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The α9α10 nicotinic acetylcholine receptor: A compelling drug target for hearing loss?

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Abstract

Introduction—Hearing loss is a major health problem, impacting education, communication, interpersonal relationships, and mental health. Drugs that prevent or restore hearing are lacking and hence novel drug targets are sought. There is the possibility of targeting the α9α10 nicotinic acetylcholine receptor (nAChR) in the prevention of noise-induced, hidden hearing loss and presbycusis. This receptor mediates synaptic transmission between medial olivocochlear efferent fibers and cochlear outer hair cells. This target is key since enhanced olivocochlear activity prevents noise-induced hearing loss and delays presbycusis.

Areas covered—The work examines the α9α10 nicotinic acetylcholine receptor (nAChR), it’s role in noise-induced, hidden hearing loss and presbycusis and the possibility of targeting. Data has been searched in Pubmed, the World Report on Hearing from the World Health Organization and the Global Burden of Disease Study 2019.

Expert opinion—The design of positive allosteric modulators of α9α10 nAChRs is proposed because of the advantage of reinforcing the MOC-hair cell endogenous neurotransmission without directly stimulating the target receptors, therefore avoiding receptor desensitization and reduced efficacy. The time is right for the discovery and development of α9α10 nAChRs targeting agents and high throughput screening assays will support this.

Keywords

α9α10 nicotinic receptors; hearing loss; positive allosteric modulators; presbycusis; tinnitus

1. Introduction

Hearing loss is one of the most prevalent sensory disabilities. It is a major public health problem, given that its impact on human communication and quality of life is

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devastating. Depending upon the age of onset, it impairs language development, education, communication, employment, mental health, interpersonal relationships and/or psychosocial well-being[1, 2]. Moreover, population-based observational studies have shown that hearing impairment is strongly related to accelerated cognitive decline and dementia risk in older adults[3–5]. Indeed, hearing loss is now known to be the largest modifiable risk factor for developing dementia, exceeding that of smoking, high blood pressure, lack of exercise, and social isolation[6]. According to the World Report on Hearing from the World Health Organization[7] and the Global Burden of Disease Study 2019[8], more than 1.5 billion people worldwide experience some decline in their hearing capacity during the course of their life and at least 430 million will require care. If unaddressed hearing loss results in an annual global cost of more than $ 980 billion. An increase of more than 1.5-fold in hearing loss is projected for the coming decades and 2.45 billion people for 2050. Most dramatic, compared with other disease categories in the Global Burden of Disease Study[8], age-related and other hearing loss was the third largest cause of global years lived with disability in 2019, after low back pain and migraine. Moreover, it ranked first among sensory disorders and was the leading cause for individuals older than 70 years. Hearing loss is sometimes accompanied with phantom sound perception, also known as tinnitus, which can be a debilitating condition on its own. Thus, tinnitus is perceived by approximately 20% and debilitating in 2–3% of the world population[9]. These striking facts indicate that hearing loss is a growing public health issue and burden, which requires an urgent call for global attention and action. In the present expert opinion I discuss the pros and cons of targeting inner ear hair cell α9α10 nicotinic acetylcholine receptors (nAChRs) for the prevention and/or treatment of hearing loss. The rational for targeting this receptor is based on the fact that it mediates synaptic transmission at the medial olivocochlear efferent fiber-outer hair cells synapse and that enhanced olivocochlear activity prevents noise-induced hearing loss and delays presbycusis[10–13].

2. Noise-induced hearing loss and related disorders

2.1. Noise-induced hearing loss

Congenital hearing loss is the most common sensory disability and affects approximately 1–2 out of 1000 newborns. In more than 50% of cases the cause is genetic, being 70–80% non-syndromic[14, 15]. To date a total of 124 non-syndromic hearing loss genes have been identified[16] and this number is constantly increasing, highlighting the wide variety of proteins involved in auditory physiology and development. Hearing loss increases with age, and age-related hearing loss or presbycusis is a multifactorial condition with contributions from, and interactions among, numerous variables including genetic factors that determine the rate and extent of hair cells and neural degeneration, pre-existing ear conditions, chronic illnesses, use of ototoxic medicines and lifestyles. Several environmental, lifestyle, or other modifiable factors contribute to the etiology of hearing impairment across the lifespan. This implies that hearing impairment in adults may be prevented or delayed[17].

Within the environmental or lifestyle preventable factors that contribute the most to hearing loss is the exposure to elevated noise, which can be of occupational, recreational or environmental origin[18–20]. High levels of workplace noise remain a problem in all regions

of the world[7]. A high risk of hearing loss is also faced due to loud levels of sound in recreational settings[21–23]. These include the prolonged listening to personal audio devices at high levels, attending to concerts or the use of firearms. The WHO estimates that over 50% of people aged 12–35 are at risk of having hearing problems due to the use of portable audio devices[7].

