Unilateral Hearing Losses Alter Loud Sound-Induced Temporary Threshold Shifts and Efferent Effects in the Normal-Hearing Ear

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Rajan, R. Unilateral hearing losses alter loud sound-induced temporary threshold shifts and efferent effects in the normal-hearing ear. J Neurophysiol 85: 1257–1269, 2001. In animals with bilaterally normal hearing, olivocochlear pathways can protect the cochlea from the temporary shifts in hearing sensitivity (temporary threshold shifts; TTSs) caused by short-duration intense loud sounds. The crossed olivocochlear pathway provides protection during binaural loud sound, and uncrossed pathways protect when monaural or binaural loud sounds occur in noise backgrounds. Here I demonstrate that when there is a chronic unilateral hearing loss, effects of loud sounds, and efferent effects on loud sound, in the normal-hearing ear differ markedly from normal. Three categories of test animals with unilateral hearing loss were tested for effects at the normal-hearing ear. In all categories a monaural loud tone to the normal-hearing ear produced lower-than-normal TTSs, apparently because of a tonic resetting of that ear’s susceptibility to loud sound. Second, in the two test categories in which the hearing-loss ear was only partly damaged, binaural loud sound exacer bated TTSs in the normal-hearing ear because it caused threshold shifts that were a combination of “pure” TTSs and uncrossed efferent suppression of cochlear sensitivity. (In normal cats, this binaural tone results in crossed olivocochlear protection that reduces TTS.) Binaural loud sound did not produce such uncrossed efferent effects in the test category in which the nonetest ear had suffered total hearing loss, suggesting that this uncrossed efferent effect required binaural input to the CNS. It is noteworthy that, in the absence of this uncrossed efferent suppression, the pure loud sound-alone induced TTSs after binaural exposure were low. Thus in the absence of any efferent effect, the normal-hearing cochlea had a reduced susceptibility to loud tone-induced damage. Finally, the results suggest that, with respect to cochlear actions at high sound levels, uncrossed and crossed efferent pathways may exert different effects at the one type of receptor cell.

INTRODUCTION

The mammalian cochlea receives a dual-component efferent innervation from the brain stem (e.g., Aschoff and Ostwald 1987; Aschoff et al. 1988; Guinan et al. 1983; Liberman et al. 1989; Robertson et al. 1987; Thompson and Thompson 1986; Warr et al. 1986). The lateral olivocochlear system (LOCS), almost exclusively from only the ipsilateral lateral superior olive nucleus, terminates on dendrites of afferent neurons. The medial olivocochlear system, from ipsilateral (uncrossed MOCs, UMOCs) and contralateral (crossed MOCs, CMOCs) periolivary nuclei, terminates on outer hair cells (OHCs).

Physiological activation of the efferent pathways by sound can reduce the temporary cochlear desensitization (temporary threshold shifts; TTSs) caused by loud tones (Rajan and Johnstone 1982; Handrock and Zeisberg 1982; Rajan 1992, 1995a,b, 1996b; Rajan and Johnstone 1988a,b). Monaural loud tones in a background of silence serve as a baseline against which such protective effects can be demonstrated, since such conditions do not activate efferent activity that modulates TTSs (Rajan 1988a, 1992, 1995a,b, 2000). Then, binaural loud tones activate CMOCs input to the OHCs to reduce TTSs, protecting the cochlea (Rajan 1992, 1995b, 1996a, 2000; Rajan and Johnstone 1988a). Uncrossed efferent pathways protect (Rajan 2000) when a loud tone is presented in a background of noise at 60 dB SPL or greater. Unlike the CMOCs effect, protection exerted by uncrossed efferents does not require binaural stimulation but occurs as long as the tone is presented in a background of noise. The uncrossed pathway consists of the LOCS pathway terminating on dendrites of afferent neurons and the UMOCs pathway terminating on OHCs. For parsimony of explanation, the protective effects of uncrossed pathways have been attributed (Rajan 2000) to efferent terminations on OHCs, i.e., to the UMOCs pathway. As well (Rajan 2000), it is difficult to see how effects on dendrites of afferent neurons (exercised by the LOCS) could prevent noise exacerbation of the loud tone-induced TTSs. In this context it is worth noting that the above-cited studies of protection measured post-loud sound effects 5 min after loud sound. At this postexposure time, the major, if not sole, contribution to TTSs appears to be damage exercised at OHCs (Patuzzi et al. 1989), and it has been shown (Rajan 1996a) that protective effects measured at this time are totally commensurate with effects predicted to occur only at OHCs (Patuzzi et al. 1989; Rajan and Patuzzi 1992). Thus with such postexposure measurements, discussion of any changes must focus on effects exercised at the OHCs.

The CMOCs protection from TTSs seen when loud tones are presented binaurally also occurs to successive loud tone exposures presented with a short inter-exposure measurement interval (Rajan 1996a). Thus in normal animals CMOCs protection is quite robust and can be demonstrated even after hearing losses are created acutely by a first exposure. (It is not yet known whether this also applies for the uncrossed pathway protection of the cochlea from TTSs caused by a loud tone in a background of noise.) However, during the experiments on CMOCs protection (Rajan 1995a,b, 1996a), a chance observation was that when animals had unilateral chronic hearing...
losses, quite different and remarkable cochlear efferent effects were obtained in the normal hearing ear to testing with loud tones in silence. These effects were explored in detail and form the basis of the present report.

METHODOLOGY

Animal treatment and measurement of hearing sensitivity

Procedures for anesthetization and treatment of test cats were as reported (Rajan 1995a,b, 1996a) for concurrently tested cats that provide comparison normative data here. Adult cats (3–6 kg) were tested under procedures approved by the Monash University Standing Committee on Ethics in Animal Experimentation and conforming to guidelines of the National Health and Medical Research Council of Australia. Cats were anesthetized (60 mg/kg ip) with pentobarbital sodium (Nembutal) and maintained with intravenous doses amounting to Nembutal at 2–3 mg · kg⁻¹ · h⁻¹. Depth of anesthesia was monitored through continuous recording of rectal temperature, the electrocardiographic (ECG) and electromyographic (EMG) activity from forearm muscles, and regular hourly checks of responses to noxious forepaw pinching, of the presence of pupillary dilatation and the absence of corneal reflexes. The ECG/EMG electrodes’ output was displayed on an oscilloscope and fed into a speaker for continuous monitoring of the cat’s condition and depth of anesthesia. Body temperature was maintained at 37.5 ± 0.5°C by a thermostatically controlled warming blanket, regulated by feedback from a rectal probe. Cats were tracheostomized but allowed to breathe independently (Rajan 1995a,b, 1996a).

