EFFERENT CONTROL OF HEARING

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The auditory system comprises both ascending (afferent) and descending (efferent) pathways. The efferent pathways, which originate in a variety of higher brain centres, are capable of altering the activity in the afferent pathways. By modulating cochlear neural output and central auditory neural circuits, these efferent pathways could play an important role in key auditory processing such as optimising the detection of acoustic signals of interest in the presence of competing background noises. The present paper focuses on the final limb of the efferent pathways, the olivocochlear system, which projects directly to the cochlea. It will describe its proposed role in normal hearing and show how dysfunction of this efferent system could contribute to generation of tinnitus and to deterioration in the detection and processing of signals such as speech, especially in non-optimum listening environments.

INTRODUCTION

The mammalian auditory system comprises parallel afferent (ascending) and efferent (descending) neural pathways (see Figure 1). The afferent pathways start at the cochlea, in the organ of Corti where sound waves are transduced into neural information. From the cochlea the information travels through different brain centres undergoing further auditory processing to the auditory cortex, where sound is perceived by the listener. Efferent pathways can be found at every level of the afferent pathway and thus enable the brain to modify the processing of the ascending auditory information at various levels, regulating peripheral cochlear function and modulating signal processing at higher stages of the auditory pathway.

THE OLIVOCOCHLEAR SYSTEM

The final limb of the efferent pathways is formed by the olivocochlear (OC) system, which projects directly to the organ of Corti within the cochlea (Figure 1). The neurons of the olivocochlear system originate in the superior olivary complex in the brainstem and can be subdivided into two major subsystems, the medial and lateral OC system, on the basis of the location of their cell bodies in the brainstem and their targets in the cochlea. The medial OC system originates bilaterally in the periolivary regions and projects via myelinated axons to the outer hair cells. The lateral OC system originates ipsilaterally in and around the lateral superior olive and projects via unmyelinated axons to the afferent dendrites contacting the inner hair cells [36,61,62,74,75,80,82].

The lateral OC system, because it synapses directly onto primary afferent dendrites, seems to be in a prime position to affect both spontaneous and sound-driven neural firing as well as excitability of the auditory nerve fibres. Because of the location of the lateral OC neurons deep in the brainstem, and their unmyelinated axons, it has proven difficult to experimentally stimulate this system and information on the role of the lateral OC system is therefore limited. Nonetheless there are several studies reporting effects of the lateral OC system on cochlear output using a variety of methods. Studies investigating the effects of de-efferentation show a decrease of spontaneous rate of the auditory nerve fibres, suggesting an excitatory role for the lateral efferents [33,35,37,77,90]. However, evidence is mounting that the lateral system actually consists of multiple subsystems whose effects on the cochlea may depend on the neurotransmitter released. A variety of different neurotransmitters has been demonstrated to exist in the lateral efferents, such as acetylcholine, γ-aminobutyric acid (GABA), dopamine, enkephalin and calcitonin gene-related peptide (CGRP) [15,55]. Acetylcholine applied close to the inner hair cell synapse and thus close to the lateral OC synapse with the afferent fibres, results in increased spontaneous firing of the afferent fibres, supportive of an excitatory role for the lateral efferents [17]. However, intracochlear application of GABA or dopamine has been shown to result in a reduction of the driven firing rate of primary afferent fibres [17,49,64], revealing a capability of the lateral OC system to inhibit the firing rate of auditory afferent fibres. Interestingly, recent indirect stimulation of the OC system showed effects on cochlear output consistent with the notion that the lateral OC system exerts both excitatory and inhibitory effects in the cochlea [20,48], which is in line with anatomical evidence that there may be two different types of lateral OC fibres [79].

The actual biological role of the lateral OC system remains as yet to be elucidated, but several hypotheses have been put forward. Increases of spontaneous firing of the afferents, as can be evoked by the lateral efferents may also contribute to amplitude-modulated sound detection [12]. Ruel et al. [63] suggested that the tonic release of dopamine by the lateral efferents prevents sound-induced excitotoxicity of the afferent dendrites.

