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Centrifugal control in mammalian hearing

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Summary

1. Centrifual contol of many sensory systems is well established, notably in the γ motorneuron of skeletal muscle stretch receptors.

2. Efferent (olivocochlear) innervation of the mammalian cochlea was first established through anatomical studies. Histological studies confirmed synaptic terminals in contact with hair cells and afferent dendrites.

3. Electrophysiology has elucidated the cellular mechanisms of efferent modulation in the cochlea.

4. The system has potential roles in noise protection, homeostatic feedback control of cochlear function and signal processing. There is some evidence in support of each, but also contraindications.

5. It is concluded that the role of the olivocochlear innervation is still contentious, but on balance the evidence appears to favour a role in enhancing signal detection in noise.

Introduction

The general concept of centrifugal or efferent control of sensory processing is familiar to physiologists and neuroscientists. Afferent neural pathways carry information to the higher centres about particular forms of stimulus energy, transduced in the sense organs and encoded as action potential firing in populations of neurons. There are also parallel descending, centrifugal, or efferent pathways at most stages by which higher centres influence and shape the activity at lower levels. These pathways are of interest because they provide a mechanism for the brain to modify sensory experience and an understanding of their action and role is clearly important for a full understanding of the link between physical events in the nervous system and perceptual performance. In addition, from the pathological perspective, there is as yet untapped potential for therapies that exploit the inherent properties of these pathways and a little researched, but potentially important area, is how malfunction of these descending pathways may contribute to sensory deficits and disturbances.

Some descending pathways operate wholly within the central nervous system. For example, descending inputs from sensory cortex are known to modify information processing in thalamic and other nuclei in a number of sensory systems. A familiar example is provided by the descending neural pathways that can modulate transmission of ascending pain information.[1] Well studied examples exist in other systems including the mammalian auditory system and visual systems.[2] Some centrifugal pathways influence sensory processing by acting even before the most peripheral sensory transduction events in the sense organ. Generally these pathways work by modulating the stimulus energy reaching the sensing elements of the sense organ itself. Familiar examples in the visual system are the control of the pupil and the lens of the eye. In the auditory system the external ear or pinna in some animals is highly mobile and this plays a special role in sound localization.[3] The tiny *tensor tympani* and *stapedius* muscles attached to the middle ear bones are also under centrifugal motor control, altering the stiffness of the ossicular chain to reduce sound transmission to the inner ear, particularly at low frequencies.[4]

This review focuses on auditory centrifugal pathways that innervate the sensory structures of the cochlea and that alter details of the primary afferent responses to sound. An early example of this kind of centrifugal control in which the peripheral sense organ itself is modulated, comes from the work of Kuffler & Eyzaguirre[5] who made an intensive study of the crustacean stretch receptor and the efferent neurons that regulate the response of the sensory afferent neuron to mechanical stimulation. The most familiar and arguably the best studied vertebrate example comes from the sensorimotor system. The length-sensitive muscle spindle organ with its afferent sensory neurons is also innervated by γ efferent motor neurons whose action is to contract the distal ends of the muscle spindle, enhancing the spindle afferent firing. Numerous studies beginning in the 1950's showed that this efferent system is activated during voluntary muscle contraction and serves to maintain the afferent spindle discharge during active muscle shortening. This shift in the dynamic range of the sense organ during active muscle shortening ensures that there is a continuing stream of precise length-related afferent sensory information going to the movement control centres during voluntary movements.[6,7]

History of auditory efferents

Efferent innervation of the vertebrate hearing organ, the cochlea, was first demonstrated by Rasmussen in the 1940s.[8] Rasmussen lesioned the auditory pathways at different levels and used histological techniques to look for degenerating nerve fibres. He concluded that neurons located in the brainstem regions called the superior olivary complex, sent their axons out through the vestibular branch of the VIIIth cranial nerve, joined the cochlear branch in the anastomosis that had been described by Oort in 1918,[9] and

entered the cochlea. Rasmussen described both crossed and uncrossed projections and called the system of efferent axons the olivocochlear bundle (Figure 1A). Not long after this, Galambos electrically stimulated the olivocochlear axons and reported that the firing of auditory nerve afferents was suppressed.[10]

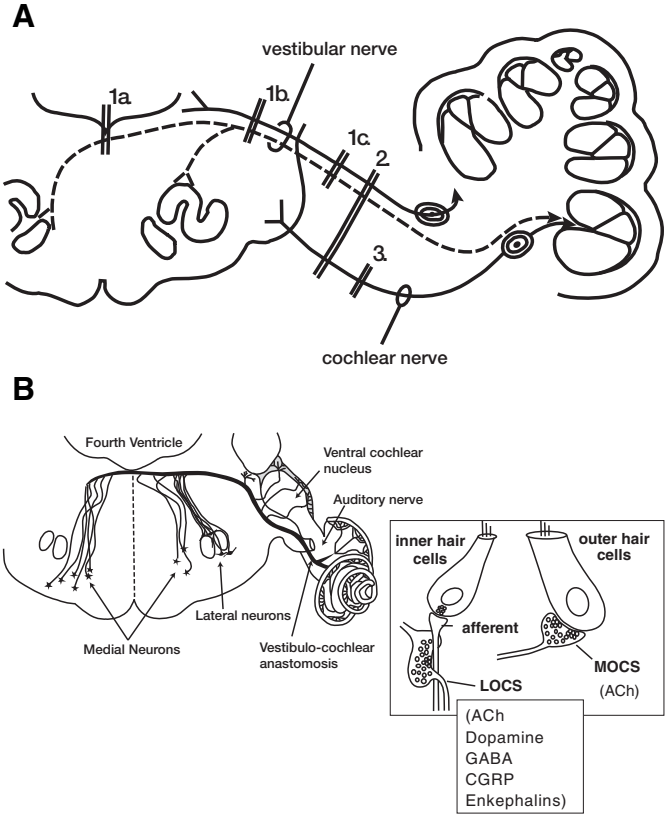

Figure 1. ***A:*** *Summary of the course of afferent (solid lines) and efferent (dotted lines) fibres of the auditory brainstem. Efferent olivocochlear axons exit the brainstem in the vestibular banch of the VIIIth neve and cross to the cochlear branch at the anastamosis of Oort. (Adapted from Rasmussen, 1953[8]).* ***B:*** *Organization of medial (MOCS) and lateral (LOCS) olivocochlear systems, their cochlear terminations and putative neurotranmsitters. (Adapted from Spoendlin, 1972[11] and Warren & Liberman, 1989[35]).*

At this point the non-specialized reader needs to be oriented with a few key facts about the structure and function of the mammalian hearing organ. There are two sets of mechano-sensitive hair cells, the inner and outer hair cells, with very different roles in auditory transduction which will be considered again later. In all mammals looked at so far, 90-95% of the primary afferent neurons are hooked up to the inner hair cells at chemical synapses.[11-13] The vibration of the basilar membrane caused by sound provides the mechanical drive to the hair cells that opens their stretch-activated transduction channels. The driving force for the movement of ions through the transduction channels is a combination of the intracellular potential of the hair cells and the large (+90mV) extracellular voltage found in the *scala media* above the hair cells – the so-called endocochlear potential that is produced by electrogenic pumps in the transporting epithelium known as the *stria vascularis*.[14] Finally, the micromechanical behaviour of the cochlea is such that there is a systematic map of sound frequency along the organ, with hair cells and nerve fibres at the base responding to high frequency sounds and those further along towards the cochlear apex responding to progressively lower frequencies.