The tympanic bullae were exposed (Rajan et al. 1991) and stainless steel electrodes implanted against the round window of both cochleas. A fine bore plastic tube was inserted into the bulla hole adjacent to the electrode, to ventilate the middle ear, and the holes sealed with dental cement. The meatuses were transected to place sound delivery tubes close to the tympanum.

Hearing sensitivity was assessed by measuring thresholds for the auditory nerve compound action potential (CAP) at frequencies from 1–40 kHz (Rajan 1995a; Rajan et al. 1991), using pure tone bursts (10–20 ms duration, 1-ms rise-fall times) presented at a rate of 7–8/s. The CAP, recorded from the round window electrode, was amplified ×1,000 and band-pass filtered (300 Hz to 10 kHz) before being displayed on an oscilloscope. Threshold criterion was a visually just-detectable CAP response on the oscilloscope; such visual detection thresholds (VDTs) correspond to a CAP amplitude of about 1–2 μV (see Rajan et al. 1991).

Tones to each ear were generated independently by one of two channels of a digital synthesis system, gated under computer control and passed into separate computer-controlled attenuators. Each attenuator fed separately into an electronic mixer box that allowed manual switching of sound delivery to either of two output channels. Cross talk between mixer box channels was greater than −100 dB up to 10 kHz, −100 dB from 10–20 kHz, decreasing thereafter to −95 dB at 40 kHz. Each output channel lead to a Stax speaker in specially designed housing with a sound delivery tube leading from the speaker into the external auditory meatus (Rajan et al. 1991).

The majority of experiments in test cats (see Classification of animals) was completed in one laboratory over a 4-yr period using the above procedures. (The long time span was due to the fact that the occurrence of 2 categories of test cats was a random process not controlled experimentally.) Three cats were tested in more recent experiments in a new laboratory (Rajan 2000) with cats being artificially ventilated on room air and maintained with continuous infusion of anesthesia, and sound being delivered through Sennheiser HD 535 speakers. Effects were identical to those seen previously in the same test category (see Classification of animals) tested in the same way. Hence these cats are not differentiated from others of that same category tested in the same manner.

Classification of animals

CAP thresholds in each cat were compared with normative data (Rajan 1995a; Rajan et al. 1991). The normal hearing group of animals, which provides data (Rajan 1995a,b, 1996a) for comparisons, had bilaterally normal hearing sensitivity from 1–40 kHz. In test groups here, cats had a unilateral hearing loss, with the other ear having normal hearing sensitivity (i.e., CAP thresholds within ±1.96 SD of mean normative thresholds; the statistically normal range, at α = 0.05, by Student’s t-test). Test groups were categorized according to the etiology of the unilateral hearing loss.

In one test category [idiopathic hearing loss (IHL), n = 27] the etiology of the unilateral hearing losses, present at initial measurement of hearing in these acute experiments, was unknown. It is presumed that these losses were chronic and possibly due to loud sound, but it was not possible to obtain enough information from the university breeding or supply services to determine their cause. In another test category (“Cyst-HL,” n = 13), animals were also not pretreated. However, during cochlear surgery in the acute experiments here, it was found that only one ear had a cholesteatoma-like highly vascular cyst completely filling the middle ear cavity. The cyst had eroded the tympanum and ossicles and had grown deep into the cochlea through the oval (and often round) window, resulting in a total hearing loss in that ear (see RESULTS). In the final test category [chronic mechanical lesion hearing loss (CMHL), n = 9], designed on the basis of early observations in the other two categories, chronic unilateral hearing losses were induced in normal-hearing cats by mechanical lesion of the basilar membrane (BM) using procedures (generally, but not always, of the left cochlea) described previously (Rajan et al. 1993). Briefly, under acute anesthesia, CAP thresholds were measured to confirm normal hearing sensitivity. Then a lesion was made with a glass micropipette into the most-apical part of the BM visible through the round window (see Rajan et al. 1993). Animals recovered for periods from 2.5 to 5.5 mo, in holding rooms in which other cats were also housed but from which loud noise was precluded, before the terminal experiment.

Different groups of animals in one of the three test categories were tested for the effects of loud sound in the normal-hearing ear, with monaural or binaural exposure being used. In some groups, brain stem lesions were made (see Surgical inactivation of cochlear efferent pathways) to all cochlear efferent pathways or, in one IHL test group, to only the crossed efferent pathways. In total, 12 test groups (5 IHL, 4 CMHL, and 3 Cyst-HL test groups) were tested as detailed in RESULTS.

Surgical inactivation of cochlear efferent pathways

Inactivation of various components of efferent pathways to the test (normal-hearing) cochlea was made using surgical lesions at the floor of the fourth ventricle, after removing the overlying cerebellum (Rajan 1995a). Because of the coursing of cochlear efferent fibers, from this location it is possible to lesion all efferents to one or both cochleas, or crossed pathways to both cochleas (Warren and Liberman 1989a) but not lesion only uncrossed pathways to a cochlea. To totally de-efferent the test cochlea, a lesion was made 1.5–2 mm lateral of the midline and on the brain stem side ipsilateral to that cochlea (Rajan 1995a,b). To cut only crossed pathways (bilaterally), a midline lesion was made (Rajan 1995a,b). Lesions were always 6–8 mm long, extending about the facial colliculi, identifiable on the floor of the fourth ventricle. Postmortem histology, occasionally combined with histochemical staining for acetylcholine esterase (which stains the efferent pathways), was used to confirm the location of the cuts (Rajan 1995a; Warren and Liberman 1989a).

