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Review

Chemical neuroprotection in the cochlea: The modulation of dopamine release from lateral olivocochlear efferents

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ABSTRACT

The prevalence of sensorineural hearing loss is increasing worldwide, mainly due to ageing, increased noise exposure and cardiovascular risk factors. Several papers dealt with the mechanisms underlying the primary causes of impaired hearing and eventual deafness, including the damage and loss of auditory hair cells; however, very little is known about the protective mechanisms that exist for hearing. Several recent investigations have implicated dopamine (DA) in a neuroprotective circuit for the cochlea. The lateral olivocochlear (LOC) efferents provide axonal innervation of the inner hair cell afferent synapses and release DA and other substances in response to different stimuli. Under ischemic conditions or during noise exposure, DA has been proven to play a neuroprotective role against glutamate excitotoxicity. This review summarises what is currently known about the modulation of DA release in the cochlea, using primarily *in vitro* experimental data. Based on recent knowledge, there could be two functional subgroups within the LOC fibres, i.e., the DA- and GABA-containing projections. In this review, we attempt to show the neurochemical interactions between these two subsystems. Other aspects of cochlear neurotransmission are also discussed to provide a complete picture of cochlear dopaminergic function in physiological and pathophysiological cases with particular reference to excitotoxicity.

1. Introduction: dopamine (DA) in the chemical transmission of the cochlea

Dopamine (DA) acts as a neurotransmitter and mediates neural transmission between the lateral olivocochlear (LOC) efferent terminals and the dendrites of the afferent nerves in the cochlea (Altschuler et al., 1986; Eybalin et al., 1993; Gil-Loyzaga and Pares-Herbute, 1989). Evidence that DA functions as a transmitter includes the following: (i) DA and its synthesising enzymes are present in LOC efferent fibres (d'Aldin et al., 1995; Eybalin et al., 1993; Gil-Loyzaga, 1995; Jones et al., 1987; Usami et al., 1988); (ii) DA is released in response to electrical stimulation, this effect is inhibited by the blockade of axonal conductance (TTX) or voltage-gated Ca^{2+} channels, proving its neural origin (Gaborjan et al., 1999), and released DA is taken up by membrane uptake carriers (DA transporters) (Gaborjan and Vizi, 1999; Halmos et al., 2005; Ruel et al., 2006); and (iii) DA receptors are present postsynaptically (Inoue et al., 2006; Karadaghy et al., 1997; Niu and Canlon, 2006). The DA-containing efferent innervation of the inner hair cell (IHC) area originates from the ipsilateral superior olivary complex. The LOC efferents reach the radial afferent auditory nerve, forming axo-dendritic synapses underneath the inner hair cells (Eybalin et al., 1993; Gil-Loyzaga, 1995; Puel, 1995; Pujol, 1994).

The functional importance of DA has been highlighted by the observations that DA has a protective effect on the IHC-afferent nerve synapse during ischemia or acoustic trauma by attenuating the post-synaptic effects of glutamate overstimulation (Darrow et al., 2007; Eybalin et al., 1993; Oestreicher et al., 1997; Pujol, 1994). Beside the potential protective role of DA released from

Abbreviations: AICA, anterior inferior cerebellar artery; CM, cochlear microphonic; CAP, compound action potential; DPOAE, distortion product otoacoustic emission; DA, dopamine; IHC, inner hair cells; LOC, lateral olivocochlear; LSO, lateral superior olive; NOS, nitric oxide synthase; NIHL, noise-induced hearing loss; OHCs, outer hair cells; OGD, oxygen–glucose deprivation; SNHL, sensorineural hearing loss; 5-HT, serotonin; SP, summating potentials; TTX, tetrodotoxin; TH, tyrosine hydroxylase; VGCCs, voltage-gated Ca^{2+}-channels.

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the LOC efferents, the exact function of the LOC system is still not clear, mainly because of technical difficulties of selective and complete lesioning and of selective stimulation of LOC neurons (Robertson, 2009). Nevertheless, its role in sound localisation (Darrow et al., 2006a; Groff and Liberman, 2003) or in relearning sound localisation during unilateral conductive hearing loss (Irving et al., 2011) were suggested.

The cochlear dopaminergic innervation is not a diffuse system within the cochlea but is distinctly localised in the vicinity of the inner hair cells. Tyrosine hydroxylase (TH; the rate limiting step enzyme in the synthesis of DA and other catecholamines) immunoreactivity is not present in the area where the outer hair cells are located (Eybalin et al., 1993). Adrenergic fibres, which show both tyrosine hydroxylase and DA beta-hydroxylase (the enzyme responsible for catalysing the conversion of dopamine to noradrenaline) immunoreactivity, do not enter the organ of Corti (Darrow et al., 2006b). These anatomical data are in agreement with functional *in vitro* studies showing that nomifensine, a selective inhibitor against DA uptake, prevents both the uptake of exogenous DA (Gaborjan et al., 1999) and the re-uptake of released DA into LOC terminals (Halmos et al., 2005). When these data are taken together, it is clear that all of the elements necessary for classical dopaminergic neurotransmission are present in the LOC fibre-afferent dendritic synapse.

