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Slow build-up of cochlear suppression during sustained contralateral noise: central modulation of olivocochlear efferents?

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Abstract

The strength of the medial olivocochlear (OC) reflex is routinely assayed by measuring suppression of ipsilateral responses such as otoacoustic emissions (OAEs) by a brief contralateral noise, e.g. (Berlin et al., 1995). Here, we show in anesthetized guinea pigs, that the magnitude of OC-mediated suppression of ipsilateral cochlear responses (i.e. compound actions potentials (CAPs), distortion product (DP) OAEs and round-window noise) slowly builds over 2–3 minutes during a sustained contralateral noise. The magnitude of this build-up suppression was largest at low ipsilateral stimulus intensities, as seen for suppression measured at contra-noise onset. However, as a function of stimulus frequency, build-up suppression magnitude was complementary to onset suppression, i.e. largest at the lowest and highest frequencies tested. Both build-up and onset suppression were eliminated by cutting the OC bundle. In contrast to “slow effects” of shock-evoked medial OC activity (Sridhar et al., 1995), which are mediated by slow intracellular changes in Ca concentration in OHCs, build-up effects of contralateral noise are immediately extinguished upon OC bundle transection and are likely mediated by central modulation of the response rates in MOC fibers due to the sustained noise. Results suggest that conventional tests of OC reflex strength may underestimate its magnitude in noisy environments.

Keywords

feedback; inner ear; brainstem plasticity; olivocochlear reflex

Introduction

Medial olivocochlear (MOC) efferents comprise a sound-evoked negative-feedback pathway to the outer hair cells (OHCs) of the inner ear (for review, see (Guinan, 1996)). When activated, this feedback reduces cochlear responses by decreasing the normal contribution of OHCs to

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cochlear amplification. The functional role of this binaurally activated feedback remains controversial, however, a strong anti-masking effect as well as protection from acoustic overexposure have been demonstrated.

Cochlear effects of OC activation can be studied by electrical stimulation of the OC bundle at the floor of the IVth ventricle (Wiederhold et al., 1970b) or by presentation of sound, either to the contralateral (Buno, 1978; Warren et al., 1989) or ipsilateral (Liberman et al., 1996) ear. OC activity, either shock- or sound-evoked, elicits a rapid (~100 ms onset time constant) reduction of cochlear responses mediated via Ca^{2+} entry through $\alpha 9/\alpha 10$ -nicotinic acetylcholine receptors (nAChR) at the MOC/outer hair cell synapse, coupled to K^{+} efflux through nearby Ca-activated K^{+} channels (Fuchs et al., 1992; Vetter et al., 2007). In addition to this ‘fast effect’, sustained electrical activation of the OC bundle also evokes a ‘slow-effect’ suppression, with an onset time constant of ~30 sec (Sridhar et al., 1995)(Brown et al., 1984b; Cooper et al., 2003). The slow effect is initiated via the same $\alpha 9/\alpha 10$ nAChRs, but downstream effects may involve a Ca^{2+} “wave” diffusing along the outer hair cell (OHC) membrane to distant (extra-synaptic) K^{+} channels (Sridhar et al., 1997).

Slow effects of sound-evoked OC activity on cochlear responses have not been well studied, however, in awake guinea pigs, sustained contralateral noise evokes both a slow and fast suppression of ipsilateral round-window noise (da Costa et al., 1997), a bio-electric signal measured in the absence of acoustic stimulation and dominated by spontaneous action potentials of cochlear nerve fibers innervating inner hair cells (IHCs). Although these sound-evoked and shock-evoked slow effects have a similar time course, they have different pharmacological profiles: whereas sound-evoked fast effects can be selectively eliminated by the MOC blocker gentamicin (Lima da Costa et al., 1997), shock-evoked slow and fast effects are blocked to a similar degree by gentamicin (Yoshida et al., 1999). This difference in pharmacology suggested that the sound-evoked slow effect might be mediated by the lateral olivocochlear (LOC) fibers (Yoshida et al., 1999), which project to terminals of cochlear nerve fibers underneath the inner hair cells (Guinan et al., 1983).

In the present study, we re-examined the effects of sustained (5-min) contralateral noise on ipsilateral cochlear responses, using the anesthetized guinea pig. To discriminate MOC from LOC effects (Groff et al., 2003), we measured a number of ipsilateral cochlear responses, including those dominated by OHC function (i.e. distortion product otoacoustic emissions and cochlear microphonics) as well as those also requiring synaptic transmission and neural activation (i.e. round-window noise and compound action potentials). We document the presence of a robust, slowly building suppression of ipsilateral responses elicited by contralateral noise, with all the characteristics of an MOC rather than an LOC effect: e.g. suppression of both otoacoustic emissions and neural responses, coupled with an enhancement of cochlear microphonics, that is larger at low ipsilateral levels than high (Groff et al., 2003). However, the further observation that this slowly building suppression is immediately extinguished upon transection of the OC bundle suggests that it is mediated by central modulation of spike activity of MOC neurons (Liberman, 1988), rather than by peripheral changes in OHC function as demonstrated for shock-evoked “slow effects” (Sridhar et al., 1995). The existence of a slow build-up of OC-mediated suppression suggests, in turn, that conventional protocols for measuring OC reflex strength underestimate its full magnitude.