In contrast to the lateral OC system, the effects of activation of the medial OC system on cochlear output have been well described. Experimental activation of the medial OC system can be relatively easily achieved by electrical stimulation of their myelinated axons since these run close to the surface of the brainstem. Activation of the medial OC system is well known to suppress cochlear neural responses to low level

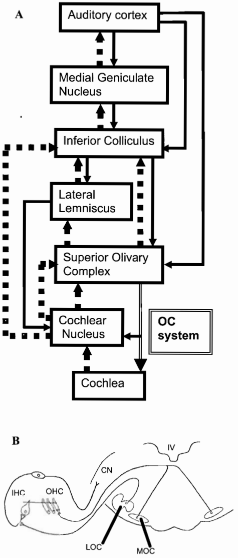

Figure 1: A: Schematic drawing of the ascending and descending pathways in the auditory system, excluding binaural pathways. Black lines are descending, dotted lines ascending projections. The olivocochlear system is indicated with a double line and illustrated in more detail in B. B: Schematic drawing of the olivocochlear system, showing the lateral OC system originating in the lateral superior olive and projecting ipsilaterally to the afferent dendrites contacting the inner hair cells and the medial OC system originating in the periolivary regions and projecting bilaterally to the outer hair cells. Abbreviations: CN: cochlear nucleus; IHC: inner hair cells; IV: IVth ventricle; LOC: lateral olivocochlear system; MOC medial olivocochlear system; OHC: outer hair cells.

acoustic stimuli [13,58,83]. Electrical stimulation of the medial OC axons results in a reduction of the compound action potential of the auditory nerve through the effects exerted on the outer hair cells [8,13,27,58,65,81,83]. The outer hair cells, which have electro-motile properties, are responsible for the cochlear gain by enhancing the vibration of the basilar membrane in response to sound. Release of acetylcholine from the medial OC synapse results in an increased conductance of the basolateral wall and subsequent hyperpolarization of the outer hair cells, thereby reducing the gain of the cochlear amplifier. Reduction of the cochlear gain leads to a decreased depolarisation and decreased neurotransmitter release from the inner hair cells, reducing auditory afferent firing, thus reducing the size of the compound action potential amplitude of the auditory nerve fibres [21].

Though the inhibitory effects of the medial OC system on cochlear output are well established, the biological role of this efferent system in hearing is still under debate. A first question to ask may be: "what activates the medial OC system in the awake, behaving organism?" Well, there is ample evidence that the medial OC neurons are excited by sound [6]. Anatomical studies have shown that the olivocochlear neurons in the brainstem receive ascending synaptic input from the cochlear nucleus [7,63,71]. Consistent with these anatomical observations, contralateral sound has been reported to result in inhibitory effects on the activity of auditory primary afferent fibres as well as the compound action potential of the auditory nerve in different mammalian species [9,34,57,81]. In addition, altered otoacoustic emissions following the application of contralateral sound have been reported in humans [41], cats [56] and guinea pigs [31,32,56]. All of the studies above indicate an excitatory action of the contralateral cochlea on medial olivocochlear neurons and suggest the olivocochlear system forms a feedback circuit at the level of the lower brainstem

One of the proposed roles for the medial OC system is consistent with it being part of a feedback loop at the level of the brainstem. It has been suggested that it serves to protect the cochlea from extensive receptor damage during intense noise exposure reducing hearing loss [52,58-60]. However, all experiments in which this protective mechanism was demonstrated used very loud sound intensities to damage the cochlea, much louder than naturally occurring sound levels. This makes it unlikely that the medial OC system evolved to serve this protective role as argued convincingly by Kirk and Smith [28], but rather that this protection that can be observed in the noisy environment of modern man is a fortuitous but convenient side-effect of the system that evolved for other reasons.

Another role put forward for the medial OC system is to provide homeostatic control of the endocochlear potential (EP). Very small fluctuations of the EP of only a few millivolt have been shown to be able to alter neurotransmitter release from the inner hair cells [51] and can alter neural firing. Increases of the EP, therefore, could lead to an increase of spontaneous activity, causing more excessive neural firing in the absence of sound, and could contribute to the generation of cochlear tinnitus. Since tinnitus, fortunately, is not a constant feature of the auditory system, this means that a control mechanism must exist that keeps the EP constant, preventing this aberrant activity from occurring. Since medial OC activation can alter the EP [8,22], Patuzzi [50] suggests that the medial OC system may serve this controlling role.

