cGMP is generated by the cGMP-forming guanylyl cyclases (GCs), the intracellular nitric oxide (NO)-sensitive (soluble) guanylyl cyclase (sGC) and transmembrane GC (e.g. GC-A and GC-B). In summarizing the particular role of cGMP signalling for hearing, we show that GC generally do not interfere significantly with basic hearing function but rather maintain a healthy state for proper temporal coding, fast discrimination and adjustments during injury. sGC is critical for the integrity of the first synapse in the ascending auditory pathway, the inner hair cell synapse. GC-A promotes hair cell stability under stressful conditions such as acoustic trauma or ageing. GC-B plays a role in the development of efferent feed-back and gain control. Regarding the crucial role hearing has for language development, speech discrimination and cognitive brain functions, differential pharmaceutical targeting of GCs offers therapeutic promise for the restoration of hearing.

**KEYWORDS**
central auditory processing, guanylyl cyclases, hearing function, temporal coding

1 | **INTRODUCTION**

Worldwide, hearing loss is considered to be the fourth leading cause of disability, which today, in industrialized countries, affects about 190 million people. The rising number of affected people in the younger population and the dramatic shift in societal demographics, will soon significantly increase the total number of people with hearing deficits. While hearing loss is not life-threatening, mid-age hearing disorder was recently shown to be a major risk factor for dementia (Livingston et al., 2017). Indeed, the prevention of hearing loss with age has been suggested as a major action on lowering the future prevalence of dementia (Montero-Odasso et al., 2020). While to date degeneration of the stria vascularis and its vasculature were considered to be a main cause of hearing loss with age (Fischer et al., 2020; Frisina & Frisina, 2013), previous studies suggested that damage to outer hair cells proceeds stria degeneration (Wu et al., 2019). Outer hair cells are electromotile and serve as a piezo-like motor in the inner ear to amplify the vibrations of the basilar membrane in the cochlea (Dallos & Harris, 1978). Gradual noise damage to outer hair cells over lifetime was labelled as a major contributor to hearing loss in humans (Wu et al., 2019). Importantly, prior to outer hair cell degeneration, a progressive and
differential degeneration of auditory fibres can occur, even before detectable elevation of hearing thresholds are identified in the clinic (Kujawa & Liberman, 2015; Plack et al., 2014; Wu et al., 2019). This so-called hidden hearing loss (Fullgrabe & Moore, 2014) has previously been linked to progressive cochlear synaptopathy, as observed in ageing animals (Bharadwaj et al., 2014) and humans (Viana et al., 2015).

It is alarming that mild hearing loss and hidden hearing loss are already prevalent in 6 to 11 year old children, an incidence higher than predicted (Moore et al., 2020). It is also alarming that in children, as a consequence of early hearing loss, important aspects of auditory and cognitive skills may be impaired. This is due to the fact that speech perception in noise and the cognitive skills underlying speech and reading, depend on the correct temporal coding of sound and correctly developed rapid auditory processing (Foss-Feig et al., 2017). As specific auditory fibres differentially contribute to proper temporal coding and sound processing (Bharadwaj et al., 2014; Plack et al., 2014), the consequences of preceding auditory fibre degeneration, whether occurring in youngsters or over age, whether hidden or additive to elevated hearing thresholds, can be manifold. They may possibly range from temporal resolution deficits (Bharadwaj et al., 2014), speech in noise problems (Muniak et al., 2018; Salvi et al., 2018), disorders such as tinnitus or hyperacusis (Knipper et al., 2020) and fast auditory processing deficits linked to autism (Rendall et al., 2017) to the point of cognitive decline and dementia (Liu et al., 2020; Livingston et al., 2017). These are all hearing-related disorders that currently lack curative therapeutic strategies.

