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Review

Cochlear hair cells: The sound-sensing machines

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ABSTRACT

The sensory epithelium of the mammalian inner ear contains two types of mechanosensory cells: inner (IHC) and outer hair cells (OHC). They both transduce mechanical force generated by sound waves into electrical signals. In their apical end, these cells possess a set of stereocilia representing the mechanosensing organelles. IHC are responsible for detecting sounds and transmitting the acoustic information to the brain by converting graded depolarization into trains of action potentials in auditory nerve fibers. OHC are responsible for the active mechanical amplification process that leads to the fine tuning and high sensitivity of the mammalian inner ear. This active amplification is the consequence of the ability of OHC to alter their cell length in response to changes in membrane potential, and is controlled by an efferent inhibitory innervation. Medial olivocochlear efferent fibers, originating in the brainstem, synapse directly at the base of OHC and release acetylcholine. A very special type of nicotinic receptor, assembled by α9α10 subunits, participates in this synapse. Here we review recent knowledge and the role of both afferent and efferent synapse in the inner ear.

1. Introduction

The inner ear of vertebrates has the unique capacity to detect sound waves and acceleration of body movements. The structure responsible for these refined tasks comprise a series of interconnected fluid-filled canals inside a bony structure at the base of the skull. Two main parts can be identified with different functionalities: the cochlea and the vestibular canals. The cochlea (Fig. 1A) houses a sophisticated machinery responsible for the detection of sounds and the conversion from mechanical energy intro electrical potentials [55,12]. The vestibular canals are responsible for the detection of changes in body position, and share many features with the cochlea [20].

The organ of Corti (Fig. 1B) is the sensory epithelium within the cochlea where hair cells, supporting cells and nerve fibers (that connect to and from the brain) interact to make hearing happen [55]. The organ of Corti rests over an acellular membrane, called basilar membrane, extending all along the cochlea and presenting unique mechanical properties [55]. It has the capacity to vibrate in response to fluid movements and propagate this mechanical energy to the entire organ of Corti. The way it vibrates in response to sound is key to understanding cochlear function. Sounds of a specific frequency produce a general wave within the cochlea, but movements of the basilar membrane are highly accelerated only in a very restricted region [122]. This phenomenon is called frequency tuning, and relies in part on the geometry of the basilar membrane, which is wider and more flexible at the apical low frequency end and narrower and stiffer at the basal high frequency end [54]. Hair cells also play a fundamental role, as will be discussed below.

The mammalian cochlea contains two classes of sensory cells, inner (IHC) and outer hair cells (OHC) [12]. They present several common characteristics, such as cellular polarity with stereocilia in the apex and synaptic connections at the base, but also, functional differences. Information about the acoustic environment is relayed primarily by synapses at IHC, whereas OHC are involved in sound amplification by electromechanical feedback.

In the following sections, we will critically discuss recent advances in some of the most important aspects of inner ear function: (1) mechano-transduction, that allows for detection of acoustic inputs; (2) afferent connections with the central nervous system, that brings information from the environment to the brain; (3) efferent connectivity, that controls cochlea amplification; and finally, (4) the association between the efferent system and the susceptibility to noise-induced hearing loss.

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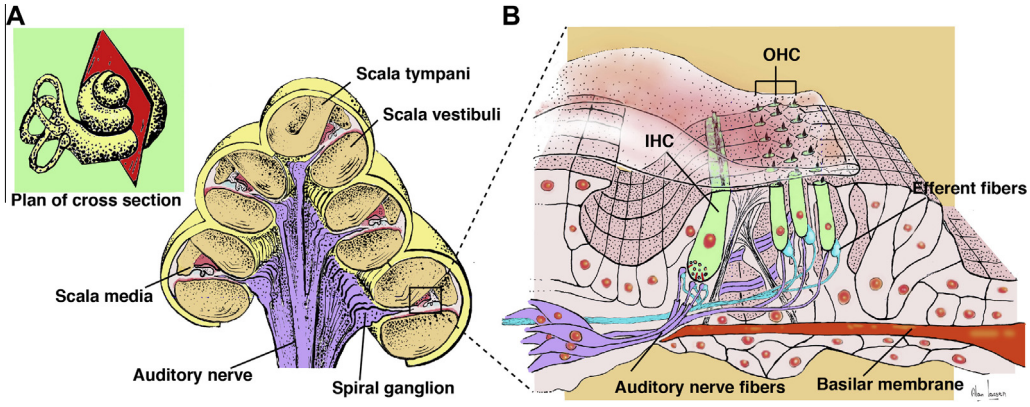

Fig. 1. Structure of the cochlea and the organ of Corti. (A) Cross-section of the cochlea (top inset shows diagram of the whole cochlea and sectioning scheme). The three compartments composing the cochlea are indicated (scala timpani, scala vestibuli and scala media). The organ of Corti is located in the scala media. The spiral ganglion comprises the somas of auditory nerve neurons innervating hair cells. (B) Structure of the organ of Corti. Inner (1) and outer (2) hair cells are indicated. Afferent dendrites belonging to auditory nerve neurons are indicated in purple, and medial olivary complex neurons in light blue. Some efferent fibers (light blue) also make axo-dendritic contacts with afferent boutons. Some afferent fibers represent a small proportion (type II) of afferent contacts on OHC. Image by Alan Larsen.

2. Mechano-transduction

Hair cells possess a set of 20–300 modified microvilli, or stereocilia, located in the cellular apex and presenting a stereotyped array (see Fig. 2A) [55]. In mammalian hair cells, stereocilia are arranged in three rows of increasing height. Each stereocilia is formed by a pack of actin filaments and inserts in the apical end of the hair cell within the so called cuticular plate. At the tip, a complex machinery devoted to transduce mechanic vibrations into electrical potentials, is located [18]. Sound waves produce coherent deflections of the cilia at their tapered base, triggering the phenomenon of mechanotransduction [55,69]. Such deflection causes the opening of a non-selective mechanotransduction (MET) cation channel (Fig. 2B, for simplicity only two stereocilia are illustrated). It has been shown that the MET channels produce a large inward current in hair cells, with an ultrafast temporal signature [27]. MET current increases with deflections toward the tallest stereocilia, and decreases in the opposite direction [57].

The biophysical properties of the MET channel have been extensively studied by electrical recordings of hair cells in *in vitro* preparations. The MET channel is a cationic channel, highly selective for Ca^{2+}, and also permeable to small organic ions [92,27]. This would explain its unusually large single-channel conductance of 100 pS or higher. The conductance of the MET channel changes along the tonotopical position within the cochlea, suggesting differential requirements at different frequencies [99]. Minute displacements of the hair bundle produce dramatic changes in MET channel open probability. Interestingly, at the bundle resting point channel's open probability is actually not zero, but approximately 20–40% of its maximum [60]. The number of MET channels opened by hair bundle deflection is relatively low. It has been estimated, using different biophysical methods, that there are 50–100 functional MET channels per bundle, translating into 1–2 MET channels per stereocilium [52,18,99,5]. Using state of the art imaging techniques, it was recently proposed that these few MET channels would exclusively be located in the second and third stereociliary rows of cochlear IHC and OHC, at the bottom of the tip links [5]. However, this finding contrasts with previous evidence indicating that channels would be located at both ends of the tip link [18,38]. More experiments would be needed to elucidate the precise MET channels location.