The details of the olivocochlear innervation of this organ were not unravelled until some 20 years after Rasmussen's original description of the olivocochlear fibre bundles. The advent of the electron microscope revealed the presence of an extensive efferent innervation with vesicle-filled efferent terminations on both receptors cells and on afferent nerve dendrites (Figure 1B). Beneath the inner hair cells vesicle-filled varicosities are found in close contact with afferent dendrites (the type I afferent neurons of the auditory nerve). In contrast, in the outer hair cell region, enormous vesicle-filled nerve endings are found actually on the receptor cells themselves. The outer hair cells themselves do possess an afferent innervation (the Type II afferent neurons) which comprises only 5-10% of the afferent cochlear neural output. However, the relationship, both anatomical and functional, between this sparse outer hair cell afferent innervation and the massive olivocochlear innervation of the outer hair cells is unclear (see for example Thiers, Nadol & Liberman, 2008[15]) and for simplicity this has been omitted from Figure 1B and from the remainder of this review.

The next major step in our understanding of the anatomical organization of the efferent innervation of the cochlea began with the autoradiographic studies of Guinan, Warr and colleagues.[16,17] They showed that injections of radio-labelled amino acids into medial zones of the superior olivary complex resulted in bilateral labelling over the outer hair cells, whereas injections into the lateral superior olive resulted in mainly labelling over the inner hair cell region. These studies were combined with the then new methods of retrograde labelling of the cell bodies of origin of the cochlear efferent innervation and as a result, Rasmussen's original division of crossed and uncrossed components was substantially modified. As shown in Figure 1B we now describe the olivocochlear efferent pathway as comprising a medial olivocochlear system (with both crossed and uncrossed components) with large cell bodies located in medial and ventral olivary regions and innervating the outer hair cells of the cochlea, and a lateral olivocochlear system of small cell bodies in and around the lateral superior olive and innervating mainly afferent dendrites beneath the inner hair cells of the ipsilateral cochlea. With minor variations this basic organization has been confirmed in several mammalian species. Various studies have shown that the large outer hair cell endings are primarily cholinergic whereas the axo-dendritic synapses beneath the inner hair cells contain a range of transmitters; acetylcholine, dopamine, enkephalins and other peptides.[18,19]

Functional effects of efferent activation

The early studies by Galambos[10] showed that stimulating the olivocochlear system resulted in suppression of auditory nerve afferent responses to sound. This stimulation can be achieved by placing stimulating electrodes at the floor of the IVth ventricle, at the level of the facial genua where the medial efferent axons coalesce to form the olivocochlear bundle. Various measures of cochlear function can be performed relatively easily in the intact animal. We can, for example record with microelectrodes the d.c. voltage in *scala media* (the endocochlear potential), and with gross electrodes in electrical continuity with the cochlear tissues we can obtain informative measures of the afferent nerve and hair cell responses to sound stimulation.

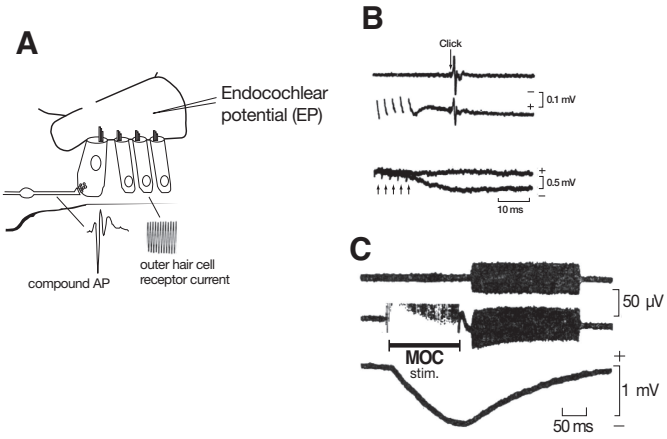

Figure 2. Effects of electrical stimulation of medial efferent axons on cochlea physiology. A: *Schematic illustration of sites of measurement of various cochlear potentials.* ***B:*** *suppression of compound action potential response to a click stimulus (top two traces) and simultaneously recorded* scala media *d.c. voltage (lower trace).* ***C:*** *simultaneous recording of cochlear microphonic potential (upper two traces -note increase caused by MOC stimulation) and fall in* scala media *voltage (lower trace). (Parts B and C adapted from Desmedt & Robertson, 1975[20])*

Figure 2 shows results obtained in the cat with John Desmedt in 1972.[20] After a train of shocks to the efferent axons, the compound cochlear action potential response to a brief acoustic stimulus is reduced in amplitude as described by Galambos. However, there are other changes that show that this effect is mediated by the efferent terminations on the outer hair cells (i.e. the medial olivocochlear system). Along with the suppression of the afferent nerve response there is a drop in the voltage above the hair cells. The endocochlear potential, normally about 90mV positive with respect to the rest of the animal, falls by up to 3mV as a result of efferent stimulation. In addition, there is a parallel increase in the externally recorded receptor current evoked by a tonal stimulus, the so-called cochlear microphonic. (Note that although the cochlear microphonic is recorded as a fluctuation in voltage between a cochlear electrode and a remote reference, it is in fact a reflection of the oscillating rise and fall in current through the hair cells, modulated by the opening and closing of their apical mechano-sensitive transduction channels.)

These latter two effects are explained by a drop in the basolateral resistance of the outer hair cells as a result of the action of the medial olivocochlear system efferent transmitter acetylcholine. We know that the α9/10 variant of the acetylcholine receptor of the outer hair cells is calcium permeable and its activation by the medial efferents leads to opening of Ca^{2+}-activated K^+ channels in the outer hair cell membrane.[21] The drop in outer hair cell resistance drains charge from the *scala media* causing the drop in its d.c. voltage, and by simultaneously increasing the standing current through the outer hair cells, also results in an increase in the modulation of external current flow by a sound stimulus as it alternately opens and closes the stretch-activated transduction channels at the top of the cells (Figure 3A).

