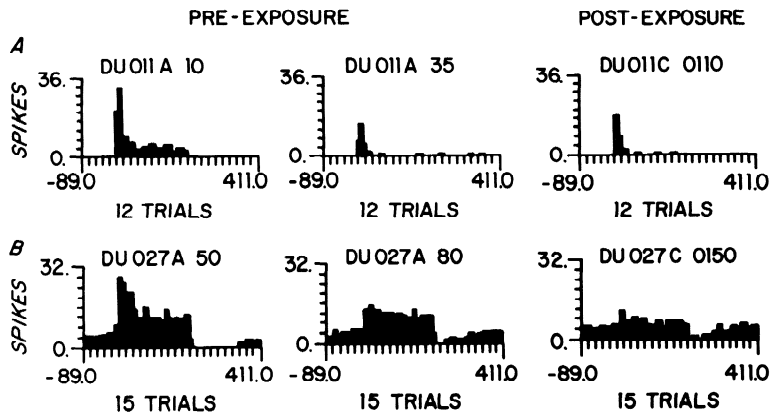

FIG. 7. Instances of apparent changes in temporal response pattern that can be ascribed to loss in sensitivity. The first histogram in *A* illustrates the preexposure primarylike response pattern evoked by intense, 86-dB (attenuation, 10 dB), CF stimuli (17.12 kHz), while the adjacent histogram shows the onsetlike response elicited by less intense, 61-dB tone-burst stimuli (attenuation, 35 dB). Immediately following exposure at $-\frac{1}{2}$ oct, the last histogram of *A* shows that the temporal response pattern averaged from the more intense signals, now resembled that of the less intense control stimuli. In *B*, the preexposure response pattern of a cochlear nucleus unit (CF, 3.74 kHz) to moderately intense, 51-dB tonal stimuli (attenuation, 50 dB) shown at the left was characterized by a prolonged inhibitory period where spontaneous discharge rate was depressed for about 120 ms following the stimulus-off pulse, while the postresponse inhibition was much less obvious at a near-threshold stimulus level of 21 dB (attenuation, 80 dB) in the middle histogram. Following exposure, the postresponse temporal pattern to the 51-dB tone bursts illustrated at the right of *B* resembled that originally elicited by the less intense 21-dB stimuli.

stimuli. As demonstrated in Figs. 9 and 10, appropriate and simultaneous changes in the distribution of the latency of the first spike to stimulus onset were also observed. Figure 9*A* illustrates that for cells demonstrating a decrement in firing during the postexposure period to all levels of test stimulation, the average latencies of the first potentials increased to stimuli representing three different intensities. Figure 9*B* clearly shows the related increase in the distribution range of the occurrence of these initial spikes along with the corresponding values computed for the next four successive potentials, i.e., for the first through fifth spikes, at the three sound intensities tested. For units showing postexposure increases in evoked activity to suprathreshold stimuli associated with a concomitant reduction in response to threshold-related signals, Fig. 10*A* illustrates the decrease and increase, respectively, in the mean spike-initiation latency at a number of representative stimulus levels. Figure 10*B* shows the corresponding tightening of the distribution of these shortened latencies for the first five spikes of the evoked responses to high-level tone bursts as well as the expected increase in onset latencies for threshold-related stimuli.

For nonmonotonic neurons, postexposure changes in dynamic-range properties were analogous to those observed for the monotonic cells of Figs. 9 and 10. Thus, for nonmonotonic units showing a postexposure decrement in evoked activity to all stimulus levels, exposure stimuli reduced the maximum discharge rate attained as well as the rate of increase and decrease in firing with increasing stimulus intensity. Similarly, for this same class unit, neurons demonstrating increased discharge to suprathreshold postexposure stimuli also showed steeper ascending and descending slopes for their nonmonotonic rate-intensity curves.

Peripheral versus central changes

Our neural data suggest that unit threshold shifts tended to be slightly but not significantly greater for more peripherally located cochlear nucleus cells ($\bar{x} = 20 \pm 13$ dB) than for inferior colliculus neurons ($\bar{x} = 18 \pm 10$ dB). Additionally, the more rostrally located neurons of the inferior colliculus appeared to recover from the effects of sustained overstimulation at a faster rate than did the second-order neurons in that given similar recording times, almost one-