Methods

Animal preparation

Results from 24 female albino guinea pigs (*Cavia Porcellus*, Hartley strain, Charles River Labs), weighing 350–800 g, are reported. Surgical and experimental procedures were approved by the Animal Care Committees of the Massachusetts Eye & Ear Infirmary and the

Massachusetts Institute of Technology. Animals were anesthetized with sodium pentobarbital (Nembutal, 25 mg/kg i.p.), Fentanyl (0.20 mg/kg i.m.) and Droperidol (10 mg/kg i.m.), with boosters given as needed to maintain an areflexive state. Animals were tracheotomized, and bullas were exposed bilaterally via a dorsal approach and opened to allow access to the round window of the cochlea. After positioning of electrodes, the bulla was covered with petroleum-jelly soaked cotton, to minimize cochlear cooling. The ear canals were severed close to the tympanic ring to allow positioning of a custom acoustic assembly. In experiments requiring access to the IVth ventricle, a posterior craniotomy was performed, and the medial portion of the cerebellum was aspirated. Lesions to the OC bundle were made with a microknife, guided by landmarks on the dorsal surface of the brainstem (Warren et al., 1989). General physiological state was monitored by electrocardiography (normal rate 280–350 per minute) and rectal temperature (maintained at 37–38° C by heating the experimental chamber and using a heating pad, if necessary). Some animals were paralyzed (tubocurarine at 0.3 mg/kg i.m.) and artificially respirated (Harvard Rodent Ventilator; tidal volume 3.5 ml at 50/min). Experiments were continued either until sufficient data were collected, or DPOAE/CAP thresholds had deteriorated significantly (>10 dB) at two or more frequencies. Typically, baseline thresholds could be maintained to within 5 dB of their initial values for the duration of the experiment (~10 hrs).

Recording cochlear responses

Experiments were conducted in a sound-proofed and electrically shielded room, heated to 30–35°. Distortion-product otoacoustic emissions (DPOAEs) were measured throughout the experiment to monitor cochlear stability.

Cochlear potentials were measured from a silver-ball electrode on the round window, referenced to an electrode in the neck muscles, filtered (300–3000 Hz) and amplified 10,000x (Grass P5 series). Gross neural activity was measured from compound action potentials (CAP) in response to 5-ms tone pips (0.5 ms rise/fall). Tone pips were presented (10/sec) in alternate-polarity pairs and averaged to obtain CAPs, or subtracted and divided by 2 to obtain cochlear microphonic (CM). CAP input-output functions were acquired at tone-pip frequencies of 4.0, 5.6, 8.0, 11.3, 16, 22.6 or 32 kHz, and CAP thresholds were defined using a response criterion of 15 μ V. CAP amplitude was calculated as the peak-to-peak voltage of the CAP waveform. CM response magnitude (to 4 kHz tones) was obtained as the magnitude of the Fourier transform component at the stimulus frequency. Round window (RW) noise, a measure of auditory nerve spontaneous activity (Dolan et al., 1990), was calculated as the integral of the power spectrum between 683 and 917 Hz (i.e. centered on the peak, which is at 800 Hz) of a 128 msec sample from the electrode signal obtained in quiet. When present, the level of the contralateral white noise was ~75 dB SPL: its spectrum was flat at the input to the earphone; the transfer function of the acoustic coupler was flat ($\pm$ 10 dB) from 500 Hz to 25 kHz.

DPOAEs were measured in the ear canal in response to two primary tones (f_1 and f_2), presented in a frequency ratio $f_2/f_1=1.22$ and level ratio $f_1=f_2+10$ dB. DPOAE input-output functions were measured with f_2 frequencies of 4.0, 5.6, 8.0, 11.3, 16, 22.6, or 32 kHz. DPOAE thresholds at each frequency were defined as the f_2 level required to obtain a $2f_1-f_2$ of 0 dB SPL. Tones were passed through custom-built precision attenuators, and commercial driver amplifiers and electrostatic loudspeakers (Tucker-Davis Technologies: ED-1 and EC-1, respectively). The cubic DPOAE at $2f_1-f_2$ was extracted from the microphone signal (Etymotics Research ER-10C, low-noise pre-amplification of 40 dB) in the custom acoustic assembly by Fourier transform. The probe-tube microphone was calibrated using a pistonphone (Bruel & Kjaer 4228) and a dedicated calibration microphone (Bruel & Kjaer 4132) in a coupler. All signal generation and online data processing was performed by custom LabVIEW (National Instruments) software and a data acquisition card (National Instruments PCI-6052E).