In all animals with brain stem lesions, prelesion checks were made of the CAP audiogram, heart rate, ECG waveform, and body temperature, and these were re-checked immediately postlesion. 
**Traumatic loud sound exposures and measurement of cochlear desensitization**

The traumatic sound to cause TTS was an 11-kHz tone at 100 dB SPL for 10 min, chosen as it was the standard loud sound (Rajan 1995a) in a series of bilaterally normal animals tested concurrently over the same period as test cats here. The frequency is from within the most sensitive part of the cat’s CAP audiogram (Rajan et al. 1991), and, of particular relevance here, frequencies from this region cause TTS more easily than do other frequencies (Rajan 1995b), and more readily activate previously described (Rajan 1995b) protective effects of crossed efferent pathways.

With monaural testing the loud tone was delivered to only the test ear and with binaural testing simultaneously to both ears. Post-loud tone CAP thresholds were re-measured only in the test (normal-hearing) ear 5 min after the loud tone, at frequencies from 7 to 24 kHz, in a constant (but not in linear) order that was the same as in the normative database (Rajan 1995a). The total time taken to measure thresholds at the eight most-affected frequencies within the test range was 2.5 min.

Frequency-specific threshold desensitizations (TTSs) were calculated as the difference between pre- and post-loud tone thresholds. Comparisons between groups or treatments were comparisons between TTSs at corresponding frequencies. Two-way repeated measures ANOVAs were used to compare effects between different experimental conditions. If the ANOVA revealed a significant difference between conditions, or a significant interaction term between experimental condition and frequency, unpaired Student’s t-tests were used to compare threshold losses at corresponding frequencies in the two conditions. Comparisons of test group data were made to normative data from normal monaurally exposed or binaurally exposed efferent-intact groups (Rajan 1995a,b) and normal efferent-cut groups. For clarity, only statistically significant P values and only comparisons of test groups to efferent-intact groups are reported. Comparisons of test groups to normal efferent-cut groups are discussed where relevant.

**RESULTS**

**Hearing sensitivity in cats with chronic unilateral hearing losses**

Figure 1 shows examples of hearing losses typical of the unilateral hearing-loss ear in each test category. In animals with idiopathic hearing losses (IHL category), this was quite varied (Fig. 1A), ranging from large losses across most of the frequency range to small losses, just worse than the normal range [i.e., greater than +1.64 SD from mean normal thresholds from a large group of animals reported by Rajan et al. (1991); significant at \( \alpha = 0.05 \)], over a small part of the test frequency range. In CMHL animals, in which unilateral hearing losses were created by mechanical lesions, losses were generally stereotyped (Fig. 1B). CAP thresholds were normal until a high-frequency at \( \approx 18-20 \) kHz and thereafter losses increased with increasing frequency. In one case (Fig. 1B, □) hearing losses also extended to low frequencies, but the pattern of increasing losses at higher frequencies was also present here. In most such animals, at higher frequencies from \( \approx 26 \) kHz onward, no CAP could be evoked even at 100 dB SPL. Finally, in the Cyst-HL category, in which a cholesteatoma-like cyst had grown into the cochlea of the hearing-loss ear, with erosion of cochlear contents, there was total loss of hearing, and no CAP could be evoked at any frequency even at 100 dB SPL (Fig. 1C).

In all three test categories the nonhearing loss ear had CAP thresholds within the statistically normal range (data not illustrated). Given that some animals (in the IHL category) suffered only small losses in their hearing-loss ear, thresholds in the normal ear were checked at least three times, about 15 min apart, to re-confirm that there were no small losses in these ears.

**Monaural loud tone causes lower-than-normal TTSs in the normal-hearing ear**

One group from each test category was tested with monaural loud sound exposure to the normal-hearing efferent-intact ear. This exposure caused only small threshold shifts (TTSs) in cochlear sensitivity, with peak threshold shift always at 15 kHz, and TTSs declining to higher and lower frequencies (Fig. 2). In individual animals of any group (Fig. 2, A–C) there was generally small variability in TTSs (cf. small SE bars in Fig. 2, A–C). There was no apparent correlation between the hearing loss in the nontest ear and the effect of the loud sound in the test, normal-hearing ear. For example, the variability in loud sound-induced hearing losses in the test ear in IHL animals

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**Fig. 1.** Typical losses in hearing sensitivity in the unilateral hearing loss ears of test animals. Data illustrated are compound action potential (CAP) thresholds, expressed as losses from normal CAP thresholds at each frequency, in the unilateral hearing-loss ears of individual cats with unilateral hearing loss of idiopathic origin [A, idiopathic hearing loss (IHL) category], or created by a cochlear mechanical lesion [B, chronic mechanical-lesion hearing loss (CMHL) category], or due to a cyst-like growth into the cochlea (C, Cyst-HL category). The 0-dB loss line represents mean normative CAP thresholds from a large group of animals reported by Rajan et al. (1991); the hatched area about this line represents the range \( \pm 1.64 \) SD (statistically significant range at \( \alpha = 0.05 \)) about that mean. Values plotted at threshold losses of 100 dB indicate that no CAP could be recorded at 90 dB SPL. Note the different scale for A.
In which nontest ear hearing losses could be quite varied (Fig. 1A), was similar to the variability in Cyst-HL animals (Fig. 2C), in which nontest ear hearing losses were stereotyped (Fig. 1C). There were no significant condition effects between pairs of test groups in the three categories (2-way repeated measures ANOVA; for all inter-group comparisons, $P > 0.15$ for all condition $F$ values). There were significant frequency effects ($P$ always $<0.001$), reflecting the frequency dependency of TTSs, but no condition $\times$ frequency interactions as the pattern and amounts of TTSs were similar in all three groups. Hence the three groups were pooled (i.e., corresponding-frequency data were pooled) for comparison to normative (efferent-intact) data (Rajan 1995a,b).

The test groups suffered significantly less TTSs than normal monaurally exposed (efferent-intact) animals (Fig. 2D), with significant effects of condition, frequency, and condition $\times$ frequency interaction (ANOVA; $P < 0.001$ for all 3 factors). In fact, the low TTSs in the monaurally exposed test groups were similar to TTSs in normal binaurally exposed (efferent-intact) animals (Fig. 2D), noting that in normal animals binaural exposure results in crossed efferent pathway reduction of TTSs (Rajan 1995a,b) compared with TTSs after monaural exposure. Comparison of pooled monaurally exposed test data to those from normal binaurally exposed animals found no significant condition differences. There was a significant frequency effect and a significant condition $\times$ frequency interaction (ANOVA; $P$, always $<0.001$ for both factors) because of differences at frequencies from 18–20 kHz (2-tailed Student’s $t$-test, $P$ always $<0.001$). However, at these frequencies TTSs were small ($<6$ dB), and at all other frequencies there were no differences between the two groups ($t$-test; $P$ always $>0.05$, generally $>0.15$). In general, over the frequency range with reasonably large TTSs, there were no differences between the pooled test groups and the normal binaurally exposed group.