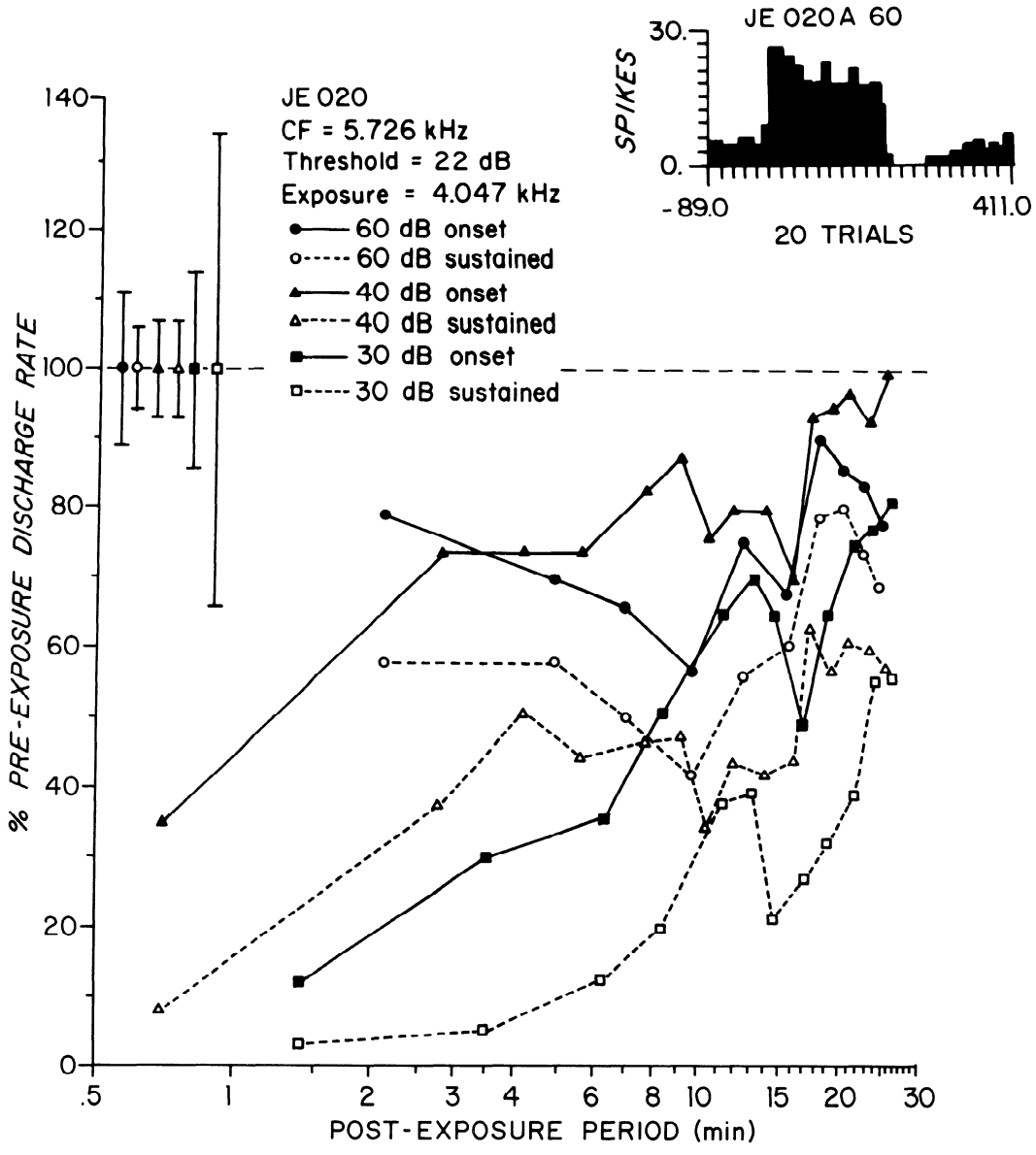

FIG. 8. Analysis of changes in the discharge rate during the onset and steady-state portions of the temporal response pattern for cochlear nucleus unit JE020 demonstrating an overall reduction in postexposure discharge rate. Both portions of the response showed reduced activity levels with the sustained component being more drastically affected by the exposure and, consequently, taking longer to approach control firing values. However, slopes of the recovery curves were approximately parallel for the two related recovery time courses.

half of the higher level units returned to their pretreatment values before electrode contact became unsatisfactory while only a few cochlear nucleus neurons recovered to control firing levels. Table 1 compares shifts and recovery times for brain stem neurons recorded from one subject demonstrating that although the magnitudes of the initial postexposure threshold shifts were almost equivalent, recovery from sustained sound stimulation tended to occur more rapidly for neurons located in late brain stem structures compared to those situated more peripherally in the cochlear nucleus.