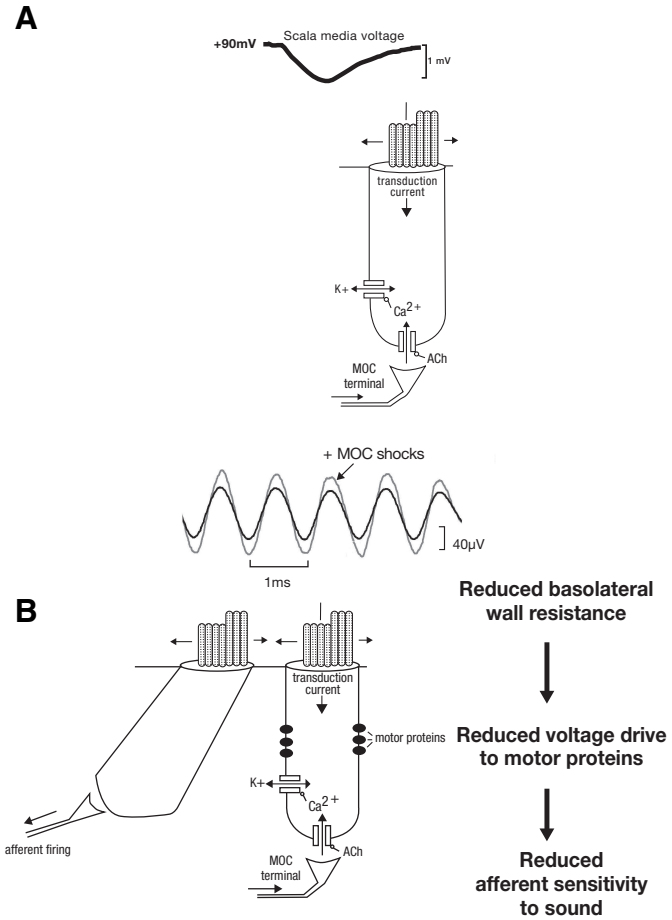

Figure 3. A: Schematic illustration of the MOC action on outer hair cell nicotinic ion channels. *Opening of K+ channels causes drop in* scala media *voltage and increase in externally recorded receptor current (measured as cochlear micophonic potential-see text for explanation).* ***B:*** *Action on outer hair cells affects cochlear amplifier function and reduces sensitivity of inner hair cell primary afferent neurons.*

So all the action in the cochlea caused by medial

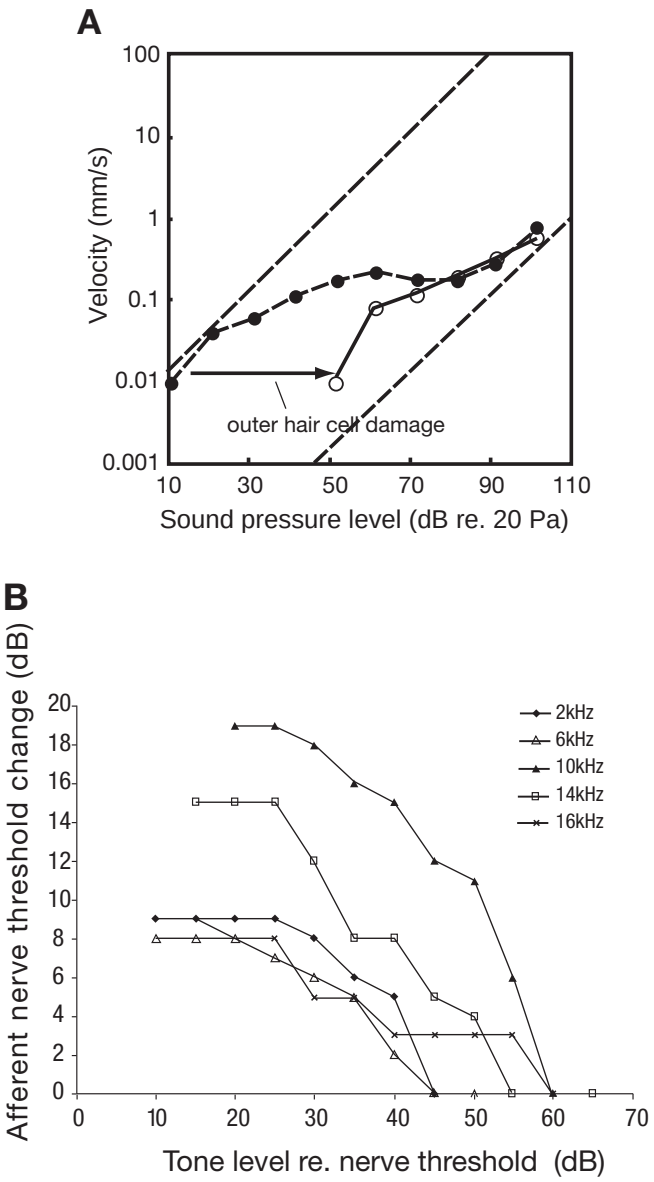

Figure 4. A: *Examples of nonlinear vibration of basilar membrane in normal cochlea (solid circles) and in the same cochlea after loud sound exposure that depresses function of outer hair cell cochlear amplifier (open circles). Note that high intensity vibration is not affected, but sensitive portion of input-output curve is lost. (Adapted from Patuzzi, Johnstone & Sellick, 1984[25]).* ***B:*** *effect of MOC stimulation on afferent nerve thresholds to sound stimulation of various intensities. Note lack of effect on responses at medium and high stimulus levels, consistent with MOC action on outer hair cell cochlear amplifier contribution to low level sensitivity. (from Seluakumaran, 2007[26]).*

efferent stimulation is occurring at the outer hair cells, and yet 90-95% of the afferent neural output of the cochlea comes from the inner hair cells. To understand how the afferent responses to sound from the inner hair cells are suppressed by action on the outer hair cells, we have to turn to the modern view of cochlear physiology, much of which was worked out with major contributions from the Perth laboratory from about 1982 onwards (for reviews see Patuzzi & Robertson, 1988[22] and Yates *et al.* 1992[23]). Transduction currents through the outer hair cells drive a fast electromechanical motor response of the hair cells that is responsible for amplifying vibration of the sense organ. This outer hair cell action, referred to as the "cochlear amplifier",[24] is an essential element in a positive feedback loop that determines the sensitivity to sound of the afferent neurons connected to the inner hair cells. The drive to the outer hair cell electromechanical motor is provided by the voltage drop across the basolateral wall of the outer hair cells and this is reduced when medial efferent action lowers the basolateral wall resistance of the outer hair cells. The overall mechanical gain of the cochlea is reduced as a consequence and the sensitivity to sound of the inner hair cells and their associated primary afferents is reduced (Figure 3B).