To characterize effects of contralateral noise (Figure 1), *blocks* of ipsilateral responses were measured in continuously interleaved fashion for 15 min, with a contralateral noise at ~75 dB SPL presented during the middle 5 min of this 15-min *trial*. Typically three to six *trials* were obtained sequentially and averaged to yield the final result. Each 10-sec *block* of ipsilateral response metrics consisted of measurement of RW noise, followed by CAPs at two to six frequency/level combinations (8 averages each), followed by one to three DPOAE frequency/level combinations (four 40-msec waveform averages per spectrum, two spectral averages each). CAP tone pip levels were typically 30–40 dB SPL and produced CAPs of 50–100 μ V; DPOAE primaries were typically 25–40 dB SPL and produced $2f_1$ – f_2 distortions of 10–15 dB re noise floor (which were 0 to –20 dB SPL depending on frequency). All metrics included an ‘artifact reject’ feature, which repeated a measurement if a criterion level was exceeded; –10 dB for RW noise, 125 μ V for CAP, and –5 dB SPL for DPOAE noise floor at the $2f_1$ – f_2 frequency band.

Data analysis

Offline analysis was done with custom software in MATLAB (The Mathworks). To average data across *trials*, each was subdivided into 10-sec bins, and for each metric, data from all available trials was averaged in the appropriate bin. All metrics were expressed in a dB scale, and the initial 300-s of measurements (silence in contralateral ear) were averaged to obtain a baseline, defined as 0 dB, to which the remaining magnitudes were referred. Where used, statistical significance was assessed by two-tailed two-sample *t*-test, at the 5% significance level ($p < 0.05$). Correlations between various metrics or time windows were assessed with the Kendall tau rank correlation coefficient (Kendall, 1938) calculated as $\tau = [4P/n(n-1)] - 1$, where P is the number of concordant pairs and n is the number of items. We used a MATLAB function (`corr`) to calculate τ : the odds ratio of the concordant to discordant sets of observations is $(1 + \tau)/(1 - \tau)$. Significance of the correlation was assessed at the 5% level ($p < 0.05$). To facilitate comparison of effects on CAP and DPOAE responses, suppression magnitudes were converted to ‘equivalent attenuation’, defined as the *decrease* in input sound pressure level required for an identical response suppression (Guinan et al., 1996). Equivalent attenuation was computed from the I/O function measured closest in time to the data being processed. Interpolation was done with piecewise cubic Hermite interpolating polynomials (PCHIP, using `interp1` in MATLAB, which makes results more accurate in regions where the function changes slope, because it creates a smooth interpolation without kinks that would result from linear interpolation).

Histology

To verify locations of brainstem lesions, brainstem sections were stained for acetylcholinesterase to mark the location of the OC bundle and the cell bodies of both MOC and LOC systems (Vetter et al., 1991). Animals were perfused intracardially with 4% paraformaldehyde, and brains were stored in the same fixative overnight. The brainstem were dissected and cryoprotected in 30% sucrose in 0.1 M phosphate buffer overnight, after which 80 μ m sections were cut in the transverse plane on a freezing microtome and stored in 0.1 M phosphate buffer. Staining for acetylcholinesterase was done by incubating at room temperature for 1 hr in a solution containing 0.0072% ethopropazine, 0.1156% acetylthiocholine iodide, 0.075% glycine, 0.05% copper sulfate, 0.68% sodium acetate (pH 5.0), followed by 1 min in a solution of 4.0% sodium sulfide (pH 7.8), and finally 1 min in a solution of 1.0% silver nitrate. Sections were placed on gel-subbed slides, air-dried overnight, dehydrated in 100% ethanol, and coverslipped with Permount.

Results

Build-up effects of sustained contralateral noise

Efferent-mediated suppression of ipsilateral cochlear responses by contralateral noise has been studied with noise durations of a few seconds (Hood et al., 1996) to a few minutes (Veuillet et al., 2001); however, the time-varying nature of such effects has not been well characterized. Here we study the slow variation in the magnitude of sound-evoked efferent suppression when the contralateral noise is sustained for 5 minutes.

As shown in Figure 2, presentation of a moderate-level (~75 dB SPL) sustained contralateral noise elicits a slowly building suppression of ipsilateral CAPs, DPOAEs and RW noise, as well as a small, but statistically significant, enhancement of the CM (Fig. 2). This constellation of cochlear effects is consistent with a slowly building activation of medial olivocochlear (MOC) effects on OHCs by the contralateral noise (Groff et al., 2003). The extinction of the effect after contralateral cochlear destruction rules out acoustic crosstalk (data not shown), and the persistence of the effect after curarization, at a dose known to block shock-evoked stapedius muscle contractions (Groff and Liberman 2003; data not shown), rules out contributions of the middle-ear muscles, as does the lack of correlated changes in the ear-canal sound pressure of the primary tones used to generate the DPOAEs, which would result from any muscle-mediated middle-ear impedance changes (Guinan, 2006).

The relatively small size of the “onset” suppression, as seen in the first ipsilateral measures after turning on the contralateral noise (Fig. 2A), is consistent with reports that anesthesia attenuates the strength of the MOC reflex (Boyev et al., 2002), when measured with brief contralateral stimuli. During the sustained noise, the “build-up” suppression reaches a maximum after 2 – 3 min, and then stabilizes (Fig. 2C), or decays (Fig. 2A,D). The return to baseline after contralateral-noise offset was variable across animals, ranging from abrupt (<10 s) to gradual (similar time constant as the suppression buildup). Overall, the build-up suppression appeared similar for neural (CAP and RW noise; Fig. 2A,D) and outer hair cell (DPOAE; Fig. 2C) responses; however the time resolution of the paradigm was not fine enough to effectively quantify the time constants.