DISCUSSION

The principal goal of the present series of investigations was to expose unanesthetized monkeys to short-lasting, pure-tone stimuli so that postexposure measures of behavioral threshold shifts could be directly related to the responses of single brain stem neurons obtained under identical stimulating conditions. To the extent that neuronal changes produced by our short-term stimulations corroborate findings based on the more intense noise exposures of other studies, we can begin to identify the cellular mechanisms underlying the well-documented transition from temporary to permanent noise-induced hearing loss under conditions of repetitive overstimulation (7).

Threshold shift and recovery

A basic finding was that the majority of our neurons were considerably more affected by loud sound in terms of amount of threshold elevation and duration of recovery course than would have been predicted by the behaviorally measured hearing losses. Sound exposure produced elevations in behavioral threshold ranging, on the average, from 7 dB for lower test frequencies to 14 dB for the more sensitive higher frequency stimuli that typically lasted no more than 15 min. However, units with CFs within even the less sensitive low-frequency hearing range routinely demonstrated shifts of 20 dB or more with correspondingly longer recovery times.

The precise mechanism whereby behavioral hearing apparently compensates for such widespread neuronal loss is at present unknown. Behavior may "fill in" for the subtle damage caused by exposure stimuli by reflecting input from a large population of neurons with hearing threshold being less affected than any one cellular element that is functionally connected to a very restricted cochlear locus. Under these conditions, neurons innervating hair cell-damaged regions of the organ of Corti may also receive an unaffected input from distant normal functioning areas, supporting the notion that remote cochlear locations contribute to the transduction of a tonal stimulus (1, 58). A similar consideration may also be consistent with the fact that unit thresholds at cochlear nucleus and inferior colliculus, in our study, and at auditory cortex (37) are often as sensitive as behavioral threshold. Thus, unit sensitivity appears to be maintained by a distinct number of neurons throughout the entire auditory system. It is reasonable to suggest that the convergence of synaptic input to these cells not only contributes to their sensitivity function, but also makes them somewhat resistant to any single exposure, so that they operate similarly following overstimulation.

A second possibility may be that discrepancies between behavioral and neural thresholds are a function of our ability to describe features of the neuronal response. Thus, for example, behavioral threshold may not rely simply on the magnitude of average discharge rate, but primarily on the nervous system's ability to detect a difference between spontaneous background activity and that evoked by the stimulus (31). In a number of cases where direct comparisons were made between neural and behavioral thresholds at CF, spontaneous versus driven discharge rates at threshold were plotted for a single unit on a trial-by-trial basis. The overall number of occasions when evoked activity was greater than spontaneous activity appeared to provide a means whereby a population of neurons could demonstrate a slightly greater response probability to the stimulus at threshold. However, these population plots did not permit a comparison of spontaneous to evoked spikes on a one-to-one basis. When such analyses were made, i.e., driven minus spontaneous rate for each stimulus presentation, spontaneous activity was more frequently greater than the corresponding driven rate at times when the animal correctly detected the presence of a threshold stimulus, suggesting that signal-to-noise ratios per se did not provide the mechanism for threshold detection.

It also is possible that a few neural spikes only discharging to stimulus onset may have resulted in a closer approximation between our behavioral and neural findings rather than the animal relying on a maintained discharge over the entire stimulus period. A number of analyses using various time windows from stimulus onset were performed to test this notion. The results revealed that the amount of activity during a short window at signal onset (e.g., 10 ms) was much less likely to yield significant differences between