Pooling data from test groups did not produce or obscure effects not already present. Comparing individual group data to normative data, TTSs in each test group (Fig. 2, A–C) were smaller than in normal monaurally exposed animals (ANOVA; $P < 0.001$ for all Condition, Frequency, and Interaction factors in pair-wise comparisons between the normal monaurally ex-
posed group and each test group). When individual test groups were compared against the normal binaurally exposed group, there were no condition differences (P always > 0.05 for Condition F values in pair-wise comparisons between the normal binaurally exposed group and each test group), as in the comparison of pooled test data against this normal group. However, as in the latter comparison, there were always significant frequency and interaction effects (P always < 0.005 for both factors in the pair-wise comparisons), but this was due to the differences at frequencies from 18–20 kHz at which TTSs were small (<6 dB) in all groups. Thus as in the pooled data, in general, there were no differences between individual test groups and the normal binaurally exposed group.

Acute cochlear efferent activity is not responsible for lower-than-normal TTSs caused by monaural exposure in the normal-hearing ear

In normal animals (Rajan 1995a,b) binaural exposure with the standard loud tone results in crossed efferent-mediated reduction of TTSs from levels caused by monaural exposure. Monaural exposure in test animals caused low TTSs similar to reduction of TTSs from levels caused by monaural exposure in normal-hearing animals (Fig. 2, G–D) as in the protected levels in binaurally exposed normal animals. However, surgical inactivation showed that acute activity in the cochlear efferent pathways was not responsible for the lower-than-normal monaural TTSs in test groups.

In three groups (one from each test category; Fig. 2, E–G) monaural exposure to the totally de-efferented normal-hearing ear produced low, and similar, TTSs for all pair-wise comparisons between pairs: P > 0.05 for Condition and Interaction factors, and <0.001 for Frequency factor, reflecting the frequency dependency of TTSs). Again there was no correlation between hearing loss in the nontest ear and the effect of loud sound in the test, normal-hearing ear; e.g., the variability in loud sound-induced hearing losses in the test ear in IHL animals (Fig. 2E), with varied hearing losses in the nontest ear (e.g., Fig. 1A) was similar to that in Cyst-HL animals (Fig. 2C), with stereotyped hearing losses in the nontest ear (e.g., Fig. 1C).

For each hearing-loss category, comparison of TTSs in the monaurally exposed test group with de-efferented ears against TTSs in the corresponding monaurally exposed efferent-intact test group showed that the status of the efferent pathways had no effect. There were never any condition effects (P always >0.15 for Condition factor in inter-group comparisons between de-efferented and efferent-intact groups in each test category). There were significant frequency effects (P always <0.001 for Frequency factor in inter-group comparisons between de-efferented and efferent-intact groups in each test category), reflecting the frequency dependency of TTSs, but there were no condition × frequency interactions. Thus lesioning efferent pathways did not alter the effects of monaural exposure in the normal-hearing ear of these test groups.

As with the efferent-intact test groups, monaural exposure in de-efferented test groups caused lower-than-normal TTS. For this comparison (Fig. 2H), corresponding frequency data from the three de-efferented test groups were pooled, given the absence of differences between them. The pooled de-efferented test groups had significantly lower TTSs than normal monaurally exposed animals (ANOVA; P always <0.001 for Condition, Frequency, and Interaction factors). When the pooled test de-efferented data were compared with the low TTSs in normal binaurally exposed animals, there were no condition differences. There was a significant frequency effect and a significant condition × frequency interaction (P < 0.001 for Frequency and Interaction factors) because of differences from 12–16 kHz (2-tailed t-test, P always <0.001), where the pooled test TTSs were significantly smaller, and at 20 and 22 kHz (t-test, P < 0.05), where the pooled test TTSs were significantly larger, than in the normative database. However, at the latter frequencies TTSs were small (<2 dB); thus generally, over the most-affected frequency range, TTSs in the pooled test groups were significantly smaller than in the normal binaurally exposed animals.

In summary, the data to date show that monaural exposure in the normal-hearing ear in test groups caused significantly lower TTSs than the same monaural exposure in normal animals, but this was not due to acute activity in the cochlear efferents.

Binaural loud tone exacerbates threshold losses in the normal-hearing ear of cats with a chronic unilateral partial hearing loss but not with a unilateral total hearing loss

In three further groups (1 group of each test category), the loud tone was presented binaurally with no manipulations of efferent pathways. In IHL and CMHL groups the exposure caused large TTSs (Fig. 3, A and B), without any differences between groups (ANOVA; P > 0.05 for Condition and Interaction factors) in the frequency-dependent pattern and amounts of TTSs (P < 0.001 for Frequency factor). The TTSs were significantly greater than in monaurally exposed test counterparts of previous sections. In this comparison, for each test category (i.e., IHL or CMHL) data from monaurally exposed efferent-intact and de-efferented groups (Fig. 2) were pooled, since the presence or absence of cochlear efferents did not alter the low TTSs caused by monaural exposure in test groups. This pooled monaural-exposure data for each test category was then compared with data from the binaurally exposed efferent-intact group of the same category (Fig. 3, D and E). For IHL and CMHL categories, there were significant differences between the binaurally exposed group and pooled monaurally exposed groups (P < 0.001 for Condition, Frequency, and Interaction factors in inter-group comparisons within each test category). Thus in these two test categories in which the nontest ear had a partial hearing loss, binaural exposure produced significantly greater TTSs in the normal-hearing ear than did monaural exposure. (In each test category separate comparisons of the binaurally exposed group against monaurally exposed efferent-intact or de-efferented groups showed the same effects as when data for the monaurally exposed test groups of that category were pooled regardless of efferent status.)