Dependence on ipsilateral frequency

The suppression of cochlear CAPs elicited by sustained MOC shock trains has a characteristic frequency dependence: shock-evoked “slow” effects are seen only in responses to high-frequency stimuli (> 10 kHz), and they peak at about 16 kHz; whereas “fast” shock-evoked effects peak at ~ 8 kHz, i.e. in the cochlear region where the density of MOC innervation is greatest (Sridhar et al., 1995). As shown in Figure 3A, the sound-evoked suppression of CAP was insensitive to ipsilateral frequency over a wide range (from 4 – 22 kHz). When the suppressive effect was decomposed into an “onset” (first sample) and a “build-up” component (see inset to Fig. 3B), the small “onset” component (open circles in Fig. 3A) had a similar frequency dependence to that seen for classic MOC “fast” effects, whether sound-evoked (Kujawa et al., 2001) or shock-evoked (Sridhar et al., 1995). Shock-evoked “slow” effects have not been measured via DPOAEs. The mean magnitude of total RW noise suppression was 0.72 dB (onset 0.19 dB, build-up 0.53 dB): this value cannot be converted to equivalent attenuation.

The frequency dependence of the build-up CAP suppression (gray circles in Fig. 3A) was complementary to that of the onset component; furthermore, the prominent build-up effects at low frequency make it distinctly different from shock-evoked “slow” effects (Sridhar et al., 1995). Averaged across ipsilateral frequency, mean total CAP equivalent attenuation (1.66 ± 0.13 dB) was larger than total DPOAE equivalent attenuation (1.08 ± 0.13 dB), mostly because the build-up component was larger (1.14 vs. 0.54 dB).

The larger size of sound-evoked MOC effects when measured via CAPs vs. DPOAEs, and the difference in their dependence on ipsilateral frequency (Figs. 3A vs. B), has been noted in previous studies of contra-sound evoked “fast” effects (Puria et al., 1996). That study argued that the differences arise because CAP reflects the simple summation of neural activity in response to a single tone pip (Kiang et al., 1976), whereas the DPOAE is a complex result of non-linear interactions in cochlear mechanics between traveling waves produced by the two primary tones, and those produced by the distortion product(s) and its cochlear reflections (Shera et al., 1999). When OC activity modulates these complex interactions, DPOAE amplitudes can be enhanced as well as reduced. As such, the CAP is arguably a more reliable metric of OC-mediated reduction of cochlear amplifier gain (Puria et al., 1996).

Dependence on ipsilateral level

The magnitude of MOC-mediated effects generally decrease with increasing ipsilateral stimulus level for both neural and OHC-based metrics (Guinan, 1996), although DPOAE suppression can be large near non-monotonicities in the amplitude-vs-level functions (Kujawa et al., 2001). In contrast, LOC effects are a constant fraction of baseline amplitudes, i.e. a constant dB of magnitude suppression, irrespective of stimulus level (Darrow et al., 2007; Groff et al., 2003; Le Prell et al., 2003). The dependence of suppression magnitude on ipsilateral stimulus level for the suppression from sustained contralateral noise (Fig. 4) is consistent with an MOC-mediated effect: suppression decreases with increasing ipsilateral stimulus level, for both CAP and DPOAE. An MOC-mediated *enhancement* of DPOAE response at high levels (as seen by the triangles in Fig. 4B) has been reported previously (Kujawa et al., 2001). At this stimulus level, the DPOAE I/O showed a notch, or local slope reversal, such that an effective input attenuation leads to an output enhancement. The onset and build-up components of the suppression magnitude showed a similar decrease with increasing stimulus level, although the pattern is noisier for the onset, because it is estimated using one sample only (data not shown).

Relations between onset and build-up effects

Previous studies of shock-evoked “fast” and “slow” effects have shown a strong positive correlation between the magnitude of these two components as shock rate is increased (Sridhar et al., 1995 - Fig. 8B). In contrast, the onset and build-up components of the sustained contralateral-noise effects tend to be (weakly) negatively correlated: the scatterplots in Figure 5A,B show that the biggest build-up suppression tends to be seen with the smallest onset effects and vice versa (correlations were -0.38 with $p<0.001$ for CAP, -0.34 with $p<0.001$ for DPOAE and -0.39 with $p=0.01$ for RW noise). Correlations for CAP and DPOAEs are tighter if both components for each trial are normalized at each frequency by the frequency-averaged total suppression magnitude for that animal (data not shown). A negative correlation would suggest a ‘ceiling’ for the total suppression magnitude and therefore with a shared common pathway for the underlying mechanisms.

Shock-evoked “slow” effects adapt during continuous stimulation: suppression magnitude decays strongly 60 – 90 sec after shock-train onset (Sridhar et al., 1995). In that respect, the present sound-evoked build-up suppression is similar, as shown in Figure 2. For both CAP and DPOAE measures, the degree of adaptation shows a slight tendency to grow with increasing size of the build-up suppression (Fig. 5 C,D): correlations were 0.34 with $p<0.001$ and 0.39 with $p<0.001$, respectively. Degree of adaptation was not significantly correlated with onset suppression magnitude (data not shown). Thus, adaptation may reflect a weakening of the build-up effect.

