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The efferent medial olivocochlear-hair cell synapse

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ABSTRACT

Amplification of incoming sounds in the inner ear is modulated by an efferent pathway which travels back from the brain all the way to the cochlea. The medial olivocochlear system makes synaptic contacts with hair cells, where the neurotransmitter acetylcholine is released. Synaptic transmission is mediated by a unique nicotinic cholinergic receptor composed of α9 and α10 subunits, which is highly Ca^{2+} permeable and is coupled to a Ca^{2+}-activated SK potassium channel. Thus, hyperpolarization of hair cells follows efferent fiber activation. In this work we review the literature that has enlightened our knowledge concerning the intimacies of this synapse.

1. Introduction

Sensory systems respond to stimulus from the surrounding world and use specialized receptor cells at the periphery to translate those stimuli into electrical signals that neurons can interpret. Further processing of sensory stimuli by the central nervous system generates a representation of the outer world called a percept. Sound detection begins when sound waves strike the eardrum, which transmits that physical stimulus to the organ of Corti within the cochlea, the sensory epithelium of the mammalian inner ear. The mechanoreceptor cells of the organ of Corti then transform this mechanical input into electrical signals that are sent to the central nervous system by the auditory nerve (Hudspeth, 1997). Different to vision, touch and the chemical senses, sound transduction is directly modulated right at the periphery by efferent fibers (olivocochlear, OC) that travel in reverse, from the brain back to the inner ear (Guinan, 1996). The present work reviews data which has helped advance our understanding of how the efferent-hair cell synapse operates.

2. Hair cells of the cochlea

Hair cells of the inner ear are very few, when compared to the millions of photoreceptors of the retina: approximately 16,000 sensory hair cells in the human cochlea. In addition, mammalian hair cells do not regenerate after damage, thus it is important to protect the inner ear from insults such us exposure to loud sound (Lim, 1986; Brigande and Heller, 2009), which leads to pathologies such as hearing loss and tinnitus (Eggermont and Roberts, 2004; Elgoyhen and Langguth, 2010). Hair cells are organized in a tonotopic fashion (arranged by frequency sensitivity): those sensitive to high frequency sound are at the basal end nearer to the tympanic middle ear and those sensitive to low frequency are at the apical end of the coiled cochlea (Hudspeth, 1997). Hair cells have a high degree of specialization, with the apical pole carrying the hair bundle specialized for mechanotransduction and the basal pole highly specialized for the release of neurotransmitter. In mammals, a further degree of specialization and division of labor is attained by the presence of two types of hair cells, arranged in rows along the organ of Corti. Inner hair cells (IHCs), of which there are approximately 3500 in each human cochlea, are the primary receptor cells and are innervated by dendrites of the auditory nerve. Outer hair cells (OHCs), approximately 11,000 in each human cochlea, are arranged in three rows and are involved in sound amplification and fine tuning of the basilar membrane (Hudspeth, 1997). They have a much less pronounced afferent innervation, but are the target of an efferent neural pathway, the medial OC (MOC) fibers, that make direct contact at the base of the OHCs (Rasmussen, 1946; Guinan et al., 1983; Warr, 1992; Guinan, 1996). IHCs are also the target of a descending pathway, the lateral OC pathway, but in this case the efferent axons form a synapse on the postsynaptic (afferent) terminal and will not be discussed further here.

3. Outer hair cells and amplification

When sound reaches the cochlea, it produces mechanical vibrations. These are sensed and transduced into an electrical response by motion of the hair bundles of hair cells and activation of the mechanically-gated ion channels. In addition, the hair cells per-

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form work and deliver energy to the system, thus increasing the magnitude of their mechanical input. This amplification of the stimulus constitutes a positive feedback that enhances the sensitivity of hearing (Dallos, 2008; Hudspeth, 2008).

In mammals, OHCs are the principal players providing the feedback underlying cochlear amplification. Two alternative mechanisms for amplification have been described: an old one, also shared by non-mammalian vertebrates, where amplification results from a nonlinearity in the transduction mechanism itself (Chan and Hudspeth, 2005; Jia and He, 2005; Kennedy et al., 2005) and a newer one in which the hair cell receptor potential drives a novel motile process within the lateral membrane of the OHC soma (Brownell et al., 1985; Dallos, 2008). In the latter case, a process known as somatic electromotility (Dallos, 2008), hyperpolarization causes the cell to expand along its longitudinal axis and depolarization causes it to contract. Somatic electromotility of OHCs, as the basis for cochlear amplification, is a mammalian novelty and is mediated by the motor-protein prestin (Zheng et al., 2000) a member of the solute carrier anion-transport family 26 (*SLC26*) (Mount and Romero, 2004; Franchini and Elgoyhen, 2006). Although prestin orthologues exist in non-mammalian vertebrates (Weber et al., 2003; Franchini and Elgoyhen, 2006; Albert et al., 2007; Elgoyhen and Franchini, 2011; Tan et al., 2011), an evolutionary analysis has shown that only mammalian prestin shows strong signatures of positive selection, most likely underlying the acquisition of amino acid substitutions to account for the motor function (Franchini and Elgoyhen, 2006; Schaechinger and Oliver, 2007; Elgoyhen and Franchini, 2011; Tan et al., 2011). The contribution of sterocilia- vs somatic-based mechanisms for amplification (or the interaction of both processes) in mammals is still a matter of debate.