Since there were no differences between binaurally exposed IHL and CMHL groups, they were pooled for comparison to normative efferent-intact data (Fig. 3G). The pooled test TTSs were significantly larger than TTSs in normal binaurally exposed animals (P < 0.001 for Condition, Frequency, and Interaction factors) or normal monaurally exposed animals (P < 0.02 for Condition factor, <0.01 for Frequency and Interaction factors). These differences are noteworthy: in normal animals binaural exposure activates the crossed efferent pathway (Rajan 1992, 1995a,b) to reduce TTSs from that caused by monaural exposure which does not (for exposures in
silence, as here) activate any efferent effect modulating loud tone-induced TTSs. In contrast, in the pooled IHL + CMHL data, binaural exposure did not protect (since it caused TTSs in the test ear greater than the low TTSs caused by monaural exposure in the same test categories), but even exacerbated TTSs beyond those caused by monaural exposure in the normal pool.

In the Cyst-HL group, binaural exposure in efferent-intact normal-hearing ears did not exacerbate TTSs (Fig. 3C) that were similar to the small TTSs in monaurally exposed Cyst-HL groups (Fig. 3F). For the latter comparison, the two previous monaurally exposed (efferent-intact or cut) Cyst-HL groups were pooled since monaural exposure produced similar low TTSs in both groups. There were no condition differences between the binaurally exposed group and the pooled monaurally exposed data. There was a significant frequency effect ($P < 0.001$) but no condition × frequency interaction indicating that the frequency-dependent pattern and amounts of TTSs were similar. (Separate comparisons between the binaurally exposed group against each monaurally exposed group showed the same effects.)

Unlike the other two test categories, the TTSs in the binaurally exposed Cyst-HL group were significantly lower than in normal monaurally exposed animals (Fig. 3H; $P < 0.001$ for Condition, Frequency, and Interaction factors). When the Cyst-HL group was compared with normal binaurally exposed animals (Fig. 3H), there were no condition differences, but there were significant frequency and condition × frequency interaction factors ($P < 0.001$ for both factors) because of differences at 13 kHz (2-tailed t-test, $P < 0.01$), at which test group TTSs were significantly smaller, and from 18 –20 kHz ($t$-test, $P$ always <0.01) at which test group TTSs were significantly larger. In the latter case it must be noted that TTSs at these frequencies in both groups were small (e.g., <3 dB from 19–22 kHz, in both groups). In general, the data suggest only small, nonsystematic differences between the Cyst-HL group and normal binaurally exposed animals.

The Cyst-HL data provide a valuable control by showing that TTS exacerbation by binaural exposure in IHL and CMHL categories is not due to physical cross-over of sound from the nontest ear to the test normal-hearing ear. In the latter categories the nontest (hearing-loss) ear had only a partial hearing loss, and, in binaural exposure, there would be some outflow to the CNS from the damaged nontest ear (even if distorted
compared with when both ears are normal) and the test ear. In the Cyst-HL category, growth of the cyst into the cochlea, with erosion of cochlear contents, means there is no neural outflow from that ear (see Fig. 1C); both monaural and binaural exposure produce an outflow to the CNS only from the normal-hearing test ear.

Cochlear efferents are responsible for the exacerbation of TTSs by a binaural loud tone in the normal-hearing ear of cats with a chronic unilateral partial hearing loss

Tests with one group each from IHL and CMHL categories demonstrated that cochlear efferent pathways contributed to the large threshold losses recorded after binaural exposure. In both groups binaural exposure after totally de-efferenting the normal-hearing ear caused small TTSs (Fig. 4, A and B) significantly lower than the large TTSs caused by binaural exposure in these test categories when efferent pathways were intact (also Fig. 4, A and B; \( P < 0.001 \) for all Condition, Frequency, and Interaction factors in comparisons within each test category). Thus in both test categories the large TTSs in the normal-hearing ear after binaural exposure with intact cochlear efferents included a component produced by the action of the efferents.

As there were no condition differences or interaction effects between binaurally exposed de-efferented groups in the IHL and CMHL categories and both had similar frequency-dependent TTSs (ANOVA; \( P < 0.001 \)), data from these groups were pooled for further comparisons.

The first comparison established that in the absence of the
efferent component, binaural exposure produced the same low “pure” loud sound-induced TTSs as monaural exposure in these test categories. Pooled data from binaurally exposed de-efferented IHL + CMHL groups were compared (Fig. 4C) with data from monaurally exposed IHL and CMHL groups (all efferent-intact and de-efferented monaurally exposed IHL and CMHL groups were pooled since, as shown above, efferent status did not affect the TTSs to monaural exposure). There were no condition differences or interaction effects, confirming that both pooled data sets had similar frequency-dependent TTSs ($P < 0.001$ for Frequency factor). (Comparisons made separately of the pooled binaurally exposed de-efferented groups against pooled IHL + CMHL monaurally exposed efferent-intact or de-efferented groups found the same effects as with the overall comparison above; there was always a significant frequency term but never any condition differences or interaction effects.) Thus in IHL and CMHL categories, binaural exposure after de-efferentation produced the same small TTSs as monaural exposure (with or without intact efferents). In contrast, as shown earlier, binaural exposure with intact efferents in these test categories produced significantly larger TTSs than did monaural exposure in all test categories. These comparisons show that the exacerbation of TTSs in binaurally exposed efferent-intact IHL and CMHL test categories is due to a CAP suppression by cochlear afferents additional to the “pure TTSs” effects of the loud tone.

In normal animals, de-efferentation abolishes the protective effect seen with binaural exposure and causes TTSs similar to the large TTSs caused by monaural exposure with or without intact efferents (Rajan 1995a,b, 2000). In contrast, as shown earlier, binaural exposure with intact efferents in these test categories produced significantly larger TTSs than did monaural exposure in all test categories. These comparisons show that the exacerbation of TTSs in binaurally exposed efferent-intact IHL and CMHL test categories is due to a CAP suppression by cochlear afferents additional to the “pure TTSs” effects of the loud tone.

In summary, lesioning efferent pathways to the normal-hearing ear prior to binaural exposure in the IHL test group prevented binaural exposure exacerbating TTSs in the normal-hearing ear. Lesioning only the crossed pathway (leaving the uncrossed pathway intact) to the normal-hearing ear did not prevent the exacerbation of TTSs by binaural exposure.