Effects of gentamicin and OC lesions

Although gentamicin at high doses can be ototoxic (Sullivan et al., 1987), at low doses (e.g. 150 mg/kg) it is an effective blocker of both fast and slow shock-evoked MOC effects. In

previous guinea pig work, gentamicin blockade of shock-evoked OC effects was maximal by 2 hrs post-injection, with no recovery after an additional 6 hours (Yoshida et al., 1999). As shown in Figure 6, gentamicin in two animals eliminated most of the onset and build-up effects of the sustained contralateral noise, consistent with a dominant role for the MOC system, and further arguing against involvement of the MEM reflex.

To further test the role of the MOC system, we measured contralateral-noise effects before and after cuts to the OC bundle. To assess the differential contributions of contralaterally vs. ipsilaterally responsive MOC pathways, cuts were first made at the midline (interrupting the ipsilaterally responsive MOC fibers) and then more laterally (at the sulcus limitans) to interrupt both pathways. As shown in Figure 7, a midline cut produces no change in the effect magnitude or time course that cannot be attributed to the run-to-run variations seen pre-manipulation. The results from the midline lesion clarify that the noise effects are not dominated by ipsilaterally responsive MOC neurons that are *facilitated* by addition of contralateral noise. In contrast, after a lateral cut, suppression is completely abolished for both CAP and DPOAE. In five additional experiments with lateral cuts that lesioned the OCB, as verified by subsequent brainstem histology, slow suppression was abolished (data not shown). In four experiments with lateral cuts that missed the OCB (as verified histologically), suppression (both onset and build-up components) was unaffected relative to the intact condition.

Central vs peripheral changes

Prior studies of shock-evoked “slow” effects showed that, once evoked by continued stimulation, the slow-effect offset was not altered by rapid transection of the OC bundle (Sridhar et al., 1995), thereby verifying a peripheral locus (i.e. OHCs) for the functionally important modifications underlying the effect. To distinguish between peripheral and central origins of build-up suppression from sustained contralateral noise, we sectioned the OC bundle *during* the contralateral noise, when suppression had reached its greatest magnitude. As shown for one such experiment in Figure 8, after cutting the OC bundle, responses immediately revert to baseline at all following samples, rather than gradually recovering, as seen for shock-evoked “slow” effects. This result is consistent with a central origin for the build-up effect, e.g. a central modulation of the sound-evoked responses of the contralaterally responsive MOC neurons.

Discussion

Mechanism of build-up suppression by contralateral noise

Many previous studies have shown that presentation of contralateral acoustic stimuli, especially broadband noise, can suppress ipsilateral cochlear responses by activating the OC bundle, more specifically the subset of medial OC fibers which originate ipsilaterally, form a portion of the uncrossed OCB and project to OHCs (e.g. (Warren et al., 1989). Indeed, the phenomenon of contra-sound suppression has, for many years, been used as an assay for the strength of the OC reflex in both human (Berlin et al., 1993; Collet et al., 1992; Mukari et al., 2008) and animal studies (Liberman, 1991). To maximize contralaterally activated OC effects, ipsilaterally driven OC activation is minimized by using transient narrow-band stimuli at low repetition rates (Liberman et al., 1986), as in the present study.

This sound-evoked efferent effect has an onset time constant of ~100 msec and thus corresponds to the “fast” component of the suppressive effects evoked by OC electrical stimulation (Warren et al., 1989). The classic MOC “fast effect” arises when ACh release from MOC terminals elicits Ca^{2+} entry through $\alpha 9/10$ ACh receptors on OHCs (Vetter et al., 2005b), and Ca^{2+} entry increases the K^{+} conductance through the associated SK2 channels on the OHCs (Vetter et al., 2005a). The result is a decrease in OHC contribution to cochlear amplification, a concomitant decrease in basilar membrane motion (Murugasu et al., 1996) and

thus a decrease in most sound-evoked cochlear responses, including the OHC-driven DPOAEs (Puria et al., 1996), inner hair cell receptor potentials (Brown et al., 1984a), as well as discharge rates of auditory-nerve fibers (Wiederhold et al., 1970a) and, correspondingly, the CAP (Puria et al., 1996). The CM, the field potential dominated by OHC receptor potentials (Dallos et al., 1976), is paradoxically enhanced by MOC stimulation, because the SK2-based increases in OHC K^+ conductance increase sound-evoked transepithelial currents (which dominate the CM) as they short-circuit the OHC transmembrane potentials which drive the motors underlying cochlear amplification (Geisler, 1974). The increase in resting transepithelial currents decreases the endolymphatic potential, which explains the reductions in auditory-nerve spontaneous discharge during OCB stimulation (Guinan et al., 1988) and, thus, the decrease in the RW electrical noise measured in silence, which is dominated by this spontaneous discharge (Dolan et al., 1990).

