Cell Tissue Res (2015) 361:301–309
DOI 10.1007/s00441-015-2158-z

REVIEW

Cochlear efferents in developing adult and pathological conditions

Régis Nouvian · Michel Eybalin · Jean-Luc Puel

Received: 12 December 2014 / Accepted: 19 February 2015 / Published online: 26 March 2015

Abstract Cochlear activity is regulated by the olivo-cochlear bundle, which originates from the brainstem and projects onto the hair cells and auditory nerve fibers. Two efferent components can be distinguished: the medial and lateral olivo-cochlear efferent originating from the medial, and the lateral nuclei of the superior olivary complex. The input of the efferent systems on hair cells occurs during development and persists in the adult cochlea. Recent studies have shown that the efferent innervations are required to set the activity pattern in developing hair cells and auditory nerve fibers and to protect the synaptic structures in adult cochlea. In addition, efferent innervations undergo plasticity during pathological conditions such as noise-trauma or aging. This review discusses the mechanisms underlying the control of the hair cells and afferent fibers excitability by efferent neurons and their putative role in developing adult and pathological conditions.

Keywords Hair cells · Auditory nerve fibers · Innervation · Cochlea · Hearing

Introduction

Many features of cochlear activity are directly regulated through innervation from the olivocochlear system, which comprises the medial olivocochlear component (MOC) originating from medial nuclei of the superior olivary complex and the lateral olivocochlear component (LOC) originating from the lateral superior olive (Guinan 2011). The MOC system projects onto outer hair cells (OHCs; see, for review, Wersinger and Fuchs 2011) and the LOC component projects onto primary auditory neurons dendrites beneath the inner hair cells (IHCs). Whereas MOC terminals likely use acetylcholine as a primary neurotransmitter and to some extent γ−amino-butyric acid (GABA), LOC efferent terminals express dopamine (DA), acetylcholine (ACh), γ−amino-butyric acid (GABA), enkephalins, dynorphins and calcitonin gene-related peptide (CGRP) (Eybalin 1993; Puel 1995; Sewell 2011). During the two last decades, significant advances in the understanding of the olivo-cochlear efferent function have been made in developmental, normal and pathological conditions, demonstrating the substantial contribution of the olivo-cochlear efferents to auditory physiology.

Efferent inhibition and ascending auditory pathway mapping

In rodents, the efferent innervation of IHCs occurs after birth and persists until the end of the second postnatal week (Katz et al. 2004; Roux et al. 2011). During this stage, the vast majority of efferent terminals are found on IHCs as well as on afferent fibers contacting IHCs (Pujol et al. 1978). Patch-clamp recordings have unambiguously demonstrated the cholinergic nature of the neurotransmitters released by the efferent fibers onto the IHCs (Glowatzki and Fuchs 2000). ACh secretion from the efferent terminals activates the α9α10 nicotinic receptors of the IHCs. Calcium influx through the α9α10 receptor opens, in turn, the small-conductance Ca^{2+} activated K^{+} channels (SK2), thereby hyperpolarizing the developing IHCs (Glowatzki and Fuchs 2000; Marcotti et al. 2004; Kong et al. 2008; Katz et al. 2011; Wersinger and Fuchs 2011; Johnson et al. 2013a). Recent work has highlighted the molecular machinery involved in ACh release by the efferent terminals. ACh secretion depends on the P/Q and N type calcium channels and is negatively regulated by the tight coupling between the L-type calcium channel and the big-conductance Ca^{2+}-activated K^{+}

R. Nouvian · M. Eybalin · J.-L. Puel
Inserm U1051 - Institute for Neurosciences of Montpellier, 34091 Montpellier cedex 5, France

R. Nouvian
e-mail: regis.nouvian@inserm.fr

M. Eybalin
e-mail: michel.eybalin@inserm.fr

R. Nouvian · M. Eybalin · J.-L. Puel
Université Montpellier, 34000 Montpellier, France

R. Nouvian · M. Eybalin · J.-L. Puel (✉)
Inserm U1051-INM, Hôpital Saint-Eloi, 80 Avenue Augustin Fliche, 34091 Montpellier cedex 5, France
e-mail: jean-luc.puel@inserm.fr

current (BK type; Zorrilla de San Martín et al. 2010). Interestingly, GABA is also released by the efferents and inhibits the ACh secretion evoked by P/Q-type calcium channels through $GABA_B$ autoreceptors signaling (Wedemeyer et al. 2013). Finally, the retrograde signaling by nitric oxide (NO), which is produced by the hair cells in a calcium-dependent manner, results in the enhancement of ACh secretion (Kong et al. 2013). Taken together, the cholinergic input can be regulated in an autonomous and dependent fashion.

Developing hair cells fire action potentials in a burst-like fashion (Johnson et al. 2011; Sendin et al. 2014; Fig. 1a, b) with each action potential triggering glutamate exocytosis onto the afferent fibers (Beutner and Moser 2001; Marcotti et al. 2003). This bursting activity has been suggested to consolidate and refine the tonotopic map along the ascending auditory pathways (Tritsch et al. 2010). The cholinergic efferent feedback inhibits the spiking pattern of the developing IHCs to coordinate peripheral and central development (Glowatzki and Fuchs 2000; Johnson et al. 2011; Sendin et al. 2014; Fig. 1c, d). This hypothesis, however, has been called into question because efferent fibers are severed during the experiments in vitro. Indeed, the loss of the α9 or α10 subunits in the mouse does not change auditory thresholds (Vetter et al. 1999, 2007; May et al. 2002), although the α9 subunit or the SK2 channel are required for the proper maturation of synaptic machinery in IHCs (Johnson et al. 2007, 2013a, b). However, mice lacking the α9 subunit show aberrant wiring of auditory pathway circuitry, i.e., impairment of the medial nucleus of the trapezoid body–lateral superior olive connections (Clause et al. 2014). These results demonstrate, therefore, that the cholinergic system in the developing cochlea contributes to the organization of the ascending structures. At the onset of hearing, cholinergic control of the IHCs ceases and the medial efferent neurons project onto the mature OHCs (for review, see Simmons 2002). The α9α10 receptors can be directly modulated by opioids (Lioudyno et al. 2002) expressed in both LOC and MOC efferents (Eybalin 1993). Because the cholinergic inhibition mechanisms are

