**INVITED REVIEW**

# Age-related hearing loss pertaining to potassium ion channels in the cochlea and auditory pathway

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## Abstract

Age-related hearing loss (ARHL) is the most prevalent sensory deficit in the elderly and constitutes the third highest risk factor for dementia. Lifetime noise exposure, genetic predispositions for degeneration, and metabolic stress are assumed to be the major causes of ARHL. Both noise-induced and hereditary progressive hearing have been linked to decreased cell surface expression and impaired conductance of the potassium ion channel $K_V7.4$ (KCNQ4) in outer hair cells, inspiring future therapies to maintain or prevent the decline of potassium ion channel surface expression to reduce ARHL. In concert with $K_V7.4$ in outer hair cells, $K_V7.1$ (KCNQ1) in the stria vascularis, calcium-activated potassium channels BK (KCNMA1) and SK2 (KCNN2) in hair cells and efferent fiber synapses, and $K_V3.1$ (KCNC1) in the spiral ganglia and ascending auditory circuits share an upregulated expression or subcellular targeting during final differentiation at hearing onset. They also share a distinctive fragility for noise exposure and age-dependent shortfalls in energy supply required for sustained surface expression. Here, we review and discuss the possible contribution of select potassium ion channels in the cochlea and auditory pathway to ARHL. We postulate genes, proteins, or modulators that contribute to sustained ion currents or proper surface expressions of potassium channels under challenging conditions as key for future therapies of ARHL.

**Keywords** Kv7.4 · Kv7.1 · BK · SK2 · Kv3.1 · Presbycusis

## Introduction

Age-related hearing loss (ARHL), or presbycusis, is the most prevalent sensory deficit in the elderly [1]. Although it is not life-threatening, this condition is associated with significant psychological and medical morbidity, including social isolation, frailty, depression, and cognitive decline [2–5]. As a major risk factor for dementia [6], the prevention of hearing loss with age has

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been recently suggested as a foremost modifying factor to lower future dementia prevalence [7]. ARHL occurs in most mammals with variations in the age of onset, rate of decline, and magnitude of degeneration in the cochlea and the auditory pathway [8–11]. The affected cochlear structures include the stria vascularis and its vasculature, spiral ligament, sensory hair cells, and auditory neurons. Until recently, the dysfunction of the stria vascularis resulting in a reduced endocochlear potential (EP) was assumed to be a primary cause of ARHL [1, 12, 13]. However, new evidence from analyzing temporal bones of the elderly challenges this long-held view, showing that hair cell loss not only occurs in predominantly high-frequency regions but also extends to low-frequency regions in ARHL preceding stria vascularis degeneration [14]. Based on this observation, lifetime acoustic noise exposure was suggested as a primary cause of hearing loss with age, particularly due to outer hair cell (OHC) damage after acoustic overexposure, which is suggested to be the major contributor to ARHL [14]. Moreover, increasing evidence suggests that even in the absence of detectable loss of hearing sensitivity, neuronal degeneration of synaptic auditory fibers or ascending auditory projections can precede hearing

threshold loss and contribute as an additional hallmark of ARHL to difficulties in speech discrimination with advancing age, especially in noisy environments [15–17]. Thus, noise exposure as a major cause of ARHL affects not only OHC over age [14] but also age-related synaptopathies and neuropathies [8], gradually leading to degeneration of spiral ganglion neurons (SGNs) [16, 18] and central auditory processing deficits [19, 20]. Furthermore, independent of lifetime noise exposure being linked to damaged hair cells and neurons, individuals with cardiovascular risk factors, e.g., hypertension, diabetes, smoking, or increased serum cholesterol, exhibit a high risk of developing hearing impairment over age [21].

We hypothesize that any limits in metabolic supply, e.g., from oxidative stress after acoustic trauma or limitations during ischemic insults, endanger particularly sensitive stages that require high energy supply or exhibit vulnerability for radical oxygen species (ROS) as the precursor of ARHL. Indeed, ROS contribute through reduced mitochondrial activity and enhanced oxidative damage to aging processes in all organs, and thus negatively affect hearing with advancing age [22]. We postulate that select potassium ion ($K^+$) channels in the cochlea and ascending auditory pathway, which are known to critically depend on continuous recycling processes for proper surface expression, are vulnerable, early targets for limitations in energy supply. $K^+$ channels show extreme genetic heterogeneity and functional diversity unmatched by other types of ion channels, which suggests them as one of the primary targets of excess ROS. Moreover, strong evidence exists that ROS-mediated oxidation of $K^+$ channels is a recurring theme in the aging nervous system and is intrinsically involved in certain neuropathies [23]. Here, we focus on functionally relevant $K^+$ channels in the cochlea and auditory pathway, which share common temporal expression during the final differentiation stages of the organ of Corti prior to hearing function in rodents, hypothesizing that late differentiation stages are the ones affected early during aging, offering a therapeutic window that could allow functional restoration before cell death [24]. We discuss the following $K^+$ channels with functional expression during or after hearing onset, that is, around postnatal day (P) 12 in rodents, and around embryonic week (EW) 27 in humans (Fig. 1): (i) $K_V7.4$ (KCNQ4) maintains OHC receptor potential [25–30]; (ii) $K_V7.1$ (KCNQ1) is expressed in marginal cells of the stria vascularis [31–33]; (iii) calcium ion ($Ca^{2+}$)-activated potassium channels BK (KCNMA1) and SK2 (KCNN2) are involved in repolarization of OHC and termination of $Ca^{2+}$ action potential (AP) firing in medial olivocochlear (MOC) efferent fibers [34, 35]; and (iv) $K_V3.1$ (KCNC1) in SGNs and ascending auditory circuits [36] are shown to be involved in temporal precision of sound processing [37]. In this review, we first summarize the expression profiles and physiological functions of these $K^+$ channels, then discuss their individual roles in the context of age- and noise-dependent hearing loss, and the contribution

of genetic predisposition to progressive hearing loss over age. Finally, we address respective possibilities and advantages in targeting $K^+$ channels for therapeutic intervention against ARHL.