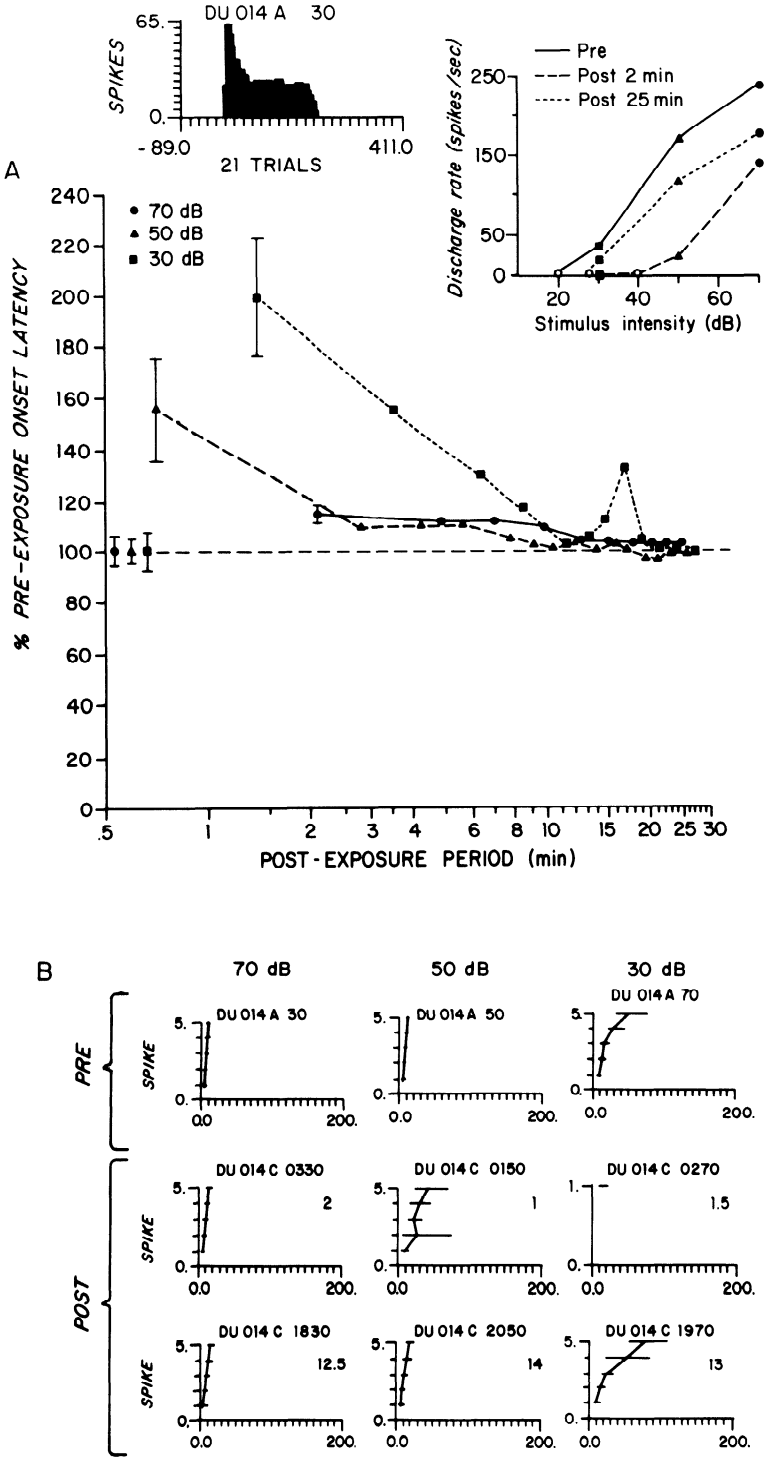

FIG. 9. Effects of a more moderate 95-dB, 2-min stimulus on postexposure dynamic-range and spike-latency functions for a cochlear nucleus unit (CF, 8.716 kHz) that showed a consistent reduction in driven discharge rate at all stimulus levels. The inset in the upper right portion of *A* demonstrates the relationship of spike discharge rate to stimulus intensity for the preexposure control period and postexposure recovery intervals at 2 and 25 min. Open circles indicate threshold intensities. To avoid confusion, it should be noted that 30 dB was below threshold

driven and spontaneous firing than total discharge rate over the entire 200-ms tone-burst period. These findings agree with those of Kitzes and associates (19) who found that for anteroventral cochlear nucleus neurons in the anesthetized cat, the longer the analysis period, the lower the threshold. A final feature specific to auditory neural activity that may contribute to detection of threshold stimuli is the periodicity phenomenon whereby evoked unit potentials phase lock to individual cycles of low-frequency stimuli (41, 44). Rose and Rhode and coinvestigators (38, 43) demonstrated that this aspect of the unit response is present at sound pressure levels well below the threshold defined by average discharge rate. Consistent with this notion is the finding by Smoorenburg and van Heusden (52) for a small number of anteroventral cochlear nucleus cells that phase locking was not disrupted by brief, intense sound exposure, thus suggesting a durable mechanism that may more closely relate postexposure neural to behavioral thresholds.

In a recent study investigating signal-detection phenomena, Kettner and colleagues (12) performed a detailed examination of anteroventral cochlear nucleus multiunit activity evoked to threshold stimuli on detect versus nondetect trials for a conditioned nictitating membrane response in the rabbit. Similar to our findings, none of their routine measures of unit activity distinguished obvious differences in neuronal discharges between the two classes of behavioral response. In short, little is presently known about the relations between behavioral and the underlying neural threshold responses. It is certain, however, that the physiological information necessary to initiate a threshold response is present but uncovering the nature of this encoding may require detailed trial-by-trial analyses involving close inspection of the fine time structure of the single-unit response.