2. Chemical anatomy of neurotransmission in the organ of Corti

2.1. The hair cell – afferent dendrite – LOC efferent terminal synaptic complex of the cochlea

The dendrites of type I afferent neurons (Nomura, 1976; Rusznak and Szucs, 2009) form synapses onto IHCs (Berglund and Ryugo, 1987; Spoendlin and Brun, 1973). Unmyelinated axons of the LOC bundle project predominantly to the ipsilateral cochlea (Aschoff and Ostwald, 1988; Safieddine et al., 1997; Szucs and Rusznak, 2002; Warr, 1975; Warr et al., 1997; Warr and Guinan, 1979) and give rise to numerous en passant varicosities and terminal boutons (Brown, 1987; Satake and Liberman, 1996; Warr et al., 1997). These boutons form mainly axo-dendritic synapses with the afferent dendrites at the synaptic release site of IHCs (Bodian and Gucer, 1980; Liberman, 1980; Liberman et al., 1990; Spoendlin, 1979). In addition to the axo-dendritic synapses, a population of efferent terminals are also in intimate contact with the cell membrane of the IHCs. The majority of these contacts lack a clear synaptic specialisation (Hashimoto et al., 1990; Liberman et al., 1990; Satake and Liberman, 1996). A special form of cellular connection, the so-called triadic synapse, can also be observed when LOC fibres synapse with both an IHC and its afferent dendrite (Sobkowicz et al., 2004). This structure is built by afferent and efferent synapses and enables the occurrence of various types of cell-to-cell communication (Ruel et al., 2007) (Fig. 1). This complex is sealed by border and inner-phalangeal cells (Ruel et al., 2007). The two synapses of LOC terminals (on IHCs and afferent dendrites) may utilise different transmitters because (1) they have different targets (i.e., different synaptic specialisations) and (2) the LOC terminals contain several different transmitter molecules (Fig. 1).

2.2. Role of glutamate in the hair cell synaptic complex

It is widely accepted that glutamate, released from IHCs, plays a major role in neurotransmission in the mammalian cochlea (Bobbin and Thompson, 1978; Eybalin et al., 1993; Eybalin and Pujol, 1983, 1989; Godfrey et al., 1976; Kataoka and Ohmori, 1994, 1996; Matsubara et al., 1998; Nordang et al., 2000; Puel, 1995). All the main types of ionotropic glutamate receptors

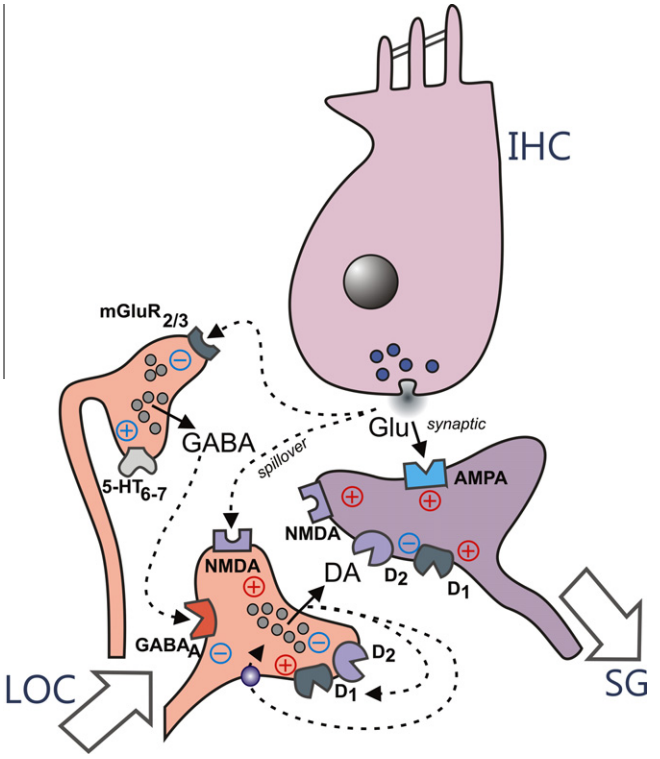

Fig. 1. Chemical anatomy of the inner hair cell – afferent dendrite – lateral olivocochlear efferent terminal complex in the cochlea. Neurochemical interactions of the inner hair cell (IHC) – afferent dendrite (SG) – lateral olivo-cochlear efferent (LOC) anatomical triad. The release of acetylcholine and neuropeptides from the LOC is not shown. Besides synaptic transmission (solid lines), non-synaptic information channels (broken lines) play important roles in mediating the interactions between the members of the triad. This schematic drawing indicates only qualitative connections and does not represent the actual proportion of the elements.