# $K^+$ channels in the auditory system

## $K_V7.4$ (KCNQ4)

OHC provide the mammalian ear with fast electromechanical amplification, which is required for the dynamic range and speed of sound encoding by the cochlea [38]. A direct mechanical gating of mechanoelectrical transduction channels modulates the input current at cochlear locations of sound stimulus-specific frequencies. This influx of $K^+$ through apical mechanosensitive channels depolarizes the membrane and drives the contraction of OHC by the motor protein prestin [39]. The speed of this action depends on the capacitance and conductance of the OHC at resting membrane potential, which in turn critically depend on determinants of OHC conductance maintained through the efflux current $I_{K,n}$, mediated by the voltage-gated potassium channel subunit $K_V7.4$ [40].

While $K_V7.4$ expression [41, 42] and its current $I_{K,n}$ [40] are detected prior to hearing onset along the entire basolateral membrane of OHC in mice (Fig. 1a), $K_V7.4$ is redistributed after the onset of hearing (P12-14), becoming restricted solely to the basal pole (Fig. 1b) [43, 44]. This localization suggests that $K_V7.4$ serves to extrude $K^+$ ions that enter OHC through the apical mechanosensitive channels [28, 29, 45, 46]. $K_V7.4$ is also detected in inner hair cells (IHCs) [25, 26], SGNs, and several nuclei along the auditory pathway, e.g., cochlear nuclei and inferior colliculus [25, 29].

Impaired surface expression of $K_V7.4$ in hair cells has been shown to be a primary step of hearing loss [47–50]. In *Kcnq4* knock-out mice, Carignano et al. [49] showed that the number of OHC slowly decreased at a young age with increasing cell loss up to complete degeneration at oldest ages. Degeneration of IHCs was also observed, but only in the adult stage. The loss of this important $K^+$ channel in OHC results in a chronic depolarization, possibly increasing $Ca^{2+}$ influx through voltage-gated $Ca^{2+}$ channels and causing their subsequent degeneration due to chronic cellular stress [51].

## $K_V7.1$ (KCNQ1)

The sensory cells of the inner ear are in contact with the fluids in the scala media which is filled with endolymph, the extracellular fluid with high $K^+$ concentration. $K^+$ is the major charge carrier for sensory transduction and its proper circulation is of great importance for the process of hearing. $K^+$ ions are secreted into the endolymph by the stria vascularis, enter the hair cells through apical mechanosensitive non-selective

cation channels, and exit these cells via their basolateral membrane, then migrate through supporting cells and fibrocytes towards the stria vascularis using a network of gap junctions where they are reabsorbed by strial marginal cells and released into the endolymph [52, 53]. $K_V7.1$ (KCNQ1) and its β-subunit KCNE1 form a channel complex that is expressed in the mature organ of Corti in the apical membrane of marginal cells of the stria vascularis where it mediates the slow delayed rectifier current $I_{K,s}$ [31–33, 54]. As components of $K^+$ circulation, $K_V7.1$ and KCNE1 are responsible for the secretion of potassium to the endolymph [55, 56], generating the EP [57, 58].

$K_V7.1$ is expressed throughout the body including the liver, lung, heart, and cochlea [31–33]. The homomeric form of $K_V7.1$ gives rise to a slowly activating and deactivating voltage-dependent potassium current [33]. However, in the inner ear, $K_V7.1$ modulates the kinetics by assembling to KCNE1 to form a heteromeric channel [32]. This results in a drastic slowdown in channel activation, a positive shift in voltage activation threshold, and an absence of inactivation [31]. During cochlear development, $K_V7.1$ was not detected at several embryonic stages in mice (Fig. 1a), indicating that its expression is first established during the postnatal stages (Fig. 1b) [59].
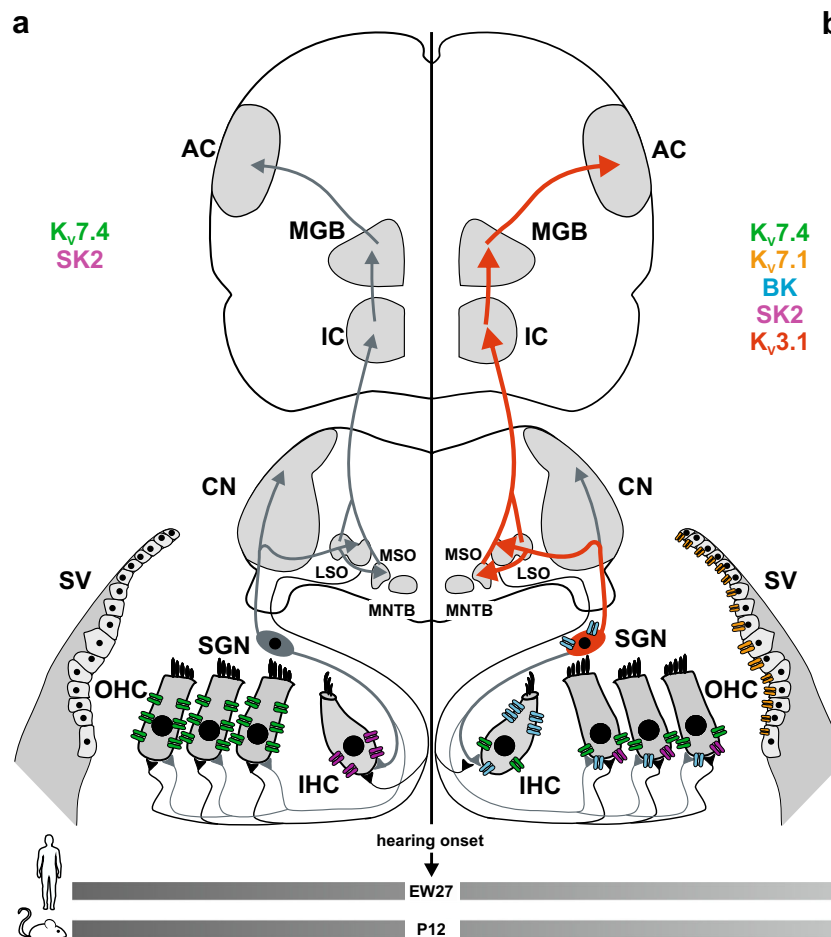