The molecular identity of many key players in the mechanotrasduction complex is still unknown, despite great research efforts. MET channel properties and evidence from invertebrates has pointed toward a channel of the 'transient receptor potential' (TRP) family as the pore forming molecule [10]. Some of the TRP channels, such as TRPA have high conductance, elevated Ca^{2+} permeability and are mechano-sensitive. However, this hypothesis

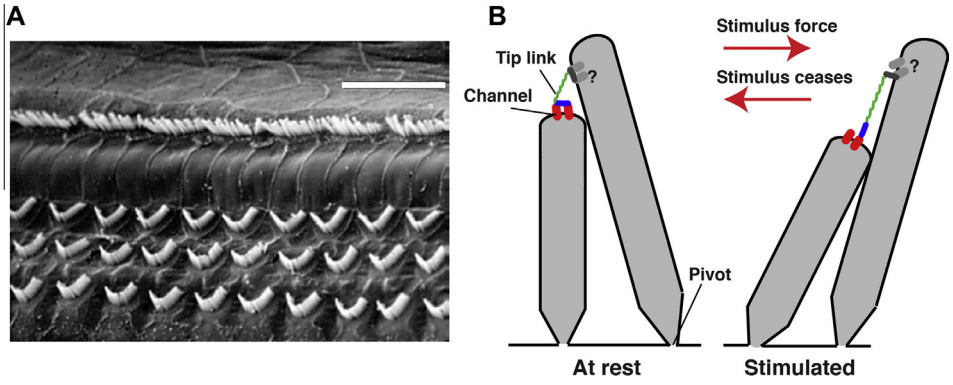

Fig. 2. Stereocilia and mechano-transduction: (A) Scanning electron-micrograph of the surface of the organ of Corti. On the top, the row of IHC stereocilia. The three bottom rows belong to OHC. Scale: 15 μm. Image by Marc Lenoir, INSERM Montpellier, from "Journey into the World of Hearing", www.cochlea.eu, edu website by Rémy Pujol et al., NeurOreille, Montpellier. (B) Mechano-transdcution scheme. In the left diagram, two stereocilia (for simplicity) are illustrated at resting state, connected by a tip link. The tip link is attached to a transduction channel. Deflection of the stereocilia, produced by mechanical force, pulls open the MET channel and activates the current through the channel (as indicated in the text, channels could be located at the bottom of the stereocilia, or even at the top).

could not be confirmed [74], and newly presented evidence indicates that members of the *transmembrane channel-like* family are part of the channel complex [93]. Recently, it has been shown that the tip link, the connecting threads between each stereocilia and its neighboring one from a different row, is formed by cadherin-23 (CDH23) and protocadherin-15 (PCDH15) [65]. Both are transmembrane proteins presenting long extracellular domains with several cadherin repeats. The tip link component PCDH15 would couple to the MET channel, not directly, but through two recently described molecules: TMHS (tetraspan membrane protein of hair cell stereocilia; also known as LHPLF5), and TMIE (transmembrane inner ear protein) forming a ternary complex [129,131]. TMHS mutations affect tip-link assembly and conductance of the transducer channel, whereas MET currents are abolished by a homozygous *Tmie*-null mutation, suggesting that both proteins are closely associated with the channel.

In OHC, MET is coupled to the extraordinary capacity of these cells to amplify sound vibrations. OHC are able to elongate (or contract) within milliseconds in response to changes in its membrane potential [7,2]. These cellular movements would further accelerate basilar membrane motion to produce amplification of a low intensity sound wave [2]. The contractile mechanism involves a protein of the chloride transporters family, called prestin [132], which is highly expressed in the basolateral membrane [53]. Conformational changes driven by the movements of chloride ions would facilitate the elongation or contraction of the cell [13,56]. Different studies on both isolated hair cells and mammalian cochleas *in vivo* have demonstrated the importance of functional prestin in healthy hearing [2]. Sound amplification and frequency discrimination are lost in mice lacking prestin [79,9]. Mice expressing a mutant prestin devoid of electromotility display a similar degraded hearing capability and auditory tuning curves [14].

3. Afferent synapse

Auditory information is conveyed to the brain through the afferent synapse onto IHC. In mammals, the afferent synapse is specialized in form and function. The active zone is defined by a slight thickening of the plasma membrane associated with a unique structure, called synaptic ribbon, that appears as a dense body in electron-micrographs (see Fig. 3A, inset) [90]. This structure is typically surrounded by clear-core synaptic vesicles [114].

The ribbon synapses between IHC and afferent dendrites of auditory nerves are glutamatergic. Release of glutamate triggers activation of AMPA receptors, composed of GluR2/3 and GluR4 subunits, in the postsynaptic terminals [87,3,40]. No NMDA component has been found in the normal operation of the synapse, although in certain conditions of intense acoustic stimulation NMDA receptors are transiently expressed [96]. Expression of NMDA receptors could be linked to the appearance of pathological conditions such as tinnitus [50,105]. As in other synapses of the auditory pathway, neurons show synaptic adaptations to efficiently respond to high frequency stimuli [120]. For instance, synaptic currents are fast, with decay times of <0.5 ms, and neurons show low input resistance which ensures fast synaptic potentials, little synaptic integration, and high fidelity responses in a cycle-by-cycle manner (Fig. 3A inset) [40,107]. The average amplitude of these currents is large, driving boutons of auditory nerve neurons to fire with short latency and little jitter [107]. However, EPSCs amplitudes present high variability (coefficient of variations: 77–95%), and quantal content present no dependence on stimulus intensity [40]. These phenomena have brought interest, but the mechanism behind the release of vesicles at this synapse is still not completely understood. It has been suggested that EPSCs are made by a highly coordinated release of multiple vesicle, and that the amplitude of each event (not the probability of occurrence) is totally in-dependent of the cytoplasmic Ca^{2+} concentration [40,44]. More recently, it has been proposed that the variability in EPSC size could be accounted for by the variable opening of the fusion pore in a single vesicle, rather than multiple [8].

Transmitter release at the hair cell's ribbon synapse occurs in response to graded changes in presynaptic membrane potential, not action potentials, similarly to some retinal synapses [88]. In the absence of sound stimulation, IHC resting membrane potential is approximately at −60 mV, and upon the arrival of a sound, transient depolarizations up to 0 mV typically occur [106,11]. Synaptic transmission at hair cells is controlled by voltage-gated Ca^{2+} channels of the L-type, that are located beneath the ribbon [100,58,31], and present low activation threshold and little inactivation [95]. These characteristics, together with the resting membrane potential of IHC, result in some degree of Ca^{2+} channel opening in the absence of sound stimulation. The function of this basal activity has been a matter of speculation. Recently, it has been proposed that it could contribute to a form of short-term plasticity, producing a noticeable increase in synaptic efficacy and also reducing latency and jitter of release events [45]. Precise timing is indispensable for the normal operation of the synapse, that should encode acoustic signals in the sub-millisecond range. Other forms of plasticity, such as short-term depression, also influences timing by delaying transmitter release. It has been suggested that a balance between synaptic depression and the speeding imposed by strong stimuli determines correct information transfer at IHC ribbon synapses [42].

The IHC is innervated by 10–20 auditory nerve fibers, and every fiber contacts the IHC with an unmyelinated single ending to form a single ribbon synapse [76]. These fibers present both overlapping and differential features. All neuronal activity is driven by transmitter release from IHC [102]. Upon acoustic stimulation, spiking increases, signaling to the brain the arrival of a given stimulus [37,68]. Persistent stimulation leads to a drop in spike rate at the auditory nerve, producing sensory adaptation, similar to that observed in other sensory modalities [68,127,117]. This phenomenon of adaptation would contribute to set the dynamic range in which neurons code sound intensities, and play an important role in speech encoding [115,17]. The cellular basis for this activity drop in spike rates is based on synaptic depression at the IHC afferent synapse. Both pre- and post-synaptic mechanisms, such as synaptic depression and desensitization of receptors, respectively, were shown to play important roles [89,47,44].