A third role proposed for the medial OC system may be improving the signal to noise ratio and the dynamic range of the auditory system. Several studies have demonstrated an unmasking effect on the responses of auditory afferent fibres in noise following medial OC activation [26,83,85]. This unmasking effect at the primary afferent level may be responsible for improving the detection of signals in a noisy background and indeed behavioural studies support a role for the medial system in signal in noise detection. Lesions of the medial OC axons resulted in a reduced capacity to discriminate signals in noise in primates [14] and cats [39]. In humans, contralateral noise, known to stimulate the medial OC system, improved intensity discrimination in a noisy background [40]. Patients that have undergone a vestibular neurotomy, which disrupts the olivocochlear axons, show no improvement in discriminating speech in noise with application of contralateral noise whereas control subjects do [19].

In 1997 a paper appeared which suggested that the olivocochlear system could improve the detection of expected signals in noise by inhibiting the perception of frequencies adjacent to the signal [68]. The authors tested human patients, undergoing a vestibular neurotomy, severing the lateral and medial OC axons, before and after surgery. Patients were asked to recognise a signal in a noisy background, in some instances an expected signal (i.e. heard before) in other instances an unexpected signal, i.e. of a frequency close but not the same as the expected signal. Their results indicated that the olivocochlear system could provide a relative enhancement of the detection of expected target signals in noise, by inhibition of the adjacent unexpected frequencies. Before surgery the expected signals were detected better than the unexpected signals, whereas after surgery the expected and unexpected signals were detected equally well. Such a role of the OC system, improving selective attention in the auditory system, strongly implies that the OC neurons are not just part of a straightforward feedback system at the brainstem level but rather that the system operates in a more active "top-down" role driven by input from higher centres. In addition, it implies that the OC system must be able to act in a selective, spatially restricted way, within the cochlea.

TOP-DOWN CONTROL

Anatomical as well as physiological studies have shown evidence that the OC system is under the influence of higher brain centres. Anatomical studies have shown that the auditory brainstem receives direct descending input from higher centres, both from auditory structures such as the inferior colliculus and auditory cortex [16,43,44,72,76] as well as from non-auditory structures such as the locus coeruleus [46,47]. Here we will discuss two of these inputs in more detail, those arising from the inferior colliculus and from the locus coeruleus.

The IC seems to play a large role in efferent processing; it receives a large input from the auditory cortex [5,11,24,67,84] and it has been shown in multiple species that the cortex can modulate the responses of IC neurons to sound [18,38,54,70,89]. Axons arising from the inferior colliculus have been shown to make direct synaptic contact with the medial OC neurons [42]. Moreover, the projection from the inferior colliculus is tonotopically organized, a common feature of the auditory pathways. Dorsal, low frequency regions of the IC project to lateral regions of the peri-olivary regions, known to project to the low frequency regions of the cochlea, whereas ventral regions of the IC project to the medial regions of the peri-olivary regions, known to project to the high frequency regions of the cochlea. This suggest that the inferior colliculus may be capable of exerting frequency-specific effects on the medial OC neurons and thus on the cochlea. This would be in accordance with the results of Scharf et al. [67], which suggested that the OC system is capable of exerting frequency-selective effects in the cochlea to aid selective attention (see above).

Is the projection from the inferior colliculus to the OC neurons biologically relevant? Physiological studies using electrical stimulation of the inferior colliculus have shown that this results in inhibition of cochlear output, an effect qualitatively similar to stimulation of the medial OC system itself, though smaller than the maximum effect that can be achieved by electrical stimulation of the OC system itself [20,43,50,53]. This smaller size inhibition is not a surprising result since the inferior colliculus is a large structure and electrical stimulation may not activate all neurons projecting to the OC neurons. In addition, it is not known whether all medial OC neurons receive input from the inferior colliculus. One study also demonstrated evidence for frequency specific effects from the inferior colliculus to the medial OC neurons. This study showed larger inhibition of low frequency compound action potentials in the cochlea when dorsal regions of the inferior colliculus were stimulated and larger inhibition of cochlear responses to high frequency tones when more ventral regions of the inferior colliculus were stimulated [49].

Interestingly, some of the effects observed with stimulation of the inferior colliculus are more consistent with stimulation of the lateral OC system [20,43,48,50,53], which lead to the hypothesis that the inferior colliculus can also indirectly affect the lateral OC system. Further studies are underway to investigate this issue.