**De-efferentation of the normal-hearing ear does not alter cochlear sensitivity prior to loud sound**

As noted previously, the normal-hearing ears had CAP thresholds within the normal range. In all animals CAP thresholds were always re-measured just prior to any brain stem surgery and immediately after (prior to any loud sound exposure). Brain stem lesions did not ever result in changes (not illustrated) in CAP thresholds in the normal-hearing ears, regardless of effects on TTSs to subsequent loud sound exposure. Thus in these test animals, there does not appear to be any tonic efferent activity to the normal-hearing ear that modulates CAP thresholds, as also reported in other studies in normal-hearing barbiturate-anesthetized cats (Rajan 1995a) or guinea pigs (Littman et al. 1991; Rajan 1989; Rajan et al. 1990). The further significance of these data are discussed later.
DISCUSSION

When there was a unilateral hearing loss in test animals, loud sounds produced effects in the normal hearing ear that differed in four respects from effects in animals with bilaterally normal hearing. 1) Monaural exposure caused lower-than-normal TTSs. 2) Binaural exposure did not produce any crossed efferent pathway protection from TTSs as in normal animals for the same exposure (Rajan 1995a,b, 1996a). 3) In test categories with a unilateral partial hearing loss (but not in test animals with a unilateral total hearing loss), binaural exposure elicited uncrossed efferent effects. In normal animals, uncrossed efferent effects are only seen with loud sound exposure in a noise background (Rajan 2000) and not with exposure in silence (Rajan 1995b, 2000). (In the noise background, uncrossed efferent effects on TTSs in normal animals are seen with a monaural loud tone exposure, and binaural exposure does not produce larger uncrossed efferent effects on TTSs.) 4) Finally, in normal animals, uncrossed efferents reduce TTSs (in noise backgrounds) (Rajan 2000), whereas in test animals with a unilateral partial hearing loss they contributed to threshold shifts measured after binaural exposure. Thus in test animals with a unilateral partial hearing loss, uncrossed efferent effects on TTSs were observed under different conditions than in normals (i.e., a noise background was not needed, but a binaural loud sound was) and resulted in changes opposite to those in normal animals.

In each test group tested under a particular experimental condition, there was generally small variability in the effects of loud sound in the normal-hearing ear despite the sometimes quite-varied pattern of hearing losses in the nonetest ear, particularly in the IHL category (Fig. 1A). There was a tendency for CMHL animals, in which unilateral hearing losses were generally stereotyped, to show the least variability. Nevertheless in any one group, there was no correlation apparent between amount of loss in the nonetest ear and effects of loud sound in the normal-hearing ear. (In reports on other studies, I will demonstrate this is not the case if hearing losses are in a test ear itself.) The pattern of losses caused by the loud sound in the normal-hearing ear was the same as seen for the same exposure in animals with bilaterally normal hearing and the variability of TTSs in the test groups was similar to (although sometimes slightly greater than) that seen for the effects of the same loud sound in normal animals (Rajan 1995a,b, 1996a). This is consistent with the fact that in test animals here, the test ear had a normal audiogram. Since it is reasonable to assume that the pattern of TTSs to a loud sound are primarily determined by cochlear mechanics, it is then not altogether surprising, in view of normal audiograms in the test ear, to find no changes in the pattern of TTSs caused by loud sound in the test, normal-hearing ear. With regard to variability of TTSs, it appears that whatever the reason (discussed later) that unilateral hearing loss resulted in changing the effects of loud sound and of the efferents in the normal-hearing ear, the change was relatively stereotyped and independent of the amount of loss in the nonetest ear, although perhaps not the frequency-extent of the loss.

In all test categories, the frequency range with hearing loss in the nonetest ear overlapped to some extent, or lay directly adjacent to, the range subsequently affected by loud sound in the other (normal-hearing) ear. Where nonetest ear losses were at frequencies that did not directly overlap with the frequency range affected later by loud sound in the normal-hearing ear, such nonetest ear losses were in the basal cochlea. In both the Cyst-HL and CMHL categories the unilateral hearing losses were large in the basal cochlea. Similar large losses may have occurred at some stage in the nonetest ear in animals in the IHL category but in some of these animals had recovered to the low levels seen at the time of experimentation. Thus the frequency range where hearing losses were present in the nonetest ear may have a bearing on the effects seen in the test, normal-hearing ear.

Reduced TTSs to monaural exposure

The lower-than-normal TTSs caused by monaural loud sound to the normal-hearing ear in all test categories were not due to acute cochlear efferent activity: lesioning these pathways did not alter the TTSs. In normal animals, efferent activity also does not modulate TTSs to monaural tone-alone exposure (Rajan 1992, 1995a) but reduces TTSs only with binaural exposure. However, in normal animals, if one cochlea is mechanically destroyed, monaural exposure in the other ear results in lower-than-normal TTSs (Rajan and Johnstone 1983a) even 1 wk after destruction of the contralateral cochlea (Robertson and Anderson 1994). This long-lasting change is consistent with the effect here in which damage to one ear either had occurred (in the mechanically lesioned, CMHL, and the Cyst-HL categories), or was presumed to have occurred (in the idiopathic loss, IHL, category) some time ago. One difference is that in normal animals the effect of contralateral cochlear destruction on ipsilateral TTSs in the short term is mediated by the crossed efferents, and lesioning this pathway prevents the reduction in ipsilateral TTSs (Rajan and Johnstone 1989). Acute involvement of cochlear efferents (but not specifically the crossed efferents) in the protective effect of long-term contralateral cochlear destruction in normal animals has also been demonstrated where such destruction was made 8–48 h before ipsilateral exposure (Robertson and Anderson 1994). Thus these effects in normal animals differ from the effects here in that here cochlear efferents were not acutely responsible for the lower-than-normal monaural TTS in the normal-hearing ear.