In contrast to the discrepancies between absolute magnitude and duration of neural and behavioral threshold losses and recovery time courses, a number of our neural findings are generally consistent with the behavioral symptoms classically associated with temporary threshold shift. Thus, the major effect of sound exposure on neural and behavioral measures was a reduction in sensitivity to pure-tone test stimuli. As indicated in Fig. 3, the frequency-related losses in neural threshold were similar to those noted in the behavioral studies with the magnitude of threshold shift being related to the frequency of the test stimulus in that the greater the CF, the larger the loss in sensitivity. Finally, although the recovery time courses for brain stem neurons did not approximate a simple exponential function as closely as the behavioral curves, they too were basically monotonic.

Several additional aspects of the neural recovery functions not evident in their behavioral counterparts were apparent. The recovery curves of evoked activity for neurons demonstrating a reduced response to tone bursts at all tested signal levels were, on the average, a positively accelerating function of time after exposure. However, as indicated in Figs. 4 and 8, for different stimulus levels, the curves demonstrated distinctly unique slopes with higher test-stimulus intensities resulting in more rapid recovery than low-intensity tone bursts. A similar level-dependent effect has also been observed during the recovery of cochlear nerve fibers following more moderate levels of stimulation (59) and may be related to the greater amount of transmitter released at the hair cell-nerve fiber synapse in re-

at 2 min postexposure. It is evident that at this time of recovery, the slope of the intensity function was decreased. The middle portion of the figure illustrates depressed latency distributions to the first evoked spike as a function of the percent preexposure latency for the three representative intensity levels indicated. SDs indicated by the vertical bars on the unconnected symbols reflect variability in latency values among stimuli for the different test levels. Immediately postexposure, mean latency to the first spike was increased by 0.6, 3, and 9 ms for the 70-, 50-, and 30-dB stimulus conditions, respectively, and variability for the two lower intensity values significantly increased. Figure 9*B* shows mean pre- and postexposure latency distributions and ranges of dispersion for the first five evoked spikes and indicates that the general effect of sound overstimulation was to increase spike latency and variability at all tested stimulus levels. Numbers inset at the upper right of each postexposure spike-distribution plot indicate the recovery time in minutes when data for a particular function were collected. The ordinate represents spike number from 1 to 5 and was automatically adjusted to a lower value if a weak stimulus evoked less than five discharges.