**Fig. 1** $K^+$ expression along the ascending auditory pathway before and after hearing onset. **a** Before the onset of hearing, potassium ion ($K^+$) channels are mainly expressed in the organ of Corti. In the outer hair cells (OHC), $K_V7.4$ (KCNQ4, green) is found along the entire basolateral membrane, while the inner hair cells (IHCs) express the calcium-activated potassium channel SK2 (KCNN2, purple) before postnatal day (P) 12 in mice, corresponding to embryonic week (EW) 27 in humans. For reference, afferent (gray) and efferent (black) neural projections are shown. **b** In the mature organ of Corti, the endolymph of the scala media contains a high concentration of $K^+$, which is mediated by $K_V7.1$ (KCNQ1, orange) channels in the apical marginal cells of the stria vascularis (SV). During auditory stimulation, endolymphatic $K^+$ enter the OHC at the basolateral membrane, and leave the cell via $K_V7.4$, BK (KCNMA1, blue), and SK2 channels. In the IHC, $K^+$ exits the cell through $K_V7.4$ and BK channels. The expression of BK channels was identified at the lateral wall of IHC as well as in the cell bodies of spiral ganglion neurons (SGNs). The auditory signal is then transmitted from the cochlea to the cochlear nucleus (CN) via rapidly firing neurons containing $K_V3.1$ (KCNC1, red arrows) channels. From here, parvalbumin-positive interneurons project onto the lateral and medial superior olive (LSO and MSO, respectively) and the medial nucleus of the trapezoid body (MNTB), whose fibers also express $K_V3.1$. The inferior colliculus (IC) receives input from the contralateral (not shown) and ipsilateral superior olivary complex. The fibers from the IC project to the medial genicular body (MGB) and the signals are then transmitted to the auditory cortex (AC) via rapid firing, $K_V3.1$ expressing neurons

Loss of functional $K_V7.1$ or KCNE1 leads to Jervell and Lange-Nielsen syndrome which is characterized by cardiac arrhythmia [60–63] and associated with congenital deafness in humans [32, 62, 64, 65]. Potassium secretion into the endolymph is consequently disturbed causing a defect of endolymph production and a collapse of the Reissner membrane [66].

## BK (KCNMA1) and SK2 (KCNN2)

Calcium-activated potassium channels are divided into two broad categories, small conductance calcium-activated SK channels and large conductance, voltage-gated, and calcium-sensitive BK channels [67]. SK channels have high $Ca^{2+}$ affinity and long open times, while BK channels are distinguished by significant differences in voltage sensitivity, single-channel conductance, $Ca^{2+}$ affinity, and gating kinetics [68]. These channels share the common functional role of coupling the increase in intracellular $Ca^{2+}$ concentration to hyperpolarization of membrane potential, thus playing an important role in cellular excitability and maintaining $K^+$ homeostasis [69].

Calcium-activated $K^+$ conductance has been described in both OHC and IHCs [45, 70]. BK decreases membrane time constants and enables the fast repolarization of hair cell receptor potentials [46] and efferent fibers [71]. BK channels in hair cells appear to show tonotopic gradients of increasing expression from apical (low frequency) to basal (high frequency) regions [34, 35, 72]. The stronger expression in high-frequency regions suggests a contribution of BK channels to high-frequency hearing in mammals. Furthermore, application of acetylcholine, a major efferent neurotransmitter, has been shown to exclusively activate BK currents in high-frequency OHC as opposed to SK currents in the lower-frequency OHC [35], and has been shown to modify efferent inhibitory synaptic responses in high-frequency OHC [73].

In the developing mouse, SK2 channel expression in IHCs was demonstrated during the first two postnatal weeks with a peak around P9 (Fig. 1a), disappearing during hearing onset with decline of cholinergic axosomatic efferent IHC innervations (Fig. 1b) [74]. BK channel expression has been identified in the cell bodies of SGN as well as in inner and outer sensory hair cells at the onset of hearing around P12 (Fig. 1b) [75, 76]. The appearance of the fast BK current, $I_{K,f}$, in IHCs has been shown to coincide with the disappearance of spontaneous action potentials, transforming mature mammalian IHCs into high-frequency signal transducers [77, 78]. During the first four postnatal weeks, $BK\alpha^{-/-}$ mice surprisingly did not show any obvious hearing deficits [51]. High-frequency hearing loss developed in $BK\alpha^{-/-}$ mice only from approximately 8 weeks postnatally onward and was accompanied by a lack of distortion product otoacoustic emissions, suggesting OHC dysfunction.

## $K_V3.1$ (KCNC1)

The *Kcnc1* gene yields two $K_V3.1$ subtypes (a and b) through alternative splicing [79], but $K_V3.1b$ has been shown to predominate in the adult rodent brain [80, 81]. Apart from the medial nucleus of the trapezoid body (MNTB) and anteroventral cochlear nucleus (AVCN), $K_V3.1$ is also expressed in neurons of the reticular thalamic nucleus and parvalbumin-positive (PV+) interneurons of the cortex and hypothalamus [81, 82]. $K_V3.1$ belongs to the delayed rectifier channel family and is located on presynaptic terminals [83–85]. Its high activation threshold and rapid activation and deactivation in response to voltage changes reduce the AP duration while simultaneously maximizing firing frequency [86]. This special characteristic of $K_V3.1$ for maximizing firing frequencies is related to its distinct expression profile in fast spiking interneurons [81, 82] and the important role it plays in the auditory system.