Exposure to loud sounds is also the main known factor leading to tinnitus or phantom sound perception, the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source[24, 25]. It is perceived by approximately 20–25 % of the word population[9]. Although the vast majority of people can live with their tinnitus, for 2–3 % of the world population, the auditory component is accompanied with suffering and so it is considered as tinnitus disorder[26]. In the latter case, the perceived sound is associated with emotional distress, cognitive dysfunction, and/or autonomic arousal, leading to behavioral changes and functional disability. Growing evidence indicates that the pathophysiology of tinnitus disorder involves changes in neuronal activity not only in different parts of the auditory pathway, but in different brain non-auditory areas as well[24, 27, 28]. At present there is not a single Food and Drug Administration (FDA) nor European Medicines Agency (EMA) approved drug on the market[25, 29–31]. Thus, there is still a significant unmet clinical need for a safe and effective drug targeting tinnitus relief. Even a drug that produces a small but significant effect would have a huge therapeutic impact. Since the exposure to overly loud sounds is the main known factor leading to tinnitus[23, 32], drugs that prevent or restore noise-induced hearing loss, would be beneficial for tinnitus.

2.2. Hidden hearing loss

Hair cell damage was classically considered as the main contributor to the hearing loss produced by exposure to loud sounds, whereas neural degeneration was regarded as a secondary event to the loss of hair cells, due to loss of neurotrophic support[33]. Moreover, the consensus indicated that cochlear neural loss occurred only after hair cell death. Thus, hair cells swell within minutes and disappear hours after an exposure to a very loud sound, leading to permanent threshold elevations[34]. In contrast, the time course of neuronal degeneration was reported to be slower, since myelinated axons of cochlear nerve fibers begin to disappear 1–2 weeks postexposure and loss of their cell bodies in the spiral ganglion is evidenced after 1 month[35]. However, it has recently been demonstrated that synaptic connections between hair cells and cochlear neurons can be damaged in the absence of hair cell loss[36]. In fact, noise exposures causing only reversible hearing threshold shifts (and no hair cell loss) cause a permanent loss of >50% of the synaptic connections between hair cells and the auditory nerve, without hair cells loss[33]. This synaptic loss or synaptopathy silences large numbers of cochlear neurons and does not affect the test of threshold detection performed in the normal audiogram. Therefore, it has been named “hidden hearing loss”. Cochlear synaptopathy compromises understanding speech in a noisy environment[37], which is a classic complaint of those who have been exposed to loud sounds or in aged people.

2.3. Presbycusis

Auditory function declines with age and includes the reduction in threshold sensitivity and poor speech discrimination and auditory processing, especially in noisy environments[38]. Genetic and ambient factors are probably involved in presbycusis. The decline in threshold sensitivity is most likely due to loss of hair cells[38]. However, even when auditory thresholds are preserved, degraded temporal resolution and the difficulty in understanding speech in background noise have been classically attributed to central and cognitive factors[38]. However, recent work in rodents has shown that synaptic aging is a key contributor to the hearing performance declines of aging listeners[39]. Thus, inner hair cell (IHC)-afferent synaptic loss progresses from youth to aged mice throughout the cochlea, long before changes in thresholds or hair cell counts are observed. Type I afferent fiber loss follows the synaptic loss, with a delay of several months[39]. This same synaptic aging most likely occurs in humans, as evidenced in a recent work performed in post-mortem human cochlea[40]. Although presbycusis occurs in the absence of exposure to loud sounds[39, 40], this ambient factor adds further insult to aging.

3. Treatment

Prevention remains the best option for limiting the effects of acoustic trauma produced by the exposure to loud sounds. This requires education, regulations, legislation and workplace noise policy enforcement. A prospective, randomized controlled assessment of the short- and long-term efficacy of a hearing conservation education program in Canadian elementary school children, has shown that a community-based health promotion project around hearing loss aids students to develop their knowledge and skills in health advocacy, highlighting the importance of hearing protection education[41]. Moreover, a Cochrane systematic review has shown that enforcement of legislation and better implementation of occupational hearing loss prevention programs can reduce noise levels in workplaces[42]. However, not all countries have and/or enforce hearing protection regulation programs[43].

In many situations prevention from exposure to loud sounds is not feasible to the extent necessary to protect hearing capabilities. A clear example is that observed in the military, where acute noise damage may result from a blast exposure, such as a discharge from a weapon or detonation of an explosive[44, 45]. In fact, hearing loss is the most common service-connected disability. Therefore, alternative strategies to merely prevention are needed. In this regard, the search for pharmacological treatments to prevent and/or treat noise-induced hearing loss is an active niche of research.