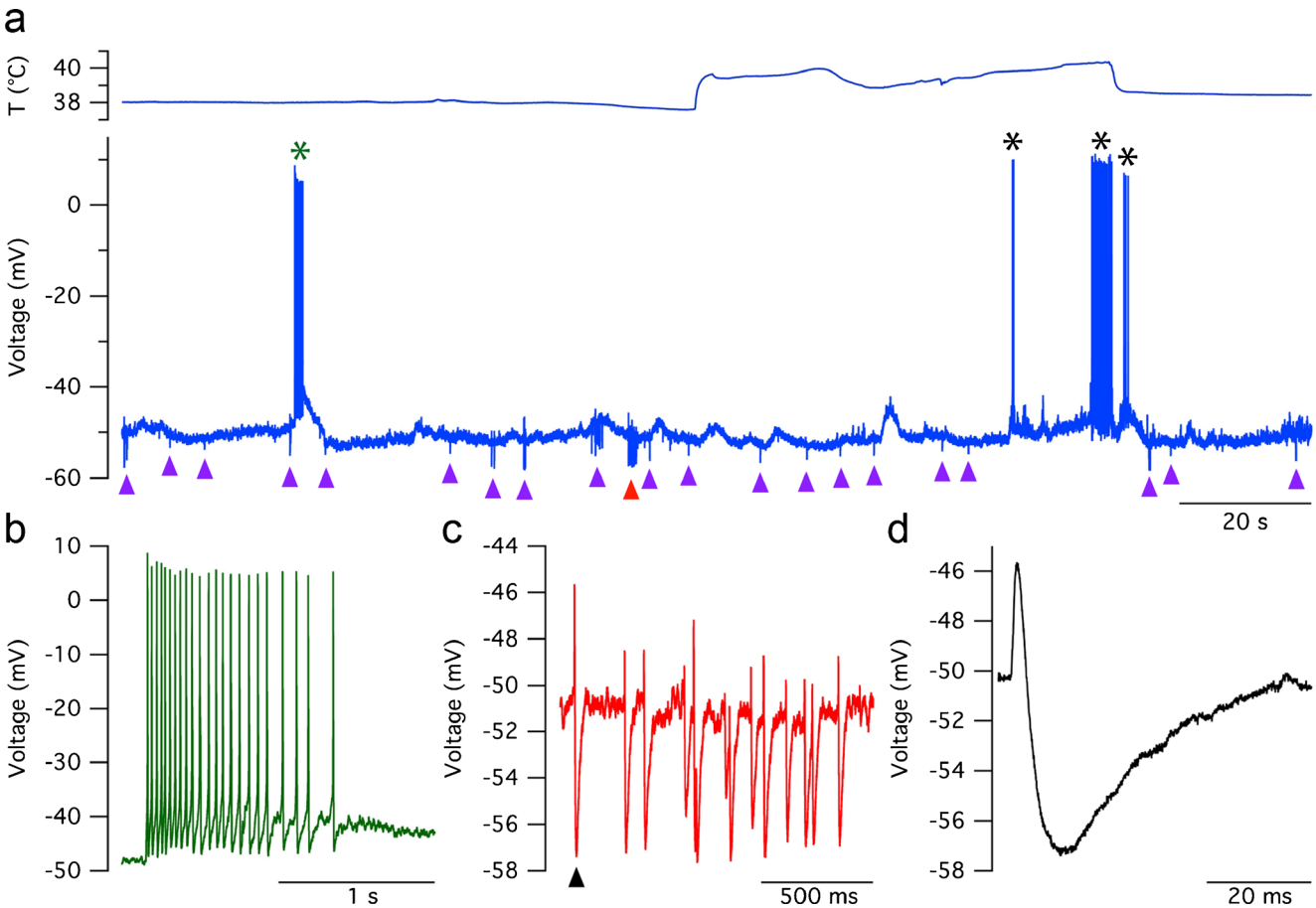

Fig. 1 Spontaneous action potentials and inhibitory post-synaptic potentials in developing inner hair cell. **a** Patch-clamp recording at physiological temperature (*top*) of the spontaneous spiking activity from an apical P6 inner hair cell in current-clamp configuration (*bottom*). Bursts of action potential (AP, *stars*) and inhibitory post-synaptic potentials (IPSPs, *arrowheads*) populate the activity of the developing hair cell. **b** Train of AP at higher temporal resolution, corresponding to the *green star* in (**a**). **c** Train of IPSPs, corresponding to the *red arrowhead* in (**a**). **d** Higher temporal resolution of a single IPSP, corresponding to the *black arrowhead* in (**c**). Please note that each IPSP consists in a small depolarization, elicited by the α9α10 activation, followed by the membrane hyperpolarization, triggered by the SK2 potassium current activation

highly similar between developing IHCs and adult OHCs, it has been proposed that the efferent fibers, which transiently connect to the immature IHCs, belong to the medial olivocochlear neuron pool (Simmons 2002; Simmons et al. 2011).

Efferents control cochlear amplification in the adult cochlea

Akin to developing IHCs, cholinergic release from MOC terminals inhibits adult OHCs through the interplay of α9α10 nicotinic receptors and SK2 or BK potassium channels in OHCs located in apical or basal regions of the cochlea, respectively (Fuchs and Murrow 1992a; Oliver et al. 2000; Wersinger et al. 2010). In addition, a calcium-induced calcium release (CICR) mechanism has been suggested to contribute to the fast inhibitory effect of the acetylcholine input. One such CICR mechanism has also been identified in the developing IHCs and adult OHCs, involving the near-membrane postsynaptic cistern facing the efferent terminals, as calcium store (Lioudyno et al. 2004; Fuchs 2014). In addition, $GABA_B$ metabotropic receptors may act on type II afferents to regulate OHC activity through reciprocal synapses (Thiers et al. 2002, 2008; Maison et al. 2009). It is thus tempting to propose that the medial efferent olivocochlear bundle controls cochlear amplification through hyperpolarization of OHCs (Murugasu and Russell 1996). Indeed, MOC efferents constitute a sound-evoked negative feedback loop (Guinan 2011). This feedback suppresses the normal contribution of OHCs to sound (Wiederhold and Kiang 1970). Therefore, it has been proposed that MOC efferent feedback provides a powerful means to improve selective attention (Oatman and Anderson 1977; Puel et al. 1988; Scharf et al. 1994), signal detection in a noisy environment (Winslow and Sachs 1987), or ear protection from acoustic injury (Rajan 1988; Maison and Liberman 2000). This latter view is now well established though the use of olivo-cochlear bundle activation, de-efferentation or its genetic manipulation: (1) electrical stimulation of the efferent pathway reduces temporary hearing loss from simultaneous acoustic overexposure (Rajan 1988; Reiter and Liberman 1995), (2) surgical de-efferented animals are more vulnerable to noise exposure (Kujawa and Liberman 1997) and (3) overexpression of α9 subunit reduced noise-induced acoustic injury (Maison et al. 2002) as well as point-mutated α9 subunit, which prolongs cochlear inhibition (Taranda et al. 2009). Beyond reducing noise trauma protection, MOC removal exacerbates the loss of IHC ribbon synapse induced by moderate sound exposure (Maison et al. 2013) or associated with aging (Liberman et al. 2014). These results suggest that fine control of OHC activity is mandatory for the preservation of the synaptic structure of the cochlea.