During auditory pathway maturation, $K_V3.1$ levels increase in SGNs between P4 and P8, reducing AP latencies and duration after hearing onset [87, 88]. The expression level of $K_V3.1$ rises dramatically near the onset of hearing along with the maturation of fast auditory processing as shown in the brainstem [89–91] and the inferior colliculus (Fig. 1b) [92, 93]. This expression profile in fast PV+ interneurons makes $K_V3.1$ a key contributor to the lowered threshold and shortened latency of cortical auditory responses, which can be measured after the sharpening of cortical receptive fields [94] at the end of the critical period after hearing onset. Thus, receptive field maturation coincides with the maturation of a network of fast-spiking GABAergic PV+ interneurons [95–98], predicted to mature in the auditory pathway with fast auditory processing after hearing onset [99]. Accordingly, given the optimal design of $K_V3.1$ for high-rate repetitive firing [100, 101], it has been identified as critical for fast-spiking PV+ interneurons [102]. Also, the key components in the auditory pathway required for auditory discrimination, the MNTB and AVCN, contain neurons that fire at very rapid rates, requiring the expression of $K_V3.1$ for rapid repolarization of AP during sound-induced activity [103–105]. MNTB neurons of $K_V3.1$ deficient mice were incapable of following high-rate stimulation or sustaining high-rate firing AP [37], demonstrating that $K_V3.1$ is essential for the rapid firing patterns. Given that hearing impairment can lead to a decline in $K_V3.1$ expression in the MNTB [36, 106], it is likely that the lack of $K_V3.1$ channels is a key contributor to deficits in fast auditory discrimination over age [107].

## Noise exposure linked to ARHL

The driving mechanisms of hearing loss over age remain largely unclear. Already in rodent animal species that are

widely used as models for human hearing, the age-related loss of cochlear function is highly variable; different mouse lines display hearing loss as early as 5 weeks after birth, determined partly by species, strain, and animal history, but also partly by lifetime auditory exposure determined by noise intensity level, duration, predictability, exposure context, and other characteristics of the sound [108]. In healthy-aged Mongolian gerbils, auditory-evoked potentials show a decrease of responses before the loss of auditory sensitivity, which is attributed to age-related pathologies in the auditory periphery [109, 110]. Studies in quiet-aged gerbils suggest that loss of synapses is the earliest age-related degenerative event (reviewed in [111]), preceding strial dysfunction and other cochlear pathologies [112]. Functional studies on aging rats have confirmed this [113] and extended the functional consequences of the loss of synapses beyond hearing sensitivity towards the loss of central compensatory action of the brain to make use of the few remaining auditory signals. In the cochlea, aging in gerbils and rats is characterized by threshold increase and concurrent loss of normal OHC phenotype from the second third of their lifespan onwards, which is related to a reduced brain-derived neurotrophic factor (BDNF) expression levels in the auditory nerve [114].

In CD-1 mice, often used as a model for human hearing, the EP is already lost at the age of 9 months, and the sensory organ is completely degenerated [115]. CBA/CaJ mice are described to have normal EP and excellent hearing for a large portion of their lifespan. Nevertheless, they display a remarkable acceleration of ARHL when repeatedly exposed to "benign" noise during their lifespan [116, 117]. By contrast, 129/SvEv mice are exceptionally resistant to noise-induced hearing loss [118], but preexisting anomalies in substrains of 129/SvJ mice predispose the ear to degenerate prematurely when interacting with K$^+$ channel deletion [118]. Finally, ROS-induced activation of DNA damage in senescence-accelerated mouse-prone 8 (SAMP8) mice are discussed as the driver for ARHL [119]. ROS can be induced in the ear by exposure to moderate, nevertheless harmful, acoustic noise [120, 121] causing an accumulation of toxic noise events throughout lifetime (reviewed in [122]). We have to assume that even the early loss of synaptic contacts between sensory hair cells and SGNs or synaptopathy [17] can be traced back to cumulative excitotoxic injury events [123], the largest source of which is likely to be noise exposure [124, 125].

One of the earliest events following metabolic limitations during noise exposure is the impairment of membrane surface expression of distinct K$^+$ channels in the cochlea, a process that is here suggested to have a pivotal role in ARHL. Both K$_V$7.4 (KCNQ4) and BK (KCNMA1) channels are required for normal hearing and have been suggested to protect OHC in cochlear regions that register high frequencies from Ca$^{2+}$ overload [47, 72]. Functional loss in OHC has been linked to the loss of K$_V$7.4 in the membrane of the OHC, preceding

their degeneration in the middle- and high-frequency coding cochlear compartments [51, 126]. The loss of BK$\alpha$ led to a similar phenotype as by pharmacological blockage of K$_V$7.4 channels, suggesting that a loss of the *BK* gene increases susceptibility for progressive ARHL, similar to *KCNQ4* mutation [26, 47, 51, 78]. Consistent with that assumption, exposure to a low-frequency, non-traumatic sound has been found to not affect hearing sensitivity of wild-type mice, but mice with *BK$\alpha$* gene deletion experienced a dramatic loss of hearing sensitivity within the stimulated low-frequency hearing range [72]. It is important to note that the affected low-frequency range was not part of the hearing range affected by accelerated ARHL in the young unexposed BK$\alpha$ deficient mice, thus confirming that the low-frequency cochlear compartments are rendered susceptible by the absence of BK. The low-frequency noise exposure extended the loss of KCNQ4 from OHC towards the low-frequency cochlear compartments affected by the noise exposure, confirming that the hearing loss resulted from the absence of KCNQ4 from hair cell plasma membrane [72]. The metabolic balance due to the fast repolarization of the receptor potential is a requirement for the healthy homeostasis of hair cells. Thus, the maintenance of KCNQ4 and BK in the OHC membrane is most critical to counteract a Ca$^{2+}$ overload of hair cells, irrespective of whether induced through excitotoxic, ototoxic, or noise exposure events, all of which are challenges that accumulate over advancing age. The activity in MOC efferent fibers contacting OHC plays an important role to activate BK and SK2 channels through acetylcholine release. Therefore, any reduction in MOC efferent fibers, which were previously shown to decline with advancing age [127], is expected to increase susceptibility to noise-induced hearing loss over age, due to reduced potential to rapidly remove K$^+$ from OHC, as can be predicted from various studies [34, 51, 72, 128, 129].

Furthermore, the protective role of BK channels is not limited to the hearing organ. In the mammalian central nervous system, BK is expressed in the neuron soma, processes, and presynaptic terminals, where it drives the membrane potential towards the potassium equilibrium potential to re- and hyperpolarize the neuron [130]. To study the importance of central BK deletion in the brain, normal hearing mice are required. Fortunately, the F1 generation of a hybrid sv129/C547/Bl6 background of mice with genetic deletion of the BK channel has documented good hearing up to the age of 15 weeks [131], which again confirms the multifactorial nature of BK gene deletion-related progression of hearing disorder. Most strikingly, these mice nevertheless display slower learning capacity and no improvement of pre-pulse inhibition of the acoustic startle response over days [131]. This strongly suggests that besides the protective role of cochlear BK channels [51, 72], they further contribute to the integrity of central neuronal circuits that are essential to process environmental auditory information. Because the top-down modulation of cochlear hair

cells' excitability is assumed to play a critical role in adaptation to and avoiding damaging influences of environmental changes [132–134], the centrifugal control of neuronal excitability may be a major factor of K⁺ channel-related ARHL.