These observations urgently indicate the need for new therapeutic approaches to counteracting or preventing these mostly acquired forms of hearing deficits. Here, we illuminate the role of cGMP signalling in hearing and recommend its differential targeting for future therapeutic intervention strategies in defined hearing disorders. The differential roles of the soluble guanylyl cyclase (sGC), transmembrane guanylyl cyclases and its ligands in the cochlea were described in an excellent review (Fitzakerley & Trachte, 2018). In the present review, we focus on newer findings of auditory function subsequent to the deletion of guanylyl cyclases (GCs) that identify (a) sGC activity as essential for the continuing integrity of inner hair cells and outer hair cells (Section 1), (b) a role of guanylyl cyclase A (GC-A) in outer hair cell function and sustained auditory fibre feed-back control during injury and ageing (Section 2) and (c) a role of guanylyl cyclase B (GC-B) in central auditory feed-back control and temporal auditory processing (Section 3). We finally refer to the particular role cGMP might play in the central auditory system, emphasizing an urgent need to put more effort into this new field. Healthy brain function and central adjustments to peripheral auditory deprivation may be interrelated through their common metabolic needs for sustained, fast auditory processing (Knipper et al., 2020; Marchetta, Savitska, et al., 2020) (Section 4). We finally conclude the review by providing a perspective for possible differential pharmaceutical targeting of distinct cGMP signalling pathways for different hearing disorders (Section 5).

2 ROLE OF SOLUBLE GUANYLYL CYCLASE (SGC) FOR HEARING

The presence of cGMP and GC activity in the cochlea was described decades ago (Guth & Stockwell, 1977), with nitric oxide (NO)-triggered cGMP formation in the cochlea observed as one of the first signalling cascades in the auditory system (Chen et al., 1995). NO stimulates the sGC (also called NO-GC) (Kuhn, 2016; Rastaldo et al., 2007), a haem-containing enzyme consisting of two subunits (α and β), the latter contains a haem-binding domain. To activate sGC, NO has to be synthesized by NOS isoforms (Murad et al., 1978) that are found in the cochlea (reviewed by Heinrich et al., 1998). NOS in the cochlea is either expressed constitutively as a calcium-activated endothelial NOS (eNOS) or as neuronal NOS (nNOS) (reviewed by Heinrich et al., 1998), two isoforms of—in total—three known forms (for review see Potter, 2011). To date, the ideas about molecular mechanisms of NO in auditory function are controversial, suggesting either protective or detrimental potentials. Thus, NO has long been predicted to damage cochlear function, as observed after, for example, exposure to loud noise (Ohinata et al., 2003; Shi et al., 2002). On the other hand, NO was shown to protect hair cells from damage through an sGC-induced counteraction of stressor-triggered Ca2+ increase, as shown for outer and inner hair cells in in vitro studies (Shen et al., 2006).

New insights into the function of sGC came from studies that began to distinguish expression profiles of the isoforms GC1 (alpha1beta1 dimer) and GC2 (alpha2beta1 dimer) (Koesling et al., 2004), GC1 and GC2 isoforms do not differ in their enzymatic or regulatory properties (Koesling et al., 2004) and have been shown to be expressed in similar amounts in the CNS (Mergia et al., 2003). Nevertheless, sGC-specific primers and RT-PCR of dissected cochlear compartments, revealed a variable localization of GC1 and GC2 in a variety of distinct cochlear compartments, including hair cells (Heinrich et al., 2000; Seebacher et al., 1999). When distinct hair cell types were analysed for differential sGC expression, a cell-specific variation of sGC expression was found in inner hair cells but not in outer hair cells, as shown through nested PCR of isolated hair cells (Figure 1a,b) or through NO-induced intracellular cGMP synthesis using FRET microscopy and cGMP sensor mice (R26-cGi500[Li1]) (Thunemann et al., 2013) in the living cochlea (Möhrle et al., 2017) (Figure 1b). The differential expression profile of sGC in inner but not outer hair cells was confirmed through hearing measurements performed in transgenic mouse strains with deletion of the specific sGC isoforms GC1 and GC2 (GC1 and GC2 knockout (KO)), generated by (Mergia et al., 2003). Neither the deletion of GC1 nor GC2 affected the threshold of auditory brainstem evoked responses, an electrical response of the auditory brainstem to short auditory stimuli (Rüttiger et al., 2017) that is determined by electromechanical outer hair cell properties (Dallos & Harris, 1978). This was true for measurements taken before and also after noise exposure, in agreement with the absence of sGC expression in outer hair cells (Möhrle et al., 2017).