A plethora of drugs have been investigated and/or used in the treatment of noise-induced hearing loss, with different levels of outcomes and, in general, with poor solid evidence to support their use. In this regard, local or systemic steroids are commonly used to address the noise post-exposure inner ear inflammatory process[46]. A systematic review and meta-analysis on the use of steroids has recommended future additional studies with the inclusion of control groups, precise definition of acoustic trauma intensity and duration, and genetic polymorphisms[46]. Since oxidative stress and the release of free radicals in the form of reactive oxygen and nitrogen species take place during noise-induced hearing loss[47, 48], antioxidants have been evaluated as a treatment option both in animal models and

humans, with contradictory results. These include N-acetylcysteine, ginseng, co-enzyme, vitamin A, vitamin C, vitamin E, and vitamin B12, glutathione, D-methionine, ebselen and resveratrol[49]. On the other hand, noise exposure leads to hair cell death displaying features of both apoptosis and necrosis as well as necroptosis, a necrotic-like process[49]. Therefore, agents that prevent hair cell apoptosis by disrupting mitogen-activated protein kinase (MAPK) cell death signaling through peptide inhibition of c-Jun N-terminal Kinase have been tested[50]. Other compounds such as calcium antagonists, vasolidators, NMDA receptor antagonists and neurothrophins also have been tested in animal models[49].

4. The α9α10 nicotinic acetylcholine receptor: a possible pharmacological target?

4.1. α9α10 nicotinic acetylcholine receptors

Nicotinic acetylcholine receptors are a subfamily of the pentameric ligand-gated ion channels involved in many physiological and pathological processes[51]. Each receptor subtype is composed of different subunits, encoded by paralogous genes. They show a similar fivefold symmetrical arrangement of subunits around a central pore, and are composed of extracellular and transmembrane (TM) domains (Figure 1). The extracellular domain contains the orthosteric ligand binding sites and folds into a highly conserved immunoglobulin-like β-sandwich. The TM domain consists of four α-helices, with TM2 lining the channel pore, surrounded by a ring made of TM1 and TM3 α-helices[51, 52]. According to their main tissue of expression, in vertebrates, they are divided into three subgroups: neuronal, muscle and hair cell nAChRs[53]. Thus, neuronal nAChRs are formed by as yet not fully characterised combinatorial arrangements of α2-α7 (α8 in non-mammals) and β2–4 subunits[54–56]. In addition, receptors formed by the same subunits, but with alternate stoichiometry[57–62], further extend the complexity of neuronal nAChRs. On the other hand, muscle receptors are formed by $\alpha 1_2\,\beta 1\gamma$, and δ, or ε subunits[63, 64]. Finally, and in contrast to neuronal receptors, the nAChR subunits expressed in cochlear hair cells have a very strict co-assembly pattern, encompassing only α9 and α10 subunits[65–67].

The α9α10 heteromeric receptor is composed only of α subunits[65, 67, 68]. Alternate stoichiometries have been reported for this receptor. Thus, at equimolar expression of both subunits, an $(\alpha 9)_2(\alpha 10)_3$ stoichiometry has been determined[69], whereas expression of a 10-fold excess of α9 compared with α10 in *Xenopus* oocytes can lead to an additional receptor isoform with a $(\alpha 9)_3(\alpha 10)_2$ stoichiometry[70]. The number of binding sites at the receptor in the different stoichiometries is unknown. However, the contribution of α9 and α10 subunits to the binding site is non-equivalent[71], and the different binding sites in alternate stoichiometries can have differential pharmacological properties[70]. Recent crystal structures of the homomeric extracellular domain of the α9 subunit bound to antagonists, is beginning to shed light into the molecular interactions between binding site residues and ligands[72]. Moreover, they serve as a template for molecular dynamics simulations of the extracellular domains of the α9α10 nAChR in pentameric assemblies[73].

α9α10 nAChRs are the most divergent within all nicotinic receptors, showing striking differences in their degree of sequence conservation compared to other nAChR subunits

and to their orthologues in different species, their restricted expression pattern, their subunit co-assembly rules and their functional properties[53, 67, 68, 74–78]. In fact, whereas all nAChRs are activated by nicotine, the agonist that gives rise to the name of the family, α9α10 are blocked by this compound[65, 67, 68, 76]. Moreover, α9α10 nAChRs are potently blocked by antagonists of glycine, $GABA_A$ and serotonin type 3 receptors, thus sharing pharmacological properties with other members of the Cys loop family[67, 75, 77]. Therefore, α9α10 has been described as an odd cousin within the old family of α9α10 nAChRs[79].