Control of auditory nerve fiber excitability in the adult cochlea

Most studies from which LOC function has been inferred rely on olivocochlear bundle lesions. In this framework, completely de-efferented cochleas showed very little change in threshold levels but a very large reduction in the spontaneous discharge rate of the auditory nerve fibers (Liberman 1990; Zheng et al. 1999). However, these studies rely on a section of the entire olivocochlear bundle, including both the LOC and MOC (medial olivo-cochlear) efferents, making interpretation difficult (Fig. 2a). Stereotaxic injection of the neurotoxin melittin has been used as an alternative method to achieve selective damage of lateral superior olive (LSO) neurons (Le Prell et al. 2003). The unilateral destruction of the LSO did not affect thresholds but rather increased the amplitude of the ipsilateral neural response together with a reduction of the contralateral neural response amplitude (Darrow et al. 2006). Taken together, this study suggests that the LOC bundle may be involved in binaural balance to achieve spatial sound localization, although protection against sound trauma has also been proposed (Darrow et al. 2007). However, the chemical ablation of the LSO i) may not result in a complete loss of the efferent neurons, ii) may provoke MOC loss in the case of neurotoxin spread (Liberman et al. 2014) and iii) does not discriminate between efferents that may employ different neurotransmitters (Fig. 2a and b).

To circumvent these issues, pharmacological manipulation of the LOC efferent neurotransmitters has been used, notwithstanding the difficulty of cochlear perfusion in vivo. Perilymphatic perfusion of dopamine (DA) has been shown to reduce the neural response, i.e., the compound action potential (CAP) that reflects the synchronous activity of auditory nerve fibers to sound stimulation (Ruel et al. 2001). Single-unit recordings show, in addition, that exogenous DA applied in the cochlea reduces spontaneous firing of action potentials (Fig. 2c) and increases the threshold of the auditory nerve fibers (Ruel et al. 2001; Garrett et al. 2011). Consistent with this effect, the selective DA transporter (DAT) inhibitors abolish the spontaneous and sound-evoked activity of auditory nerve fibers as they increase the endogenous level of extracellular DA (Ruel et al. 2006). To know whether DA is released in a tonic fashion, the effect of dopamine receptor antagonists on spontaneous activity was examined. In this case, auditory nerve fibers increased their spontaneous firing with a reduction of the auditory threshold (Ruel et al. 2001; Garrett et al. 2011). Altogether, these data suggest that a tonic release of dopamine operates in the cochlea, which can therefore control the behavior of the afferent fibers. Because fibers with different spiking rates and auditory thresholds populate the auditory nerve, it is conceivable that the tonic inhibition dictates, or at least modulates, the phenotypes of these fibers. In addition, morphological observation shows that a fraction of the IHC–auditory fiber synapses are swollen after DA antagonists perfusion (Ruel et al. 2001). The pool of auditory fibers showing swollen