SK2 (KCNN2) is expressed in OHC as a postsynaptic marker apposing synapses of MOC efferent fibers and required for $Ca^{2+}$-activated SK2 channel activation through MOC's cholinergic function [135]. The number of SK2-positive foci is remarkably reduced in mouse strains that exhibit fast progression of ARHL, such as the C57BL/6J [136], thus representing a general trait in the pathophysiological progression of ARHL. The protective role of MOC efferent fibers during aging and noise only recently received support through the discovery that loss of MOC efferent fibers is an early event of ARHL [127]. We may thus conclude that loss of BK, SK2, and KCNQ4 is likely to be early contributors to ARHL, with their dysfunction discussed as a primary event of OHC loss over age.

$K_V7.1$ (KCNQ1) is a major component of the K⁺ circulation by the stria vascularis and is responsible for the secretion of potassium to the endolymph and maintaining the EP, to assist motility in OHC, perform synaptic activity, and maintain the spontaneous and evoked activity of SGNs. The cells of the stria vascularis contain high numbers of mitochondria [137, 138] and $Na^+/K^+$ATPase [139, 140]. In quiet-aged gerbils, the stria vascularis and spiral ligament showed a decrease in $Na^+/K^+$ATPase activity in these tissues [141], as well as degeneration of strial capillaries at both ends of the cochlear spiral [142] and decreased blood flow [143]. In aged CBA/CaJ mice, $Na^+/K^+$ATPase expression was largely reduced, and the stria vascularis was found to be atrophied [139]. However, it remains difficult to determine whether the lack of blood flow or the cellular dysfunction leads to the strial atrophy. As such, most of these studies did not specifically analyze membrane expression patterns of KCNQ1 during stria vascularis degeneration over age. Interestingly, 12-month-old C57BL/6 mice displayed notable hearing loss and morphological examination showed a significant OHC loss in the cochlear basal turn accompanied by atrophy of the stria vascularis, with immunohistochemical analysis revealing dramatically decreased KCNJ10 and KCNQ1 expression [144]. While these studies observed a conservation of the EP in these aging C57BL/6 mice, and suggested that the stria vascularis can generate a new balance for potassium influx and efflux at relatively low turnover [144], other studies found a clear requirement of adequate KCNQ1 recycling in marginal stria vascularis membranes for hearing and OHC cell survival [145]. On the whole, age-dependent decline of KCNQ1 from the marginal surface of the stria vascularis should be urgently reconsidered with regard to ARHL.

The expression of $K_V3.1$ (KCNC1) subtype b, which is predominant in the adult rodent brain [80, 81], has been shown to decrease in neurons of the MOC efferent system by middle age in CBA/CaJ mice, and these changes appeared to correlate with functional declines in efferent activity in both middle-aged CBA/CaJ mice and $K_V3.1b$ knockout mice [106, 146], suggesting age-dependent decline of $K_V3.1b$ as a possible cause of MOC efferent decline over age [127]. Also, C57BL/6 mice have been shown to lose sensory basal hair cells during early adulthood progressing towards the apex with age [147], which was linked to a concurrent decrease in levels of $K_V3.1b$ in brainstem neurons [106]. In Sprague-Dawley rats, both the intensity of $K_V3.1$ immunostaining and number of $K_V3.1$-positive neurons have been shown to decline with age in the cochlear nucleus [148]. Age-dependent $K_V3.1$ modifications are expected to contribute to age-dependent temporal discrimination deficits [149]. This is particularly important when considering the special role $K_V3.1$ activity displays as a modulator for fast-spiking inhibitory PV+ interneurons, which control feedforward and feedback inhibitory modalities [150], suggested to be essential for fast auditory processing circuits [99]. Reduced PV expression levels have also been found in the auditory cortex in aged animal models [151], which implies a potential relation between the decline of $K_V3.1$ expression over age and PV-mediated processing deficits in ARHL.

Based on evidence from different animal models and from human temporal bones, it seems likely that aging or senescence alone is not necessarily a major risk factor for hearing impairment over advancing age. Convincing evidence that aging per se is not necessarily the main cause for ARHL comes from geriatric cats that have normal hearing sensitivity and auditory brainstem functions over the whole frequency range of hearing, developing ARHL only late in their lifespan [152]. The current evidence suggests that an accumulation of noise events may most likely be the origin of ARHL in humans (Fig. 2a), with excessive noise able to overstimulate sensory hair cells and requires fast and effective K⁺ recycling within the inner ear. This suggests that ARHL may rather be an accumulation of damage from minor toxic events instead of an inevitable progressing loss of cells, structures, and the ability for regeneration.