4.2. The efferent medial olivocochlear system

The best described function of the α9α10 nAChR is at the organ of Corti of the inner ear, where it mediates synaptic transmission between cholinergic medial olivocochlear fibers and outer hair cells (OHCs)[53, 66–69, 74, 76–78, 80–86]. This nicotinic synapse is inhibitory, since the activation of the α9α10 hair cell nAChR leads to an increase in intracellular Ca^{2+} and the subsequent opening of small conductance Ca^{2+}-activated K^+ (SK2) channels, thus leading to hyperpolarization of hair cells (Figure 2)[87–93]. Outer hair cells are responsible for amplification of incoming sounds and fine tuning of the basilar membrane through a mechanism known as somatic electromotility based on the motor protein prestin[94, 95]. The MOC neurons constitute a sound-evoked negative feedback loop. As sound pressure level increases, the firing rate of MOC fibers increases[96]. This results in the suppression of the contribution of OHCs to amplification of sound-induced motion in the sensory epithelium[97]. Thus, the MOC system reduces the gain of the cochlea through a direct inhibition of OHC function. Moreover, the strength of cochlear inhibition is proportional to the rate of MOC activity[97–99]. Thus, the MOC efferent system is part of a cochlea-brainstem-cochlea reflex pathway, which enables the central nervous system to modulate hearing at the periphery through the activation of α9α10 nAChRs, providing a stimulus-related control of the cochlea[100].

4.3. α9α10 nicotinic acetylcholine receptors and protection from noise-induced hearing loss

The MOC system has been implicated in several functions of the auditory process; important for this Expert Opinion is the protection from damage produced by the exposure to loud sounds[11, 12, 101–105]. The protective effect of the MOC system from acute and chronic noise-induced hearing loss has been described in different animal models[103, 106–109]. In addition, the strength of the MOC system is inversely correlated with the degree of noise-induced hearing loss[102]. Moreover, activation of the MOC system also reduces neuropathy produced during hidden hearing loss[10]. Short-term plasticity of the MOC-OHC synapse is responsible for shaping MOC inhibition and encodes the transfer function from efferent firing frequency to the gain of the cochlear amplifier[110]. In this regard, the activity of the α9α10 nAChR is key in the protective effect of the MOC system. Thus, overexpression of the α9 nAChR subunits in OHCs reduces acoustic injury from exposures causing either temporary or permanent damage[11]. In addition, a *Chrna9L9T* "gain-of-function" knockin mice with a threonine for leucine change at position 9′ in the second transmembrane domain of the α9 nAChR subunit, leading to an enhanced strength of MOC-mediated cochlear inhibition[12, 111], shows less permanent hearing loss following exposure to intense noise[12]. The introduction of this threonine for leucine change, results in an α9α10 nAChR with

a decrease in the desensitization rate, an increase in the potency of ACh and spontaneous receptor openings when expressed in an heterologous expression system[112] and in prolonged synaptic currents with slower desensitization kinetics when assessed in an *ex-vivo* organ of Corti preparation (Figure 3)[12, 110, 111]. *Chrna9L9T* knockin, with enhanced efferent activity, have also proven that the extent of hidden hearing loss produced by noise exposure is dependent upon the level of MOC cholinergic activity[113]. Thus, strengthening MOC feedback by enhancement of α9α10 nAChR activity can reduce noise-induced hearing loss.

The mechanism/s underlying the protective effect of the MOC system are poorly understood. One can propose that they could be the consequence of either a mechanical or a metabolic OHC effect. The former would derive from the reduction of amplification of cochlear vibrations produced by OHC electromotility and the latter from a direct protection from damage of the very acoustic vulnerable OHCs[11]. A mechanical effect is less favored, since the magnitude of the reduction of cochlear vibrations by MOC activation is higher at low-mid, but probably not at high levels of acoustic input[114]. This suggests that the MOC protective effects are likely independent of SK2 activation that leads to the OHC K^+ efflux, cell hyperpolarization and inhibition of electromotility. This is further supported by the finding that, contrary to that observed when overexpressing the α9 nAChR subunit[11], a mouse model that overexpresses SK2 and shows enhanced MOC-evoked cochlear suppression, does not exhibit resistance to acoustic injury[115].