The specialized synaptic organelle present in hair cells, the ribbon, also called synaptic rod or body, is a matter of intense investigation. It is thought that by concentrating vesicles in the active zones, the ribbon would increase the supply rate of these vesicles, supporting the capacity of the synapse to continuously release neurotransmitter [88]. Complementary to this role, ribbons could also serve as a diffusional barrier for Ca^{2+} ions entering the cell through voltage-gated channels, producing a high ionic concentration in the vicinity of active zone [46]. The first molecular component of the ribbon to be identified was named *ribeye* and it is only found in this type of synapses [111]. It has been shown that ribeye can interact with itself and that multiple ribeye–ribeye aggregation might generate the three dimensional scaffold of the synaptic ribbon [84]. *Bassoon*, a presynaptic protein found ubiquitously in the brain, has a special role at the ribbon synapse. It binds to ribeye, and is responsible for anchoring ribbons to the presynaptic plasma membrane and clustering Ca^{2+} channels in the active zones [66,119,30]. In bassoon deficient synapses, ribbons appear floating freely in the cytoplasm and synaptic transmission is profoundly impaired [66]. Synaptic currents occur almost normally, but at a lower rate and with a deficient recovery process [59].

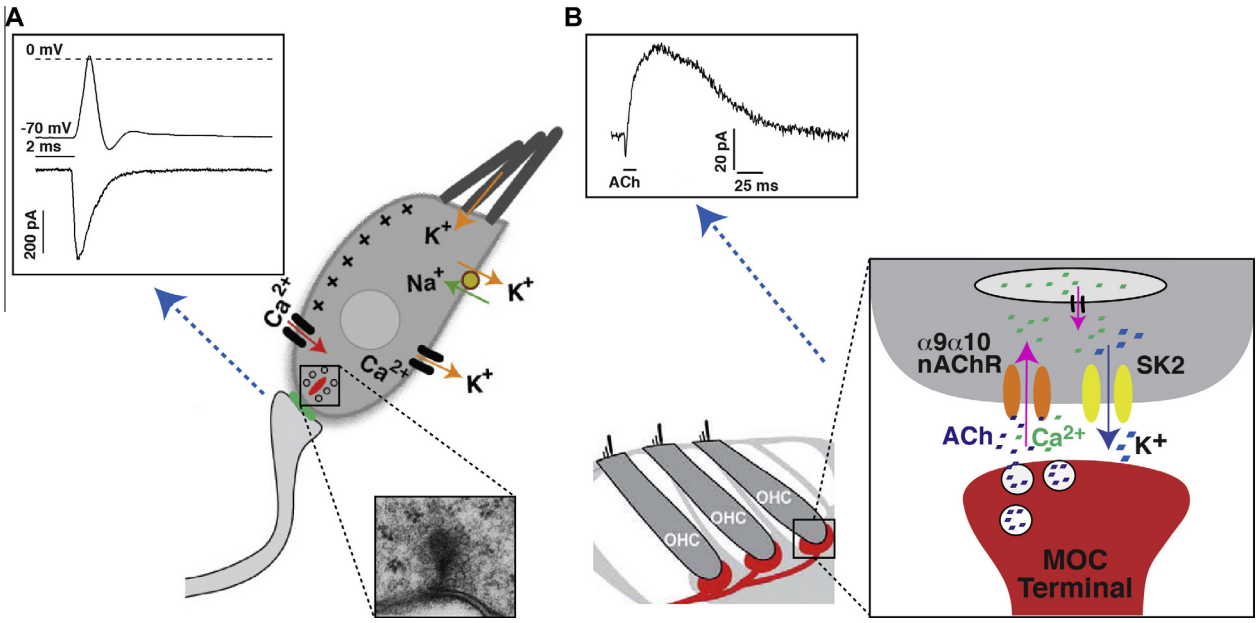

Fig. 3. Afferent and efferent synapse on hair cells of the cochlea. (A) Scheme of the IHC afferent synapse. A postsynaptic bouton of auditory nerve neuron is included (size is overemphasized for illustration purposes). Between 10 and 20 neurons innervate each IHC. A synaptic ribbon is observed opposing to the postsynaptic bouton. An electronmicrograph of the ribbon is shown in detail. Ca^{2+} influx, through voltage-activated calcium channels, is coupled to release of synaptic vesicles. Inset: detail of a synaptic current elicited by the release of a glutamate-filled vesicle/s, and also a synaptic potential followed by an action potential. (B) Detailed diagram of the synaptic terminal of MOC neurons onto OHC. MOC terminals release acetylcholine, which activates α9α10 nicotinic receptors in OHCs. Ca^{2+} influx through these receptors activates SK channels. A Ca^{2+} store (included in the diagram) is always observed in direct opposition to the location of the nicotinic receptors. Top inset: typical response of a hair cell to acetylcholine release. Note the initial and small inward current (carried by the nicotinic receptors) followed the larger outward component due to SK activation. Modified from [118].

Other molecular components of the release machinery are only partially shared with those of central synapses. Synaptotagmin, the canonical Ca^{2+} sensor present in synaptic vesicles, does not intervene in exocytosis at hair cells [108]. Instead, another candidate called *otoferlin*, with various Ca^{2+} binding domains, has been identified in a genetic screening in hearing impaired patients [104]. Otoferlin presents high affinity for Ca^{2+} and also binds to the SNARE (N-ethylmaleimide sensitive factor attachment protein receptor) complex in a Ca^{2+} dependent manner, two fundamental properties required for a Ca^{2+} sensor candidate. Transgenic mice with a null otoferlin mutation show strongly impaired hearing and non-functional afferent synapses, albeit structurally normal [104,94]. It has been also suggested, based on both physiological and structural studies, that otoferlin could mediate the replenishment of vesicles at active zones after prolonged synaptic activity [94]. Other key players of vesicular exocytosis, such as SNARE complex proteins, have also been investigated at IHC afferent synapses. It was initially described that neuronal isoforms of SNAP-25, syntaxin I and synaptobrevin I were expressed at the IHC afferent synapse [108]. More recently this idea has been challenged by a study indicating that release at this synapse is totally independent of the SNARE complex [91]. More experiments are required to determine how vesicles are released at the hair cell ribbon synapse.

The afferent neurons that have been described so far contact only IHC, are classified as type I, and represent 95% of all afferents [67]. There is a minor percentage of neurons, called type II, that receive inputs from several OHC with *en passant* synapses. Glutamate also mediates synaptic transmission at these synapses, and ribbons have been found in OHC, with somewhat different shapes [125]. Expression of kainate receptors subunits (GluK2 and GluK5) have been detected in type II fibers [35]. However, it is unlikely that type II neurons also encode acoustic information, given that the activity level in these synapses is very low and insufficient to drive neurons to fire in basal conditions [124]. Alternatively, it has been suggested that type II neurons may have a role in coding pain in the ear [28].

4. The efferent synapse

In addition to the ascending afferent neural pathway, the mammalian auditory system comprises descending efferent or centrifugal neural projections originating in the auditory brainstem and going all the way to the inner ear. Two efferent components can be distinguished originating in the medial, and the lateral, nuclei of the superior olivary complex (MOC and LOC respectively) [49]. The LOC system has been far less studied than the MOC system. The LOC consists of unmyelinated axons projecting to the dendrites of auditory nerve fibers near the IHC afferent synapses [49]. The role of the LOC system is still unknown, but the presence of several neurotransmitter and modulators in its terminals, such as dopamine, acetylcholine and GABA, suggest that it has complex functions [25].