Surprisingly, GC2 deletion and, to less extent GC1 deletion, protected cochleae from noise-induced inner hair cell synaptopathy,
as shown by a smaller reduction of inner hair cell ribbons and of auditory brainstem response wave I amplitudes in sGC KO after noise trauma (Möhrle et al., 2017). This indicated that the global deletion of sGC may induce an immature, less vulnerable, state that might be explained through the absence of a mediator that, in the presence of GC1 and GC2, renders inner hair cell synapses and their auditory fibres more vulnerable to acoustic trauma. Such a mediator that renders the inner hair cell pre/postsynapse vulnerable might be the hyperpolarization-activated cation inward current $I_h$ generated by hyperpolarization-activated cyclic nucleotide–gated (HCN) channels, that were described in hair cells and cochlear neurons (Cho et al., 2003; Kopp-Scheinflug et al., 2015; Luque et al., 2020). HCN channels can be modified in their open kinetics through sGC, thereby shifting the membrane depolarization to less depolarized states and
facilitated N-methyl-D-aspartate-(NMDA) receptor activation (Koesling et al., 2016; Neitz et al., 2014) (Figure 1c). While NMDA receptor activation through sGC subtype-induced HCN modification may be beneficial for memory-linked plasticity responses (Koesling et al., 2016; Neitz et al., 2014), the same process may contribute to excitotoxic events, including Ca2+ overload leading to afferent neurodegeneration as shown after acoustic noise trauma or cochlear injury (Ruel et al., 2000, 2008). To test the impact of sGC on the maturation of pre- and postsynaptic function of inner hair cell, future experiments may consider the effects of sGC function on cochlear HCN expression or physiology. Further, it would be very interesting to analyse the hearing of different NOS KO mice (eNOS (Ueda et al., 2015) and/or nNOS (Ishizuka et al., 2019)), to clarify the enzymatic source of NO-related effects in the hearing organ.

When the function of sGC in hearing was tested through sGC stimulators, this treatment had positive effects only in young animals (Figure 1c). Thus, BAY 41-8543, which stimulates the sGC directly and, furthermore, makes the enzyme more sensitive to its endogenous activator NO [Bayer AG, Leverkusen, Germany (Stasch et al., 2002)], led to a stabilization of auditory nerve response amplitudes (auditory brainstem response wave I) prior to noise exposure and to a preservation after exposure. By contrast, long-term treatment of BAY 41-8543 exacerbated the noise-induced loss of auditory nerve responses in aged animals (Möhrle et al., 2017). It was suggested that NO-induced signalling cascades, resulting in the activation of poly (ADP-ribose) polymerase (PARP), a nuclear enzyme for DNA repair (Figure 1c, red), can elevate stress resistance early in life, but may act detrimentally in older organisms. This mechanism of NO/sGC/cGMP signalling may also provide support for the idea that “ageing” promotes a host of degenerative pathologies with debilitating losses of tissue or cellular function (Campisi, 2013).

In agreement with the possibility that sGC activates pro-survival cascades in young, but not in aged animals, pro-survival PARP activity was observed downstream of cGMP-dependent protein kinase G 1 (PKG1) signalling in the cochlea of young animals (Jaumann et al., 2012), as it was in neurons (Kim et al., 1999). A pro-survival PARP activity downstream of sGC was, however, suggested to be lost in various species with age (Grube & Burkle, 1992).

To summarize, sGC in the hearing organ: (1) is unlikely to affect basic hearing thresholds or outer hair cell functions, (2) during maturation modifies inner hair cell pre- and postsynapses towards higher vulnerability for excitotoxic events, (3) perhaps protects inner hair cell pre- and postsynapses through pro-survival PARP activity at young ages, but (4) may lose protective effects when pro-survival downstream cascades are lost with age.