(NMDA, AMPA, and kainate) have been identified in postsynaptic sites of the cochlea (Bobbin and Thompson, 1978; Ehrenberger and Felix, 1991; Eybalin et al., 1993; Jenison and Bobbin, 1985; Puel, 1995). The fast excitatory transmission between IHCs and radial dendrites has been shown to be mediated by AMPA receptors (Glowatzki and Fuchs, 2002; Puel et al., 2002; Ruel et al., 2000). Antagonists of AMPA and kainate receptors (CNQX and DNQX) can change the activity of afferents (Littman et al., 1989). Even prolonged hair cell depolarisation does not saturate or desensitise postsynaptic AMPA receptors at single ribbon synapses, highlighting the potency of glutamate as a neurotransmitter in the cochlea (Li et al., 2009).

So far, the role of NMDA receptors in postsynaptic excitatory actions within the IHC synaptic complex has been rather controversial. NMDA receptors do not appear to mediate afferent neurotransmission (Fex and Martin, 1980; Ruel et al., 2007). Direct recordings from postsynaptic nerve endings below the IHCs failed to show NMDA receptor-mediated EPSPs (Glowatzki and Fuchs, 2002). NMDA had no effects on freshly isolated spiral ganglion cell soma (Nakagawa et al., 1990; Ruel et al., 1999). In spite of the apparent lack of NMDA-mediated EPSPs in the postsynaptic afferents, NR1/NR2B NMDA receptors exist at the ribbon synapse (Ruel et al., 2008). These receptors are likely silent under normal circumstances but become active under special conditions, such as COX2 enzyme inhibition, which enables NMDA responses (Ruel et al., 2008). NMDA autoreceptors that control glutamate release could also be present at the basal pole of IHCs (Ruel et al., 2008). Furthermore, *in vivo* experiments revealed excitatory actions on auditory nerve fibres following the application of NMDA (Felix and Ehrenberger, 1990). NMDA was reported to have effects on

cultured ganglion cells (Peng et al., 2003). In these experiments, NMDA could reach its receptors at any location, particularly high-affinity NMDA receptors located outside of the synapse.

How can the results showing the actions of NMDA be explained in the context of AMPA-mediated fast transmission in IHC-type I dendrite synapses? The most likely explanation comes from the consideration of local non-synaptic interactions. Non-synaptic transmission, i.e., when cells can communicate outside of synapses (Vizi, 2000; Vizi et al., 2010, 2004), may contribute to the operation of the IHC synaptic complex. Because of the special structure of the IHC synaptic complex, it is possible that, following sustained activation of the IHC, glutamate spillover occurs from the IHC-auditory dendritic synapse, reaching non-synaptic high affinity NMDA receptors (NR2B) at other sites. Because it has been shown that spiral ganglion neurons also express NMDA receptors, one could make the assumption that NMDA receptors are present on the surface of auditory dendrites away from the synapse (Fig. 1). These NMDA receptors can detect glutamate spillover and initiate various responses. This hypothetical arrangement of NMDA receptors is in accordance with the finding that the soma of freshly isolated ganglion cells are not responsive to NMDA. In this scenario, NMDA receptors would be present in the dendritic region but not the soma. However, under physiological conditions, extrasynaptic NMDA receptors are unlikely to contribute to fast synaptic transmission between IHCs and auditory dendrites. Supporting the possible existence and importance of non-synaptic excitatory transmission in the cochlea, glutamate transporters are present in the supporting cells surrounding the IHC and in the satellite cells that surround auditory dendrites (Furness and Lehre, 1997; Rebillard et al., 2003), indicating that glutamate surrounds virtually the entire IHC synaptic complex and not exclusively localised to the IHC-auditory dendritic synapse. Recent data have described a neurotrophic role for NMDA receptors (Ruel et al., 2007), showing that NMDA receptors are involved in the functional recovery seen following re-innervation (d'Aldin et al., 1997; Puel, 1995).

2.3. Excitotoxicity

Besides its physiological role at the IHC-afferent synapse, glutamate also has an important pathophysiological aspect in the cochlea. The excessive release of glutamate causes excitotoxicity (Ruel et al., 2007). Regarding the clinical importance of this excitotoxicity, AMPA receptors appear to play an important role in the development of acoustic trauma (Puel et al., 1998), while NMDA receptors appear to be responsible for the generation of salicylate-induced tinnitus (Guitton et al., 2003). In this model, salicylate inhibits cochlear cyclooxygenase, leading to increased levels of arachidonate. Arachidonate interacts with NMDA receptors, enhancing responses to glutamate released from inner hair cells (Ruel et al., 2008). Furthermore, the cochlear application of the NR2B subtype-selective NMDA antagonist ifenprodil reduced the effects of a noise insult (Guitton and Dudai, 2007). Glutamate spillover and the extensive activation of extrasynaptic NMDA receptors lead to massive Na^+ and Ca^{2+} influxes through the receptor (Fig. 1), which in turn causes the swelling of the afferent dendrities (Gil-Loyzaga and Pujol, 1990; Jager et al., 2000; Pujol and Puel, 1999; Pujol et al., 1993). Ca^{2+} entering the cell through NMDA receptors, and activates proteases and lipases to induce irreversible cell damage (Choi et al., 1987). Glutamate spillover can occur during ischemia or noise exposure. We therefore suggest that the activation of non-synaptic NMDA receptors (NR2B) could cause cellular damage (Vizi et al., 2010), resulting in temporary or long-term definitive sensorineural hearing loss (SNHL).