If an alternative metabolic effect of MOC activation leads to protection of OHCs damage, a downstream effect of Ca^{2+} signaling needs to be considered, due to the high calcium permeability of mammalian α9α10 nAChR[74, 76, 116]. An increase in intracellular Ca^{2+} might activate protein phosphorylation of the motor protein prestin or of cytoskeletal components, leading to changes in OHC axial stiffness[117, 118]. On the other hand, a traumatic insult leads to the activation of multiple cellular signaling pathways that affect gene expression and are a balancing act between those involved in cell survival to restore homeostasis and in cell death via apoptotic or necrotic pathways. Although in general one considers that calcium overload leads to cell death, the controlled Ca^{2+} entry through ion channels is also involved in pro-survival or anti-apoptotic pathways, through the activation of protein kinase C[119]. One accepted mechanism of hair cell damage is the accumulation of reactive oxygen and reactive nitrogen species[120, 121], which are mainly produced in the mitochondria and increased by the accumulation of extracellular calcium[120]. On the other hand, mitogen-activated protein kinases (MAPKs) are important mediators of both damage and survival signals[120]. Thus, stress-activated MAPKs include c-Jun-N-terminal kinase (JNK) isoforms and p38 MAPK can lead to apoptosis and necrosis, whereas the extracellular regulated kinase (ERK) is associated with cell survival and proliferation[120]. The ERK protective pathway is dependent upon Ca^{2+} activation[122]. In addition, the phosphoinositide-3 kinase/protein kinase B (PI3K/Akt) pathway is implicated in hair cell survival[123]. One can propose that Ca^{2+} entry at the base of OHC through α9α10 nAChRs could participate in hair cell survival mechanisms. In this regard, Ca^{2+} entry and distribution at the base of OHCs is tightly controlled[93]. Electron micrographs have shown postsynaptic cisterns within OHCs, closely aligned in apposition with presynaptic efferent synaptic contacts (Engström, 1958; Fuchs et al., 2014; Saito, 1980; Smith & Sjöstrand, 1961). These might serve as a barrier for free calcium diffusion in the cytoplasm. Moreover, they can serve as a Ca^{2+} store,

modulating efferent synaptic responses through both Ca^{2+} ATPases (of the sarcoplasmic type, SERCA) and ryanodine receptors (RyR) (Evans et al., 2000; Grant et al., 2006; Lioudyno et al., 2004; Sridhar et al., 1997).

4.4. α9α10 nicotinic acetylcholine receptors and presbycusis

Recent experiments in mice have shown that MOC efferents are important for the long-term maintenance of cochlear function during aging, even in the absence of acoustic overexposure[124]. Thus, MOC de-efferentation accelerates age-related amplitude reduction in cochlear neural responses and increases the loss of afferent synapses, a characteristic of hidden hearing loss[124]. Moreover, C57 mice, which are used as a model for presbycusis, show decline in the neural population of the trapezoid body nuclei and efferent inhibition[125] and in MOC-OHC synaptic terminals, independent of OHC loss[126]. In addition, experiments in mice have shown that MOC decline precedes age-related hearing loss[125]. Recent work has shown that, compared to rodents, MOC efferent innervation in humans is less abundant and also decreases with aging[127]. Functional studies have further indicated that the contralaterally evoked MOC reflex is weakened for frequencies <1500 Hz (where medial efferent effects are largest) in middle age human subjects[128]. Taken together, the presented evidence suggests that loss of MOC function may play a role in the development of presbycusis in both humans and animal models[127]. Therefore, the MOC-OHC synapse plays a key function in age-related hearing loss. In the absence of high levels of sounds as a confounding factor, aged *Chrna9L9T* knockin mice with enhanced MOC strength, are protected from the loss of acoustic sensitivity, cochlear synaptopathy and hair cell loss, compared to aged wild-type mice which exhibit elevated acoustic thresholds together with loss of afferent synapses of IHCs throughout the cochlea and some OHC loss[13]. The mechanisms underlying the protective effect of the MOC system on inner ear aging are mainly unknown, but could derive from the activation of pro-survival or anti-apoptotic pathways as suggested above for noise-induced hearing loss. Taking together, these results suggest that strengthening MOC feedback by enhancement of α9α10 nAChR activity can slow cochlear aging.

4.5. α9α10 nicotinic acetylcholine receptors in pharmacoterapeutics

In general, nicotinic receptor ligands can be classified into agonists, allosteric agonists, antagonists and allosteric modulators[129]. Orthosteric agonists and antagonists contact highly conserved amino acids in the ACh-binding site at the interface of two adjacent subunits[129]. An additional unorthodox orthosteric ACh-binding site has been recently discovered at some α/α and β/α subunit interfaces, in nAChRs with alternative stoichiometries bearing 3 α and 2 β subunits. Unorthodox sites synergize with orthodox sites to promote activation[130–134]. Allosteric agonists induce nAChR activation but do not bind to the orthosteric binding site. On the other hand, allosteric modulators may stimulate (PAM) or inhibit (NAM) nAChR function elicited by the agonist by binding to regulatory sites other than ACh binding sites[129, 135–137]. In addition, silent allosteric modulators (SAMs) have also been reported for nAChRs. These compounds can block the effect of other allosteric modulators (PAMs, NAMs or allosteric agonists) by binding competitively at an allosteric binding site. Three types of effects from PAMs have been identified for nAChRs. Type I PAMs increase the agonist peak responses in the absence of changes in desensitization

kinetics[138–140]; type II PAMs increase agonist peak responses, slow desensitization kinetics and reactivate desensitized receptors[138, 139, 141]; type III PAMs are allosteric agonists, they increase agonist activation and can also activate nAChRs directly in the absence of agonists[142, 143]. Nicotinic receptor agonists (both full and partial) have beneficial effects in clinical and/or preclinical studies for CNS disorders. This include addiction, obsessive–compulsive disorder, pain, schizophrenia, autism, attention deficit/hyperactivity disorder and Parkinson's and Alzheimer's disease (for reviews see[129, 144, 145]). However, chronic treatment with agonists may provide suboptimal benefit because sustained receptor activation leads to desensitization. Moreover, the fact that neuronal subunits assemble into different combinatorial assemblies giving rise to a plethora of nAChRs that play a role in a number of different neural functions, leads to agonists with considerable off target side effects. On the other hand, PAMs which can reinforce the endogenous cholinergic neurotransmission without directly stimulating the target receptors, do not lead to desensitization, have less side effects and have recently appeared as attractive pharmacotherapeutic compounds for CNS disorders[129].