## Genetic predisposition to ARHL

The human genome contains roughly 70 K⁺ channel-encoding genes [153]. Many of these genes play essential roles in normal physiological processes, including those involved in hearing, as evidenced by the clinical appearance of syndromic and/or non-syndromic hearing loss with genetic variation. As ARHL has a delayed onset and progressive nature, it is plausible to hypothesize that genetic variation may directly contribute to an inter-individual variability and susceptibility to ARHL or to other indirect processes of aging such as metabolic status. One way to test this is to perform statistical
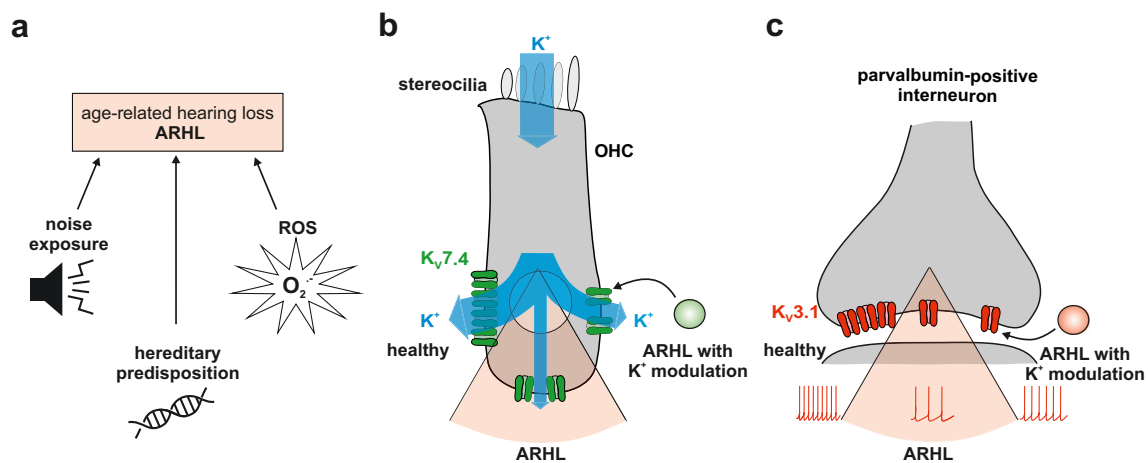
**Fig. 2** **a** In the challenged auditory system leading to age-related hearing loss (ARHL), the key causing factors are postulated to be lifetime noise exposure, hereditary predisposition, and the accumulation of reactive oxygen species (ROS). **b** In a healthy outer hair cell (OHC), potassium ions ($K^+$) enter the cell through apical mechanosensitive channels and are then transported to the supporting cells through $K_V7.4$ (KCNQ4, green) channels on the basolateral membrane of OHC. However, in the challenged system, the expression of $K_V7.4$ is reduced, resulting in a poor $K^+$ efflux. This state can be influenced by the addition of $K^+$ channel modulators (green circle) in a way where cell surface expression remains stable but the efflux rate can be increased. **c** In fast-spiking, parvalbumin-positive interneurons, $K_V3.1$ (KCNC1, red) is required for the high-frequency repetitive firing. A decline in $K_V3.1$ cell surface expression leads to an incapacity of neurons to maintain high-frequency firing action potentials. Modulators that bind to $K_V3.1$ (red circle) may lower action potential latencies and duration and increase the firing pattern of these neurons

analyses in the form of association testing to identify genetic regions or variants, in either genes of interest or across the entire genome, to identify associations with ARHL. This type of analysis has not been performed for all of the genes encoding the channels discussed in this review. However, in the following section, we summarize the current body of genetics knowledge for our selected $K^+$ channels and make connections to ARHL.

The *KCNQ4* gene encodes the potassium voltage-gated channel subfamily Q member 4 protein ($K_V7.4$). Deleterious variants in *KCNQ4* cause autosomal dominant non-syndromic hearing loss (MIM* 603537) [30]. A significant association between *KCNQ4* and ARHL has been identified by Van Eyken et al. [154] in two independent populations. However, except for one single nucleotide polymorphism (SNP), i.e., SNP12 (rs2149034), different SNP spanning a 13-kb region of *KCNQ4* were positively associated in both populations. *KCNQ4* was regarded by the authors as a strong susceptibility gene for ARHL; however, replication studies have not reproduced this observation. *KCNQ4* expression increases with age, supporting a hypothesis that an increased defective protein load may lead to progressive cellular dysfunction [154, 155]. Van Laer et al. [156] also found significant differences between individuals susceptible and resistant to noise exposure for the allele, genotype, and haplotype frequencies for a *KCNQ4* SNP (rs34287852). A genome-wide association study (GWAS) meta-analysis from the Cohorts for Heart and Aging Research in Genomic Epidemiology or CHARGE Consortium was performed with the aim to identify genetic factors associated with overall mortality and healthy longevity [157]. This study identified 14 independent SNP that predicted risk of death and eight that predicted healthy longevity. Several of these SNP were located either in or near genes that are involved in neurological processes. A *KCNQ4* SNP (rs2769255) was significantly associated with both mortality and healthy longevity and is located approximately 4.4 kb upstream from the gene. The enrichment of SNP, either in or adjacent to genes involved in neurological processes, suggests the importance of these genes in regulating healthy aging and longevity.

The *KCNQ1* gene encodes the potassium voltage-gated channel subfamily Q member 1 protein ($K_V7.1$). *KCNQ1* variants have been associated with long QT syndrome, short QT syndrome, atrial fibrillation, and Jarvell and Lange-Nielsen syndrome (MIM* 607542) [158]. The same study by Van Laer et al. [156] also found one significant difference between noise susceptible and resistant individuals in one *KCNQ1* SNP (rs163171). The most interesting literature linking KCNQ1 to ARHL comes from the diabetes field, which constitutes a risk factor for ARHL [21]. With respect to a broader biological context, *KCNQ1* is also expressed in the heart, stomach, intestine, liver, kidney, and insulin-producing cells [159, 160]. Several GWAS have uncovered many independent intronic regions in *KCNQ1* that harbor type 2 diabetes mellitus risk alleles (rs231362, rs2283228, rs2237892, rs2237895, and rs2237897) in Europeans, East Asians, and Native Americans [161–164]. It is unclear if the SNP exert a functional effect and whether this would involve *KCNQ1* or the neighboring genes, *KCNQ1OT1*, or *CDKN1C*, a known regulator of pancreatic beta-cell development [163]. Neither

*Kcnq1* null mice nor patients with deleterious variants show impaired hyperglycemia or glucose intolerance; therefore, it is thought that an increase in expression in pancreatic beta-cells may be linked to the development of type 2 diabetes [163]. Interestingly, *KCNQ1* resides on chromosome 11p15.5, a maternally imprinted region [161]. This means that maternally inherited variants in this imprinted region confer disease risk. There is compelling evidence that diabetes risk at the *KCNQ1* locus is medicated through a gene with imprinted gene expression that may be mediated by *KCNQ1* or neighboring genes (*KCNQ1OT1* or *CDKN1C*) [165]. The confirmation of so-called parent-of-origin effects that have been identified in every organ system of the human body so far except the auditory system would fundamentally re-shape the way the genomics field views genetic contributors of ARHL [166].