2.4. Functional segregation of the lateral olivocochlear efferents

Several other neurotransmitters, including acetylcholine, GABA, DA, enkephalins, dynorphins, calcitonin gene-related peptide and serotonin, can be released from cochlear LOC terminals (Eybalin et al., 1993; Gil-Loyzaga, 1995; Puel, 1995; Safieddine et al., 1997). It has long been debated which molecules, among the possible candidates, actually transmit the message from the LOC efferents to target structures.

Currently, at least two functional subgroups, each containing different transmitters, have been suggested to exist within the LOC system; dopaminergic neurons represent one such subpopulation (Darrow et al., 2006b). Evidence of the distinct dopaminergic subgroup within the LOC fibres arises from the observation that TH-positive cell bodies only comprise a fraction of the LOC system (5–35%), which can be detected by the retrograde transport of horseradish peroxidase (Campbell and Henson, 1988; Mulders and Robertson, 2004; Niu et al., 2004). Furthermore, the TH-positive cell bodies of the LOC fibres appear to localise to the shell region of the lateral superior olive (Darrow et al., 2006b; Mulders and Robertson, 2004). Nevertheless, not all of the shell neurons appear to be dopaminergic (Vetter et al., 1991). As GABA co-localises with acetylcholine in olivocochlear efferent terminals in mice (Maison et al., 2003), and the cholinergic marker vesicular acetylcholine transporter (VAT) does not co-localise with the dopaminergic marker tyrosine hydroxylase (TH; Darrow et al., 2006b), it is reasonable to assume that, within the LOC fibres, acetylcholine- and GABA-containing terminals may represent the second functional subgroup. Electrical stimulation in the inferior colliculus could reveal selective LOC effects in the cochlea, allowing for the observation of long-lasting (5–20 min) enhancement or suppression of compound action potentials (CAPs) without changes in the cochlear responses dominated by OHCs (Groff and Liberman, 2003). This heterogeneity of LOC effects, after the stimulation of brainstem nuclei, also supports the existence of subgroups within the LOC system (Groff and Liberman, 2003). Unfortunately, no direct immunostaining evidence has been obtained to prove the existence of these distinct subgroups (Darrow et al., 2006b).

3. Receptor modulation of cochlear DA release

3.1. Dopaminergic autoreceptors

There is strong evidence suggesting the presence of presynaptic DA autoreceptors on LOC terminals. The activation of D_1 DA receptors induces DA release at rest and can also modulate, i.e., enhance, the electrical stimulation (depolarisation)-evoked release of DA, which can be prevented by specific antagonists (Gaborjan et al., 1999). These results clearly indicate a presynaptic modulatory site for D_1 receptors. The selective block of D_2 receptors by sulpiride at low concentrations (10 μM) or by another specific D_2 antagonist, L-741,626, induced a significant enhancement of the electrical stimulation-evoked release of DA from isolated cochlea (Halmos et al., 2005, 2002). The most likely mechanism for this increased DA release is that D_2 antagonists act on presynaptic D_2 autoreceptors and removing this feedback inhibition increases DA release (Gaborjan et al., 1999; Vizi, 1979). Based on these data, we conclude that, in addition to D_1 receptors, there are pre-synaptic D_2 receptors on dopaminergic LOC efferent terminals (Fig. 1). The functional importance of dopaminergic autoregulation in the cochlea was highlighted when piribedil, a dopaminergic agonist used clinically in the treatment of DA system dysfunction, was investigated in cochlear superfusion systems. Although piribedil had previously been characterised primarily as a D_3 agonist with little affinity for D_1 receptors (Cagnotto et al., 1996), *in vitro* piribedil

treatment enhanced DA release through presynaptic D_1 receptors (Gaborjan et al., 1999). This raises a question as to how this dual DA receptor regulation might work. The presence of both inhibitory and excitatory (auto)receptors on a bouton is not unprecedented (Ciruela et al., 2006). The D_1 and D_2 receptors have opposite functions; the actual balance between the action of the two receptor types determines the overall effect of DA. We can speculate that the extracellular concentration of DA can be maintained at a sufficiently high enough level for neuroprotection by activating the D_1-mediated pathway. This would increase extracellular DA levels, which is then turned off by the activation of D_2 receptors leading to subsequent reduction in DA release.

