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The Role of Purinergic P2X and P2Y Receptors in Hearing Loss

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Abstract

Hearing loss is the most common form of sensorineural impairment, affecting 5.3% of the worldwide human population. Whereas 1 in 500 children is born with hearing disorders, sudden or progressive forms of hearing loss can appear at adult age. However, the physiological and molecular mechanisms involved in this pathological process remain unclear. Interestingly, an increasing number of studies have demonstrated that purinergic receptors could play a key role on hearing disorders and auditory pathway dysfunctions. This mini review summarizes the current data suggesting a key role of purinergic signaling in cochlear hair cell functions and their involvement in progressive hearing loss. Taken together, these studies provide new knowledge in the biochemical and physiological mechanism of purinergic receptors in cochlear cell functions and open the door for the development of new drugs candidates involved in hearing loss treatment.

Keywords: Hair cells; Hearing loss; Purinergic receptor; Cochlear supporting cells; P2X receptor mutations

Cochlea and Hearing Loss

The cochlea is the sensory organ capable of perceiving sound over a range of pressure. The sensorineural organ responsible for the sound detection is the organ of Corti. This organ is located in the mammalian cochlea and harbors the auditory sensory epithelium containing the hair cells. These cochlear hair cells are classified in outer hair cells (OHCs) and inner hair cells (IHCs) and are organized in three and one rows respectively (Figure 1 Left panel) [1,2]. Each hair cell contains, at its apical surface, a mechanically sensitive stereocilia that respond to fluid motion. An extracellular matrix, the tectorial membrane, covers the apical surface of the organ of Corti and is attached to the hair bundles of OHCs (Figure 1 Left panel). The cell bodies of hair cells form specialized adhesive contacts with inner and outer supporting cells (ISC and OSC) that adhere at their basolateral surfaces to the basilar membrane, an extracellular matrix assembly with a different molecular composition from the tectorial membrane [3].

Hearing is initiated when sound waves that reach the outer ear travel through the ear canal to the tympanic membrane. Then, the vibrations are transferred onto the hair cells, leading to the deflection of the hair cell stereocilia [4]. This deflection causes mechanoelectrical channels to open leading to a massive influx of potassium ions from the endolymph to the hair cell [5], cell depolarization and the release of glutamatergic vesicles. The electrical signals are propagated to the nervous system through spiral ganglion neurons (SGN) and processed in the brainstem and auditory cortex [6].

Hearing loss affects 360 million persons worldwide, with a prevalence of 183 million adult males and 145 million adult females, and it is classified as the most common sensorineural disorder in humans [7]. The two principal causes of hearing loss in humans are environmental factors such as noise exposure, or ototoxic drugs and aged related auditory system senescence. Acoustic trauma is responsible for 10% of hearing impairment in adults, in particular military veterans [8]. Interestingly, the damaging effects of noise exposure are extremely variable among individuals, suggesting that genetics factors could play an essential role in the development of this disorder [9].

On the other hand, the most common form of sensorineural pathology in aging people is age-related hearing loss. This disorder is characterized by a symmetric and progressive hearing impairment that starts at high frequencies with a prevalence of 35% of individuals over 65 years of age [10]. However, as observed in hearing loss induced by noise exposure, not all humans suffer from age-related hearing loss, suggesting that both genetic and environmental factors play a key role in age-related hearing loss development.

Purinergic Receptors

Since the role of adenosine 5'-triphosphate (ATP) as an extracellular signaling molecule was discovered, a great deal of research has revolved around the purinergic receptors. Currently, it is firmly established that two structurally and functionally distinctive families of P2 purinergic receptors mediate intracellular signaling evoked by extracellular ATP: the ligand-gated ion channel P2X receptors and the G-protein-coupled P2Y receptors (GPCR) [11].

Seven different P2X receptor subunits (P2X1–P2X7) encoded by seven genes are expressed in mammalian cells [12] and these subunits are able to form functional homomeric or heteromeric receptors, except for the P2X6 subunit [13]. P2X receptors are widely expressed in several cell types, regulating a diversity of primary physiological processes from hearing neurotransmission to cell signaling.

P2X receptors function as classical ligand-gated ion channels selectively permeable to small physiological cations such as Ca^{2+}, Na^{+}, and K^{+}, with the exception of the human P2X5 receptor which exhibits significant Cl^{-} permeability. In response to brief agonist receptor activation, these receptors allow the entrance of cations playing an essential function in cell signaling and neurotransmitter release. However, the prolonged activation of P2X receptors leads to the formation of big cell pores conferring membrane permeability to large molecules of up to 900 Daltons [12].