There is an important basic property of this mechanism of efferent-mediated suppression. The outer hair cell active feedback loop has a limited dynamic range as shown here in measurements made of the organ vibration in the Perth lab (Figure 4A). At the most sensitive frequency the vibration amplitude near threshold grows roughly linearly with sound intensity but then flattens off markedly as the active amplification reaches saturation. At much higher sound levels vibration is dominated by the passive linear mechanical properties. This is shown dramatically by the data in which loud sound was used to damage the outer hair cells.[25] This results in a loss of the sensitive outer hair cell-assisted vibration whereas the higher level linear vibration is untouched. The consequence of this is that in the normal cochlea, the medial efferent action on the cochlear amplifier (and hence on afferent neuron sensitivity to sound) is most effective at low to medium sound levels as shown in Figure 4B. Electrical stimulation of the medial efferent axons causes a maximum suppression of the afferent nerve response equivalent to a sound pressure reduction of about 20dB, but this suppression declines to almost nothing for sound levels only 40-50dB above threshold.[26] This issue of the limited dynamic range of medial efferent effects is pertinent when considering the possible roles of the system in hearing.

Medial efferent neuron activation can also affect the spontaneous firing rate of primary afferents. This can also be explained by the effect on the basolateral resistance of the outer hair cells. The drop in the standing voltage above the hair cells results in a hyperpolarization of the inner hair cell membrane potential and hence reduced spontaneous transmitter release. It has been shown by independently altering the *scala media* voltage that a change of only a few millivolts in this d.c. voltage is sufficient to cause measurable changes in spontaneous afferent firing.[27]

What is the mode of action of the lateral olivocochlear system that terminates on the primary afferent dendrites? We would expect this system to modulate primary afferent excitability independently of the cochlear electromechanical gain. In fact it has proved extremely difficult to demonstrate reliable effects of electrical

stimulation of this component of the efferent system probably because of its very small diameter unmyelinated axons and the diverse range of neurotransmitters that it employs. Lesions of the nucleus of origin, the lateral superior olive, have been reported to have a variety of effects on compound afferent nerve activity.[28-30] Although suggestive, some of these effects may not reflect an immediate loss of tonic drive but rather a longer term effect of loss of neuromodulatory input. Data from our own lab (Garrett unpublished results) show that selective antagonists to receptors for one of the lateral system transmitters dopamine, when perfused into the cochlea, cause reductions in the afferent nerve responses to sound. This suggests that there is a tonic excitatory action of some lateral system efferents on the primary afferent dendrites beneath the inner hair cells, but data from other labs suggest that both inhibitory and excitatory actions are possible.[28-33]

Functional organization of inputs

What is known about the normal synaptic inputs to the efferent neurons in the brainstem? First, there are inputs at the brainstem level that are driven by sound. Recordings of the activity of single efferent axons combined with intracellular tracing methods, have shown that individual efferent neurons respond sensitively to sound and show responses that are highly frequency selective, with each neuron tuned to a specific sound frequency in a manner very similar to the sharp tuning of primary afferents. Single efferents responded to sound in one or other ear and sometimes both. These responses to sound arise because of connections to the efferent neurons in the brainstem from either the ipsilateral or contralateral cochlear nucleus which have been demonstrated using double labelling methods.[34]

Numerous studies have shown that acoustic activation of these brainstem inputs to medial efferent neurons, can result in measurable effects on cochlear responses, in a manner consistent with a reduction in the gain of the outer hair cell amplifier.[35]

Most important of all, in the microelectrode studies of single efferents, it was possible to map the region of the cochlea innervated by single medial efferents that had been characterized physiologically. The data from such experiments showed that the position along the cochlea where individual medial efferent neurons terminated on outer hair cells closely corresponded to that expected from the sound frequency to which they were most sensitive, based on the well-known place-frequency map of the cochlea. These findings established that medial efferent neurons are able, in principle, to influence outer hair cell function in a more or less precise, tonotopically organized feedback manner.[37]

No-one has succeeded in recording from single lateral system neurons so we do not know how they respond to sound, but indirect evidence suggests that a similar precise organization exists here too. Robertson *et al.*,[38] injected the fluorescent retrograde label DY into the cochlea and looked at the location of labelled cell bodies in the brainstem nucleus of origin of the lateral system. Injections into basal cochlear regions (the high frequency parts of the place-frequency map) labelled efferent cell bodies in a region of the lateral superior olivary nucleus that is known to receive afferent input from high frequency cochlear regions. Injections into other turns of the cochlea labelled efferent neurons located in systematically lower frequency coding zones of the brainstem nucleus. These data strongly suggest that, like the medial efferents, the lateral efferents can also act in a precise feedback manner to alter cochlear neural output from the same frequency region from which they receive their input.

Do the efferent neurons receive synaptic input from higher centres? Medial and lateral olivocochlear neurons are contacted by noradrenergic terminals that arise from the *locus coeruleus*[39,40] and these inputs may activate both medial and lateral efferent systems.[41] Substance P–positive synaptic terminals are found on medial olivocochlear neurons and these possibly arise directly from substance P-positive neurons in the primary auditory cortex.[42,43] Electrical stimulation of the inferior colliculus results in reduction of primary afferent nerve responses to sound and increases in outer hair cell receptor current consistent with activation of medial efferents by descending projections from the midbrain, although the nature of the neurotransmitter involved is still unknown.[44] Xueyong Wang carried out a series of extensive studies on olivocochlear neurons in brainstem slices. The neurons were identified as efferent by pre-labelling them using intracochlear injections of retrograde label. Wang recorded the responses of these identified neurons to a range of transmitters and agonists. In both sharp electrode and whole cell patch recordings, medial efferents were found to be strongly excited by noradrenaline and substance P.[45-48]

In summary, although there are many details still to be unravelled, the olivocochlear pathways comprise an organized set of projections to the cochlea, driven by auditory brainstem inputs and probably by a variety of higher centres as well. The medial and lateral systems offer two different ways of regulating cochlear neural output, either by altering outer hair cell gain and the *scala media* d.c. voltage, or by directly manipulating the excitability of the afferent dendrites. Furthermore the system does not constitute a diffuse non-specific projection. On the contrary, the innervation of the cochlea and the wiring in the brainstem is such that efferent neurons innervate the discrete cochlear regions close to the region from which they receive their most effective acoustic input.

Role in hearing

One possible role is in early development of the peripheral sense organ. Efferent innervation of the cochlea is present in neonates well before the onset of hearing[49] and it has been shown that early de-efferentation results in a failure of the normal outer hair cell amplification process to fully develop.[50] This effect could be because of a loss of trophic factors supplied by the efferent endings.

It is important however to stress that the centrifugal

innervation is not required in any way for the normal baseline operation of the normal adult organ. The basic functional properties of the cochlear afferent output are achieved without neural networks, by the micromechanical behaviour of the organ and its receptors cells. Interrupting the centrifugal pathways acutely in adult animals does not interfere with this basic operation. So if the efferents have a role it must be in altering cochlear function under particular circumstances. The roles which have been attributed to the efferent system in the mature cochlea are: 1) protection from acoustic overstimulation; 2) homeostatic regulation; 3) enhanced signal processing. These are considered in turn below.