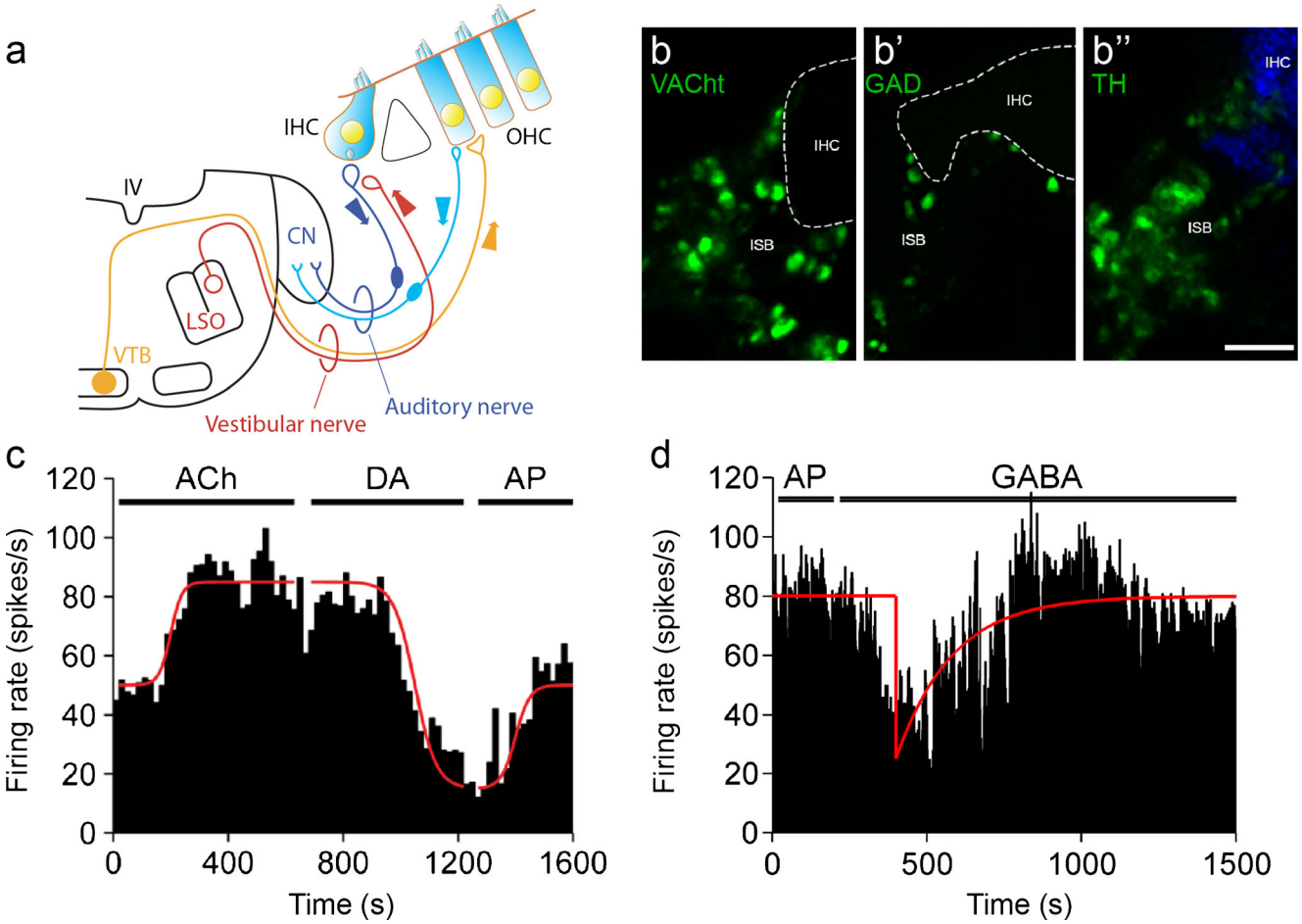

Fig. 2 Modulation of the synaptic transmission by acetylcholine, dopamine and GABA. **a** Schematic representation of afferent and efferent olivocochlear innervation of the organ of Corti in adult cochlea (modified from Puel 1995). Inner hair cells are innervated by type I afferent auditory fibers, which approximate about 90–95 % of the total afferent fiber population of the auditory nerve. Outer hair cells (OHCs) are innervated by the 5 % remaining afferent fibers of the auditory nerve (type II). Both type I and type II project to the cochlear nuclei. Two types of efferents innervate the cochlea: the efferents projecting underneath the inner hair cells (IHCs) and those connecting directly the OHCs. These efferents originate from different areas in the superior olivary complex in the brainstem and run through the vestibular nerve. The efferents connecting the afferent type I fibers originate in the lateral superior olive (LSO). The OHCs efferent neurons are located in the ventral nuclei of the trapezoid body (VTB). Consequently, most of the authors use the terms lateral and medial efferent systems to designate the efferents below the IHC and those of the OHCs. The lateral efferents, which represent about 50~65 % of the olivocochlear bundle fibers, are unmyelinated and project towards the ipsilateral cochlea. The medial efferents are myelinated and reach the OHCs via the crossed and uncrossed components of the olivocochlear bundle. The crossed component predominates and forms about 70–75 % of the medial efferent innervation. **b**–**b**" Cryostat sections through the second turn of a guinea pig cochlea showing immunoreactivities to the vesicular acetylcholine transporter (**b**, VAChT, *green*), glutamic acid decarboxylase (**b'**, GAD, *green*) and tyrosine hydroxylase (**b**", TH, *green*) in lateral efferent fibers. For VAChT and GAD immunostaining, IHC is outlined with *dashed lines*. For TH immunostaining, IHC is labelled with anti-calbindin antibody (*blue*). *IHC* Inner hair cell; *ISB* inner spiral bundle. *Scale bar* 5 μm. **c**, **d** Spontaneous activity of a single afferent fiber modulated by LOC neurotransmitters. **c** Perfusion with artificial perilymph (*AP*) containing 100 μM ACh + 10 μM strychnine (α9α10 antagonist) increases the spiking rate of the auditory nerve fiber. Subsequent perfusion of AP containing 1 mM dopamine (*DA*) has the opposite effect as decreasing the discharge rate. **d** Perfusion with artificial perilymph (*AP*) containing 1 mM GABA transiently reduces the discharge rate of the afferent fibers. Spiking rate was fitted using sigmoidal (**c**, *red line*) or transient exponential recovery models (**d**, *red line*)

terminals after the DA inhibition removal may correspond with the high spontaneous rate fibers. This may explain why DA antagonists increase the firing rate of the lowest spontaneous rate fibers but completely suppress high spontaneous rate fibers (Ruel et al. 2001). Dopamine release may adjust the activity of the auditory fibers and prevent the excitotoxic side effect of glutamate at the first auditory synapse. Accordingly, dopamine receptor (D4 and D5) knock-out mice have been shown to be more susceptible to noise trauma than wild-type (Maison et al. 2012).

The inhibitory control of afferent fibers activity is not restricted to DA release by the LOC terminals. For example, micro-iontophoretic application of GABA reduces the afferent spiking rate increase evoked by glutamate (Arnold et al. 1998). Also, single unit recordings show a clear reduction of the spontaneous rate following GABA perfusion into the cochlear fluids (Fig. 2d). Because the GABA-induced reduction does not persist throughout the time course of application, i.e., the response elicited by GABA shows a strong desensitization, it contradicts