The main effect of the MOC efferent innervation is to inhibit cochlear responses by decreasing the gain of the OHC amplifier. This effect is observed as a reduction in basilar membrane motion, and also as a transient loss in auditory nerve sensitivity to sound [49]. MOC neurons directly contact OHC producing inhibitory synaptic currents once activated [1,39]. The nature of this inhibitory input was a matter of debate over a long period of time, due to its complex biophysical and pharmacological characteristics.

Although ACh was identified in the late 50 s as the principal neurotransmitter released by MOC efferent fibers [97], the molecular nature of the postsynaptic receptor remained unknown for roughly five decades. Both metabotropic muscarinic receptors linked to second messenger cascades as well as ionotropic, nicotinic, ligand-gated ion channels had been proposed, and were the basis of a large quantity of contradictory literature in the field [25,24,6]. The cloning of two new receptor subunits of the nicotinic family, α9 and α10, deciphered the molecular nature of the hair cell cholinergic receptor and established its addition within the nicotinic family of cholinergic receptor subunits [21,23]. Recombinant receptors assembled from these subunits present a mixed nicotinic-muscarinic pharmacology [21,23,103,121], similar to

responses found years before in multiple end-organ preparations [33]. The α9α10 receptor is a cationic channel with high Ca^{2+} permeability [123,41]. In hair cells, Ca^{2+} influx leads to the activation of a Ca^{2+}-dependent small potassium conductance, SK2, producing cellular hyperpolarization (Fig. 3B, see also inset for detail of the currents) [33]. The coupling of α9α10 and SK2 underlies the biphasic shape of efferent synaptic currents, as can be observed in Fig. 3B [32,86,6,39]. However, it is still a matter of debate whether Ca^{2+} entering through α9α10 receptors is sufficient to activate the SK2 channels or if alternatively, Ca^{2+} release from an internal store might also take place. This latter possibility is supported by the finding of an extensive cistern tightly juxtaposed to the synaptic contact in OHC [109,34], and also some evidence indicating that the phenomenon of Ca^{2+}-induced Ca^{2+} release could occur [81].

Recent data indicates that Ca^{2+} permeability of the α9α10 nicotinic receptors varies among species, being high in mammals and low in non-mammalian vertebrates, such as chicken [83,82]. Evolutionary analyses indicate that the mammalian α9α10 has been under strong selective pressure, acquiring non-synonymous substitutions in the coding regions of α9 and α10 [29,82]. An increased Ca^{2+}-permeable mammalian receptor might have been the phenotypic consequence of this evolutionary process. This could have been necessary to drive the activation of the large conductance, Ca^{2+}- and voltage-gated potassium channels, BK, present in efferent contacts of OHC in high frequency regions of the mammalian cochlea [126]. The Ca^{2+} affinity of BK channels is two orders of magnitude lower than that of SK channels [26], requiring higher Ca^{2+} influx for activation.

MOC neurons can fire at high frequencies in response to sound [77]; the louder the stimuli, the faster neurons fire. Inhibition of OHC is strongly dependent on the firing rate of these neurons, as transmitter release presents a robust enhancement when triggered at short succession [4]. While significant progress has been made in defining the cellular mechanisms of hair cell inhibition [22], the functional role(s) of this sound-evoked feedback system, including control of the dynamic range of hearing [49], improvement of signal detection in background noise [19,128,64], mediating selective attention [16], and protection from acoustic injury [98,118], remain controversial.

It is important to note that OHC are not the only targets of MOC fibers. During a critical period of postnatal development of the altricial rodent cochlea, IHC transiently receive cholinergic innervation which is also mediated by α9α10 receptors [33,39,63]. During this period, comprising the first 2 weeks after birth, mice are deaf, but spontaneous electrical activity in the organ of Corti has been shown to occur. IHC are able to fire Ca^{2+} action potentials [70], driving neurons in the auditory pathway to respond rhythmically. This activity would be important for the normal maturation of synapses and circuits of the entire auditory pathway, and ceases after the onset of hearing [62]. Activity of the MOC to IHC input is also inhibitory during this developmental period, and would control the excitability of the hair cells [39,43,61,113].

5. Noise-induced hearing loss

Noise-induced hearing loss (NIHL) is a worldwide condition that leads to considerable communication problems in affected individuals and presents an important socio-economic risk factor [112]. Despite several identified details about its etiology, the underlying mechanisms that lead to NIHL have been only partially resolved. Depending on the kind, duration and intensity, overexposure to loud sounds causes trauma to the ear, deteriorating our ability to hear [110], and leads to tinnitus (phantom sound perception) [15]. It has been demonstrated that mechanical damage, as well as metabolic disturbances induced by intense sound exposure, lead to NIHL [110]. Changes in cellular structures in the organ of Corti include: stereocilia disarrangement, synaptic terminal swellings, supporting cells with altered morphology, and even hair cell death [80]. OHC are the most vulnerable to acoustic over-exposure. Above a specific intensity level, OHC show signs of metabolic exhaustion with the accumulation of reactive oxygen and nitrogen species [130]. Given that mammalian hair cells do not regenerate [48], the loss of cells determines an irreversible loss of hearing capacity.

Temporary and/or permanent auditory threshold shifts can occur in response to exposure to overly loud sounds. Permanent NIHL is due to the irreversible destruction of cochlear hair cells and/or damage to their mechano-sensory hair bundles [78]. It has been proposed that temporary NIHL is due to swelling of cochlear nerve terminals at their hair-cell synapses [116,101]. However, recent work in both mouse [72] and guinea pig [36] has shown that acoustic overexposures causing reversible threshold elevations can lead to an irreversible degeneration of auditory nerve fibers. The loss of hair cell synapses and auditory nerve terminals is rapid (within hours post-exposure), while the loss of auditory nerve cell bodies in the spiral ganglion is slow (months to years) [72,73,75]. Thus, these recent studies indicate that the damage due to exposure to loud sounds go beyond that previously described.

Several lines of evidence suggest that the MOC system has an important role in the protection from trauma produced by overly loud sounds. Stimulation of the MOC fibers during sound overexposure produces a reduction of sensitivity loss [98] and chronic sectioning of the olivocochlear bundle renders the ear more vulnerable to permanent acoustic injury [51,71]. Moreover, the strength of this sound-evoked olivocochlear feedback pathway to the inner ear (in humans) is inversely correlated with the degree of hearing loss after acoustic trauma [85]. A transgenic mouse line was recently engineered carrying an enhanced MOC–OHC synapse due to an α9α10 receptor with increased gating properties [118]. Mutant mice exhibit higher tolerance to noise-induced trauma, further pinpointing to the participation of the MOC in protection of the inner ear. It is still unknown whether protection is due to reduced mechanical vibration of the sensory epithelium, or if Ca^{2+} entry through α9α10 produces downstream effects impacting on OHC function. Since hearing loss and tinnitus are a worldwide burden [112], and exposure to loud sounds is one of the main underlying causes, the development of drugs that target α9α10 receptors has been recently suggested [22].