Protection from overstimulation

Excessive exposure to loud sound can cause both temporary and permanent loss of neural sensitivity in the cochlea. This is believed to be essentially a modern problem created by the industrialization of society – noise-induced deafness was first described as "boilermakers' deafness". For most types of loud noise exposure, we know from a host of experiments, that the deafness is the result of either temporary or permanent damage to the outer hair cells and the loss of their unique amplification function. In our laboratory, Alan Cody[51] first showed in an animal model that binaural exposures to loud sound resulted in less cochlear damage than monaural exposures. Cody showed that this binaural effect was eliminated if animals were administered strychnine prior to the loud noise exposure, implicating the olivocochlear pathways. Ramesh Rajan followed up these observations in his PhD work in Perth and showed conclusively that stimulation of the olivocochlear efferents protects the cochlea from loud sound induced damage.[52,53]

Patuzzi & Thompson[54] followed up these studies by looking at the relationship between the loss of neural sensitivity and the outer hair cell receptor current after loud noise exposure. Their results indicated two things; first that protection is mediated somehow by protecting the outer hair cell receptor current from the damaging effect of loud sound and second, that individual variations in the neural threshold change resulting from loud sound exposure may be a result of individual variations in the effectiveness of the efferent protection.

There are two puzzling aspects to the protective effect. The first is to do with the mechanism. Because of the saturation of the outer hair cell amplifier, the classical medial efferent effect on outer hair cells should be completely ineffective at the sort of intensities of sound employed to produce the acoustic trauma. If efferent activation does protect by reducing the basilar membrane vibration amplitude during the loud sound it is unclear how this is achieved. It is possible that the efferent protective effect is mediated not by an effect on vibration amplitude, but by triggering some intracellular pathway in the outer hair cells that leads to protection of the outer hair cell transduction current. It is known that there are a number of other slower Ca^{2+}-dependent processes in outer hair cells. These are thought to result in slow cellular length changes mediated by conventional contractile proteins. Such length changes might affect parameters such as the set point of the hair bundle angle which could have an important influence on the effect of loud sound on the transduction channels, resulting in a protection of the transduction currents.

In addition to this unresolved issue of the mechanism of protection, the functional significance of the protective effect is unclear. It has been argued that it is unlikely that the efferent innervation of the cochlea could have evolved for this purpose in a pre-industrial world.[55] It is therefore possible that the protective effect is an accidental result of efferent-mediated processes that have other functions.

Homeostatic regulation?

The cochlea presents a classic example of the need for physiological regulation. Two fundamental aspects of cochlear neural output need to be tightly regulated. One is the sensitivity to sound of the primary afferents emanating from the inner hair cells and the other is their spontaneous firing rate.

Sensitivity to sound is highly dependent on the outer hair cell electromechanical gain. This gain needs to be controlled carefully because it forms part of a positive feedback loop that is inherently in danger of running out of control and causing spontaneous mechanical oscillation. We know that such runaway oscillations can occur because of the presence of otoacoustic emissions in which sound energy can be spontaneously emitted from the ear, sometimes accompanied by the perception of phantom sounds.[56]

Spontaneous afferent firing rate also needs to be carefully regulated. Any changes in spontaneous firing rate could result in confusion in the central nervous system as to what constitutes sound and what constitutes silence and potentially could give rise to phantom auditory sensations or tinnitus. On the presynaptic side, we know that a change in inner hair cell membrane potential of less than 1mV is sufficient to alter spontaneous firing rates in primary afferents. Because of its influence on inner hair cell membrane potential, the *scala media* voltage needs to be tightly controlled. On the post-synaptic side, changes in afferent dendrite excitability could lead to altered spontaneous firing and in addition could lead to hypersensitivity to sound or to sudden deafness. Figure 5, inspired in part by Patuzzi[57] illustrates the ways in which lateral and medial efferents could provide feedback regulation of these two parameters of cochlear neural output. Both spontaneous and driven afferent firing rates provide the inputs to these feedback circuits.

The problem with these plausible theoretical notions of a long term homeostatic role for the olivocochlear efferents, is that there is little compelling evidence to support them. Adult animals whose cochleae have been completely de-efferented show no obvious fluctuations or gross abnormalities of neural threshold. In cats it has been reported that the mean spontaneous firing rate across all primary afferents falls some weeks after de-efferentation,[28]

and in mice with lesioned lateral superior olivary nuclei, there is a reduction in the amplitude of the auditory nerve response to moderate intensity sounds.[58] As argued already however, these effects could represent a loss of some trophic influence rather than a loss of ongoing neural feedback control. Similarly, human patients in whom the efferent input to the cochlea has been severed in the course of vestibular nerve section as a treatment for intractable vertigo, show no significant alteration in standard measures of threshold and a host of other audiometric parameters.[59,60] The incidence of phantom auditory sensation (or tinnitus) in such patients has also been investigated and the results are interesting but inconclusive. Such patients frequently suffer from tinnitus before surgery. About equal numbers of patients show an amelioration, a worsening, or no change in their tinnitus after de-efferentation.[61]

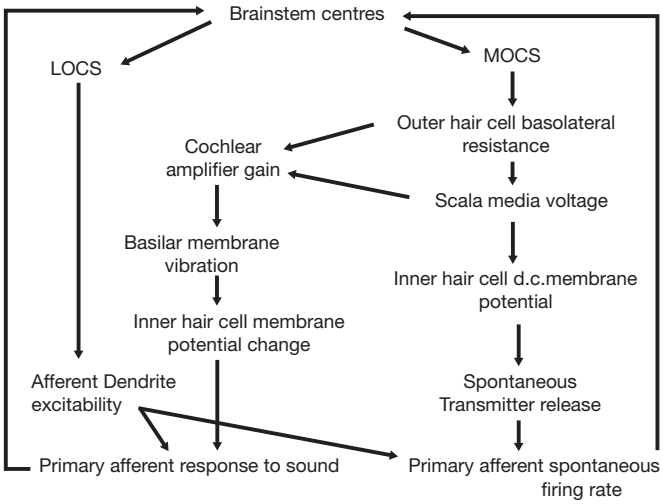

Figure 5. *Schematic illustration of the various ways in which MOCS and LOCS pathways could act in a homeostatic feedback mode to regulate afferent nerve firing.*

It is perhaps not surprising that animal experiments and clinical data have not provided compelling evidence for a homeostatic regulatory role for olivocochlear efferents. There are almost certainly other homeostatic mechanisms that may be operating either in tandem or as backups. For example, Housley and co-workers in Auckland have extensively studied purinergic signalling pathways in the cochlea and shown that the voltage in the *scala media* may be controlled by P2X receptor ion channels allowing more or less current drain through the cellular boundaries of the *scala media* compartment. In addition, P2Y receptors in the ion pumping cells of the stria may help to regulate the voltage by directly controlling the electrogenic ion pumping.[62] O'Beirne and Patuzzi[63] provide evidence that the outer hair cell is itself a complex homeostatic machine with multiple feedback loops in which membrane potential, voltage and stretch-activated ion channels, intracellular calcium, slow hair cell length changes and hair bundle operating point all interact with the *scala media* driving potential to regulate overall gain and *scala media* voltage. In this scheme of things, the medial efferent action on outer hair cell conductance is only one of many control elements.