Conditioning or priming an ear with a moderate-to-loud sound can reduce TTSs in the same ear to later loud sounds (e.g., Campo et al. 1991; Canlon et al. 1988; Miyakita et al. 1992; Rajan and Johnstone 1983b; Ryan et al. 1994; Zheng et al. 1997a), even many days after conditioning. Such conditioning is unlikely to account for the effects here. In IHL animals some prior binaural loud sound may have overstimulated the normal-hearing ear (without damaging it, unlike the other ear, or creating damage such that only one ear had recovered by these experiments). However, there was no previous prolonged stimulation in CMHL animals where a mechanical lesion created chronic unilateral hearing losses in normal-hearing animals that recovered without overstimulation. Nor is it likely that previous overstimulation was involved in causing unilateral hearing loss in Cyst-HL animals.

The consistency of effects of monaural exposure in all test categories suggests that the pertinent feature here is a unilateral hearing loss in the nonetest ear. It is also likely pertinent that the unilateral hearing losses were chronic. In normal animals,
monaural exposure (with the same loud sound used here) of each of the two ears in succession with some delay (=90 min) does not cause different TTSs in the second-exposed ear compared with the first-exposed ear (Rajan 1995a).

Finally, the present data show only that acute activity in cochlear efferents is not needed for lower-than-normal TTSs to monaural exposure in test animals, but does not preclude an efferent role. Unilateral chronic hearing losses may have influenced efferent outflow to the normal-hearing ear to produce changes that chronically reset the susceptibility of that ear to loud sound. Acute cochlear efferent activity, driven by the loud sound, is then not necessary to cause lower-than-normal TTSs to that loud sound. Such re-setting of the normal-hearing cochlea’s susceptibility to loud sounds did not manifest in a change in CAP thresholds prior to the monaural loud sound. However, it has been proposed (Rajan 1992, 1995b) that the protective efferent system manifests actions only on the effects of loud damaging sound. CAP thresholds are not measured using such sounds and any chronic efferent-induced change in cochlear “responses” would not be detectable prior to the loud sound.

**Uncrossed efferent pathways contribute to the large TTSs after binaural exposure**

When the nontest ear had only a partial hearing loss (IHL and CMHL categories) but not when it had a total hearing loss (Cyst-HL), binaural loud sound exacerbated TTSs beyond those caused by monaural loud sound in all test categories. TTSs were considerably higher than those caused by binaural exposure in normal animals and similar to or higher than those caused by monaural exposure in normal animals. Since, in the first two test categories only, binaural exposure would produce some output from both ears, the exacerbation of TTSs in these two categories only appears to require input to the CNS from the nontest damaged ear as well as from the normal-hearing test ear.

The TTS exacerbation by binaural exposure in these categories was prevented by lesioning all efferent pathways but not only the crossed pathway. Thus in these test categories TTSs in the normal-hearing ear after binaural exposure were due to “pure” loud sound-induced cochlear desensitization and also uncrossed efferent effects elevating CAP thresholds. (The present results do not show whether this TTS exacerbation was due to an exacerbation of the damaging effects of the loud tone during its binaural presentation or whether a prolonged post-loud tone efferent suppression of afferent activity contributed to the overall TTSs.)

It is well documented that, when activated with brain stem electrical stimulation (Desmedt 1975; Fex 1962; Galambos 1956; Gifford and Guinan 1987; Guinan 1988; Rajan 1988a; Weiderhold 1986), cochlear efferents can elevate CAP thresholds, and both crossed and uncrossed medial olivocochlear system (CMOCS and UMOCS) neurons can act so (Gifford and Guinan 1987). Binaural tones can evoke uncrossed efferent suppression of the CAP (Liberman 1989), i.e., afferent neural responses (cf., Warren and Liberman 1989a,b), to nondamaging sounds. Finally, in guinea pigs with idiopathic losses in CAP thresholds (Rajan 1989), cochlear efferents were found to be tonically active to cause some CAP threshold elevations. Although that result was interpreted as due to the crossed pathway, at least some brain stem lesions in that report would also have damaged uncrossed pathways.

Nevertheless, an efferent effect contributing to post-loud sound elevation in CAP thresholds is a novel demonstration. In normal animals, monaural exposure with intact or cut efferents produces the same TTSs, binaural exposure with intact efferents reduces these TTSs through CMOCS action, and binaural exposure after de-efferentation results in the same TTSs as monaural exposure (Rajan 1995a, 2000; Rajan and Johnstone 1988a). Thus, normally, TTSs are due to damage to cochlear processes without any exacerbation by centrifugal pathways.

Uncrossed efferent pathways consist of LOCS neurons terminating on dendrites of cochlear afferent neurons and MOCS neurons terminating on OHCs (Guinan et al. 1983; Warr et al. 1986). While it is generally held (e.g., Gifford and Guinan 1987; Guinan 1988; Weiderhold 1986) that all cochlear efferent effects described to date, and responses from single efferent neurons, are due solely to MOCS neurons terminating on OHCs, the present results do not allow attribution of the novel efferent contribution to postbinaural exposure threshold desensitizations to either one of the two uncrossed pathway components.

Finally, in normal animals, binaural exposure after de-efferentation results (Rajan 1995a,b, 2000) in large TTSs identical to those produced by monaural tone exposure (with or without efferents). In the present study when uncrossed efferent effects were eliminated by lesioning prior to exposure in IHL and CMHL categories, binaural exposure resulted in pure loud tone-induced desensitizations significantly lower than TTSs produced by monaural tone exposure in normal animals. This means (as confirmed by analyses not reported here) that the pure loud tone-induced desensitizations in the de-efferented binaural exposure condition here were also significantly lower than TTSs in normal animals with the same experimental condition (Rajan 1995a,b). Thus in the test categories here, the normal-hearing ear had a reduced susceptibility to loud tone-induced damage, and, in the absence of any efferent effect, monaural and binaural exposure resulted in low “pure TTSs” in test categories with a unilateral partial hearing loss. In effect, it appears that the unilateral hearing losses resulted in changes in the normal-hearing ear that “scaled” its susceptibility to loud sound.