6. Conclusions and perspectives

During the past 20 years, important advances have been made in order to uncover the molecular basis of hearing. Given the peculiarities of this sensory modality, detection of the simplest sound requires a very complex series of cellular events. The biophysical and physiological details of phenomena such as mechano-transduction, non-exhausting afferent synaptic transmission and efferent control of the hearing sensitivity are only starting to emerge. An in-depth understanding of the underpinnings of how hearing takes place at the cellular and molecular level, will enable the development of more powerful tools for preventing and treating hearing loss.

References

[1] Art, J.J., Fettiplace, R. and Fuchs, P.A. (1984) Synaptic hyperpolarization and inhibition of turtle cochlear hair cells. J. Physiol. 356, 525–550.
[2] Ashmore, J. (2008) Cochlear outer hair cell motility. Physiol. Rev. 88, 173–210.

[3] Bailey, G.P. and Sewell, W.F. (2000) Contribution of glutamate receptors to spontaneous and stimulus-evoked discharge in afferent fibers innervating hair cells of the Xenopus lateral line organ. Hear. Res. 144, 8–20.
[4] Ballestero, J., Zorrilla de San Martin, J., Goutman, J.D., Elgoyhen, A.B., Fuchs, P. A. and Katz, E. (2011) Short-term synaptic plasticity regulates the level of olivocochlear inhibition to auditory hair cells. J. Neurosci. 31, 14763–14774.
[5] Beurg, M., Fettiplace, R., Nam, J. and Ricci, A.J. (2009) Localization of inner hair cell mechanotransducer channels using high-speed calcium imaging. Nat. Neurosci. 12, 553–558.
[6] Blanchet, C., Erostegui, C., Sugasawa, M. and Dulon, D. (1996) Acetylcholine-induced potassium outer hair cells: its dependence receptors current of guinea pig on a calcium influx through nicotinic-like receptors. J. Neurosci. 16, 2574–2584.
[7] Brownell, W.E., Bader, C.R., Bertrand, D. and de Ribaupierre, Y. (1985) Evoked mechanical responses of isolated cochlear outer hair cells. Science 227, 194–196.
[8] Chapochnikov, N.M., Takago, H., Huang, C., Pangršič, T., Khimich, D., Neef, J., Auge, E., Gottfert, F., Hell, S.W., Wichmann, C., Wolf, F., Moser, T. and Go, F. (2014) Uniquantal release through a dynamic fusion pore is a candidate mechanism of hair cell exocytosis i c. Neuron 83, 1–15.
[9] Cheatham, M.A., Huynh, K.H., Gao, J., Zuo, J. and Dallos, P. (2004) Cochlear function in Prestin knockout mice. J. Physiol. 560, 821–830.
[10] Christensen, A.P. and Corey, D.P. (2007) TRP channels in mechanosensation: direct or indirect activation? Nat. Rev. Neurosci. 8, 510–521.
[11] Dallos, P. (1986) Neurobiology of cochlear inner and outer hair cells: intracellular recordings. Hear. Res. 22, 185–198.
[12] Dallos, P. (1996) Overview: cochlear neurobiology in: The Cochlea (Dallos, P., Popper, A.N. and Fay, R.R., Eds.), pp. 1–43, Springer-Verlag New York Inc., New York.
[13] Dallos, P. (2008) Cochlear amplification, outer hair cells and prestin. Curr. Opin. Neurobiol. 18, 370–376.
[14] Dallos, P., Wu, X., Cheatham, M.A., Gao, J., Zheng, J., Anderson, C.T., Jia, S., Wang, X., Cheng, W.H.Y., Sengupta, S., He, D.Z.Z. and Zuo, J. (2008) Prestin-based outer hair cell motility is necessary for mammalian cochlear amplification. Neuron 58, 333–339.
[15] De Ridder, D., Elgoyhen, A.B., Romo, R. and Langguth, B. (2011) Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc. Natl. Acad. Sci. U.S.A. 108, 8075–8080.
[16] Delano, P.H., Elgueda, D., Hamame, C.M. and Robles, L. (2007) Selective attention to visual stimuli reduces cochlear sensitivity in chinchillas. J. Neurosci. 27, 4146–4153.
[17] Delgutte, B. (1999) Auditory neural processing of speech in: The Handbook of Phonetic Sciences (Hardcastle, W.J. and Laver, J., Eds.), pp. 507–538, Blackwell Publishing, New York.
[18] Denk, W., Holt, J.R., Shepherd, G.M.G. and Corey, D.P. (1995) Calcium imaging of single stereocilia in hair cells: localization of transduction channels at both ends of tip links. Neuron 15, 1311–1321.
[19] Dolan, D.F. and Nuttall, A.L. (1988) Masked cochlear whole-nerve response intensity functions altered by electrical stimulation of the crossed olivocochlear bundle. J. Acoust. Soc. Am. 83, 1081–1086.
[20] Eatock, R.A. and Songer, J.E. (2011) Vestibular hair cells and afferents: two channels for head motion signals. Annu. Rev. Neurosci. 34, 501–534.
[21] Elgoyhen, A.B., Johnson, D.S., Boulter, J., Vetter, D.E. and Heinemann, S.F. (1994) Alpha 9: an acetylcholine receptor with novel pharmacological properties expressed in rat cochlear hair cells. Cell 79, 705–715.
[22] Elgoyhen, A.B., Katz, E. and Fuchs, P.A. (2009) The nicotinic receptor of cochlear hair cells: a possible pharmacotherapeutic target? Biochem. Pharmacol. 78, 712–719.
[23] Elgoyhen, A.B., Vetter, D.E., Katz, E., Rothlin, C.V., Heinemann, S.F. and Boulter, J. (2001) Alpha10: 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.
[24] Erostegui, C., Norris, C.H. and Bobbin, R.P. (1994) In vitro pharmacologic characterization of a cholinergic receptor on outer hair cells. Hear. Res. 74, 135–147.
[25] Eybalin, M. (1993) Neurotransmitters and neuromodulators of the mammalian cochlea. Physiol. Rev. 73, 309–373.
[26] Fakler, B. and Adelman, J.P. (2008) Control of K(Ca) channels by calcium nano/microdomains. Neuron 59, 873–881.
[27] Fettiplace, R. and Hackney, C.M. (2006) The sensory and motor roles of auditory hair cells. Nat. Rev. Neurosci. 7, 19–29.
[28] Flores, E.N., Duggan, A., Madathany, T., Hogan, A.K., Márquez, F.G., Kumar, G., Seal, R.P., Edwards, R.H., Liberman, M.C. and García-Añoveros, J. (2015) A non-canonical pathway from cochlea to brain signals tissue-damaging noise. Curr. Biol., 606–612.
[29] Franchini, L.F. and Elgoyhen, A.B. (2006) Adaptive evolution in mammalian proteins involved in cochlear outer hair cell electromotility. Mol. Phylogenet. Evol. 41, 622–635.
[30] Frank, T. et al. (2010) Bassoon and the synaptic ribbon organize Ca^{2+} channels and vesicles to add release sites and promote refilling. Neuron 68, 724–738.