4. Efferent innervation of the mammalian cochlea

While OHC respond to auditory stimulation and modulate the micromechanics of the cochlear partition independent of central nervous system control, they are targets of efferent or centrifugal fibers which originate in the brain (Guinan, 1996). Olivocochlear efferent neurons permit the central nervous system to control the way that sounds are processed in the auditory periphery. Lateral OC efferents originate from small neurons in or around the lateral superior olivary nucleus and project predominately to the IHC area of the ipsilateral cochlea. They make synaptic contacts on the radial dendrites of Type I auditory afferents postsynaptic to the IHCs. MOC efferents originate from larger neurons located ventral, medial and anterior to the medial superior olivary nucleus and project mostly contralaterally to make synaptic contacts directly onto OHCs (Rasmussen, 1946; Warr, 1975, 1992). In addition, before the onset of hearing, OC efferents make functional transient direct synaptic contacts with IHCs (Glowatzki and Fuchs, 2000; Katz et al., 2004).

Efferent inhibition can be activated by sound presented to the contralateral ear (Kujawa et al., 1994). However, most studies of efferent inhibition have been performed by electrical stimulation of efferent axons and measurement of effects in the cochlea (Guinan, 1996). Medial efferents are myelinated, whereas lateral efferents are not. Myelinated fibers have a lower threshold for extracellular current stimulation than do unmyelinated fibers. Moreover, MOC axons travel nearer to the floor of the fourth ventricle where stimulating electrodes are usually placed. Taken together, these observations imply that electrical stimulation activates medial but not lateral efferents. Thus, most efferent effects that have been described so far are attributed to the MOC system (Guinan, 1996).

Electrical stimulation in the floor of the fourth ventricle activates contra- and ipsilateral axons of the MOC efferents to reduce the amplitude of the compound action potential ('N1') produced by a brief acoustic stimulus (Galambos, 1956), especially at low sound levels. Moreover, basilar membrane motion is diminished by efferent activity (Murugasu and Russell, 1996; Russell and Murugasu, 1997). These effects most likely result from an inhibition of the motor function of OHCs, which is required for sensitive IHCs responses, thus indicating that MOC activity reduces amplification. Efferent inhibition also affects the cochlear tuning mechanism. Thus, efferent activity suppresses the response of a single auditory nerve fiber such that a louder tone is required to produce a threshold response (Wiederhold and Kiang, 1970; Gifford and Guinan, 1987). This threshold shift is maximal at the fiber's characteristic frequency, but smaller for frequencies above and below the characteristic frequency. This results in a broader tuning curve and therefore a diminished frequency selectivity of the afferent neuron.

The ultimate effect and functional role/s of MOC activity on audition is still a matter of active research. This include, the control of the dynamic range of hearing (Guinan, 1996), improvement of signal detection in background noise (Dolan and Nuttall, 1988; Winslow and Sachs, 1988; Kawase et al., 1993), mediating selective attention (Oatman, 1976; Delano et al., 2007), and protection from acoustic injury (Liberman, 1991; Rajan, 2000; Taranda et al., 2009b).

5. Neurotransmitters at the MOC-hair cell synapse and hair cell responses

Acetylcholine (ACh) is the main neurotransmitter released at the MOC–OHC synapse and for which a clear hair cell response has been described (Housley and Ashmore, 1991; Fuchs and Murrow, 1992a,b; Fuchs, 1996). The first hints of the cholinergic nature of the cochlear efferents were provided by the histochemical reaction for acetylcholinesterase labeled processes in the intact cochlea, which disappear in surgically deefferented cochleas (Churchill et al., 1956; Schuknecht et al., 1959). Extensive biochemical and immunohistochemical studies have further supported the hypothesis that ACh is the main neurotransmitter of the MOC system (Eybalin, 1993). At the electron microscopic level, choline acetyltransferase-like immuno-labeled patches were shown to correspond to large axosomatic synapses on the OHCs (Eybalin and Pujol, 1987).

Antibodies made directly against either gamma amino butyric acid (GABA) or its synthesizing enzyme glutamate decarboxylase, show immunoreactivity in cell bodies located in the superior olivary complex and in terminals located below hair cells, suggesting GABA as a second neurotransmitter of the efferent system (Eybalin, 1993). Fibers forming large axosomatic synapses with the OHCs would belong to the medial efferent system (Eybalin and Altschuler, 1990; Maison et al., 2003a). ACh and GABA might be colocalized in the same neurons. Thus, immunoelectron microscopy studies provided strong evidence for choline acetyltransferase and glutamate decarboxilase colocalization in efferent terminals on OHCs throughout the rat cochlea (Dannhof et al., 1991). A study in mice suggests the complete congruence of GABAergic and cholinergic markers in the OHC area (Maison et al., 2003a). The role of efferent gabaergic neurons to OHCs is mostly unknown.

Based largely on chemical neuroanatomical studies, the neuropeptide calcitonin gene-related peptide (CGRP) has been proposed as a neurotransmitter or neuromodulator in the auditory system (Kuriyama et al., 1990). CGRP-containing terminals have been identified in radial afferents beneath IHCs and medial efferent synapses with OHCs (Tohyama et al., 1989; Kuriyama et al., 1990; Cabanillas and Luebke, 2002; Maison et al., 2003a). However, the