The significance of dopaminergic neurotransmission in the cochlea is manifested in its influence on functional auditory measures. Intracochlear infusion of DA reduced the CAP and increased the thresholds and decreased the spontaneous and driven discharge rates of single units of auditory nerve fibres without changing their frequency-tuning properties (Ruel et al., 2001). Perilymphatic perfusion with $D_{1/5}$ agonist resulted in marked suppression of CAP amplitudes without changing summating potential (SP) amplitudes, suggesting an inhibitory action of these receptors on afferent dendrites. Antagonism of D_2 receptors also caused a significant suppression of CAP, what seems to be in accordance with the presence of presynaptic D_2 negative feedback autoreceptors on LOC efferent terminals (Halmos et al., 2005). However, reduction in hair cell measures like SP, cochlear microphonic (CM) and distortion product otoacoustic emission (DPOAE) amplitudes for perfusion of D_2 antagonist suggests that D_2 receptors are not solely confined to LOC efferent terminals or primary afferent dendrites (Garrett et al., 2011).

3.2. Ionotropic glutamate receptors: NMDA and AMPA receptors

AMPA and NMDA receptor antagonists failed to alter stimulation-evoked DA release, suggesting a lack of a tonic glutamatergic component in the regulation of cochlear DA release (Halmos et al., 2000). However, the application of NMDA onto isolated cochleae induces the release of DA and enhances the electrical stimulation-evoked release of DA (Halmos et al., 2008). The modulatory effect of NMDA on stimulation-evoked release favours the presence of NMDA receptors on LOC terminals (Fig. 1). In practice, electrical field stimulation releases transmitters from all axon terminals regardless of the upstream (somatodendritic) inhibitory or excitatory tone (Doleviczenyi et al., 2008; Halmos et al., 2008).

3.3. Metabotropic glutamate receptors

Several different types of metabotropic glutamate receptors (mGluRs) on both spiral ganglion cells and IHCs in the cochlea have been demonstrated by different laboratories (Bilak and Morest, 1998; Niedzielski et al., 1997; Safieddine and Eybalin, 1995). mGluRs have both slower and longer kinetics than ionotropic receptors; therefore, they typically mediate modulatory actions in the cochlea (Kleinlogel et al., 1999). Using an *in vitro* cochlea preparation, it was demonstrated that specific group I and III mGluR ligands failed to alter the release of DA from the cochlea, while group II mGluRs can modulate DA release, since the administration of the agonist 2R,4R-APDC increased DA release at rest (Doleviczenyi et al., 2005). Furthermore, electrical stimulation-evoked DA release is not affected by group II agonists in this study, suggesting that these receptors are not functionally present on dopaminergic axon terminals (Doleviczenyi et al., 2005). As the polarity of the modulation is opposite to what would be expected for an inhibitory receptor, it is reasonable to assume that mGluR2 receptors are located on other, presumably inhibitory, neurons, while the dopaminergic terminals themselves do not contain this receptor. Suppression of GABAergic inhibitory activity induces the disinhibiton of the dopaminergic terminal and underlies the observed DA-releasing effects (Doleviczenyi et al., 2005). These GABAergic fibres most likely express functional mGluR2/3 (Fig. 1). Through these mGluRs, glutamate released from IHCs can decrease GABA release, which leads to the disinhibition of DA-containing LOC terminals.

Disinhibitory mechanisms are widespread throughout the central nervous system. For example, in the hippocampus, GABA-containing projections innervate inhibitory interneurons, leading to the disinhibition of their target cells (Toth et al., 1997). More specifically, in the brain, the modulation of DA release by mGluRs located on GABAergic interneurons is also known to occur (Diaz-Cabiale et al., 2002; Feenstra et al., 1998). What could be the functional significance of mGluR-induced elevation in cochlear DA release? The facilitated outflow of DA inhibits the activity of afferent dendrites and counteracts their IHC-induced activation. Since the excess release of glutamate may lead to excitotoxic damage of afferent dendrites (e.g., in response to ischemia or acoustic trauma), the inhibition of afferent nerve overactivation provides an example of protective autoregulation; the "toxic" glutamate itself causes the release of the protective transmitter DA, thus reducing the consequences of overactivating ionotropic glutamate receptors. Taking these results together, dopaminergic terminals most likely lack group II mGluRs, but other GABA-containing LOC terminals express functional group II mGluRs (Doleviczenyi et al., 2005). It is important to note that group II and III mGluR agonists are widely considered to act as neuroprotective compounds (Nicoletti et al., 1996). The neuroprotective role of mGluRs has been described in other regions of the nervous system (David and Abraini, 2001; Moldrich et al., 2001).