[31] Frank, T., Khimich, D., Neef, A. and Moser, T. (2009) Mechanisms contributing to synaptic Ca^{2+} signals and their heterogeneity in hair cells. Proc. Natl. Acad. Sci. U.S.A. 106, 4483–4488.
[32] Fuchs, P.A. and Murrow, B.W. (1992) Cholinergic inhibition of short (outer) hair cells of the chick's cochlea. J. Neurosci. 12, 800–809.
[33] Fuchs, P.A. (1996) Synaptic transmission at vertebrate hair cells. Curr. Opin. Neurobiol. 6, 514–519.
[34] Fuchs, P.A., Lehar, M. and Hiel, H. (2013) Ultrastructure of cisternal synapses on outer hair cells of the mouse cochlea. J. Comp. Neurol..
[35] Fujikawa, T., Petralia, R.S., Fitzgerald, T.S., Wang, Y.-X., Millis, B., Morgado-Díaz, J.A., Kitamura, K. and Kachar, B. (2014) Localization of kainate receptors in inner and outer hair cell synapses. Hear. Res. 314, 20–32.
[36] Furman, A.C., Kujawa, S.G. and Liberman, M.C. (2013) Noise-induced cochlear neuropathy is selective for fibers with low spontaneous rates. J. Neurophysiol. 110, 577–586.
[37] Galambos, R. and Davis, H. (1943) The response of single auditory nerve fiber to acoustic stimulation. J. Neurophysiol. 6, 39–58.
[38] Gillespie, P.G. and Cyr, J.L. (2004) Myosin-1C, the hair cell's adaptation motor. Annu. Rev. Physiol., 521–545.
[39] Glowatzki, E. and Fuchs, P.A. (2000) Cholinergic synaptic inhibition of inner hair cells in the neonatal mammalian cochlea. Science 288, 2366–2368.
[40] Glowatzki, E. and Fuchs, P.A. (2002) Transmitter release at the hair cell ribbon synapse. Nat. Neurosci. 5, 147–154.
[41] Gomez-Casati, M.E., Fuchs, P.A., Elgoyhen, A.B. and Katz, E. (2005) Biophysical and pharmacological characterization of nicotinic cholinergic receptors in rat cochlear inner hair cells. J. Physiol. 566, 103–118.
[42] Goutman, J.D. (2012) Transmitter release from cochlear hair cells is phase locked to cyclic stimuli of different intensities and frequencies. J. Neurosci. 32, 17025–17036.
[43] Goutman, J.D., Fuchs, P.A. and Glowatzki, E. (2005) Facilitating efferent inhibition of inner hair cells in the cochlea of the neonatal rat. J. Physiol. 566, 49–59.
[44] Goutman, J.D. and Glowatzki, E. (2007) Time course and calcium dependence of transmitter release at a single ribbon synapse. Proc. Natl. Acad. Sci. U.S.A. 104, 16341–16346.
[45] Goutman, J.D. and Glowatzki, E. (2011) Short-term facilitation modulates size and timing of the synaptic response at the inner hair cell ribbon synapse. J. Neurosci. 31, 7974–7981.
[46] Graydon, C.W., Cho, S., Li, G., Kachar, B. and von Gersdorff, H. (2011) Sharp Ca^{2+} nanodomains beneath the ribbon promote highly synchronous multivesicular release at hair cell synapses. J. Neurosci. 31, 16637–16650.
[47] Griesinger, C.B., Richards, C.D. and Ashmore, J.F. (2005) Fast vesicle replenishment allows indefatigable signalling at the first auditory synapse. Nature 435, 212–215.
[48] Groves, A.K. (2010) The challenge of hair cell regeneration. Exp. Biol. Med. (Maywood) 235, 434–446.
[49] Guinan, J.J. (2006) Olivocochlear efferents: anatomy, physiology, function, and the measurement of efferent effects in humans. Ear Hear. 27, 589–607.
[50] Guitton, M.J., Caston, J., Ruel, J., Johnson, R.M., Pujol, R. and Puel, J.-L. (2003) Salicylate induces tinnitus through activation of cochlear NMDA receptors. J. Neurosci. 23, 3944–3952.
[51] Handrock, M. and Zeisberg, J. (1982) The influence of the effect system on adaptation, temporary and permanent threshold shift. Arch. Otorhinolaryngol. 234, 191–195.
[52] Howard, J. and Hudspeth, A.J. (1988) Compliance of the hair bundle associated with gating of mechanoelectrical transduction channels in the bullfrog's saccular hair cell. Neuron 1, 189–199.
[53] Huang, G. and Santos-Sacchi, J. (1993) Mapping the distribution of the outer hair cell motility voltage sensor by electrical amputation. Biophys. J. 65, 2228–2236.
[54] Hudspeth, A.J. (1985) The cellular basis of hearing: the biophysics of hair cells. Science 230, 745–752.
[55] Hudspeth, A.J. (1989) How the ear's works work. Nature 341, 397–404.
[56] Hudspeth, A.J. (2008) Making an effort to listen: mechanical amplification in the ear. Neuron 59, 530–545.
[57] Hudspeth, A.J. and Corey, D.P. (1977) Sensitivity, polarity, and conductance change in the response of vertebrate hair cells to controlled mechanical stimuli. Proc. Natl. Acad. Sci. U.S.A. 74, 2407–2411.
[58] Issa, N.P. and Hudspeth, A.J. (1994) Clustering of Ca^{2+} channels and Ca(2+)-activated K+ channels at fluorescently labeled presynaptic active zones of hair cells. Proc. Natl. Acad. Sci. U.S.A. 91, 7578–7582.
[59] Jing, Z., Rutherford, M.A., Takago, H., Frank, T., Fejtova, A., Khimich, D., Moser, T. and Strenzke, N. (2013) Disruption of the presynaptic cytomatrix protein bassoon degrades ribbon anchorage, multiquantal release, and sound encoding at the hair cell afferent synapse. J. Neurosci. 33, 4456–4467.
[60] Johnson, S.L., Beurg, M., Marcotti, W. and Fettiplace, R. (2011) Prestin-driven cochlear amplification is not limited by the outer hair cell membrane time constant. Neuron 70, 1143–1154.
[61] Johnson, S.L., Eckrich, T., Kuhn, S., Zampini, V., Franz, C., Ranatunga, K.M., Roberts, T.P., Masetto, S., Knipper, M., Kros, C.J. and Marcotti, W. (2011) Position-dependent patterning of spontaneous action potentials in immature cochlear inner hair cells. Nat. Neurosci. 14, 711–717.
[62] Kandler, K., Clause, A. and Noh, J. (2009) Tonotopic reorganization of developing auditory brainstem circuits. Nat. Neurosci. 12, 711–717.
[63] Katz, E., Elgoyhen, A.B., Gomez-Casati, M.E., Knipper, M., Vetter, D.E., Fuchs, P. A. and Glowatzki, E. (2004) Developmental regulation of nicotinic synapses on cochlear inner hair cells. J. Neurosci. 24, 7814–7820.
[64] Kawase, T., Delgutte, B. and Liberman, M.C. (1993) Antimasking effects of the olivocochlear reflex. II. Enhancement of auditory-nerve response to masked tones. J. Neurophysiol. 70, 2533–2549.