In the present study, in anesthetized guinea pigs, sustained contralateral noise elicited both immediate and slowly building suppression of cochlear ipsilateral responses, including CAPs, DPOAEs and RW noise, while it slightly enhanced the CM (Fig. 2). Loss of these effects after contralateral cochlear destruction ruled out acoustic crosstalk as a mechanism, and lack of susceptibility to paralysis eliminated a role for the middle-ear muscles. Blockade of the effects by systemic gentamicin (Fig. 6) and by lesion of the OC bundle (Fig. 7) provided compelling evidence that this efferent neural pathway is involved. The strong suppression of OHC-driven DPOAEs (e.g. Figs. 2, 3B) argues strongly against a major role for the lateral (L)OC system, since these unmyelinated LOC projections terminate exclusively in the inner hair cell area (Maison et al., 2003), where they evoke changes in auditory nerve responses without affecting DPOAEs or CM (Groff et al., 2003). Correspondingly, the constellation of effects observed on cochlear responses is qualitatively consistent with known effects of the MOC system, e.g. small effects in anesthetized animals (Boyev et al., 2002-Fig. 5), slightly larger suppression of CAPs than DPOAEs (Puria et al., 1996-Fig. 3), and larger magnitude suppression at low than high ipsilateral stimulus levels (Wiederhold et al., 1970a - Fig. 4).

The slow build-up suppression seen here, though largely MOC-mediated, is probably not the “slow effect” of shock-evoked MOC activity, a CAP suppression and CM enhancement with an onset time constant of ~30 sec (DPOAEs and RW noise were not measured in previous studies of shock-evoked slow effects (Sridhar et al., 1997; Sridhar et al., 1995). The shock-evoked “slow effect” is thought to arise from a wave of calcium-induced Ca^{2+} release, triggered by the same $\alpha 9/\alpha 10$ ACh receptors that mediate the “fast” effect. However, insensitivity to the SK2 blocker apamin suggests that shock-evoked “slow effects” are mediated by different, and possibly extrasynaptic, K^+ channels (Yoshida et al., 2001). The build-up suppression observed here differed from the shock-evoked “slow effect” in several important ways. First, shock-evoked slow effects are exclusively a high-frequency phenomenon (evoked only when ipsilateral tone frequency is > 10 kHz, peaking at 16 kHz: (Sridhar et al., 1995)), whereas build-up CAP suppression is as large at 4 kHz as it is at 22.6 kHz (Fig. 3A). Second, the magnitudes of fast and slow shock-evoked effects are highly correlated (Sridhar et al., 1995), whereas onset and buildup sound-evoked CAP suppression are complementary in size (Fig. 5A). Third, and most compellingly, transection of the OCB at peak effect immediately extinguished the sound-evoked build-up suppression (Fig 8); whereas, after OCB transection, shock-evoked slow effects slowly return to baseline with an offset time constant similar to that seen after shock-train termination with an intact OCB (Fig. 4C in Sridhar et al., 1995).

An alternate view is that the build-up suppression elicited by contralateral noise could reflect a slow modulation of response rate in MOC neurons, i.e. it may arise from slow changes in the excitability of the MOC central circuitry rather than via slow effects on OHCs. Indeed, single-fiber recordings in anesthetized cats have shown that a 10-minute exposure to ipsilateral, contralateral or binaural noise can elicit a lingering enhancement of MOC fiber response, seen

as a 10–20 dB increase in threshold sensitivity (Liberman, 1988), as well as a lingering increase in spontaneous discharge rate in MOC fibers (Liberman, unpublished). Although the onset time course of this slow enhancement has not been well characterized in single MOC fibers, the offset time course is appropriate: the enhancement dissipates by 5 minutes post noise-offset (Liberman, 1988 - Fig. 13). Thus, the basic phenomenon of central response facilitation is consistent with the effects we observe in suppression of CAPs, DPOAEs and RW noise, and with their immediate extinction upon OC bundle transection. The modest effects of midline MOC cuts on build-up suppression (Fig. 7), which interrupt only the ipsilaterally driven MOC fibers (Liberman et al., 1986), suggest that it is not their binaural facilitation by contralateral sound that mediates delayed suppression. Rather, it must be mediated by the contralaterally responsive fibers, which comprise the uncrossed OC bundle (Liberman et al., 1986). Prior studies of OC-mediated protection from acoustic overstimulation have suggested that OC activation may be slowly modulated in the presence of continuous noise (Rajan, 2000; Rajan, 2001), and, furthermore, that these protective effects are mediated primarily by the contralaterally responsive fibers of the uncrossed OC bundle (Rajan, 1991).

Previous investigators documented both onset and slowly building suppression of RW noise in awake guinea pigs (da Costa et al., 1997) in response to sustained contralateral noise (sound-evoked ipsilateral responses were not measured). The larger suppression magnitudes observed in awake animals (3, 1.5, and 5.5 dB, respectively, for onset, build-up and total suppression) compared to the anesthetized animals (0.2, 0.5, and 0.7 dB, respectively) used here, is consistent with anesthesia-induced attenuation of MOC effects in guinea pigs (Boyev et al., 2002). However, the awake state adds background noise (e.g. from animal movements), thus the RW noise measured “in silence” in the awake study must include both spontaneous and sound-evoked nerve discharge, which will enhance the magnitude of MOC-mediated suppression compared to that measured in a sound-proof room with an anesthetized animal (Guinan et al., 1988). Spontaneous rates in auditory nerve fibers can be reduced by as much as 25% (i.e. 2.5 dB) during maximal shock-evoked MOC activity, because of the drop in endolymphatic potential caused by the MOC-mediated increase in resting K^+ conductance in OHCs (Guinan et al., 1988). Given that sound-evoked rates in MOC fibers are never as high as shock-evoked rates, the values from all these studies appear to be consistent. Although, the previous investigators ascribed their slowly building suppression to the MOC “slow effect” (da Costa et al., 1997), it is likely the same phenomenon reported here.