3.4. The role of serotonin (5-HT)

The 5-hydroxytryptamine (5-HT)-containing efferent cochlear innervation originates in the periolivary area of the superior olivary complex system and projects to the cochlea. Serotonergic fibres, which belong to the LOC bundle, have been identified recently by immunocytochemistry in the cochlea around the inner and outer hair cells (Gil-Loyzaga et al., 1997, 2000). The concentration of 5-HT and its metabolite (5-HIAA) from rat cochleae has been quantified by a special HPLC method (Vicente-Torres et al., 2002), and 5-HT receptors have been detected in the organ of Corti by an RT-PCR study (Oh et al., 1999). 5-HT transporters have also been reported to be present in cochlear serotonergic fibres (Vicente-Torres et al., 2003). Blocking $5\text{-HT}_{1/2}$ receptors inhibits the compound action potentials of the auditory nerve (Bobbin and Thompson, 1978). 5-HT has been proposed to play a role in tinnitus; disrupted or modified 5-HT function may cause a reduction in auditory filtering and in tinnitus habituation (Simpson and Davies, 2000). In the cochlea, 5-HT_6 and 5-HT_7 receptors indirectly modulate DA release from LOC terminals (Fig. 1); because they are located on GABAergic neural elements, their primary action is to induce GABA release, which results in the inhibition of DA release (Doleviczenyi et al., 2008). In the CNS, 5-HT_6 receptors influence the activity of DA (Lacroix et al., 2004) and GABA (Cole et al., 2007; Schechter et al., 2005), whereas 5-HT_7 receptors modulate the release of glutamate and 5-HT itself (Harsing, 2006).

3.5. GABAergic mechanisms

As previously mentioned, GABA is one of the transmitters released from LOC efferents. Structural studies have revealed GABA-like immunoreactivity in the vicinity of OHCs and IHCs (Schrott-Fischer et al., 2002). It is also important to note that not all efferent fibres were GABA-positive (Schrott-Fischer et al.,

2002). This observation raises the possibility that GABAergic terminals can communicate with other non-GABAergic terminals within the olivocochlear bundle. It has been shown that functional $GABA_A$ receptors are required in dopaminergic LOC terminals; bicuculline, a selective antagonist of the $GABA_A$ receptor, significantly increases the release of DA at rest and elevates the electrical stimulation-evoked release of DA (Doleviczenyi et al., 2005). In addition, these GABA-containing fibres also express functional 5-$HT_{6/7}$ receptors (Doleviczenyi et al., 2008). GABAergic LOC fibres were also shown to be present in the human cochlea (Schrott-Fischer et al., 2002), thus highlighting the potential importance of GABAergic mechanisms in therapy. Using RT-PCR, in situ hybridisation and immunohistochemistry, it was shown that subunits of the inhibitory glycine receptor (GlyR), GlyRα3, GlyRβ and gephyrin, are expressed in the organ of Corti and in spiral ganglion neurons. Thus, this receptor also serves as a target molecule of efferent transmission in the cochlea (Dlugaiczyk et al., 2008).

4. The role of DA uptake in the cochlea

DA transporters, as essential components of dopaminergic neurotransmission, are present in LOC fibres, participate in the termination of DA action by taking up the released transmitter (Gaborjan et al., 1999) and play important roles in maintaining the spontaneous activity of auditory nerve neurons (Ruel et al., 2006). Indeed, the high-affinity DA uptake blocker, nomifensine, inhibited both the uptake of tritiated DA and, consequently, the electrical stimulation-evoked release of DA (Gaborjan et al., 1999). However, when nomifensine is applied between two electrical stimulations, the acute effect becomes visible; the electrical stimulation-evoked release of DA is significantly increased, but resting DA levels are not affected (Gaborjan et al., 1999; Halmos et al., 2005). In the presence of nomifensine, experimental ischemia fails to induce the release of cochlear DA (Halmos et al., 2005), suggesting the reversal of the transporter under ischemic conditions. There are several examples for the reverse operation of transporters in the central nervous system (Lendvai et al., 1996; Santha et al., 2000), particularly under ischemic conditions (Buyukuysal and Mete, 1999; Jabaudon et al., 2000; Vizi, 1998), and this transport in the opposite direction is also blocked by reuptake inhibitors (Buyukuysal and Mete, 1999; Lonart and Zigmond, 1991; Zelles et al., 1995).