The *KCNMA1* (BK), *KCNN2* (SK2), and *KCNC1* ($K_V$3.1) genes presently do not have compelling evidence linking them to ARHL, but several already have gene-disease associations. The *KCNMA1* gene encodes the potassium calcium-activated channel subfamily M alpha 1 protein (BK). Deleterious *KCNMA1* variants are associated with paroxysmal nonkinesigenic dyskinesia with or without generalized epilepsy, Liang-Wang syndrome and cerebellar atrophy (MIM* 600150). Although no current genetic-based studies linking *KCNMA1* SNP to presbycusis and aging exist, BK channels appear to be sensitive to oxidative stress [167]. The *KCNN2* gene encodes the potassium calcium-activated channel subfamily N member 2 protein (SK2) and is currently not associated with any human phenotypes. The SK channel has been linked to neuroprotection in the form of mitochondrial resilience against neuronal death [168]. SK channels may involve attenuation of mitochondrial calcium uptake upon SK channel activation. Mitochondrial activation calcium uptake across the mitochondrial membrane is essential for the numerous calcium-sensitive processes required for mitochondrial metabolism and respiration [169]. Oxidative stress in neurons leads to a series of detrimental effects such as intracellular calcium overload that induces changes in mitochondrial metabolism such as alterations in ATP synthesis and NADP(H) oxidation that lead to an increase in ROS [168, 170]. Finally, the *KCNC1* gene encodes the potassium voltage-gated channel subfamily C member 1 protein ($K_V$3.1). It has been associated with autosomal-dominant progressive myoclonic epilepsy (MIM* 176258) [171] and intellectual disability without seizure or epilepsy [172].

On the whole, the current literature lacks conclusive human genetic evidence to link ARHL and *KCNQ1* ($K_V$7.1), *KCNMA1* (BK), *KCNN2* (SK2), and *KCNC1* ($K_V$3.1), but contains limited information to link it to *KCNQ4* ($K_V$7.4). These genes are still intriguing due to possible gene-environment interactions in processes such as aging and metabolism that are presently unknown (Fig. 2a). ARHL is a complex disorder with environmental, e.g., noise exposure,

and genetic factors. Twin studies for ARHL have estimated the heritability of ARHL, or importance of a genetic component in a disease [154] and found that twin similarity of monozygotic twins decreased with age and dizygotic twins increased with age [173]. This suggests that environmental factors may become more prominent with age. Of note, SNP in $K^+$ channel genes have not been noted with significance in the more recent large-scale genomics studies [174, 175]. However, if $K^+$ channel genetic targets are identified with future ongoing studies, they have the potential to make excellent therapeutic targets.

# $K^+$ channels as therapeutic targets against ARHL

Having given a comprehensive view about the role select potassium channels play in the cochlea and the ascending auditory pathway for ARHL in the context of noise exposure and genetic predispositions, we may next illuminate therapeutic intervention strategies with a potential to prevent or repair hearing dysfunction as future ARHL therapies. Provided that noise exposure, age-related synaptopathies and neuropathies, and cardiovascular risk factors are major contributors of ARHL [8, 14, 21], substantial evidence points to oxygen metabolism as one of the main culprits for $K^+$ channel dysfunctions with aging given that these dysfunctions are not only based on channel mutations. Numerous studies evidenced that ROS increases with age [176] and by statistical probability alone preferentially affects $K^+$ channels (Fig. 2a). The extreme genetic heterogeneity and functional diversity of $K^+$ channels are unparalleled to that of other types of channels [23]. ROS can indirectly modulate $K^+$ channel function by acting on cellular pathways that regulate gene transcription, trafficking, turnover, and proteasomal degradation [177]. On the other hand, direct age-related oxidation of particular voltage-dependent $K^+$ channels that include the aforementioned $K_V$7 channels, $Ca^{2+}$-activated BK and SK2, and $K_V$3.1 underlie a specific type of neuronal aging [23]. In the auditory system, several lines of evidence hint to the importance of these channels with respect to ARHL as discussed above.

*KCNQ* genes have a considerable physiological impact in many cell types. This reliance upon $K_V$7 channels for normal cellular function is evident by hereditary disorders caused by mutations in *KCNQ* genes, meaning that pharmacological targeting of these channels has broad appeal. Consequently, a plethora of chemical entities that modulate $K_V$7 channel activity has been developed. Moreover, $K_V$7 channels are influenced by many disparate intracellular mediators and trafficking processes, making upstream targeting an appealing prospect for therapeutic development to overcome deficits related to these channels [178]. Until now, however, modulation of $K_V$7 channels has been recognized mainly as a

potential to prevent neurodegenerative disorders linked to epilepsy and cognitive deficits [179]. Although efforts have not reached ARHL, pharmacological approaches in trials targeting $K_V7.2$ to $K_V7.5$ channels with the novel antiepileptic drug retigabine (or ezogabine) have been used to overcome hearing loss [180, 181]. Retigabine increases the probability of opening these $K_V7$ channels upon causing a negative 15-mV leftward shift in the voltage-dependence of activation and a decrease in the rate of deactivation (Fig. 2b) [178, 182–184].

Given a hereditary origin of progressive hearing loss through *KCNQ4* dysfunction, as it occurs in DFNA2 non-syndromic autosomal-dominant progressive high-frequency hearing loss [155, 157], genetic therapeutic approaches have been envisioned, e.g., those following heterologic expression of wild-type channels that could be combined with $K_V7$ channel openers such as retigabine [181]. Correspondingly, retigabine has already proven successful to rescue hearing deficits in Korean families with co-segregating *KCNQ4* pathogenic variants [180]. Also, a combination of zinc pyrithione plus retigabine has been used in Chinese hamster ovary cells either transfected with wild-type *Kcnq4* sequences or ones containing variants that encode mutated channels, evidencing a restoration of channel function that was dependent on the location of the DFNA2 mutation within the gene [185]. This further provides an interesting approach to rescue progressive ARHL linked with mutations of *KCNQ* genes on the personalized medicine level.