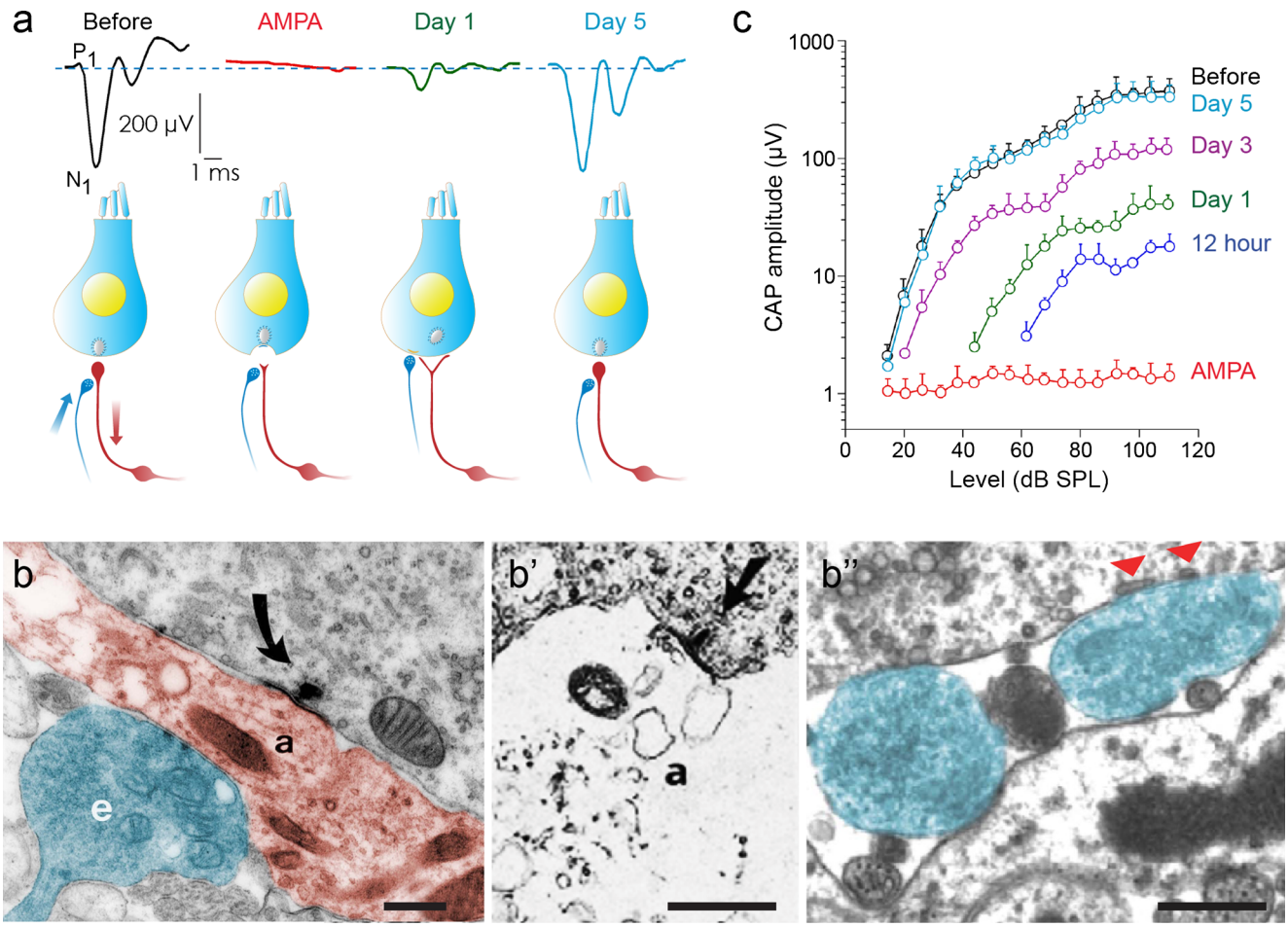

Fig. 3 Synaptic re-arrangement after AMPA-induced excitotoxicity. **a** The compound action potential (CAP), which reflects the synchronous activation of the auditory fibers, is completely abolished following intracochlear 200 μM AMPA perfusion and recovers during the next days (*top*). Schematic representation of the innervation changes during excitotoxic injury in the cochlea. Swelling of the afferent terminals caused by AMPA application accounts for the loss of CAP. During the repair of the afferent fibers terminals, efferent terminals connect in a transient fashion the hair cells (*bottom*). **b–b"** Electron microcopy examination shows a synaptic body (*arrow*) facing a neurite terminal (*a*) and the efferent (*e*) making axo-dentritic contact in normal condition (**b**, *scale bar* 0.5 μm). Ten-minute perfusion of AMPA provoked a massive swelling of radial dendrites, which ends in a disruption of membranes and a loss of cytoplasmic content (**b'**, *scale bar* 1 μm). One day later, efferents contact the hair cell (**b"**, *scale bar* 1 μm). Efferents show a very high density of vesicles, sometimes with postsynaptic cisterns in the hair cell (*red arrowheads*). **c** CAP amplitude (N_1–P_1) plots against the intensity of the sound-stimulation (probed at 8 kHz, 80 dB SPL). Note that the CAP amplitude recovers completely within 5 days after the excitotoxic injury, according to (**c**). (**a**) and (**c**) are adapted from Ladrech et al. (2003)

a tonic effect of GABA in the cochlea. It should also be stressed that deletion of GABA receptors sub-unit β3 leads to a loss of afferent innervation (Maison et al. 2006), suggesting a role for GABA in synaptic maintenance.

In addition to inhibitory input, auditory nerve fibers undergo excitatory modulation. Indeed, excitatory action of LOC efferents is supported by the fact that micro-iontophoretic injections of ACh in the IHC synaptic area increase the spontaneous and glutamate-induced firing activity of radial afferent fibers in a dose-dependent manner (Felix and Ehrenberger 1992; Arnold et al. 1998). However, the very low spontaneous rate firing of fibers recorded in the vicinity of the afferent synapses suggested that micro-iontophoresis may have damaged fibers. To probe the cholinergic component of the LOC, ACh was applied by intracochlear perfusion. In order to block the effect of ACh on the MOC efferents, ACh was perfused together with strychnine, a potent blocker of the α9α10 receptors (Fuchs and Murrow 1992b; Kujawa et al. 1994; Elgoyhen et al. 1994, 2001). ACh/strychnine perfusion increased the spontaneous and sound driven activities of single auditory nerve fibers, suggesting an excitatory role for the cholinergic LOC efferents (Fig. 2c).

In addition to classical neurotransmitters, dynorphin may modulate the neural output of the cochlea as the CAP amplitude is depressed following diffusion of the kappa-opioid receptor agonist (−) pentazocine across the round window membrane (Le Prell et al. 2014). Finally, CGRP application increases the spike rate and decreases the mechanically driven response of primary afferents in the lateral line (Bailey and

Sewell 2000a, b). Conversely, targeted gene deletion of CGRP in mice decreased suprathreshold neural responses, without the corresponding changes in DPOAE amplitudes that would be expected if OHCs were affected (Maison et al. 2003).

Altogether, these results show that LOCs can cause opposing effects on afferent fiber activity. One working hypothesis is that the LOCs adjust the sensitivity of the auditory nerve fibers according to the level of environmental sound. Thus, the ability of the auditory nerve to encode sound level in a noisy environment could be driven by LOC neurotransmitter release onto the afferent fibers, as when, for example, DA modifies auditory thresholds (Ruel et al. 2001).

Pathophysiological consequences

After environmental injury (excitotoxic injury, noise trauma, ototoxic drugs) or during aging, synaptic rearrangements occur in the cochlea. In all these cases, afferent synaptic contacts are lost and efferent neurons appear to form synapses with IHCs, at least transiently. Major challenges remain in determining the mechanisms that drive these changes and to understand what functional consequences they may have.

The IHC-afferent synapse is vulnerable to glutamate excitotoxicity and acoustic trauma, with potentially adverse consequences for long-term spiral ganglion neuron survival. In our hands, the excitotoxicity caused by intracochlear perfusion of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) induced a massive swelling of radial dendrites, which resulted in a disruption of membranes and a loss of cytoplasmic content (Puel et al. 1991, 1994). Structural rearrangements were clearly seen 1 day after excitotoxic injury (Fig. 3a, b). The basal pole of the IHC was surrounded by neurites, which appeared relatively normal at low magnification. However, upon closer examination, thin filopodia appeared to make elongated contact with the IHC membrane (covering up to 20–30 μm), with multiple dense thickenings, mimicking what has been described early in development (Pujol et al. 1978). At higher magnification, both afferent boutons (auditory nerve dendrites) and efferents could be recognized in direct contact with the IHC membrane (Fig. 3b). Five days after excitotoxic exposure, the pattern of IHC innervation seemed, at least qualitatively, almost normal, correlating with the full recovery of the compound action potential (CAP) (Puel et al. 1995; Ladrech et al. 2003; Fig. 3c). Normal synaptic differentiation between IHCs and auditory nerve endings was more frequently observed, together with efferents connecting to the afferent dendrites. Finally, the number of spiral ganglion neurons was not significantly different in AMPA-treated cochleas (24,293±976) versus the non-treated contralateral cochleas (23,598±852) when counted 1 month after exposure (Puel 1995).

Efferents are therefore able to synapse onto the hair cell during excitotoxic injury until the auditory nerve fiber terminals repair. The nature of the efferent fibers remains undetermined (LOC vs. MOC), although the loss of the afferent dendrite, as target of the LOC, may drive the LOC terminals to contact the nearby IHC. It is not known whether this efferent projection to the presynaptic hair cell is functional or whether this efferent connection is involved in afferent neuron survival. Worthy of note is that noise exposure also shows a change in innervation patterns (i.e., efferent neurons reinnervate the IHCs) during synaptic repair (Puel et al. 1998). Similar features of innervation have also been observed with aminoglycoside intoxication (Lenoir et al. 1999; Ladrech and Lenoir 2002). It might be conjectured that the projection of efferent neurons onto the hair cells favors the activity-dependent stabilization of afferent neurons by regulating hair cell excitability.