There are several lines of evidence to indicate that the OC system receives information from non-auditory structures. Within the auditory brainstem a variety of neurotransmitters have been shown to exist such as serotonin [73], substance P [88] and noradrenaline [45,87]. With respect to the latter, it has been demonstrated that noradrenaline containing varicosities make direct synaptic contacts with both lateral and medial olivocochlear neurons [45,86]. Anatomical tracing studies have demonstrated that the noradrenergic input to the olivocochlear neurons arises from the locus coeruleus [46,47]. This nucleus also supplies noradrenergic input to other auditory brainstem nuclei, such as the cochlear nucleus and inferior colliculus [29,30].

In line with these anatomical data, electrophysiological *in vitro* studies in rat brain slices have demonstrated that noradrenaline exerts a generally excitatory action on medial olivocochlear neurons [78]. The effect of noradrenaline on

OC neurons has also been investigated in anaesthetized guinea pigs. These experiments revealed inhibitory effects on compound action potentials when noradrenaline was injected close to the medial OC neurons and excitatory effects when noradrenaline was injected close to the lateral OC neurons. These results are thus consistent with the notion that noradrenaline has an excitatory effects on both the medial and lateral OC neurons.

The question remains as to what function this projection from the locus coeruleus to the OC system has. The locus coeruleus is well known to play a role in attentive processes, showing high tonic activity during arousal, moderate, phasic activity during selective attention and low tonic activity during drowsiness and sleep [1,2]. Since the olivocochlear system has been hypothesized to play a role in selective auditory attention, attenuating unattended signals and in improving speech detection in noisy environments (see above), noradrenaline may be modulating this process.

CLINICAL IMPLICATIONS AND FUTURE STUDIES

Dysfunction of both the lateral and medial OC system has been associated with hearing associated pathologies. This is not surprising if one considers effects of both systems on cochlear neural output and their proposed roles in normal hearing. When the lateral OC neurons can affect spontaneous neural firing, abnormal activity can well lead to tinnitus, the phenomenon where noise is perceived in the absence of an external physical sound [3,66]. An interesting observation in this respect is that stress is known to exacerbate tinnitus [23,25]. This may well be an example of top-down control, since stress activates the locus coeruleus. This in its turn may increase the noradrenaline release to the lateral OC system, causing activation, enhancing the spontaneous neural firing of primary auditory afferent fibres. This may provide the perception of tinnitus, either directly, or by secondary alterations of activity in central pathways.

If the medial OC system serves a homeostatic role, keeping the endocochlear potential constant, then disruption of this control could also lead to increased spontaneous firing from auditory afferent fibres as explained above. In patients that suffer from tinnitus the medial OC system has been shown to be less effective, showing less suppression in otoacoustic emissions with contralateral noise [10]. However, it must be mentioned that studies of patients with ablated OC axons, i.e. patients that received a vestibular nerve section to alleviate Menière's disease, did not reveal a clear link between disruption of the OC systems and tinnitus. Baguley and co-workers using an extensive literature search found that in the majority of patients undergoing the procedure tinnitus symptoms were not worsened [4], but the effects were highly variable.

With regard to a proposed role for the OC systems in signal detection in noisy environments, a common complaint in patients with auditory processing disorders and sensory deafness is the difficulty in understanding speech in noisy environments. Interestingly, in some of these patients a low activity of the MOC system was demonstrated [42] by measuring oto-acoustic emissions. Malfunctioning medial OC pathways have also been demonstrated in auditory neuropathy patients, which showed an absence of the suppression of oto-acoustic emissions with contralateral noise [69]. In these patients of course it is unclear whether the OC system itself is dysfunctional or whether it is driven less by the reduced cochlear afferent input. All of these patients, with the exception of a very young child, reported speech comprehension as a major problem, which may be connected to the malfunction of the efferent pathway.

More research will be necessary to elucidate the biological role of the efferent pathways and to reveal whether and how malfunctioning of these pathways is involved in the generation of hearing associated pathologies. Moreover, when more information is gathered on how the system is activated biologically, it may well have future therapeutic benefits. It may then be possible by pharmacological or other intervention to alleviate symptoms associated with dysfunction or to modulate abnormal afferent activity associated with tinnitus.

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