5. Influence of nitric oxide production on cochlear DA release

NO is a highly diffusible transmitter in the brain that freely crosses biological membranes (Gally et al., 1990). The neuronal form of NOS is connected to NMDA receptors and primarily produces NO in response to NMDA receptor activation following stimulation by glutamate (Brenman and Bredt, 1997). In the organ of Corti, different isoforms of the nitric oxide synthase (NOS) enzyme have been identified (Michel et al., 1999). In support of the structural data, significant NO activity has been reported to occur in the cochlea, and this activity can be increased by the NOS substrate L-arginine and inhibited by N_{ω}-nito-L-arginine methyl ester (L-NAME) (Shi et al., 2002). It has also been suggested that NO in the human cochlea could act as a neurotransmitter or neuromodulator (Popa et al., 2001). nNOS is present in spiral ganglion cells and nerve fibres, fibre endings below the inner and outer hair cells, IHCs and OHCs, and Deiters' cells (Takumida et al., 2001). Neurochemical evidence indicates that the activation of NMDA receptors induces DA release in the cochlea. The NMDA-evoked release of DA results from a non-synaptic action; within the organ of Corti, the applied NMDA reaches receptors at different cellular targets (including the afferent dendrite) and induces the production of nitric oxide (NO), which in turn diffuses out to dopaminergic terminals and stimulates DA release (Halmos et al., 2008). The non-synaptic nature of NO has been suggested by recent findings that demonstrated the inhibition of monoamine transporters by NO (Kiss et al., 1999, 2004). Nevertheless, it is worth mentioning that, in the cochlea, NMDA receptor activation-induced DA release, which involves NO production, is not dependent on the DA transporter (Halmos et al., 2008). It has also been suggested that tinnitus can be initiated by increasing NO levels (Pall and Bedient, 2007). Glutamate perfusion can cause an elevation in the threshold of compound action potentials that could be prevented by pretreatment with the neuronal NOS inhibitor 7-nitroindazole, suggesting that NO mediates excitotoxicity during high glutamate exposure (Patel et al., 2008).

6. An ultra-short feedback loop via the local regulation of DA release

The feedback loop of the olivocochlear system involves the release of DA in the cochlea, which in turn influences the afferents, thereby modulating dopaminergic activity in the superior olive and the firing of the LOC system (Fig. 2). Based on our results (Doleviczenyi et al., 2005, 2008; Halmos et al., 2005, 2008), we suggest an additional ultra-short feedback loop not involving the brainstem; released glutamate can reduce its own excitatory effect on the auditory nerve by acting within the cochlea on the boutons of the lateral olivocochlear efferent system (Fig. 2). More specifically, glutamate released from IHCs, besides activating afferent dendrites through AMPA receptors, can reduce activity locally in the cochlea by releasing DA from the LOC system. The release of DA can be induced directly through NMDA receptors located on the dopaminergic boutons (Halmos et al., 2008) or indirectly

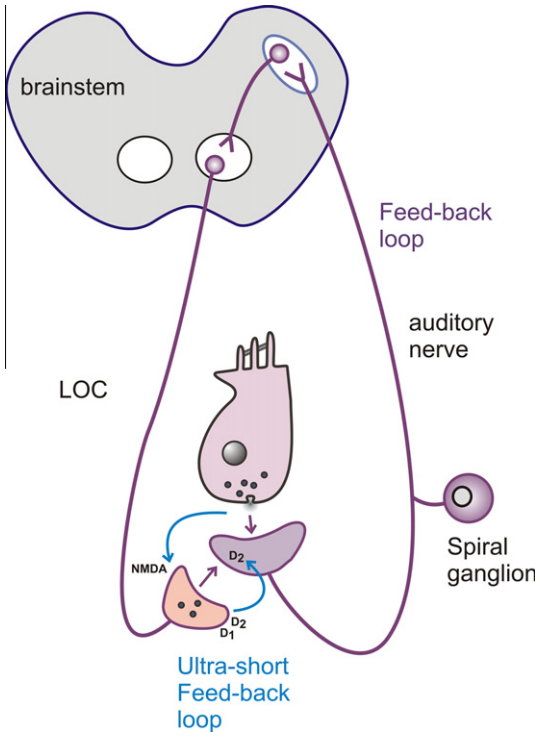

Fig. 2. Dopaminergic feedback loops in the cochlea. Schematic drawings of feedback loop mechanisms to protect cochlear cells against various types of damage. The ultra-short feedback mechanism is restricted to the cochlea, whereas the larger feedback loop requires an intact LOC and auditory nerve. The two loops converge at the level of DA mobilisation in the cochlea.

through group II mGluRs (Doleviczenyi et al., 2005) located on GABAergic boutons (Fig. 1). The activation of 5-HT_{6-7} receptors on GABAergic boutons has the opposite effect, i.e., it enhances the release of GABA, which reduces DA release (Fig. 1) (Doleviczenyi et al., 2008). The upregulation of DA release by local modulatory mechanisms may occur during harmful environmental changes and does not require brainstem activity. Given the widely accepted theory of dopaminergic protection in the cochlea, the pharmacological enhancement of such feedback mechanisms could be a potential target for the future therapy of SNHLs. D_2 antagonists, NMDA agonists, mGluR group II agonists, GABA antagonists or 5-HT_{6-7} antagonists, all of which can enhance DA release from LOC terminals, may serve as boosters of the ultra-short local feedback loop in the cochlea and can protect cochlear cells against harmful noxae during various physiological and pathophysiological processes. The administration of a 5-HT_7/D_4 receptor antagonist produced an even more pronounced enhancement of cochlear DA release (Doleviczenyi et al., 2008), i.e., increases during both the resting and electrical stimulus-evoked outflow. An augmented, multiple-target DA release action may form the basis of a potentially effective and novel therapy for SNHLs.