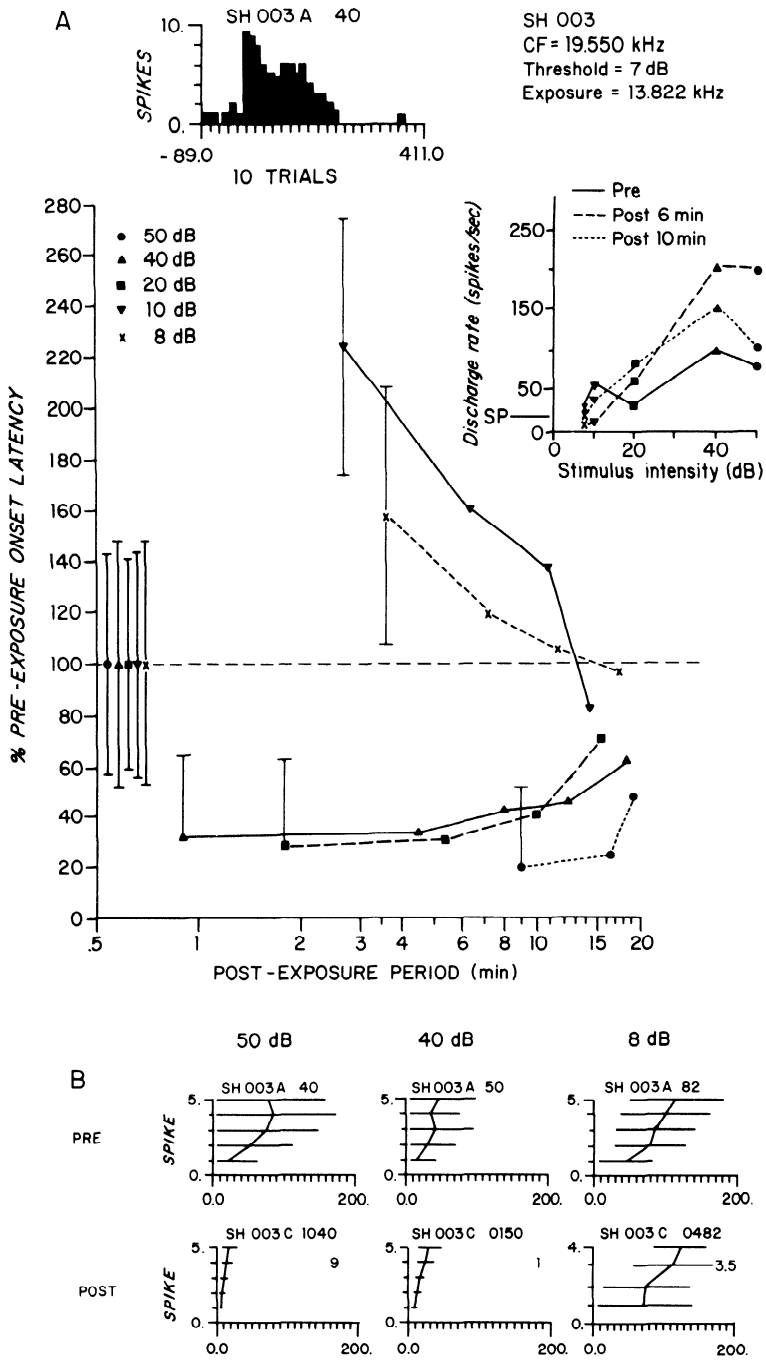

FIG. 10. Similar input-output intensity functions as described in Fig. 9 for a cochlear nucleus unit showing reduced discharge rates to near-threshold stimuli associated with increased firing to suprathreshold tone-burst stimuli. Following exposure, slopes of the recovering intensity functions (upper right) appeared significantly increased. The principal plot in *A* shows that latency to the first spike was greatly increased for near-threshold stimuli at the same time that it was decreased for suprathreshold test signals. The spike-latency functions in *B* demonstrate postexposure decreases in latency for the first five spikes at 40 and 50 dB of test stimulation associated with decreased variability in occurrence and the converse effect for low-intensity 8-dB stimuli. For the three representative stimulus-intensity values shown, mean firing latency was decreased by 14.5 and 8 ms for the 50- and 40-dB levels, respectively, and increased by 25 ms for the low-intensity 8-dB near-threshold condition.

TABLE 1. *A comparison of magnitude of threshold shift for two postexposure intervals and recovery times for cochlear nucleus and inferior colliculus units for monkey (DU)76-314*

Unit	CF, kHz	Threshold Shift, dB		Recovery Time, min
		2 min	10 min	
Cochlear nucleus				
DU009	0.398	4	0	8
DU008	0.846	12	5	17*
DU010	1.626	30	10	11*
DU003	2.064	16	10	15*
DU027	3.740	35	20	29*
DU016	4.605	14	8	15*
DU014	8.716	22	15	35*
DU021	9.030	40	22	56*
DU028	16.240	18	10	15*
DU020	21.615	28	14	14*
$\bar{x}$		22	11	
SD		11	7	
Inferior colliculus				
DU006	0.908	5	0	5
DU029	1.089	10	0	5
DU017	1.127	6	0	10
DU018	5.210	20	4	12
DU019	5.744	23	10	25*
DU023	14.560	30	20	11*
DU025	21.130	8	0	10
DU024	22.010	40	30	12*
$\bar{x}$		18	8	
SD		13	11	

* Unit lost at this time before recovery to within ±1 SD of control discharge rate.

sponse to high-level test signals (11). The rapid recovery processes for high-intensity tone bursts was not as pronounced for units demonstrating poststimulatory supradischarge rates (see Fig. 5) and may be evidence that this facilitated effect was mediated by more central mechanisms.

Exposure stimuli also appeared to have different degrees of effectiveness on the onset and sustained components of the temporal activity pattern (see Fig. 8) in that each portion appeared to be reduced independently of the other, with the later tonic response always being more severely depressed, thus requiring longer recovery intervals. Although the rate-reducing effects of exposure were specific to each portion of the temporal response, the underlying processes determining their recovery time constants appeared to be related since both onset and steady-state responses recovered in parallel.

Finally, the recovery functions for inferior colliculus units tended to be slightly faster than those for the lower level cochlear nucleus neurons, suggesting that either synaptic input other than that from the periphery contributed to the more rapid recovery rate at higher brain stem levels, or that the multiplicity of synaptic inputs at more rostral neural centers includes significant signal transmission by contributing response areas along the cochlear partition less affected by the exposure stimulus.