Implications for MOC reflex-testing protocols

The strength of the MOC reflex in humans is often measured by quantifying what corresponds, in the present study, to the onset suppression of ipsilateral responses by contralateral noise, i.e. the contralateral noise is often no more than 2–3 sec in duration (e.g. (Backus et al., 2006; Berlin et al., 1995)). The present results show that the strength of the reflex can be significantly enhanced relative to that onset value by sustained presentation of the contralateral noise. Thus, the conventional metrics for reflex testing appear to underestimate the full power of OC feedback. The single-fiber studies of MOC response enhancement suggest that these long-lasting effects might be even greater with sustained exposure to bilateral noise (Liberman, 1988) than with the contralateral noise used here. The fact that the strength of sound-evoked OC effects is dependent on acoustic history, with a “memory” of several minutes, suggests that, to reduce variability in contra-sound suppression tests, care should be taken to control the overall degree of noise stimulation, especially immediately before the OC reflex testing.

In other protocols for MOC reflex testing, the contralateral noise can be on for longer periods of time, during which ipsilateral OAE-evoking clicks or tone pips are presented, and responses are averaged (Veuillet et al., 2001). In such longer-noise paradigms, the averaging of responses over a period in which MOC effects may be slowly building will also underestimate the full

size of the suppression. Furthermore, the variability in the duration of the contralateral noise, which is introduced because of variations in the numbers of ipsilateral stimuli that are “rejected” because of noisy responses, will introduce variability from subject to subject in the degree of suppression build-up, assuming that the same phenomenon is present in awake humans.

The slow changes in contralateral sound suppression observed here in anesthetized guinea pigs can presumably be measured non-invasively in awake human subjects using ipsilateral measurement of OAEs. If the present hypothesis is correct, such a test provides a window into plasticity in neural circuitry in the auditory brainstem. This information could prove useful in clinical diagnosis as well as in studying plasticity in normal auditory processing.

Functional implications of noise-induced build-up of MOC reflex strength

All the putative functional roles of the MOC system, protection against acoustic injury, anti-masking and dynamic-range extension (Kawase et al., 1993; Maison et al., 2000; Rajan, 1991; Winslow et al., 1987) are likely enhanced by the slowly building sound-induced effects reported here. Given that the build-up suppression 1) can be larger than onset suppression (Fig. 5), 2) is likely larger in awake than in anesthetized animals (Boyev et al., 2002), and 3) as studied here (with contralateral sound) is activating only 1/3 of the MOC innervation to the ipsilateral ear (Liberman et al., 1986; Liberman et al., 1996), its impact on cochlear physiology could be substantial.

Dynamic-range adjustment due to MOC build-up suppression should be additive with that arising from MOC fast effects. Given its long integration time, the build-up component of MOC feedback could adapt to the long-term sound-level distribution and shift the operating point of auditory nerve response to be more sensitive to changes in input level, improving intensity discrimination and perhaps other auditory tasks. Indeed, neurons in the inferior colliculus shift their rate-level functions in response to the input-level statistics (Dean et al., 2005), and the underlying mechanism may include contributions from the MOC reflex via the phenomenon of build-up suppression.

In its anti-masking role, MOC feedback increases the response of auditory-nerve fibers to transient stimuli in a continuous background noise (Kawase et al., 1993; Winslow et al., 1987) by reducing the vesicle depletion at the inner hair cell-neural synapse elicited by the response to the continuous noise. Any slowly building enhancement of MOC responsivity (and therefore of its feedback suppression) during prolonged noise should add to the anti-masking effect. However, from a teleological perspective, the utility of such a build-up enhancement of an anti-masking function is not obvious: if the anti-masking is useful, it would seemingly be most useful immediately after noise onset.

The role of MOC feedback in protection against acoustic injury is well established, both for temporary (Rajan, 1991) and permanent threshold shifts (Kujawa et al., 1997). The mechanism of buildup suppression, whereby the magnitude of inhibitory feedback slowly increases for long-duration stimuli, seems particularly well suited for a role in cochlear protection. Increasing discharge rates in the OC bundle, via increasing rates of electrical stimulation, decreases the vulnerability of the ear to temporary threshold shifts by as much as 20 dB (Rajan, 1988). In the present experiment, the increase in effective stimulus attenuation associated with the putative slow response facilitation of the MOC system was on the order 2 – 3 dB (Fig. 3). Given the expansive relationship whereby each dB decrease in effective stimulus level can translate into a 6 – 7 dB decrease in noise-induced permanent threshold shift (Yoshida et al., 2000), the protective effects of delayed suppression in unanesthetized animals could be as great as 20 – 30 dB.

