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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

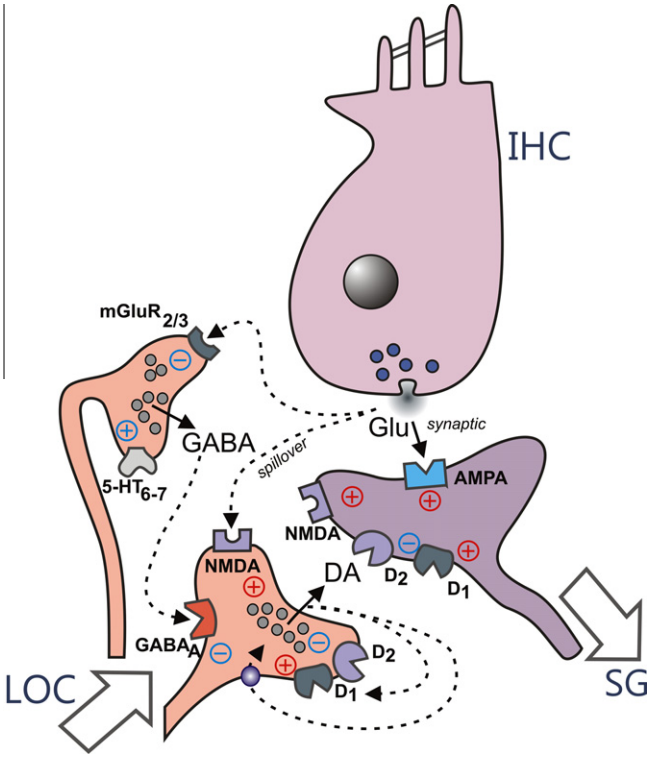

Fig. 1. Chemical anatomy of the inner hair cell – afferent dendrite – lateral olivocochlear efferent terminal complex in the cochlea. Neurochemical interactions of the inner hair cell (IHC) – afferent dendrite (SG) – lateral olivo-cochlear efferent (LOC) anatomical triad. The release of acetylcholine 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