The observation that the α9α10 nAChR has a restricted expression pattern, are not expressed in the brain[66, 84, 146–148] and have a different pharmacological profile when compared to other nAChRs, makes this receptor a suitable pharmacotherapeutic target for the design of drugs with less side effects, specially of central origin. The pharmacotherapeutic activity of α9 and/or α9α10 nAChR antagonists have been investigated in several types of pain in animal models, probably due to the expression of α9α10 nAChR in different immune cells involved in inflammatory processes[149–152]. Moreover, α9 and/or α10 nAChR subunit blockers have been also suggested to be of use in animal models of immune diseases such as experimental autoimmune encephalomyelitis[153, 154]. In addition, the NMDA and α9α10 nAChR antagonist neramexane[155, 156], has been tested in clinical trials for the treatment of tinnitus without success (https://clinicaltrials.gov/). The allosteric α9α10 nAChR antagonist alphaO-Conotoxin GeXIVA, has resulted in antitumor effects[157, 158]. However, the potential use of α9α10 nAChR PAMs in therapeutics has not been investigated. The observation that in *Chrna9L9T* knockin mice, which are resistant to permanent noise-induced and hidden hearing loss and have a delayed presbycusis[12, 111], efferent synaptic responses are prolonged and ACh responses are potentiated and have a slower desensitization kinetics (Figure 3), poses putative α9α10 nAChR type II PAMs as potential inner ear pharmacotheraputic drugs. The serendipitous discovery that the store active compound ryanodine[159] and the serotonin type 3 receptor agonist 1-(*m*-chlorophenyl)-biguanid, potentiate α9α10-mediated ACh-responses[77], with no intrinsic activity *per se*, opens a possible avenue for the design of positive allosteric modulators for this nAChR subtype. So far the search for α9α10 PAMS has been hampered by the lack of high throughput screening assays of small molecule libraries. The recent successful expression of these receptors in HEK cells coupled to FLIPR calcium assay[160] opens a new area in the search for α9α10 nAChR selective lead compounds as otoprotectants. Moreover, the availability of the crystal structure of the α9 subunit extracellular domain[72], and the feasibility of radioligand binding assays of compounds to purified extracellular α9 protein fragments, will further aid to decipher the orthosteric or allosteric interaction of novel α9α10 nAChR ligands[161].

5. Conclusions

Hearing loss is a major health problem that affects the quality of life if left unattended. The exposure to loud sounds is the most prevalent and modifiable environmental risk factor leading to hearing loss. Thus, prevention from exposure to damaging sound levels is the most efficient and safe way to proceed. This requires education and regulation enforcement. However, protection from and/or avoiding the exposure to loud sounds is not always possible. Therefore, a plethora of drugs have been used to prevent from or treat noise-induced hearing loss, with very limited efficacy. Medial olivocochlear fibres that contact OHCs, protect the inner ear from the damage produced by the exposure to overly loud sounds. Thus, compounds that enhance MOC activity appear as a near physiological way to approach the problem. In this regard, the properties of the α9α10 nAChR, which mediates synaptic transmission between MOC fibres and OHCs, has been extensively studied in recent years and appears as a possible pharmacotherapeutic target. Positive allosteric modulators of nicotinic receptors, compounds which can reinforce the endogenous cholinergic neurotransmission without directly stimulating the target receptors, do not lead to desensitization, have less side effects and have recently appeared as attractive pharmacotherapeutics for CNS disorders. Similar compounds that target α9α10 nAChRs would be an alternative way to tackle the debilitating condition resulting from noise-induced hearing loss.