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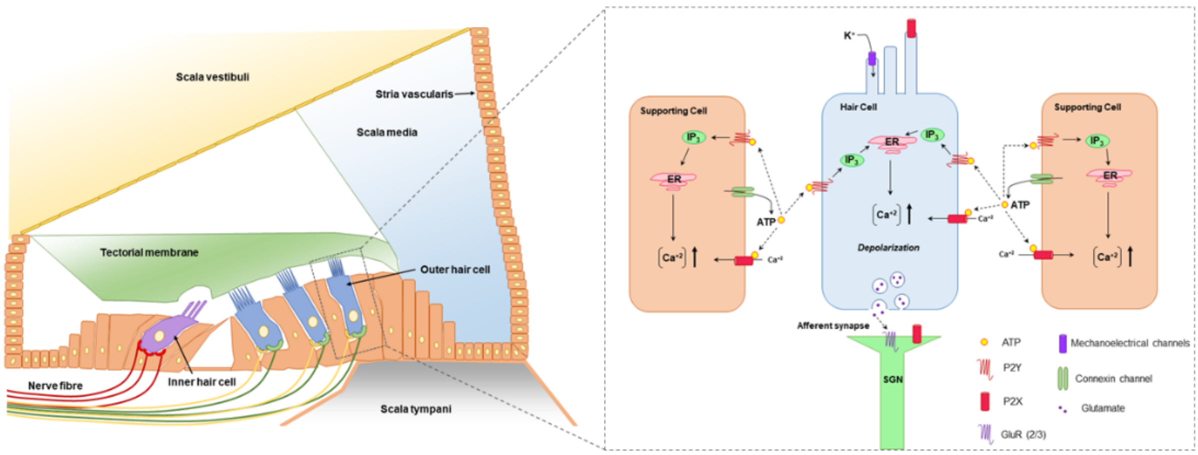

Figure 1: Left panel: Schematic representation of the auditory sensory organ. The scheme shows a cross section of the mammalian cochlea. Right panel: Scheme illustrating the relationship between purinergic receptors expressed in the hair cells and the supporting cells. ATP is released by supporting cells *via* connexin channels and binds P2X and P2Y receptors. Activation of P2X receptor allows entry of calcium into the hair cell and supporting cell. P2X receptors are also localized at the apical region of the cochlear hair cells, in association with the mechanoelectrical channels, and providing the entry of K^+ into the cells. The activation of P2Y receptors induces an increase of IP3 leading to endoplasmic reticulum (ER) calcium release. Increase of intracellular calcium concentration induces hair cell depolarization and release of glutamate vesicles. A possible association of P2X receptor with glutamate 2/3 receptor on the postsynaptic membrane of afferent SGN synapses has also been suggested.

Particularly, P2X2 receptors are largely expressed in the central and peripheral nervous system [14]. Moderate permeability to Ca^{2+} ions has been described for P2X2 compared to P2X1 and P2X4 receptors, however, this cation permeability is significantly higher than P2X3 receptors. In presence of short-term exposure to ligand, P2X2 displays slow desensitization compared to the fast desensitization observed in P2X1 and P2X3 receptors [15].

Until now, eight different functional mammalian P2Y receptors have been identified. As previously stated, P2Y are GPCR superfamily receptors with significant differences in ligand selectivity and G-protein coupling. Interestingly, these molecular differences have been explained by the low sequence homology between P2Y receptors.

Whereas the activation of P2Y1, P2Y2, P2Y4 and P2Y6 receptors leads to the activation of phospholipase C and inositol triphosphate (IP3) increasing intracellular Ca^{2+}, the activation of P2Y12, P2Y13 and P2Y14 inhibits adenylate cyclase reducing cAMP intracellular levels. P2Y11 is unique receptor that presents affinity to both Gq/11 and Gi proteins and therefore couple ligand binding to both intracellular signaling pathways [16]. In addition to these signaling mechanisms, the P2Y receptors mediate their cellular effects modulating other pathways such as inhibition of N-type voltage-gated Ca^{2+} channels in neurons and endocrine cell lines and activation of G protein-gated inward rectifier K^+ channels in neurons [17].

Role of Purinergic Receptors in Cochlear Functions

Several studies demonstrated that extracellular ATP plays an essential role in the embryonic cochlea development and regulates many different physiological functions in adult cochlea [18,19]. Importantly, P2X2 receptors are expressed in sensory hair cells and supporting cells of the organ of Corti and the afferent SGNs of cochlea [20]. In this way, whereas the complete role of P2X2 in cochlea cells remains poorly studied, increasing studies suggest that these receptors participate in many hearing function processes [21] such as sound transduction, auditory neurotransmission [20], OHC motility, gap junctions maintaining and hair cell cation recycling [22].

Recently, Morton-Jones and collaborators demonstrated that loss of the P2X2 receptor function in epithelial cells of the Reissner's membrane leads to extracellular ATP sensitivity loss affecting the functionality of the organ of Corti [23]. Moreover, high noise exposure leads to upregulation of P2X2 protein in the organ of Corti, probably due to a strong release of ATP into the endolymphatic compartment [24,25]. This increase of ATP in endolymph activates inner and outer hair cell P2X2 receptors leading to a cation shunt across the cochlear partition and then decreasing sound transduction mediated by the electromotive force of hair cells [19,20].