If efferent re-innervation somehow sustains the hair cell to enable spiral ganglion neuron survival, the death of hair cells would be expected to lead to spiral ganglion death. However, it has been found that spiral ganglion neurons can survive in the absence of IHCs (Zilberstein et al. 2012). In this latter case, however, it should be noted that efferent neurons still contact the auditory nerve fibers so that they may provide an input required for afferent fiber survival (Zilberstein et al. 2012). Finally, it has been found that efferent neurons re-innervate inner hair cells during the aging process (Lauer et al. 2012), perhaps to slow down the degenerative loss of the auditory nerve fibers due to multiple injuries throughout the life span.

Conclusions

The activity of the cochlea is under the regulation of efferent terminals that originate from the brainstem. During the two last decades, new roles for the efferent systems have emerged. Beside their contribution to the circuitry organization and activity, the olivo-cochlear bundle protects the cochlear structures. MOC innervation is required for auditory pathway development and to prevent the loss of synaptic structure in IHCs via the inhibition of cochlear amplifier in noise- and age-related hearing loss. In parallel, LOC innervation governs the excitability of the auditory nerve fibers to prevent glutamate-induced excitotoxicity and to promote synaptic repair. Others have suggested that LOC efferents are involved in binaural balance to achieve spatial sound localization. Based on the resistance of low-spontaneous rate fibers to masking noise (Costalupes et al. 1984), the larger number of efferent synapses connected onto the auditory nerve fibers of the modiolar side of the IHCs (i.e., the lowest spontaneous rate fibers) may also explain the better discrimination in background noise. In other words, LOC efferent may adjust the sensitivity of the fibers to improve the signal -to -noise ratio.

Finally, Yin et al. (2014) demonstrated a role for the efferents in maintaining functional heterogeneity in the cochlear nerve. Although a vast amount of data on functional roles for these two efferent synapses in the regulation of cochlear development, maintenance and pathophysiology has been identified, we are still far from a clear and comprehensive portrait. A better understanding of cochlear efferent function will not only increase our knowledge of sound coding but also improve our understanding of the cellular changes that take place after cochlear trauma.

Acknowledgments The authors acknowledge Jérôme Bourien, Jing Wang, Jérôme Ruel and Marc Lenoir for collaborative work on experimental protocols. Part of the work on acoustic trauma is supported by the association "Gueules Cassées". We would like to thank Dr. A. Woehler for constructive comments on the manuscript. This work has been supported by the Inserm and the Agence Nationale pour la Recherche (ANR-13-JSV1-0009-01).

References

Arnold T, Oestreicher E, Ehrenberger K, Felix D (1998) GABA(A) receptor modulates the activity of inner hair cell afferents in guinea pig cochlea. Hear Res 125:147–153

Bailey GP, Sewell WF (2000a) Calcitonin gene-related peptide suppresses hair cell responses to mechanical stimulation in the Xenopus lateral line organ. J Neurosci 20:5163–5169

Bailey GP, Sewell WF (2000b) Pharmacological characterization of the CGRP receptor in the lateral line organ of Xenopus laevis. J Assoc Res Otolaryngol 1:82–88

Beutner D, Moser T (2001) The presynaptic function of mouse cochlear inner hair cells during development of hearing. J Neurosci 21:4593–4599

Clause A, Kim G, Sonntag M et al (2014) The precise temporal pattern of prehearing spontaneous activity is necessary for tonotopic map refinement. Neuron 82:822–835. doi:10.1016/j.neuron.2014.04.001

Costalupes JA, Young ED, Gibson DJ (1984) Effects of continuous noise backgrounds on rate response of auditory nerve fibers in cat. J Neurophysiol 51:1326–1344

Darrow KN, Maison SF, Liberman MC (2006) Cochlear efferent feedback balances interaural sensitivity. Nat Neurosci 9:1474–1476. doi:10.1038/nn1807

Darrow KN, Maison SF, Liberman MC (2007) Selective removal of lateral olivocochlear efferents increases vulnerability to acute acoustic injury. J Neurophysiol 97:1775–1785. doi:10.1152/jn.00955.2006

Elgoyhen AB, Johnson DS, Boulter J et al (1994) Alpha 9: an acetylcholine receptor with novel pharmacological properties expressed in rat cochlear hair cells. Cell 79:705–715

Elgoyhen AB, Vetter DE, Katz E et al (2001) Alpha 10: a determinant of nicotinic cholinergic receptor function in mammalian vestibular and cochlear mechanosensory hair cells. Proc Natl Acad Sci U S A 98:3501–3506. doi:10.1073/pnas.051622798

Eybalin M (1993) Neurotransmitters and neuromodulators of the mammalian cochlea. Physiol Rev 73:309–373

Felix D, Ehrenberger K (1992) The efferent modulation of mammalian inner hair cell afferents. Hear Res 64:1–5

Fuchs PA (2014) A "calcium capacitor" shapes cholinergic inhibition of cochlear hair cells. J Physiol Lond 592:3393–3401. doi:10.1113/jphysiol.2013.267914

Fuchs PA, Murrow BW (1992a) Cholinergic inhibition of short (outer) hair cells of the chick's cochlea. J Neurosci 12:800–809

Fuchs PA, Murrow BW (1992b) A novel cholinergic receptor mediates inhibition of chick cochlear hair cells. Proc R Soc Lond B 248:35–40. doi:10.1098/rspb.1992.0039

Garrett AR, Robertson D, Sellick PM, Mulders WHAM (2011) The actions of dopamine receptors in the guinea pig cochlea. Audiol Neurootol 16:145–157. doi:10.1159/000316674

Glowatzki E, Fuchs PA (2000) Cholinergic synaptic inhibition of inner hair cells in the neonatal mammalian cochlea. Science 288:2366–2368

Guinan JJ (2011) Physiology of the Medial and Lateral Olivocochlear Systems. In: Ryugo DK, Fay RR (eds) Auditory and Vestibular Efferents. doi: 10.1007/978-1-4419-7070-1

Johnson SL, Adelman JP, Marcotti W (2007) Genetic deletion of SK2 channels in mouse inner hair cells prevents the developmental linearization in the Ca2+ dependence of exocytosis. J Physiol Lond 583:631–646. doi:10.1113/jphysiol.2007.136630

Johnson SL, Eckrich T, Kuhn S et al (2011) Position-dependent patterning of spontaneous action potentials in immature cochlear inner hair cells. Nat Neurosci 14:711–717. doi:10.1038/nn.2803

Johnson SL, Kuhn S, Franz C et al (2013a) Presynaptic maturation in auditory hair cells requires a critical period of sensory-independent spiking activity. Proc Natl Acad Sci U S A. doi:10.1073/pnas.1219578110

Johnson SL, Wedemeyer C, Vetter DE et al (2013b) Cholinergic efferent synaptic transmission regulates the maturation of auditory hair cell ribbon synapses. Open Biol 3:130163