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Abbreviations

CAP	Compound action potential
CM	Cochlear microphonic
DPOAE	Distortion product otoacoustic emissions
IHC	Inner hair cell
LOC	Lateral Olivocochlear
MOC	Medial Olivocochlear
OC	Olivocochlear
OHC	Outer hair cell
RW	Round window

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Figure 1.

Schematic of the ipsilateral and contralateral stimuli for one 15-min 'trial' of the paradigm used in the present study. The ipsilateral ear is used to monitor efferent effects by measuring CAPs and DPOAEs (each at multiple frequency/level combinations) and RW noise in interleaved fashion. A complete measurement of all these metrics, defined as a 'block', required about 10 sec. Blocks were repeated until the trial was ended. The contralateral ear was used to evoke efferent effects using a 5-min broadband noise flanked by prior and subsequent silent intervals (5 min each). In most experiments, data from multiple trials were averaged to produce an estimate of contralateral-noise effects.

Figure 2.

Slow modulation of ipsilateral responses by sustained contralateral noise. Each panel shows a different ipsilateral response metric; each point is the average ipsilateral response amplitude during one block of the trial, averaged over 4 consecutive trials, and normalized to the mean value for that response before noise onset. The mean magnitude of the contralateral-noise effect on each ipsilateral response (open square in each panel) is computed as the mean change from pre-noise baseline during the 13th – 17th blocks (130–170 sec) post noise onset. CAPs (**A**) were evoked by 4 kHz tone pips at 45 dB SPL; DPOAEs (**C**) with f_2 at 4 kHz and 48 dB SPL and CM (**B**) by 4 kHz tones at 75 dB SPL; RW noise (**D**) was measured in silence. Negative values indicate response suppression.

Figure 3.

Frequency dependence of the contralateral noise effect. Mean ($\pm$ s.e.m.) CAP (**A**) and DPOAE (**B**) suppression evoked by contralateral noise is plotted as a function of ipsilateral stimulus frequency, decomposed into onset, build-up, and total components, as defined in the inset to **B**. Suppression values are given as 'equivalent attenuation' (see Methods). The number of data points (1 per frequency per animal) per half-octave bin is indicated just above the x-axis. Negative values indicate response suppression.

Figure 4.

Dependence of contralateral noise suppression on ipsilateral stimulus level. Mean total suppression (defined as described in Figure 3) for CAPs (A) and DPOAEs (B) evoked by contralateral noise is plotted as function of ipsilateral stimulus level. Data are from four animals (a different frequency in each animal: see key); results from 3–6 trials are averaged for each point ($\pm$ s.e.m.). Negative values indicate response suppression.

Figure 5.

Relations among suppression components for CAP (A,C), RW noise (inset to A) and DPOAE (B,D). Suppression components are defined in Figure 4; adaptation is the difference between “total” suppression and the suppression seen for the last block during the contralateral noise. Each point is from a different trial. Data from all trials, at all ipsilateral frequencies and levels are included. Dashed lines are for reference only. Solid lines in C and D are best-fit straight lines to the data. Negative values indicate response suppression.

Figure 6.

Blockade of contralateral noise effects with systemic gentamicin. Mean total suppression magnitude ($\pm$ s.e.m.) for CAP (**A**) and DPOAE (**B**) before (filled symbols) and 2 hours post-injection (open symbols) of gentamicin (150 mg/kg i.m.). CAP stimuli were ~ 20 dB above CAP threshold (35 – 70 dB SPL); DPOAE primaries were ~ 5 dB above DPOAE threshold (30 – 55 dB SPL). Negative values indicate suppression of ipsilateral responses. Data are from two animals (EL29: circles, EL45: squares). In each case, at least 8 15-minute “trials” (Fig. 1) were obtained pre-injection, and at least 8 more were obtained post-injection: blockade of contra-noise effects is maximal roughly 2 hours after intramuscular injection (Yoshida et al., 1999).

Figure 7.

Elimination of contralateral-noise suppression after OC bundle transection. Modulation of CAPs (**A**) and DPOAEs (**B**) by contralateral noise before (filled symbols) and after a midline cut of the crossed OC bundle (COCB: open circles) and, finally, after a complete OC bundle cut (gray squares). Pre-lesion data are averaged from 5 trials, post-COCB-cut data from 4 trials and post-OCB-cut from 3 trials. CAPs were evoked by 16 kHz tones at 43 dB SPL; DPOAEs by primaries with f2 at 16 kHz and 28 dB SPL.

Figure 8.

Immediate extinction of contralateral-noise suppression by OC bundle cut during the sustained contralateral noise. Modulation of CAPs (**A**) and DPOAEs (**B**) by contralateral noise before (filled symbols) and after a complete OC bundle lesion (open circles) created midway through the contralateral noise on the 5th trial. Pre-lesion data are averaged from 4 trials. For the single lesion trial, the number of stimuli per block (see Figure 1) was decreased (one stimulus level and frequency was chosen for both CAP and DPOAE measures) so that the stimulus averaging from one trial could match that achieved pre-lesion by combining results from 4 trials. CAPs were evoked by 16 kHz tones at 35 dB SPL; DPOAEs by primaries with f_2 at 16 kHz and 25 dB SPL.