[65] Kazmierczak, P., Sakaguchi, H., Tokita, J., Wilson-kubalek, E.M., Milligan, R.A., Muller, U. and Kachar, B. (2007) Cadherin 23 and protocadherin 15 interact to form tip-link filaments in sensory hair cells. Nature 449, 87–92.

[66] Khimich, D., Nouvian, R., Pujol, R., tom Dieck, S., Egner, A., Gundelfinger, E.D. and Moser, T. (2005) Hair cell synaptic ribbons are essential for synchronous auditory signalling. Nature 434, 889–894.

[67] Kiang, N.Y.S., Rho, J.M., Northrop, C.C., Liberman, M.C. and Ryugo, D.K. (1982) Hair-cell innervation by spiral ganglion cells in adult cats. Science 217, 175–177.

[68] N.Y.S. Kiang, T. Watanabe, L.F. Clark, Discharge Patterns of Single Fibers in the Cat's Auditory Nerve, 35 MIT Research Monograph N, Ed., 1965.

[69] Kozlov, A.S., Risler, T. and Hudspeth, A.J. (2007) Coherent motion of stereocilia assures the concerted gating of hair-cell transduction channels. Nat. Neurosci. 10, 87–92.

[70] Kros, C.J., Ruppersberg, J.P. and Rusch, A. (1998) Expression of a potassium current in inner hair cells during development of hearing in mice. Nature 394, 281–284.

[71] Kujawa, S.G. and Liberman, M.C. (1997) Conditioning-related protection from acoustic injury: effects of chronic deefferentation and sham surgery. J. Neurophysiol. 78, 3095–3106.

[72] Kujawa, S.G. and Liberman, M.C. (2009) Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. J. Neurosci. 29, 14077–14085.

[73] Kujawa, S.G. and Liberman, M.C. (2015) Synaptopathy in the noise-exposed and aging cochlea: primary neural degeneration in acquired sensorineural hearing loss. Hear. Res..

[74] Kwan, K.Y., Allchorne, A.J., Vollrath, M.A., Christensen, A.P., Zhang, D.-S., Woolf, C.J. and Corey, D.P. (2006) TRPA1 contributes to cold, mechanical, and chemical nociception but is not essential for hair-cell transduction. Neuron 50, 277–289.

[75] Liberman, L.D. and Liberman, M.C. (2015) Dynamics of cochlear synaptopathy after acoustic overexposure. J. Assoc. Res. Otolaryngol. 16, 205–219.

[76] Liberman, M.C. (1982) Single-neuron labeling in the cat auditory nerve. Science 216, 1239–1241.

[77] Liberman, M.C. and Brown, M.C. (1986) Physiology and anatomy of single olivocochlear neurons in the cat. Hear. Res. 24, 17–36.

[78] Liberman, M.C. and Dodds, L.W. (1984) Single-neuron labeling and chronic cochlear pathology. III. Stereocilia damage and alterations of threshold tuning curves. Hear. Res. 16, 55–74.

[79] Liberman, M.C., Gao, J., He, D.Z.Z., Wu, X., Jia, S. and Zuo, J. (2002) Prestin is required for electromotility of the outer hair cell and for the cochlear amplifier. Nature 419, 300–304.

[80] Liberman, M.C. and Kiang, N.Y.S. (1984) Single-neuron labeling and chronic cochlear pathology. IV. Stereocilia damage and alterations in rate- and phase-level functions. Hear. Res. 16, 75–90.

[81] Lioudyno, M., Hiel, H., Kong, J., Katz, E., Waldman, E., Parameshwaran-Iyer, S., Glowatzki, E. and Fuchs, P.A. (2004) A "synaptoplasmic cistern" mediates rapid inhibition of cochlear hair cells. J. Neurosci. 24, 11160–11164.

[82] Lipovsek, M., Fierro, A., Perez, E.G., Boffi, J.C., Millar, N.S., Fuchs, P.A., Katz, E. and Elgoyhen, A.B. (2014) Tracking the molecular evolution of calcium permeability in a nicotinic acetylcholine receptor. Mol. Biol. Evol. 31, 3250–3265.

[83] Lipovsek, M., Im, G.-J., Franchini, L.F., Pisciottano, F., Katz, E., Fuchs, P.A. and Elgoyhen, A.B. (2012) Phylogenetic differences in calcium permeability of the auditory hair cell cholinergic nicotinic receptor. Proc. Natl. Acad. Sci. U.S.A. 109, 4308–4313.

[84] Magupalli, V.G., Schwarz, K., Alpadi, K., Natarajan, S., Seigel, G.M. and Schmitz, F. (2008) Multiple RIBEYE-RIBEYE interactions create a dynamic scaffold for the formation of synaptic ribbons. J. Neurosci. 28, 7954–7967.

[85] Maison, S.F. and Liberman, M.C. (2000) Predicting vulnerability to acoustic injury with a noninvasive assay of olivocochlear reflex strength. J. Neurosci. 20, 4701–4707.

[86] Martin, A.R. and Fuchs, P.A. (1992) The dependence of calcium-activated potassium currents on membrane potential. Proc. R. Soc. Lond. B: Biol. Sci. 250, 71–76.

[87] Matsubara, A., Laake, J.H., Davanger, S., Usami, S. and Ottersen, O.P. (1996) Organization of AMPA receptor subunits at a glutamate synapse: a quantitative immunogold analysis of hair cell synapses in the rat organ of corti. J. Neurosci. 16, 4457–4467.

[88] Matthews, G. and Fuchs, P.A. (2010) The diverse roles of ribbon synapses in sensory neurotransmission. Nat. Rev. Neurosci. 12, 812–822.

[89] Moser, T. and Beutner, D. (2000) Kinetics of exocytosis and endocytosis at the cochlear inner hair cell afferent synapse of the mouse. Proc. Natl. Acad. Sci. U.S.A. 97, 883–888.

[90] Moser, T., Brandt, A. and Lysakowski, A. (2006) Hair cell ribbon synapses. Cell Tissue Res. 326, 347–359.

[91] Nouvian, R., Neef, J., Bulankina, A.V., Reisinger, E., Pangršič, T., Frank, T., Sikorra, S., Brose, N., Binz, T. and Moser, T. (2011) Exocytosis at the hair cell ribbon synapse apparently operates without neuronal SNARE proteins. Nat. Neurosci. 14, 411–413.

[92] Ohmori, H. (1985) Mechano-electrical transduction currents in isolated vestibular hair cells of the chick. J. Physiol. 359, 189–217.

[93] Pan, B., Géléoc, G.S.G., Asai, Y., Horwitz, G.C., Kurima, K., Ishikawa, K., Kawashima, Y., Griffith, A.J. and Holt, J.R. (2013) TMC1 and TMC2 are components of the mechanotransduction channel in hair cells of the mammalian inner ear. Neuron 79, 504–515.

[94] Pangršič, T., Lasarow, L., Reuter, K., Takago, H., Schwander, M., Riedel, D., Frank, T., Tarantino, L.M., Bailey, J.S., Strenzke, N., Brose, N., Müller, U., Reisinger, E. and Moser, T. (2010) Hearing requires otoferlin-dependent efficient replenishment of synaptic vesicles in hair cells. Nat. Neurosci..

[95] Platzer, J., Engel, J., Schrott-Fischer, A., Stephan, K., Bova, S., Chen, H., Zheng, H. and Striessnig, J. (2000) Congenital deafness and sinoatrial node dysfunction in mice lacking class D L-type Ca^{2+} channels. Cell 102, 89–97.

[96] Puel, J.-L., Safieddine, S., Gervais d'Aldin, C., Eybalin, M. and Pujol, R. (1995) Synaptic regeneration and functional recovery after excitotoxic injury in the guinea pig cochlea. C.R. Acad. Sci. III 318, 67–75.

[97] Rasmussen, G.L. (1955) Descending, or "feedback-back" connections of the auditory system of the cat. Am. J. Physiol. 183, 653.

[98] Reiter, E.R. and Liberman, M.C. (1995) Efferent-mediated protection from acoustic overexposure: relation to slow effects of olivocochlear stimulation. J. Neurophysiol. 73, 506–514.

[99] Ricci, A.J., Crawford, A.C. and Fettiplace, R. (2003) Tonotopic variation in the conductance of the hair cell mechanotransducer channel. Neuron 40, 983–990.