When endolymphatic ATP is elevated, K^+ entry into scala media is limited by a P2Y4 receptor pathway in the marginal cells of the stria vascularis. This complements the activation of ATP-gated ion channels assembled from P2X receptor subunits in the epithelial cells and hair cells which line the compartment. The K^+ efflux causes a fall in endocochlear potential which is a major component of the driving force for sound transduction. Direct depolarization of the hair cells *via* intrinsic ATP-gated channels would further reduce the sound-evoked receptor potential [26].

ISCs also spontaneously release ATP leading to IHCs excitation and neurotransmitter release, and ultimately inducing action potentials in

SGN that propagate to central auditory centers [27] (Figure 1 Right panel). At the same time, this released ATP also activates P2X and P2Y autoreceptors present in the ISCs increasing intracellular Ca^{2+}concentration and leading to a transient shrinkage of groups of ISCs [28].

Moreover, endolymphatic surface of the sensory epithelium also expresses purinergic P2Y2 and P2Y4 receptors. Thus, the ATP released into the endolymph also binds these receptors leading to phosphatidylinositol 4,5-bisphosphate hydrolysis and generating the second messengers IP3 and diacyl-glycerol [29]. Then, IP3 binds to intracellular receptors leading to an increase of cytosolic Ca^{2+} concentration from the endoplasmic reticulum (Figure 1 Right panel).

Finally, neurons of the cochlea display brief periods of high-frequency potential actions in the absence of sound. Tritsch and collaborators suggested that these spontaneous firings could be explained by the release of ATP from ISCs [27] due to the correlated activity between ISCs, IHCs and SGNs. Nevertheless, the role of ATP in cochlea cell functions remains controversial; Johnson and collaborators demonstrated that the inhibition of purinergic receptors with specific antagonists can also lead to hair cell excitation and that the effects of ATP in P2X and P2Y receptors can induce depolarization or hyperpolarization depending on the experimental conditions [30]. Taken together, these data suggest that purinergic receptors and ATP released by ISC play an essential role in cochlear cell signaling and sound transduction. However, additional studies need to be performed to understand the complex role of purinergic signaling in hearing system.

Mutations in Purinergic Receptors and Hearing Loss

The mutations in P2X2 receptors have been directly correlated with noise-induced hearing loss in humans. Since 2002, an increasing number of studies identified four mutations in P2X2 receptors, expressed in the cochlear sensory epithelium and the SGN, that cause sensorineural hearing loss: DNFA41 locus, p.Val60Leu, p.GLy353Arg and p.Asp201Tyr mutation.

In DFNA 41 locus mutation the P2RX2 gene has recently been identified as a progressive sensorineural hearing loss in two Chinese and one Italian family characterized by a late-onset. This mutation has an autosomal dominant trait with a bilateral non-syndromic sensorineural hearing loss at all frequencies [31]. This mutation leads to a phenotype starting in the second decade of life and reaching a plateau at the fourth decade.

The p.Val60Leu mutation, described for the first time by Yan and collaborators, leads to a progressive hearing impairment starting at the second decade of life. In this mutation, the valine is substituted with leucine in P2X2 receptors that are localized on the hair cells leading to a disruption of the disulfide bond that opens the channel when ATP binds [32].

More recently, another study identified a new autosomal dominant P2X2 receptor mutation p.GLy353Arg through a large Italian family. This mutation leads to a bilateral and progressive hearing impairment mainly affecting medium high frequencies between 1,000 and 4,000 Hz. Faletra and collaborators suggested that the change of a glycine to an arginine could destabilize the protein, affecting channel assembly, gating, ion selectivity and permeability [33].

Finally, a new mutation in the mitochondrial DNA, p.Asp201Tyr, was identified in 2015 in a family suffering myopathy, encephalopathy, lactic acidosis, stroke-like episodes and a severe progressive sensorineural hearing loss. This phenotype has been linked to the decrease in mitochondrial ATP production that might suppress the activation of P2X2 receptors and hence hearing loss [34]. However, the molecular and cellular mechanism leading to the progressive hearing loss in these patients remains unclear.

Purinergic Receptors as a Pharmacological Target for Hearing Disorders

The field of study on P2X receptors is relatively young. Because the role of P2X receptors in inner ear biology and hearing disorders remains poorly known, the development of pharmacological therapies becomes a difficult task. Nevertheless, in the last years some groups have developed new drug candidates targeting purinergic receptors and their efficacies in P2X signaling have been characterized by cell-based high-throughput screening methods.

Pharmaceutical companies are developing potent and selective P2X antagonists useful for the treatment of other pathologies such as pain, HIV-1 infection and arthritis and some of which are currently in phase I and IIa of clinical trials for several therapeutic applications [35,36].

Conclusion

In conclusion, because studies of the role of P2X2 receptors in the auditory system are quite recent, it is crucial to deepen the molecular mechanism of P2X2 in hearing loss in order to develop pharmacological and gene therapies for noise-induced hearing loss, for the whole population as well as for patients suffering from progressive hearing loss induced by purinergic receptor mutations.

Competing Interests

Author declares no competing interests.

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