Katz E, Elgoyhen AB, Gómez-Casati ME et al (2004) Developmental regulation of nicotinic synapses on cochlear inner hair cells. J Neurosci 24:7814–7820. doi:10.1523/JNEUROSCI. 2102-04.2004

Katz E, Elgoyhen AB, Fuchs PA (2011) Cholinergic Inhibition of Hair Cells. In: Ryugo DK, Fay RR (eds) Auditory and Vestibular Efferents. doi: 10.1007/978-1-4419-7070-1

Kong J-H, Adelman JP, Fuchs PA (2008) Expression of the SK2 calcium-activated potassium channel is required for cholinergic function in mouse cochlear hair cells. J Physiol Lond 586:5471–5485. doi:10.1113/jphysiol.2008.160077

Kong J-H, Zachary S, Rohmann KN, Fuchs PA (2013) Retrograde facilitation of efferent synapses on cochlear hair cells. J Assoc Res Otolaryngol 14:17–27. doi:10.1007/s10162-012-0361-0

Kujawa SG, Liberman MC (1997) Conditioning-related protection from acoustic injury: effects of chronic deefferentation and sham surgery. J Neurophysiol 78:3095–3106

Kujawa SG, Glattke TJ, Fallon M, Bobbin RP (1994) A nicotinic-like receptor mediates suppression of distortion product otoacoustic emissions by contralateral sound. Hear Res 74:122–134

Ladrech S, Lenoir M (2002) Changes in MAP2 and tyrosinated alpha-tubulin expression in cochlear inner hair cells after amikacin treatment in the rat. J Comp Neurol 451:70–78. doi:10.1002/cne.10334

Ladrech S, Lenoir M, Ruel J, Puel J-L (2003) Microtubule-associated protein 2 (MAP2) expression during synaptic plasticity in the guinea pig cochlea. Hear Res 186:85–90

Lauer AM, Fuchs PA, Ryugo DK, Francis HW (2012) Efferent synapses return to inner hair cells in the aging cochlea. Neurobiol Aging 33:2892–2902. doi:10.1016/j.neurobiolaging.2012.02.007

Le Prell CG, Shore SE, Hughes LF, Bledsoe SC (2003) Disruption of lateral efferent pathways: functional changes in auditory evoked responses. J Assoc Res Otolaryngol 4:276–290. doi:10.1007/s10162-002-3018-6

Le Prell CG, Hughes LF, Bledsoe SC (2014) Dynorphin release by the lateral olivocochlear efferents may inhibit auditory nerve activity: a cochlear drug delivery study. Neurosci Lett 571:17–22. doi:10.1016/j.neulet.2014.04.024

Lenoir M, Daudet N, Humbert G et al (1999) Morphological and molecular changes in the inner hair cell region of the rat cochlea after amikacin treatment. J Neurocytol 28:925–937

Liberman MC (1990) Effects of chronic cochlear de-efferentation on auditory-nerve response. Hear Res 49:209–223

Liberman MC, Liberman LD, Maison SF (2014) Efferent feedback slows cochlear aging. J Neurosci 34:4599–4607. doi:10.1523/JNEUROSCI. 4923-13.2014

Lioudyno MI, Verbitsky M, Glowatzki E et al (2002) The alpha9/alpha10-containing nicotinic ACh receptor is directly modulated by opioid peptides, endomorphin-1, and dynorphin B, proposed efferent cotransmitters in the inner ear. Mol Cell Neurosci 20:695–711

Lioudyno M, Hiel H, Kong J-H et al (2004) A "synaptoplasmic cistern" mediates rapid inhibition of cochlear hair cells. J Neurosci 24: 11160–11164. doi:10.1523/JNEUROSCI. 3674-04.2004

Maison SF, Liberman MC (2000) Predicting vulnerability to acoustic injury with a noninvasive assay of olivocochlear reflex strength. J Neurosci 20:4701–4707

Maison SF, Luebke AE, Liberman MC, Zuo J (2002) Efferent protection from acoustic injury is mediated via alpha9 nicotinic acetylcholine receptors on outer hair cells. J Neurosci 22:10838–10846

Maison SF, Emeson RB, Adams JC et al (2003) Loss of alpha CGRP reduces sound-evoked activity in the cochlear nerve. J Neurophysiol 90:2941–2949. doi:10.1152/jn.00596.2003

Maison SF, Rosahl TW, Homanics GE, Liberman MC (2006) Functional role of GABAergic innervation of the cochlea: phenotypic analysis of mice lacking GABA(A) receptor subunits alpha 1, alpha 2, alpha 5, alpha 6, beta 2, beta 3, or delta. J Neurosci 26:10315–10326. doi: 10.1523/JNEUROSCI. 2395-06.2006

Maison SF, Casanova E, Holstein GR et al (2009) Loss of GABAB receptors in cochlear neurons: threshold elevation suggests modulation of outer hair cell function by type II afferent fibers. J Assoc Res Otolaryngol 10:50–63. doi:10.1007/s10162-008-0138-7

Maison SF, Liu X-P, Eatock RA et al (2012) Dopaminergic signaling in the cochlea: receptor expression patterns and deletion phenotypes. J Neurosci 32:344–355. doi:10.1523/JNEUROSCI. 4720-11.2012

Maison SF, Usubuchi H, Liberman MC (2013) Efferent feedback minimizes cochlear neuropathy from moderate noise exposure. J Neurosci 33:5542–5552. doi:10.1523/JNEUROSCI. 5027-12.2013

Marcotti W, Johnson SL, Rusch A, Kros CJ (2003) Sodium and calcium currents shape action potentials in immature mouse inner hair cells. J Physiol Lond 552:743–761. doi:10.1113/jphysiol.2003.043612

Marcotti W, Johnson SL, Kros CJ (2004) A transiently expressed SK current sustains and modulates action potential activity in immature mouse inner hair cells. J Physiol Lond 560:691–708. doi:10.1113/jphysiol.2004.072868

May BJ, Prosen CA, Weiss D, Vetter D (2002) Behavioral investigation of some possible effects of the central olivocochlear pathways in transgenic mice. Hear Res 171:142–157

Murugasu E, Russell IJ (1996) The effect of efferent stimulation on basilar membrane displacement in the basal turn of the guinea pig cochlea. J Neurosci 16:325–332

Oatman LC, Anderson BW (1977) Effects of visual attention on tone burst evoked auditory potentials. Exp Neurol 57:200–211

Oliver D, Klöcker N, Schuck J et al (2000) Gating of Ca2+−activated K+ channels controls fast inhibitory synaptic transmission at auditory outer hair cells. Neuron 26:595–601

Puel JL (1995) Chemical synaptic transmission in the cochlea. Prog Neurobiol 47:449–476