7. Role of cochlear DA release in certain forms of sensorineural hearing loss

7.1. Protection against excitotoxicity

Several forms of SNHLs (e.g., noise-induced hearing loss (NIHL), ischemia of the cochlea or presbycusis) involve excitotoxic damage of auditory neurons (Puel et al., 1998; Pujol and Puel, 1999; Pujol et al., 1992, 1993, 1990a; Ruel et al., 2007; Tabuchi et al., 2010).

Overstimulation of extrasynaptic Glu receptors (NR2B) leads to extreme Na^+ and Ca^{2+} influxes and the constant depolarisation of the cells. Increases in the concentration of intracellular sodium is always followed by water entry and the subsequent acute swelling of the afferent nerve (Billett et al., 1989; Pujol et al., 1990b). It is known that the accumulation of intracellular Ca^{2+} levels results in mitochondrial ROS production and the activation of different enzymes that degrade cellular components (Abi-Hachem et al., 2010; Fekete et al., 2008).

In the cochlea ischemia and noise exposure can induce afferent dendritic swelling under the IHCs (Puel et al., 1994; Pujol et al., 1990a). The acute application of glutamate receptor agonists can also result in afferent dendritic swelling (Gil-Loyzaga and Pujol, 1990; Puel et al., 1994; Pujol et al., 1985), which can be prevented by pre-perfusion with AMPA antagonists (Ruel et al., 2000). DA, released from the LOC efferents, has a protective effect against this excitotoxicity (Niu et al., 2007). LOC input is known to be important in noise-induced trauma; after LOC removal, noise can induce larger and more harmful effects in the cochlea compared to cases with functional LOC fibres (Darrow et al., 2007; Le Prell, 2007).

Under intense noise stimulation, significant effluxes of glutamate from the cochlea have been shown (Jager et al., 1998; Puel et al., 1998). Ischemic insults of the cochlea also result in an excessive release of glutamate from IHCs, likely from supporting cells adjacent to hair cells as well (Matsubara et al., 1998; Pujol et al., 1992), and increased levels of non-synaptically released Glu in the perilymph (Hakuba et al., 1997, 2000). It is worth mentioning that intense noise reduces cochlear blood supply, i.e., ischemia is part of the NIHL pathology (Le Prell et al., 2007; Nakashima et al., 2003; Okamoto et al., 1990; Thorne and Nuttall, 1987, 1989; Vass et al., 1995).

Ischemia can be studied *in vitro* with oxygen–glucose deprivation (OGD). OGD, by mimicking ischemic effects in a cochlear preparation, induced the elevation of basal DA levels via the reverse operation of the DA transporter (Halmos et al., 2005). This effect was revealed by the inhibition of D_2 receptors in LOC efferent terminals. These negative feedback receptors are not exclusively involved in the regulation of synthesis and the vesicular release of DA but are also involved in the activation of its reuptake into the terminal. Thus, D_2 receptor antagonism additionally interferes with the powerful reuptake that clears away DA and prevents its measurement in the extracellular space during the *in vitro* superfusion experiment (Halmos et al., 2005). In conclusion, the level of cochlear extrasynaptic DA appears to be an important factor during ischemia. Selective pharmacological interventions on D_2 receptors might provide a therapeutic approach for treating cochlear ischemia, which involves the excitotoxic damage of the primary afferent neurons.

Veratridine is an alkaloid, which is known to maintain the open state of voltage-sensitive Na^+ channels. Veratridine has been used as a simplified model of ischemia, mimicking the persistent Na^+ influx that is one characteristic event in the ischemic cascade (Malgouris et al., 1994; Pauwels et al., 1989). The application of veratridine induces significant DA release at rest and markedly enhances the electrically evoked release of DA (Halmos et al., 2002). We suggest that the influx of Na^+ and the elevation of intracellular Na^+ during ischemia also induces the release of DA. This is an inherently protective mechanism that can attenuate the overactivation of auditory dendrites by excessive glutamate release caused by ischemia (excitotoxicity). It has been shown previously that sound conditioning upregulates TH in the cochlea and LSO (Niu et al., 2007). At the same time, sound conditioning can protect against subsequent acoustic trauma, suggesting that the dopaminergic component of the LOC is likely to play an important role in cochlear neuroprotection (Niu et al., 2007).

7.2. Involvement in aminoglycoside induced ototoxicity

Neomycin, an ototoxic aminoglycoside antibiotic, can inhibit the electrically evoked release of DA *in vitro* (Gaborjan et al., 2001). This dopaminergic mechanism could be one potential cause of neomycin-induced damage in the cochlea. However, after a two week-long pretreatment with neomycin *in vivo*, acute doses of this antibiotic failed to induce significant effects on DA release, suggesting the existence of a preconditioning mechanism (Gaborjan et al., 2001). It is known that subdamaging or mildly injurious doses of aminoglycosides confer protection against a later, more injurious aminoglycoside insult (Maudonnet et al., 2008) or even NIHL (Fernandez et al., 2010).

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