Dynamic range

One basic finding was that exposure did not produce a parallel shift along the firing-rate coordinate of the intensity function or a change in overall dynamic range but instead, within the limits of our measures, appeared to alter both the maximum firing rate and the rate at which it was attained. For the majority of neurons, exposure to loud sound produced a reduction in maximum rate without an apparent alteration in the

operating range of the unit, resulting in smaller slopes for the rate-level curves of both monotonic and nonmonotonic functions. Conversely, neurons showing supradischarge rates following exposure demonstrated steeper slopes associated with higher maximum-rate plateaus, again without appearing to extend dynamic range.

A number of studies investigating the responses of single auditory nerve fibers have shown that for approximately one-third of the fiber population, the most effective frequency for eliciting maximum discharge rate decreases systematically as stimulus intensity increases (6, 32, 43). Preliminary studies using below-CF test stimuli suggest that the ventral cochlear nucleus cells showing similar nonlinear behavior are the units that demonstrated the increase in postexposure firing to suprathreshold stimuli. Although little is known about the underlying mechanisms associated with this phenomenon, it appears that the generally moderate exposure tones used in the present study may have temporarily interfered with the micromechanical processing of test signals by the basilar membrane so that during recovery, CF test stimuli behaved in a manner similar to that of preexposure, below-CF stimuli. This suggestion is supported by other recent electrophysiological evidence that exposure stimuli similar to those used here temporarily disrupted the generation of nonlinear distortion-product responses in primary nerve fibers routinely observed under bitonal conditions so that combination tones equivalent to fiber CF no longer elicited evoked activity (47, 48).

Spontaneous activity

Exposure to loud sound frequently produced changes in spontaneous firing rates for moderate- and high-spontaneous-rate neurons that resulted in either temporarily facilitated or reduced activity levels in the absence of deliberate stimulation that did not persist beyond the first few minutes of the recovery period. On the other hand, low-spontaneous-rate units were relatively unaffected by the exposures of the present study.

The observed transitory reduction in spontaneous discharge firing is consistent with the results of Kiang (18) and Young and Sachs (59) showing that comparable reductions in the spontaneous activity of primary nerve fibers rapidly recovered after exposure to sustained tones of more moderate levels. Conversely, the finding of an initial excitatory increase in spontaneous firing followed by a rapid recovery process has not been observed in primary afferents other than for a short-lasting facilitation in interstimulus-interval-related activity occuring in the few milliseconds between rapidly presented test stimuli (25). For inferior colliculus neurons, following exposure to much longer stimuli of similar intensity, Salvi (46) also observed increased spontaneous discharge rates, but only for units categorized as onset responders. We failed to observe a similar relationship between temporal discharge pattern and facilitated spontaneous firing in the unanesthetized monkey preparation at either the cochlear nucleus or inferior colliculus brain stem levels.

The functional significance of increased or decreased spontaneous activity is at present unclear. Increased spontaneous discharge rates appeared to be of a more temporary nature since, in our sample of units (see Fig. 6), they returned to control firing levels, on the average, slightly faster than did reduced spontaneous discharge rates. Although Young and Sachs (59) observed only depressed spontaneous rates following the application of more moderate stimuli, they noted a tendency for high-spontaneous-rate neurons to recovery more rapidly, which is consistent with our findings that neurons demonstrating increased postexposure spontaneous firing tended to be high-rate units, which also recovered fastest.

The rapid recovery times of facilitated spontaneous activity suggest that this phenomenon may be the physiological counterpart of the rapidly fading "rushing noise" tinnitus commonly observed in man immediately following similar pure-tone exposures (57). On the other hand, decreased spontaneous activity may signal more serious damage to the cell. This notion is consistent with the repeated demonstrations of Kiang and Liberman and associates (15, 17, 21, 23) that low spontaneous discharge rates are significantly correlated with increased thresholds in permanently, noise-damaged cochlear nerve fibers. The fact that reduced

spontaneous activity recovered before depressed evoked discharge rates both in primary nerve fibers (25, 59) and the brain stem cells of the present study following short-term sound exposure supports the suggestion that the underlying mechanisms responsible for the generation of evoked and spontaneous unit potentials may be initially distinct and separate (14), but as the severity of cochlear damage progresses, this independence may deteriorate.