Despite this uncertainty about a homeostatic role for the olivocochlear efferents we do have some quite compelling evidence from animal studies, that abnormal levels of efferent activity can actually produce peripheral hearing pathology.[36,64] Some animals show a pre-existing hearing losses of 20dB or more in a restricted frequency range (assessed by measuring the thresholds of the afferent nerve response to tones). Remarkably, when the medial efferent axons in the brainstem are cut, the hearing thresholds show substantial and immediate recovery of sensitivity, in some cases to normal levels. Such results clearly show that spontaneous tonic activity of efferents can result in reversible hearing losses in limited regions of the cochlea. We do not know what factors trigger such abnormal efferent firing, but these results are interesting from the perspective of spontaneous fluctuations and sudden hearing loss in humans. Perhaps some of these cases are due to hyperactivity in efferent pathways to the cochlea and the hearing loss might be alleviated by pharmacological agents that block peripheral efferent action.

Signal detection and discrimination?

The final postulated role for the olivocochlear efferents is the one that on balance, I favour. Listening in the real acoustic world is a messy business as anyone trying to follow a conversation in a noisy restaurant knows. There are many mechanisms by which the auditory system strives to select signals of interest from the extraneous background noise, but for some years now it has been proposed that the medial efferent neurons are one element in this important aspect of auditory signal processing.

Winslow & Sachs[65] first showed the neural basis of this proposed role of the medial efferents. Figure 6A shows a typical input-output curve of a single primary auditory afferent showing its firing rate in response to a pure tone of different intensities. There is a spontaneous firing rate in the absence of sound and above threshold a rapid increase in firing to reach a saturation rate. When the medial efferents are activated, the curve is shifted to the right because of the action of the medial efferents on the outer hair cell gain.

The situation in the presence of background noise is very different (Figure 6B). Note firstly that the neuron increases its background firing rate in response to the noise. This results in increased adaptation of the neuron and a consequent reduction in the maximum firing rate. The result is that the range of output firing rates in response to the tone is now significantly compressed and the slope of the input output curve decreases. There is also a shift to the right because the background noise partly "jams" the outer hair cell amplifier and reduces cochlear sensitivity. This interaction between background noise and a tone signal is known as "masking" and it is one of the major problems that we encounter in trying to listen to signals such as speech in the presence of competing noisy backgrounds.

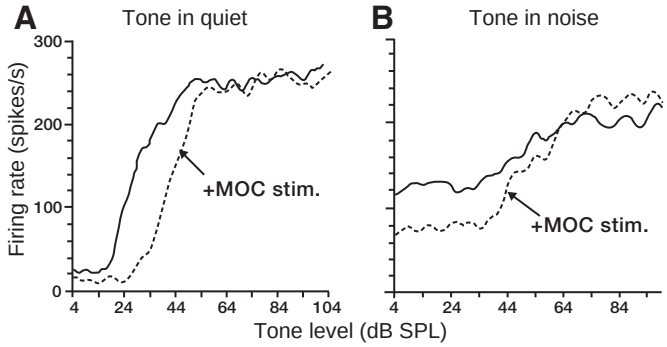

Figure 6. *Effects of MOC electrical stimulation on input-output curves of single auditory afferent neuron in quiet and in presence of background noise. (Adapted from Winslow & Sachs, 1987[65]).*

Now, when medial efferents are activated in the presence of masking noise, the effect on the input-output curve to tones is rather different from that in quiet. The efferents cause a suppression of the response to the relatively low level background noise, so the background firing rate is reduced. As explained earlier, the efferents have little or no effect on the responses of the neuron to the higher level tones, and in addition the drop in firing to the noise causes reduced adaptation, resulting in an improvement in the maximum firing rate. The net result is a substantial recovery of the output dynamic range and the slope of the input-output curve, a phenomenon that has been referred to as "anti-masking". We have investigated this anti-masking effect in the inferior colliculus and cochlear nucleus. Although the input-output curves of these neurons vary in shape, some being similar to those of primary afferents and others showing various degrees of non-monotonicity, we still found strong evidence of the expected anti-masking in many neurons.[66,67]

What evidence is there that this anti-masking action of the efferents is translated into meaningful behavioural performance? The vestibular neurectomy patients lacking olivocochlear efferents, referred to before, showed a spectacular absence of any effects of the de-efferentation on basic auditory function. However, they did show a change in performance in a particular listening task. In normal subjects, accuracy in detection of a tone in noise is much better when the frequency of the tone is "expected", either because that frequency is presented more often than others, or because the tone to be detected is preceded by a clearly audible cue of the same frequency.[68] This effect has been described as an "attentional filter", the idea being that the auditory cue sets in motion some unspecified process that directs attention to the cue frequency and so improves the detection of matching probes. In de-efferented human subjects, this attentional filter has been found to be absent, with cue and non-cue frequencies being detected with equal probability.[59,60]

We have recently shown that in normal subjects with completely randomized cue and probe frequency combinations, there is still a significant effect of a cue, equivalent to about a 3dB improvement in probe detection when cue and probe are matched.[68] This is an important result because it shows that a component of the cue effect is available on a trial-by-trial basis, and is not simply the result of some built up expectation of a particular frequency being presented. In further studies Tan has shown that in subjects with a hearing loss resulting from outer hair cell damage, remembering that the outer hair cells are the targets of the medial efferents, the enhancing effect of the cue was absent at most frequencies studied. So we think that the neurectomy data of Scharf[59,60] and our own psychophysical results constitute some evidence that under certain conditions, medial efferent activation can enhance the detection of particular signals in background noise. Our working hypothesis is that in the particular experiments described, the cue sound activates the medial olivocochlear neurons via the brainstem circuits that were described earlier and the anti-masking effect improves the detectability of the probe tones in the noise. The effect is frequency-selective, both because of the sharply-tuned response areas of the efferent neurons, and because of their projection back to the outer hair cells at the place close to where the cue tone frequency is represented. This mechanism might be optimized in certain sorts of tasks in which excitatory descending projections from higher centres such as auditory cortex, *locus coeruleus* and elsewhere might act synergistically with the brainstem inputs to produce strong activation of the olivocochlear efferents in response to the cue. It is possible that important everyday listening tasks such as focussing on the stream of information in speech in the presence of other competing sounds, or listening for repeated low intensity signals of strong significance for communication or survival, could activate these processes. Our results also suggest that the most common form of sensorineural deafness in which the outer hair cells are damaged or degenerated may be accompanied by a loss of this efferent-mediated attentional filter mechanism. Further study is needed to determine whether this loss of centrifugal function contributes to the loss of functionality in signal discrimination in noise that is commonly experienced by sufferers of this condition.