8. Expert opinion

The market for a drug indicated for prevention of noise-induced, hidden hearing loss and presbycusis is huge and will grow further. In spite of the existence of such a huge market, compounds in pharma pipelines are scarce. Although a wide range of compounds with different cellular targets have been tested in animal models and some used in the clinics, their effectiveness is limited, and serendipitous discoveries of effective pharma treatments are lacking. In this regard, the α9α10 nAChR emerges as a new target to be investigated. The rationale behind this new avenue of research is that activation of the α9α10 nAChRs present in OHCs prevents noise-induced, hidden hearing loss and presbycusis. Two alternative compounds could be developed: agonists that bind to the orthostheric ligand bind site or positive allosteric modulators that enhance agonist activity. Compared to other nAChRs, very few agonists of α9α10 nAChRs have been described so far and most classical nAChR agonists act as antagonists of this receptor[67]. The crystal structure of the α9 extracellular domain, together with molecular docking simulations and mutagenesis experiments, are beginning to decipher residues that impair agonist binding in α9α10 compared to other nAChRs[72, 162, 163]. In this regard, very recent discoveries shed light into novel α9α10 nAChR agonists[164].

In the absence of α9α10 nAChRs agonists, positive allosteric modulators, appear as the best option. In fact, PAMS of nAChRs in general are considered as a better pharmacotherapeutic tool, since *in vivo* efficacy of ligands binding to the orthosteric site is limited due to desensitization. This is circumvented by using PAMs, which lack any intrinsic activity, but can enhance the effect of the orthosteric endogenous agonists[138, 139, 141]. The best example of PAMs used in clinical settings are the benzodiazepines which enhance $GABA_A$

receptor activity, another member of the pentameric ligand-gated ion superfamily[165]. Although no nAChR PAMS are approved for therapeutics yet, a wide range of them have been developed for neuronal receptors with promising results. The proof of concept that allosteric potentiation of α9α10 nAChRs responses is feasible is provided by the results with ryanodine[159] and the serotonin type 3 receptor agonist 1-(*m*-chlorophenyl)-biguanid[77]. However, the first next step in order to prove that α9α10 nAChRs PAMS are effective in hearing disorders, is to test them in animal models of noise-induced hearing loss. Moreover, additional α9α10 nAChRs PAMS need to be discovered and tested. This is now facilitated by the recent success in the expression of these receptors in cells coupled to calcium imaging, which allows high throughput small molecule screening[160]. Moreover, the known crystal structure of the α9 subunit, coupled to molecular modelling, will aid to decipher the binding site of PAMS and facilitated further virtual screening for compounds[166].

Targeting α9α10 nAChRs as a pharmacotherapeutic approach leads to several open questions that will need to be addressed in the future. First, although it is well established that enhancement of the MOC system prevents noise-induced and hearing hidden loss, will this approach be efficacious as otoprotectants immediately after the damage is produced? This would be ideal in order not only to prevent, but to treat these disorders. Second, the pharmacokinetics of these compounds and the passage through the blood-cochlea barrier need to be taken into consideration for a systemic versus a local drug delivery. Finally, auditory perceptual side effects due to the activation of the MOC system and the reduction of the gain of the cochlea need to be investigated. Despite these caveats, much progress has been made in understanding cochlear physiology and the biophysical and pharmacological properties α9α10 nAChRs, an odd member of the nicotinic cholinergic family of receptors. The time is right for the search of α9α10 nAChRs targeting compounds.

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Article highlights

- Hearing loss is one of the most prevalent sensory disabilities. It is a major public health problem, given that its impact on human communication and quality of life is devastating.
- Within the environmental or lifestyle preventable factors that contribute the most to hearing loss is the exposure to elevated noise, which can be of occupational, recreational, or environmental origin.
- Several drugs have been investigated and/or used in the treatment of noise-induced hearing loss; a spectrum of outcomes has been observed and there is poor evidence to support their use.
- The protective effect of the medial olivocochlear system from acute and chronic noise-induced hearing loss has been described in animal models. Thus, enhancing the strength of the MOC system appears is a means to protect from noise-induced hearing loss.
- Since the α9α10 nAChR mediates synaptic transmission between MOC fibers and cochlear hair cells, it appears to be a novel target for the development of drugs that prevent noise-induced hearing loss.
- The development of positive allosteric modulators of α9α10 nAChRs is proposed as a novel approach in the prevention from hearing disorders produced by exposure to loud sounds.