Puel JL, Bonfils P, Pujol R (1988) Selective attention modifies the active micromechanical properties of the cochlea. Brain Res 447:380–383

Puel JL, Pujol R, Ladrech S, Eybalin M (1991) Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid electrophysiological and neurotoxic effects in the guinea-pig cochlea. Neuroscience 45:63–72

Puel JL, Pujol R, Tribillac F et al (1994) Excitatory amino acid antagonists protect cochlear auditory neurons from excitotoxicity. J Comp Neurol 341:241–256. doi:10.1002/cne.903410209

Puel JL, Saffiedine S, Gervais d'Aldin C et al (1995) Synaptic regeneration and functional recovery after excitotoxic injury in the guinea pig cochlea. C R Acad Sci III Sci Vie 318:67–75

Puel JL, Ruel J, Gervais d'Aldin C, Pujol R (1998) Excitotoxicity and repair of cochlear synapses after noisetrauma induced hearing loss. Neuroreport 9:2109–2114

Pujol R, Carlier E, Devigne C (1978) Different patterns of cochlear innervation during the development of the kitten. J Comp Neurol 177: 529–536. doi:10.1002/cne.901770311

Rajan R (1988) Effect of electrical stimulation of the crossed olivocochlear bundle on temporary threshold shifts in auditory sensitivity. I. Dependence on electrical stimulation parameters. J Neurophysiol 60:549–568

Reiter ER, Liberman MC (1995) Efferent-mediated protection from acoustic overexposure: relation to slow effects of olivocochlear stimulation. J Neurophysiol 73:506–514

Roux I, Wersinger E, McIntosh JM et al (2011) Onset of cholinergic efferent synaptic function in sensory hair cells of the rat cochlea. J Neurosci 31:15092–15101. doi:10.1523/JNEUROSCI. 2743-11.2011

Ruel J, Nouvian R, Gervais d'Aldin C et al (2001) Dopamine inhibition of auditory nerve activity in the adult mammalian cochlea. Eur J Neurosci 14:977–986

Ruel J, Wang J, Demêmes D et al (2006) Dopamine transporter is essential for the maintenance of spontaneous activity of auditory nerve neurones and their responsiveness to sound stimulation. J Neurochem 97:190–200. doi:10.1111/j.1471-4159.2006.03722.x

Scharf B, Magnan J, Collet L et al (1994) On the role of the olivocochlear bundle in hearing: a case study. Hear Res 75:11–26

Sendin G, Bourien J, Rassendren F et al (2014) Spatiotemporal pattern of action potential firing in developing inner hair cells of the mouse cochlea. Proc Natl Acad Sci U S A 111:1999–2004. doi:10.1073/pnas.1319615111

Sewell WF (2011) Pharmacology and Neurochemistry of Olivocochlear Efferents. In: Ryugo DK, Fay RR (eds) Auditory and Vestibular Efferents. doi: 10.1007/978-1-4419-7070-1

Simmons DD (2002) Development of the inner ear efferent system across vertebrate species. J Neurobiol 53:228–250. doi:10.1002/neu.10130

Simmons DD, Duncan J, Crapon de Caprona D, et al. (2011) Development of the Inner Ear Efferent System. In: Ryugo DK, Fay RR (eds) Auditory and Vestibular Efferents. doi: 10.1007/978-1-4419-7070-1

Taranda J, Maison SF, Ballestero JA et al (2009) A point mutation in the hair cell nicotinic cholinergic receptor prolongs cochlear inhibition and enhances noise protection. PLoS Biol 7:e18. doi:10.1371/journal.pbio.1000018

Thiers FA, Burgess BJ, Nadol JB (2002) Reciprocal innervation of outer hair cells in a human infant. J Assoc Res Otolaryngol 3:269–278. doi:10.1007/s101620020024

Thiers FA, Nadol JB, Liberman MC (2008) Reciprocal synapses between outer hair cells and their afferent terminals: evidence for a local neural network in the mammalian cochlea. J Assoc Res Otolaryngol 9:477–489. doi:10.1007/s10162-008-0135-x

Tritsch NX, Rodríguez-Contreras A, Crins TTH et al (2010) Calcium action potentials in hair cells pattern auditory neuron activity before hearing onset. Nat Neurosci 13:1050–1052. doi:10.1038/nn.2604

Vetter DE, Liberman MC, Mann J et al (1999) Role of alpha9 nicotinic ACh receptor subunits in the development and function of cochlear efferent innervation. Neuron 23:93–103

Vetter DE, Katz E, Maison SF et al (2007) The alpha10 nicotinic acetylcholine receptor subunit is required for normal synaptic function and integrity of the olivocochlear system. Proc Natl Acad Sci U S A 104: 20594–20599. doi:10.1073/pnas.0708545105

Wedemeyer C, Zorrilla de San Martín J, Ballestero J et al (2013) Activation of presynaptic GABA(B(1a,2)) receptors inhibits synaptic transmission at mammalian inhibitory cholinergic olivocochlear-hair cell synapses. J Neurosci 33:15477–15487. doi:10.1523/JNEUROSCI.2554-13.2013

Wersinger E, Fuchs PA (2011) Modulation of hair cell efferents. Hear Res 279:1–12. doi:10.1016/j.heares.2010.12.018

Wersinger E, McLean WJ, Fuchs PA, Pyott SJ (2010) BK channels mediate cholinergic inhibition of high frequency cochlear hair cells. PLoS ONE 5:e13836. doi:10.1371/journal.pone.0013836

Wiederhold ML, KIANG NY (1970) Effects of electric stimulation of the crossed olivocochlear bundle on single auditory-nerve fibers in the cat. J Acoust Soc Am 48:950–965

Winslow RL, Sachs MB (1987) Effect of electrical stimulation of the crossed olivocochlear bundle on auditory nerve response to tones in noise. J Neurophysiol 57:1002–1021

Yin Y, Liberman LD, Maison SF, Liberman MC (2014) Olivocochlear innervation maintains the normal modiolar-pillar and habenular-cuticular gradients in cochlear synaptic morphology. J Assoc Res Otolaryngol 15:571–583. doi:10.1007/s10162-014-0462-z

Zheng XY, Henderson D, McFadden SL et al (1999) Auditory nerve fiber responses following chronic cochlear de-efferentation. J Comp Neurol 406:72–86

Zilberstein Y, Liberman MC, Corfas G (2012) Inner hair cells are not required for survival of spiral ganglion neurons in the adult cochlea. J Neurosci 32:405–410. doi:10.1523/JNEUROSCI.4678-11.2012

Zorrilla de San Martín J, Pyott S, Ballestero J, Katz E (2010) Ca(2+) and Ca(2+)-activated K(+) channels that support and modulate transmitter release at the olivocochlear efferent-inner hair cell synapse. J Neurosci 30:12157–12167. doi:10.1523/JNEUROSCI. 2541-10.2010