Undoubtedly, $K_V7.1$ (KCNQ1) expression decreases with advancing age in the stria vascularis [144], but, as previously highlighted, it may only contribute to ARHL in a secondary manner [14]. Hormone changes may be considered as contributors to the decline of $K_V7.1$ surface expression loss in the stria vascularis with age. Thus, throughout the lifespan, the steroid hormone estrogen (17β-oestradiol, E2) declines with age in females [186]. Estrogen decline has been suggested to induce $K_V7.1$ dysfunction through changes in estrogen-dependent control of its internalization from the plasma membrane by a clathrin-mediated endocytosis process [187]. Estrogen has been shown to modulate the association between $K_V7.1$ and the clathrin adaptor AP-2, required for endocytosis, rather than degrading the ion channel, and a biphasic recycling mechanism involving Rab4 and Rab11 is involved in this process, as shown in colon epithelium [187]. Modulators of $K_V7.1$ may thus contribute to overcome postmenopausal-related hearing loss reported to occur with aging [188].

Within this context, it may be interesting to note that a spatio-temporal correlation of the loss of KCNQ1 and KCNE1 surface expression and loss of hearing thresholds has been reported following loss of proteins involved in KCNQ1 recycling, such as SCARB2 [145]. Human SCARB2 is a key regulator of lysosome integrity, motility,

and dynamics, and its loss has been shown to cause rupture of lysosome membranes and significantly shortened lifespan [189]. This may suggest any disturbance of proper membrane recycling or insufficient targeting of KCNQ1 and KCNE1 in the stria vascularis, might be a possible rationale for ARHL [190], and renders lysosomal enzymes that stimulate trafficking as potential candidates for targeting ARHL [191].

The $Ca^{2+}$-activated channels BK (KCNMA1) and SK2 (KCNN2) play an important role in noise-induced ARHL, counteracting noise-induced hyperpolarization of OHC. These may be particularly sensitive for age-dependent ROS damage, being both susceptible to redox modifications [23, 192]. The noise-induced rise in $Ca^{2+}$ in OHC (i.e., $Ca^{2+}$ overload) is expected to induce slow cellular after-hyperpolarizations for SK2 and fast ones for BK channels, both possibly contributing to the prevention of noise damage to OHC [34]. Within this context, the specific role of BK in IHCs, shown to rapidly and robustly shape IHC receptor potential [193], needs to be considered. An oligonucleotide antisense against SK channels was shown to compensate an age-related memory decline in mice, resulting from ROS-induced modification of SK channel function [194, 195], providing viral-mediated expression of SK2 channel as a potential means to target its deficits with advancing age. For BK channels, specific blockers have been shown to counteract the negative redox effects in the brain, indicating that ROS-signaling on BK channels leads more to active, rather than inactive, channels [196]. This would expectedly lead to reduced neuronal excitability of hair cells, through upregulation of $K^+$ channel activities as a hallmark of the aging process. This hypothesis for the aging cochlea awaits further studies and requires reflection in the context of age-dependent deficits of fast auditory processing [197, 198].

A-type voltage-gated potassium ($K_V$) channels, to which the $K_V3.1$ (KCNC1) channel belongs, are sensitive for age-dependent ROS changes [199], resulting through oxidation of channels in slowed inactivation and increased open channel currents, modifications that would dampen neuronal excitability as shown for the hippocampus [200, 201]. $K_V3.1$ has not only been shown as important for sustained temporally accurate firing, being susceptible to deprivation, but also to its deficits partially restored in animals by the compound AUT00063 (Fig. 2c) [197]. AUT00063 has also been shown to improve auditory synchronization and support more accurate decoding of temporal sound features in the inferior colliculus and auditory cortex in adult mice with a near-complete loss of auditory nerve afferent synapses in the contralateral ear [197], rendering $K_V3.1$ modulators an attractive candidate for pharmaceutical targeting against fast auditory processing deficits due to ARHL. Furthermore, antidepressants, such as p11, have been shown to control $K_V3.1$ expression level and intracellular localization in PV+ interneurons of

the hippocampus [202]. With reduced $K_V$3.1 levels, the capacity of PV+ interneurons to adapt to high-frequency firing is abolished [202], underscoring the crucial role that sustained expression levels of $K_V$3.1 may have over age for preserving temporal auditory processing and speech discrimination. Importantly, the high metabolic vulnerability of particular PV+ interneuron synapses [203] should be reconsidered in the context of required sustained $K_V$3.1 channels for its proper function in the ascending auditory pathway. $K_V$3.1 channel modulators have recently been shown to enable faster activating kinetics and increase firing frequency in fast-spiking GABAergic interneurons [204, 205]. This renders these modulators as promising candidate pharmaceutical drugs to overcome ARHL, with a potential to improve speech in noise deficits, especially with regard to the reconsidered role that maintained PV+ interneuron-mediated feedforward and feedback circuits have in fast auditory processing [99].

## Outlook

In humans, the classification of various presbycusis profiles over age is manifold, but despite profound heterogeneity, most of the presbycusis profiles are characterized by a dominant loss of sensitivity to high-frequency tones [206]. Therefore, loss of auditory sensory function with age must be classified by the probable excessive noise exposure as a main contributor [14]. The current review suggests that noise-induced overstimulation of sensory hair cells and neurons most critically depends on fast and effective $K^+$ recycling in the cochlea, including sustained fast auditory processing that may be required for $K_V$3.1-driven, fast PV+ interneuron function over age. Pharmaceutical targeting of $K^+$ channels to enable fast recycling through stimulators, modulators, or activators has future potential to arrest or even prevent ARHL before the inevitable progression of loss of cells, structures, and degeneration.

An important caveat to consider with respect to different functional consequences of oxidation for the reviewed $K^+$ channels is the rationale against considering therapies based on generic anti-oxidants for the treatment of ARHL. Modes of interventions aimed at targeting more specific channel proteins or distinctly responsible ROS species, which is not a simple task, may be more likely to succeed. The ability to pharmacologically separate the impact of individual $K^+$ channel subunits needs further refinement, beginning with existing compounds and reinforcement with molecular interference techniques.

Although many clinicians inform patients that ARHL cannot be prevented, animal model studies provide insight and future prospects for clinical trials and even clinical interventions to prevent or slow the progression of ARHL.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

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