Conclusions

After more than 60 years of research, the anatomical organization and mode of action of the olivocochlear efferent pathways is relatively well understood. However, the functional role of this centrifugal control system in normal and abnormal hearing, is still contentious. Numerous roles are possible although on balance the evidence appears to favour a role in enhancing signal detection in noise.

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References

1. Basbaum AI, Fields HL. Endogenous pain control mechanisms: review and hypothesis. *Ann Neurol.* 1978; **4**: 451-62.
2. Zhang Y, Suga N. Modulation of responses and frequency tuning of thalamic and collicular neurons by cortical activation in mustached bats. *J. Neurophysiol.* 2000; **84**: 325-33.
3. Populin LC, Yin TC. Pinna movements of the cat during sound localization. *J. Neurosci.* 1998; **18**: 4233-43.
4. Liberman MC, Guinan Jr JJ. Feedback control of the auditory periphery: anti-masking effects of middle ear muscles vs. olivocochlear efferents. *J. Commun Disord.* 1998; **31**: 471–82.
5. Kuffler SW, Eyzaguirre C. Synaptic inhibition in an isolated nerve cell. *J. Gen Physiol.* 1955; **39**: 155-84.
6. Kuffler SW, Hunt CC. The mammalian small-nerve fibers: a system for efferent nervous regulation of muscle spindle discharge. *Res. Publ. Assoc. Res. Nerv. Ment .Dis.* 1952; **30**: 24-47.
7. Tock Y, Inbar GF, Steinberg Y, *et al*. Estimation of muscle spindle information rate by pattern matching and the effect of gamma system activity on parallel spindles. *Biol. Cybern.* 2005; **92**: 316-32.
8. Rasmussen GL. Further observations of the efferent cochlear bundle. *J. Comp. Neurol.* 1953; **99**: 61-74.
9. Oort H. Über die verästelung des nervus octavus bei säugetieren. Modell des utriculus und sacculus des kaninchens. *Anat. Anz.* 1918; **51**: 272-280.
10. Galambos R. Suppression of auditory nerve activity by stimulation of efferent fibers to cochlea. *J. Neurophysiol.* 1956; **19**: 424-37.
11. Spoendlin H. Innervation densities of the cochlea. *Acta Otolaryngol*. 1972; **73**: 235-48.
12. Kiang NY, Rho JM, Northrop CC, Liberman MC, Ryugo DK. Hair-cell innervation by spiral ganglion cells in adult cats. *Science* 1982; **217**: 175-7.
13. Robertson D. Horseradish peroxidase injection of physiologically characterized afferent and efferent neurones in the guinea pig spiral ganglion. *Hear. Res.* 1984; **15**: 113-21.
14. Sellick PM, Johnstone BM. Production and role of inner ear fluid. *Prog Neurobiol.* 1975; **5**: 337-62.
15. Thiers FA, Nadol Jr JB, Liberman MC. Reciprocal Synapses between outer hair cells and their afferent terminals: Evidence for a local neural network in the mammalian cochlea. *J. Assoc. Res. Otolaryngol.* 2008; **9**: 477 - 89.
16. Guinan Jr JJ, Warr WB, Norris BE. Differential olivocochlear projections from lateral versus medial zones of the superior olivary complex. *J. Comp. Neurol.* 1983; **221**: 358-70.
17. Guinan Jr JJ, Warr WB, Norris BE, Topographic organization of the olivocochlear projections from the lateral and medial zones of the superior olivary complex. *J. Comp. Neurol.* 1984; **226**: 21-7.
18. Warr WB, Guinan Jr JJ. Efferent innervation of the organ of corti: two separate systems. *Brain Res.* 1979; **173**: 152-5.
19. Eybalin M. Neurotransmitters and neuromodulators of the mammalian cochlea. *Physiol Rev.* 1993; **73**: 309-73.
20. Desmedt JE, Robertson D. Ionic mechanism of the efferent olivo-cochlear inhibition studied by cochlear perfusion in the cat. *J. Physiol.* 1975; **247**: 407-28.
21. Fuchs P. The synaptic physiology of cochlear hair cells. *Audiol. Neurootol.* 2002; **7**: 40-4.
22. Patuzzi R, Robertson D. Tuning in the mammalian cochlea. *Physiol. Rev.* 1988; **68**: 1009-82.
23. Yates GK, Johnstone BM, Patuzzi RB, Robertson D. Mechanical preprocessing in the mammalian cochlea. *Trends Neurosci.* 1992; **15**: 57-61.
24. Davis H. An active process in cochlear mechanics. *Hear. Res.* 1983; **9**: 79–90.
25. Patuzzi R, Johnstone BM, Sellick PM. The alteration of the vibration of the basilar membrane produced by loud sound. *Hear. Res.* 1984; **13**: 99-100.
26. Seluakumaran K. Descending control of responses in the auditory midbrain. PhD Thesis The University of Western Australia. 2007.
27. Sewell WF. The effects of furosemide on the endocochlear potential and auditory-nerve fiber tuning curves in cats. *Hear. Res.* 1984; **14**: 305-14.
28. Liberman MC. Effects of chronic cochlear de-efferentation on auditory-nerve response. *Hear. Res.* 1990; **49**: 209-23.
29. Le Prell CG, Shore SE, Hughes LF, Bledsoe SC Jr. Disruption of lateral efferent pathways: functional changes in auditory evoked responses. *J. Assoc. Res. Otolaryngol.* 2003; **4**: 276-90.
30. Le Prell CG, Halsey K, Hughes LF, Dolan DF, Bledsoe SC Jr. Disruption of lateral olivocochlear neurons via a dopaminergic neurotoxin depresses sound-evoked auditory nerve activity. *J. Assoc. Res. Otolaryngol.* 2005; **6**: 48-62.
31. Ruel J, Nouvian R, Gervais d'Aldin C, Pujol R, Eybalin M, Puel JL. Dopamine inhibition of auditory nerve activity in the adult mammalian cochlea. *Eur. J. Neurosci.* 2001; **14**: 977-86.
32. Niu X, Canlon B. The signal transduction pathway for the dopamine D1 receptor in the guinea-pig cochlea. *Neuroscience* 2006; **137**: 981-90.
33. Groff JA, Liberman MC. Modulation of cochlear afferent response by the lateral olivocochlear system: activation via electrical stimulation of the inferior colliculus. *J. Neurophysiol.* 2003; **90**: 3178-200.
34. Robertson D, Winter IM. Cochlear nucleus inputs to olivocochlear neurones revealed by combined anterograde and retrograde labelling in the guinea pig. *Brain Res.* 1988; **462**: 47-55.
35. Warren 3rd EH, Liberman MC. Effects of contralateral sound on auditory-nerve responses. I. Contributions of cochlear efferents. *Hear. Res.* 1989; **37**: 89-104.
36. Thompson ML. An investigation of the involvement of descending pathways in the neurophysiology of hearing and deafness. PhD Thesis The University of Western Australia. 1993.