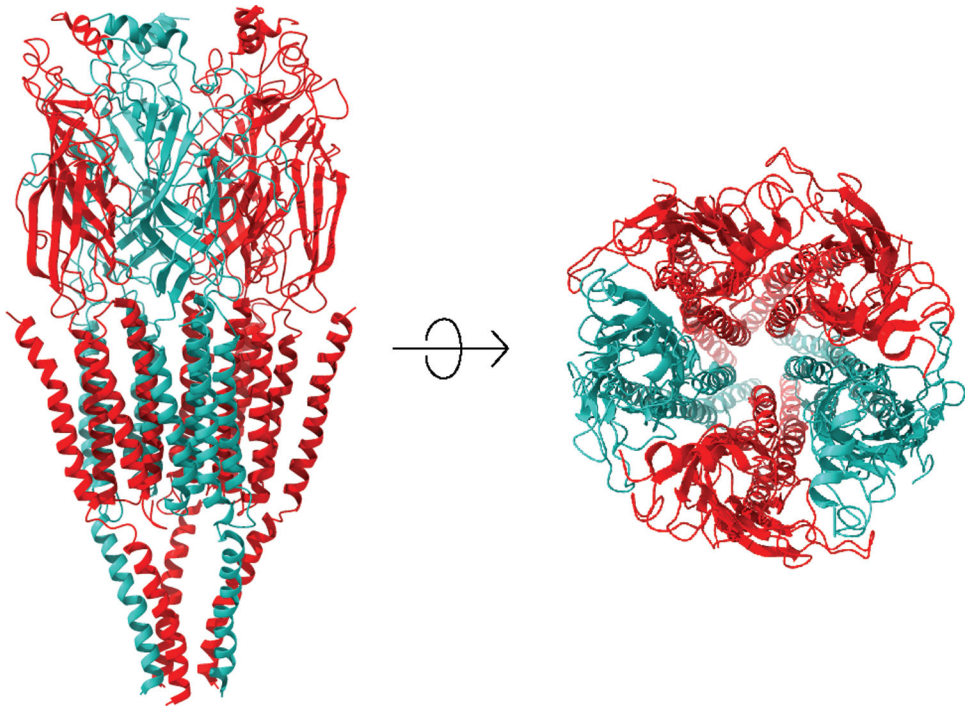

Figure 1.

Ribbon structure of a heteromeric pentameric nicotinic acetylcholine receptor, showing the arrangement of subunits around the channel pore. Front and upper views are provided. The extracellular domain contains the orthosteric ligand binding sites and folds into a highly conserved immunoglobulin-like β-sandwich. The transmembrane domain consists of four α-helices, with TM2 lining the channel pore, surrounded by a ring made of TM1 and TM3 α-helice. Reproduced from Lipovsek et al (2021)[79] under Creative Commons Attribution (CC BY) license.

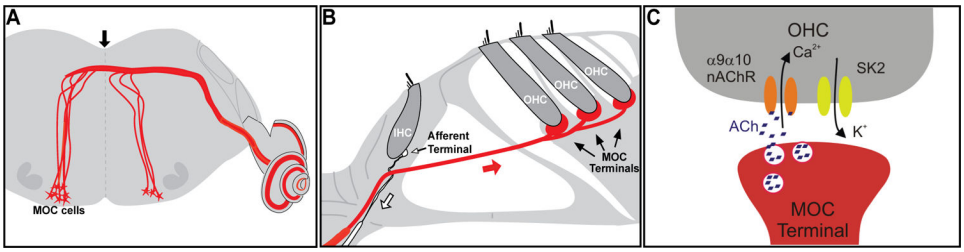

Figure 2.

Schematics of the MOC System. (A) MOC efferent neurons are located in the superior olivary complex of the brainstem and project to the cochlea; (B) MOC fibers make direct synaptic contacts at the base of the OHCs; (C) At the MOC-OHC synapse ACh is released. It binds to α9α10 nAChRs present at the OHCs, leading to Ca^{2+}- influx and the subsequent activation of Ca^{2+}-dependent K^+ (SK2) channels and hair cell hyperpolarization. The white arrow in (B) indicates the afferent fibers that bring the information from the IHCs to the central nervous system, and the red arrow indicates the MOC fibers. Reproduced from Taranda et al (2009)[12] under Creative Commons Attribution (CC BY) license.

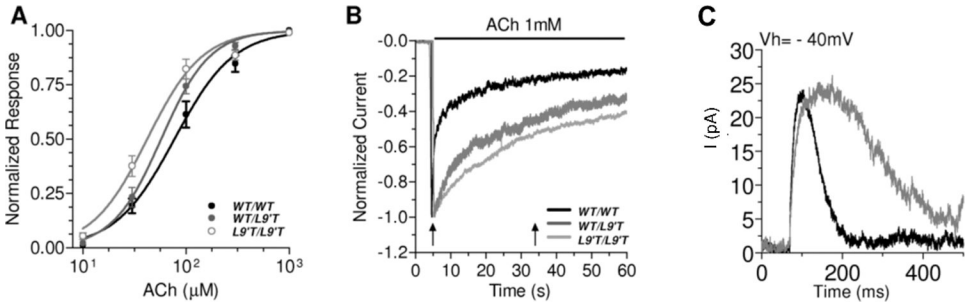

Figure 3.

Hypersensitive and Slowly Desensitizing responses in *Chrna9L9T* knockin mice. (A) Acetylcholine is more potent in α9α10 nAChRs of mutant mice; (B) Hair cell responses to 1 mM ACh during 1 min show slower desensitization kinetics in mutant mice; (C) Spontaneous synaptic MOC-hair cell currents are prolonged in mutant mice. Adapted from Taranda et al (2009)[12] under Creative Commons Attribution (CC BY) license.