Peripheral versus central changes

The principal finding common to all our units was that the moderately intense exposure tones produced a severe reduction in response rate and increased the latency of spikes evoked by threshold and near-threshold tone bursts. Similar reductions in driven discharge rate have been observed for cochlear nerve fibers following short-duration, intense stimulation (25, 59) and are presumably related to peripheral receptor processes involving, for example, a depletion in sensory cell-related metabolic and/or transmitter materials, changes in basilar membrane characteristics leading to an altered excitation pattern for primary receptors, or a disruption in the micromechanical events that delicately couple hair cells to the tectorial and basilar membranes.

For brain stem neurons, the mechanism(s) underlying the threshold-related decrement in response rate accompanied by a consistent increase in spike-onset latency probably involve a variety of complex factors, including the loss in sensitivity of peripheral components, as well as potential modifications in neural inputs that cause delays in synaptic transmission or differential changes in the number or efficacy of synaptic linkages. The similarity in the initial percent reduction of threshold-related, postexposure activity for both early and late brain stem units to that observed in primary afferent fibers following stimulation with comparable sound exposure (25) supports the conclusions that the loss in sensitivity to low-intensity test stimuli primarily reflected receptor alterations projected to the higher order cells by the affected hair cell-nerve fiber elements. It seems likely that neurons demonstrating consistent postexposure reductions in discharge rate involving coincident increases in spike latencies to stimuli at all test levels (see example in Fig. 9) were part of a system of very secure synaptic pathways (19) that reliably transmitted the peripheral response decrement.

Similarly, the temporarily decremented spontaneous activity of a number of our brain stem neurons could also have been mediated by depressed cochlear processes, which would result in a reduction in spontaneous-rate input to the central auditory system. This intepretation is consistent with the finding that the spontaneous firing of ventral cochlear nucleus cells is dependent on the integrity of the cochlea and cochlear nerve in that once disrupted, these neurons do not exhibit unitary discharges in the absence of externally applied stimuli (20).

One important finding was that the population of brain stem cells studied here appeared not to be homogenous with respect to the general features of sound-induced depression in that an appreciable fraction exhibited a decrease in discharge rate associated with a corresponding increase in onset latency to low-intensity stimuli while at the same time, high-level test signals elicited shorter latency, increased firing. These paradoxical findings may be attributable to a modification in any one of the multiple sources of input impinging on higher order cells. Although a facilitation of driven activity has been observed for both primary nerve fibers and cochlear nucleus cells under special experimental conditions involving either hypoxic physiological states (5) or stimulation with noise-band stimuli centered at CF (10, 45), supradischarge rates have not been observed to our knowledge for short-term, sound-exposed primary afferents. However, the appropriate experimental design permitting a comparison of the discharges of primary nerve fibers under similar test-retest conditions to those of higher order afferents has not yet been systematically tested since either exposure stimuli have been much more severe or tone-burst stimuli restricted to threshold-related intensity values have been routinely used to elicit postexposure responses at the peripheral level (25, 59). Consequently, the possibility remains that the increased driven rates we observed were mediated by an as yet unidentified peripheral process.

Threshold shift model

Recent anatomical-behavioral studies have demonstrated significant losses of hair-cell receptors following moderate exposures to restricted bands of noise in the absence of permanent, pure-tone threshold shifts (4). In contrast to these findings, several neurophysiological investigations have reported permanent abnormalities in cochlear nerve fiber properties not reflected by hair-cell loss (15, 23), but apparently correlated with subtle changes in the arrangements of receptor-cell stereocilia (22). The findings of the present study are consistent with the growing body of literature indicating the sensitivity of neuronal measures in detecting subtle cochlear damage. Thus, according to our measures, unit thresholds were more severely elevated than their behaviorally measured counterparts and took substantially longer to recover. The similarity between alterations in dynamic-range function and spontaneous activity of higher order neurons to the permanent changes noted in neural responsiveness resulting from the more drastic overstimulations of other physiological investigations suggests that such long-term changes can be mimicked by more moderate exposure stimuli in unanesthetized subjects highly similar to man. All these findings support recent work (4) indicating that sound-induced cochlear damage is a continual process involving an accumulation of the effects of the initial exposure episode rather than a series of discontinuous events. Whether more complex aspects of single-unit behavior involving, for example, frequency selectivity, two-tone interaction phenomena, or low-frequency tuning-curve sensitivity, all known to demonstrate permanent abnormalities following more severe noise exposure, occur during brief periods of overstimulation remains to be determined. To the extent that such changes occur, a model based on short-lasting temporary threshold shifts in which pre- and poststimulation measures can be sequentially examined within the same cell promises to provide further insights into the mechanisms of noise-induced hearing loss.

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