**Factors responsible for the absence of protective effects of the crossed efferent pathway**

In normal animals the binaural exposure used here activates CMOCS protection to reduce TTSs from those caused by the same exposure monaurally (Rajan 1995a, 1996a). The absence of TTS protection by the CMOCS with binaural exposure in test animals may be due to a change in excitability of the pathway so it is no longer acutely activated to modulate TTSs. Changes in excitability in single efferent neurons have been reported after acute prolonged stimulation with moderate and high-level noise stimuli (Liberman 1988) or 5 days after a 10-day conditioning stimulus (Brown et al. 1998). (The latter study found no change in drive to stimulation of the ear providing the main drive but a slight, significant, increase in the facilitatory influence of the other ear.) However, these aftereffects of prior long-lasting stimulation are increases in efferent discharge rate, and it seems
unlikely that this should result in absence of protection. Further, the studies showed effects on responses of efferent neurons in one ear after prolonged stimulation of that ear. Such previous overstimulation did not occur in CMHL animals, nor is it likely to have been an issue in the unilateral hearing loss in Cyst-HL animals. The consistency of effects between IHL and CMHL groups for monaural and binaural exposures, and between IHL and Cyst-HL groups for monaural exposures (reasons for differences with binaural exposure have been suggested above), makes it unlikely that in IHL animals alone previous acoustic overstimulation of the normal-hearing ear is responsible for TTS effects seen here.

Alternatively, the absence of CMOCS protection with binaural exposure may be because CMOCS end-effects no longer reduced TTSs. If the CMOCS protects by acting only on one component of the TTSs and if this component is not affected significantly or at all by loud sound, then protection may not ensue. In support of this idea neither direct electrical stimulation of cochlear efferents (Rajan 1988b; Rajan and Johnstone 1988b) nor binaural acoustic stimulation (Rajan 1995b; Rajan and Johnstone 1989) evoke protection from TTSs to loud sounds at levels that cause small TTSs (Rajan 1995a,b; Rajan and Johnstone 1988a) even if they strongly drive efferent neurons (Liberman 1988; Liberman and Brown 1986; Robertson and Guummer 1985). The same manipulations do result in CMOCS-mediated protection at higher exposure levels that produce larger TTSs, presumably because now the putative “protected” component is affected. Consistent with this hypothesis, in IHL and CMHL categories, TTSs after de-efferentation and binaural exposure were similar to TTSs after monaural exposure in all test categories. Thus as in normal animals (Rajan 1988b, 1995b; Rajan and Johnstone 1988b, 1989), when TTS is low, binaural exposure does not result in CMOCS-mediated protection.

In summary, the absence of CMOCS-mediated protection in test animals in the binaural conditions that reveal protection in normal animals is proposed to be likely due to a re-setting of the susceptibility of one particular cochlear component/process in loud sound-induced damage in the normal-hearing ear. If this effect is specific to cochlear processes at high SPLs, then it would not result in any changes in CAP thresholds prior to the loud sound, consistent with the absence of any changes in CAP thresholds in the normal-hearing ear. The present results do not indicate what mechanisms may have been re-set in such a way.

Finally, the pure TTSs in test animals to monaural or binaural exposure (for 11 kHz, 100 dB SPL, 10-min exposure) were similar to the low TTSs in normal animals to a monaural 7-min exposure at the same frequency and level (Rajan 1995a). Yet, in normal animals, the latter exposure evokes protection (Rajan 1995a): there are lower TTSs with binaural compared with monaural exposure. In contrast, in test animals here the “pure TTSs” to binaural and monaural exposure were similar, suggesting that the CMOCS may no longer protect at all in the test animals or that its protective effect has been shifted to a higher part of its TTSs “operating” range (Rajan 1992, 1995b).

In normal animals, when protecting from TTSs to a loud tone (in a noise background only), uncrossed efferents do not appear to act directly on the mechanism(s) whereby loud sound causes TTSs but prevent noise from exacerbating loud tone-induced TTSs (Rajan 2000). Thus normally, as long as the CMOCS pathway is lesioned, the “pure TTSs” caused by a monaural or binaural tone in a background of silence are not affected by the presence or absence of uncrossed efferents (Rajan 1995b, 2000). The present data provide further support for differentiating uncrossed efferent effects on TTSs from “pure TTSs” of loud sound. Binaural exposure after de-efferentation (in IHL animals in which this manipulation was tested) resulted in small TTSs similar to those after monaural exposure in test animals. The extra TTSs with binaural exposure in efferent-intact test animals were due to uncrossed efferent effects additional to the pure loud tone-induced cochlear desensitization.

It may be most parsimonious, for reasons detailed in the introduction, to assume that uncrossed efferent effects here are due to uncrossed MOCS (UMOCS) neurons, terminating on OHCs. Then, previous results in normal animals and the present results suggest that although CMOCS and UMOCS neurons exert effects on OHCs, they may do so through very different mechanisms of action or have different requirements for their activation.

With regard to activation, the only effects seen here in animals with unilateral hearing losses after loud tone–alone exposures were due to uncrossed pathways. In normal animals, the only effects seen after loud tone exposures in silence were due to the CMOCS (Rajan 1995a,b) and uncrossed pathway effects are seen with monaural loud tones only in a noise background (Rajan 2000). This suggests different activation requirements for CMOCS and (presumed) UMOCS. For unknown reasons, the activation requirements for UMOCS appear changed when there is a chronic unilateral loss: UMOCS effects are now seen when the loud tone is presented in a background of silence.

With regard to mechanisms of action, CMOCS effects during (binaural) loud sound in normal animals protect from TTSs, whereas, as noted above, in normal animals uncrossed efferent (presumed UMOCS) effects, seen only to a loud sound in a noise background, prevent exacerbation of TTSs by noise but do not directly protect from TTSs (Rajan 2000). In test animals here, uncrossed efferent (presumed UMOCS) effects during loud sound (in a background of silence) exacerbated post-loud sound threshold shifts, but appeared to be additional to the “pure TTS” effects of loud sound. These differences suggest different end-effects of the CMOCS and (presumed) UMOCS with respect to actions during, or on the effects of, loud traumatic sounds. If true this represents an important distinction that has not previously been made. Both CMOCS and UMOCS neurons are cholinergic, and cholinergic effects on OHCs appear to be exercised through a single nicotinic-type receptor (e.g., Nenov et al. 1996; Puel 1995). Current studies, either implicitly or explicitly, assume that effects exercised by UMOCS and CMOCS are made through the same end-mechanism on OHCs. However, such studies have concentrated only on MOCS effects at atraumatic sound levels, and it may be that
at traumatic levels, there are distinctions of the sort speculated about here.

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