[100] Roberts, W.M., Jacobs, R.A. and Hudspeth, A.J. (1990) Colocalization of ion channels involved in frequency selectivity and synaptic transmission at presynaptic active zones of hair cells. J. Neurosci. 10, 3664–3684.

[101] Robertson, D. (1983) Functional significance of dendritic swelling after loud sounds in the guinea pig cochlea. Hear. Res. 9, 263–278.

[102] Robertson, D. and Paki, B. (2002) Role of L-type Ca^{2+} channels in transmitter release from mammalian inner hair cells. II. Single-neuron activity. J. Neurophysiol. 87, 2734–2740.

[103] Rothlin, C.V., Katz, E., Verbitsky, M. and Elgoyhen, A.B. (1999) The alpha9 nicotinic acetylcholine receptor shares pharmacological properties with type A gamma-aminobutyric acid, glycine, and type 3 serotonin receptors. Mol. Pharmacol. 55, 248–254.

[104] Roux, I., Safieddine, S., Nouvian, R., Grati, M., Simmler, M., Bahloul, A., Perfettini, I., Le Gall, M., Rostaing, P., Hamard, G., Triller, A., Avan, P., Moser, T. and Petit, C. (2006) Otoferlin, defective in a human deafness form, is essential for exocytosis at the auditory ribbon synapse. Cell 127, 277–289.

[105] Ruel, J., Chabbert, C., Nouvian, R., Bendris, R., Eybalin, M., Leger, C.L., Bourien, J., Mersel, M. and Puel, J.-L. (2008) Salicylate enables cochlear arachidonic-acid-sensitive NMDA receptor responses. J. Neurosci. 28, 7313–7323.

[106] Russell, I.J. and Sellick, P.M. (1978) Intracellular studies of hair cells in the mammalian cochlea. J. Physiol. 284, 261–290.

[107] Rutherford, M.A., Chapochnikov, N.M. and Moser, T. (2012) Spike encoding of neurotransmitter release timing by spiral ganglion neurons of the cochlea. J. Neurosci. 32, 4773–4789.

[108] Safieddine, S. and Wenthold, R.J. (1999) SNARE complex at the ribbon synapses of cochlear hair cells: analysis of synaptic vesicle- and synaptic membrane-associated proteins. Eur. J. Neurosci. 11, 803–812.

[109] Saito, K. (1983) Fine structure of the sensory epithelium of guinea-pig organ of Corti: subsurface cisternae and lamellar bodies in the outer hair cells. Cell Tissue Res. 229, 467–481.

[110] Saunders, J.C., Dear, S.P. and Schneider, M.E. (1985) The anatomical consequences of acoustic injury: a review and tutorial. J. Acoust. Soc. Am. 78, 833–860.

[111] Schmitz, F., Königstorfer, A. and Südhof, T.C. (2000) RIBEYE, a component of synaptic ribbons: a protein's journey through evolution provides insight into synaptic ribbon function. Neuron 28, 857–872.

[112] Seidman, M.D. and Standring, R.T. (2010) Noise and quality of life. Int. J. Environ. Res. Public Health 7, 3730–3738.

[113] Sendin, G., Bourien, J., Rassendren, F., Puel, J.-L. and Nouvian, R. (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.

[114] Smith, C.A. and Sjöstrand, F.S. (1961) A synaptic structure in the hair cells of the guinea pig cochlea. J. Ultrastruct. Res. 5, 184–192.

[115] Smith, R.L., Brachman, M.L. and Goodman, D.A. (1983) Adaptation in the auditory periphery. Ann. N.Y. Acad. Sci. 405, 79–93.

[116] Spoendlin, H. (1971) Primary structural changes in the organ of Corti after acoustic overstimulation. Acta Otolaryngol. 71, 166–176.

[117] Taberner, A.M. and Liberman, M.C. (2005) Response properties of single auditory nerve fibers in the mouse. J. Neurophysiol. 93, 557–569.

[118] Taranda, J., Maison, S.F., Ballestero, J.A., Katz, E., Savino, J., Vetter, D.E., Boulter, J., Liberman, M.C., Fuchs, P.A. and Elgoyhen, A.B. (2009) A point mutation in the hair cell nicotinic cholinergic receptor prolongs cochlear inhibition and enhances noise protection. PLoS Biol. 7, e18.

[119] tom Dieck, S., Altrock, W.D., Kessels, M.M., Qualmann, B., Regus, H., Brauner, D., Fejtová, A., Bracko, O., Gundelfinger, E.D. and Brandstätter, J.H. (2005) Molecular dissection of the photoreceptor ribbon synapse: physical interaction of Bassoon and RIBEYE is essential for the assembly of the ribbon complex. J. Cell Biol. 168, 825–836.

[120] Trussell, L.O. (1999) Synaptic mechanisms for coding timing in auditory neurons. Annu. Rev. Physiol. 61, 477–496.

[121] Verbitsky, M., Rothlin, C.V., Katz, E. and Elgoyhen, A.B. (2000) Mixed nicotinic–muscarinic properties of the alpha9 nicotinic cholinergic receptor. Neuropharmacology 39, 2515–2524.

[122] Von Bekesy, G. (1960) Experiments in Hearing, McGraw-Hill, New York.

[123] Weisstaub, N., Vetter, D.E., Elgoyhen, A.B. and Katz, E. (2002) The alpha9alpha10 nicotinic acetylcholine receptor is permeable to and is modulated by divalent cations. Hear. Res. 167, 122–135.

[124] Weisz, C., Glowatzki, E. and Fuchs, P.A. (2009) The postsynaptic function of type II cochlear afferents. Nature 461, 1126–1129.
[125] Weisz, C., Lehar, M., Hiel, H., Glowatzki, E. and Fuchs, P.A. (2012) Synaptic transfer from outer hair cells to type II afferent fibers in the rat cochlea. J. Neurosci. 32, 9528–9536.
[126] Wersinger, E., Mclean, W.J., Fuchs, P.A. and Pyott, S.J. (2010) BK channels mediate cholinergic inhibition of high frequency cochlear hair cells. PLoS One 5.
[127] Westerman, L.A. and Smith, R.L. (1984) Rapid and short-term adaptation in auditory nerve responses. Hear. Res. 15, 249–260.
[128] Winslow, R.L. and Sachs, M.B. (1988) Single-tone intensity discrimination based on auditory-nerve rate responses in backgrounds of quiet, noise, and with stimulation of the crossed olivocochlear bundle. Hear. Res. 35, 165–189.
[129] Xiong, W., Grillet, N., Elledge, H.M., Wagner, T.F.J., Zhao, B., Johnson, K.R., Kazmierczak, P. and Müller, U. (2012) TMHS is an integral component of the mechanotransduction machinery of cochlear hair cells. Cell 151, 1283–1295.
[130] Yamane, H., Nakai, Y., Takayama, M., Konishi, K., Iguchi, H., Nakagawa, T., Shibata, S., Kato, A., Sunami, K. and Kawakatsu, C. (1995) The emergence of free radicals after acoustic trauma and strial blood flow. Acta Otolaryngol. Suppl. 519, 87–92.
[131] Zhao, B., Wu, Z., Grillet, N., Yan, L., Xiong, W., Harkins-Perry, S. and Müller, U. (2014) TMIE is an essential component of the mechanotransduction machinery of cochlear hair cells. Neuron 84, 954–967.
[132] Zheng, J., Shen, W., He, D.Z.Z., Long, K.B., Madison, L.D. and Dallos, P. (2000) Prestin is the motor protein of cochlear outer hair cells. Nature 405, 149–155.