37. Robertson D, Gummer M. Physiological and morphological characterization of efferent neurones in the guinea pig cochlea. *Hear. Res.* 1985; **20**: 63-77.
38. Robertson D, Anderson CJ, Cole KS. Segregation of efferent projections to different turns of the guinea pig cochlea. *Hear. Res.* 1987; **25**: 69-76.
39. Mulders WH, Robertson D. Origin of the noradrenergic innervation of the superior olivary complex in the rat. *J. Chem. Neuroanat.* 2001; **21**: 313-22.
40. Mulders WH, Robertson D. Catecholaminergic innervation of guinea pig superior olivary complex. *J. Chem. Neuroanat.* 2005; **30**: 230-42.
41. Mulders WH, Robertson D. Noradrenergic modulation of brainstem nuclei alters cochlear neural output. *Hear. Res.* 2005; **204**: 147-55.
42. Mulders WH, Robertson D. Evidence for direct cortical innervation of medial olivocochlear neurones in rats. *Hear. Res.* 2000; **144:** 65-72.
43. Mulders WH, Robertson D. Morphological relationships of peptidergic and noradrenergic nerve terminals to olivocochlear neurones in the rat. *Hear. Res.* 2000; **144**: 53-64.
44. Mulders WH, Robertson D. Effects on cochlear responses of activation of descending pathways from the inferior colliculus. *Hear. Res.* 2000; **149**: 11-23.
45. Wang X, Robertson D. Two types of actions of norepinephrine on identified auditory efferent neurons in rat brain stem slices. *J. Neurophysiol.* 1997; **78**: 1800 -10.
46. Wang X, Robertson D. Effects of bioamines and peptides on neurones in the ventral nucleus of trapezoid body and rostral periolivary regions of the rat superior olivary complex: an in vitro investigation. *Hear. Res.* 1997; **106**: 20 - 8.
47. Wang X, Robertson D. Substance P-induced inward current in identified auditory efferent neurons in rat brain stem slices. *J. Neurophysiol.* 1998; **80**: 218-29.
48. Wang X, Robertson D. Substance P-sensitive neurones in the rat auditory brainstem: possible relationship to medial olivocochlear neurones. *Hear. Res.* 1998; **116**: 86 - 98.
49. Cole KS, Robertson D. Early efferent innervation of the developing rat cochlea studied with a carbocyanine dye. *Brain Res.* 1992; **575**: 223 -30.
50. Walsh EJ, McGee J, McFadden SL, Liberman MC. Long-term effects of sectioning the olivocochlear bundle in neonatal cats. *J. Neurosci.* 1998; **18**: 3859-69.
51. Cody AR, Johnstone BM. Temporary threshold shift modified by binaural acoustic stimulation. *Hear. Res.* 1982; **6**: 199-205.
52. Rajan R. Effect of electrical stimulation of the crossed olivocochlear bundle on temporary threshold shifts in auditory sensitivity. I. Dependence on electrical stimulation parameters. *J. Neurophysiol.* 1988; **60**: 549-68.
53. Rajan R. Effect of electrical stimulation of the crossed olivocochlear bundle on temporary threshold shifts in auditory sensitivity. II. Dependence on the level of temporary threshold shifts. *J. Neurophysiol.* 1988; **60**: 569-79.
54. Patuzzi RB, Thompson ML. Cochlear efferent neurones and protection against acoustic trauma: protection of outer hair cell receptor current and interanimal variability. *Hear. Res.* 1991; **54**: 45-58.
55. Christopher KE, Smith DW. Protection from acoustic trauma is not a primary function of the medial olivocochlear efferent system. *J. Assoc Res Otolaryngol.* 2003; **4**: 445 - 65.
56. Kemp DT. Physiologically active cochlear micromechanics--one source of tinnitus. *Ciba Found. Symp.* 1981; **85**: 54 - 81.
57. Patuzzi R. Outer hair cells, EP regulation and tinnitus. *Proc. VIIth Interntl. Tinnitus Seminar* Fremantle. 2002; p16–24.
58. Darrow KN, Maison SF, Liberman MC. Cochlear efferent feedback balances interaural sensitivity. *Nat. Neurosci.* 2006; **9**: 1474-6.
59. Scharf B, Magnan J, Collet L, Ulmer E, Chays A. On the role of the olivocochlear bundle in hearing: a case study. *Hear. Res.* 1994; **75**: 11-26.
60. Scharf B, Magnan J, Chays A. On the role of the olivocochlear bundle in hearing: 16 case studies. *Hear. Res.* 1997; **103**: 101-22.
61. Baguley DM, Axon P, Winter IM, Moffat DA. The effect of vestibular nerve section upon tinnitus. *Clin. Otolaryngol. Allied Sci.* 2002; **27**: 219-26.
62. Housley GD, Jagger DJ, Greenwood D, *et al*. Purinergic regulation of sound transduction and auditory neurotransmission. *Audiol. Neurootol.* 2002; **7**: 55-61.
63. O'Beirne GA, Patuzzi RB. Mathematical model of outer hair cell regulation including ion transport and cell motility. *Hear. Res.* 2007; **234**: 29-51.
64. Rajan R. Tonic activity of the crossed olivocochlear bundle in guinea pigs with idiopathic losses in auditory sensitivity. *Hear. Res.* 1989; **39**: 299-308.
65. Winslow RL, Sachs MB. Effect of electrical stimulation of the crossed olivocochlear bundle on auditory nerve response to tones in noise. *J. Neurophysiol.* 1987; **57**: 1002-21.
66. Mulders WH, Seluakumaran K, Robertson D. Effects of centrifugal pathways on responses of cochlear nucleus neurons to signals in noise. *Eur. J. Neurosci.* 2008; **27**: 702-14.
67. Seluakumaran K, Mulders WH, Robertson D. Unmasking effects of olivocochlear efferent activation on responses of inferior colliculus neurons. *Hear. Res*. 2008; **243**: 35 - 46.
68. Tan MN, Robertson D, Hammond GR. Separate contributions of enhanced and suppressed sensitivity to the auditory attentional filter. *Hear. Res.* 2008; **241**: 18-25.

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