3 | ROLE OF GC-A IN HEARING

The archetypical transmembrane GC-A, which was known as natriuretic peptide receptor 1 (NPR1), is activated by atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) (Potter, 2011). ANP and BNP have emerged as key regulators of energy consumption and metabolism, since they promote lipid oxidation and mitochondrial respiration (Kuhn, 2016). Strikingly, when GC-A was analysed in isolated mature hair cells, the expression was found to be restricted to outer hair cells and spiral ganglia but not inner hair cells (Figure 2a,b) (Marchetta, Möhrle, et al., 2020). Also, in agreement with previous studies, the RNA of GC-A ligands ANP and BNP was observed in outer hair cells, spiral ganglia and inner hair cell (Dornhoffner et al., 2002; Marchetta, Möhrle, et al., 2020; Möhrle et al., 2017; Suzuki et al., 1998). When the hearing of GC-A KO mice was analysed (Marchetta, Möhrle, et al., 2020), no profound effect on basic hearing function was observed, as also described for sGC KO mice (Möhrle et al., 2017). Thus, the hearing thresholds, when measured using distortion product otoacoustic emission as a metric for electromotile properties of outer hair cells (El-Badry & McFadden, 2007; Rüttiger et al., 2017), were similar between WT and GC-A KO mice for all young, middle aged and old GC-A KO mice. Analysis of frequency-specific thresholds of distortion product otoacoustic emission signals, however, revealed that outer hair cell-specific responses at higher frequencies (11.3 kHz) were already reduced in young GC-A KO mice and remaining constantly lower throughout all ages (Marchetta, Möhrle, et al., 2020). This suggested a role of GC-A in maintaining the basic integrity of outer hair cells particular in high-frequency cochlear turns. This deficit in the function of outer hair cells in high-frequency regions in GC-A KO mice could be linked to a decline in the surface expression of the voltage-dependent K+ channel, KCNQ4 (KCNQ4) across life span. This potassium channel maintains the outer hair cell resting potential and its time constant, and is not only vital for outer hair cell survival (Kharikovets et al., 2006; Marcotti & Kros, 1999), but, as for other KC7 channels, has a high membrane turnover and is influenced by many disparate intracellular mediators and trafficking processes (Barrese et al., 2018).

This challenges the hypothesis that GC-A, as a key regulator for energy consumption and metabolism (Kuhn, 2016), may maintain metabolically demanding proper surface expression of KCNQ4 in outer hair cells (Peixoto Pinheiro et al., 2020). PARP drives a polymerase-mediating PAR polymerization that was shown to be involved in DNA repair and transcriptional activity in a PKG1-dependent manner (Kim et al., 1999; Paquet-Durand et al., 2007) and can also be directly activated by cGMP (Paquet-Durand et al., 2007). Interestingly, GC-A KO exhibited a decline of PARP, particularly in outer hair cells of high-frequency cochlear turns (Marchetta, Möhrle, et al., 2020), suggesting that the observed deficits in outer hair cell function, KCNQ4 and PARP expression in GC-A KO in high-frequency regions may be causally linked (Figure 2c), a perspective for future interaction studies.

GC-A was not only shown to play a role in the basal integrity of outer hair cells, but also in the integrity and stability of pre- and postsynaptic contacts of inner hair cells when the cochlea is challenged through acoustic trauma or ageing (Figure 2c). Thus, when suprathreshold auditory brainstem response wave amplitudes were measured in ageing GC-A KO mice in comparison to same-aged controls, a reduction in auditory brainstem response wave I amplitude (reflecting auditory nerve activity) and auditory brainstem response wave IV amplitude (reflecting midbrain activity) was found in middle-aged and
old GC-A KO mice. When, moreover, GC-A KO mice were exposed to acoustic trauma, reduced auditory brainstem response wave I and IV amplitudes and reduced inner hair cell ribbon numbers, as a marker for inner hair cell synaptopathy, were already seen in mice exposed at young and middle age, a feature that also agreed with a reduction in PARP (Marchetta, Möhrle, et al., 2020) (Figure 2c). These observations suggested a protective GC-A/cGMP/PKG1/PARP cascade influencing outer hair cells, inner hair cells and their downstream ascending auditory neural circuits under challenging conditions (Figure 2c). This was confirmed when the gene-expression profiles of cGMP-dependent protein kinases (Prkg1, coding for PKG1), or functional assays in mouse mutants with deleted Prkg1 were analysed. Prkg1 was found to...
be expressed in supporting cells and spiral ganglion neurons as well as in inner hair cells and outer hair cells within the cochlea (Jaumann et al., 2012; Shen et al., 2015). Deletion of Prkg1, like GC-A KO, exhibited deficits in outer hair cell function and inner hair cell synapse integrity following noise trauma, a process that was linked to altered PARP levels (Jaumann et al., 2012). These findings suggest a beneficial role of GC-A in maintaining hair cell integrity under challenging conditions.

GC-A KO mice develop arterial hypertension (Kuhn, 2005). Whether arterial hypertension itself together with changes in the glucose metabolism may contribute to age-related hearing loss is controversially discussed (Reed et al., 2018). To prove whether the observed beneficial effect of GC-A for maintaining hearing function, is the result of GC-A induced vasodilation instead of GC-A effects on hair cell integrity, future studies of tissue-specific GC-A KO mice with deletion of GC-A in either endothelial (Kuhn et al., 2009) or hair cells are needed.

In conclusion, a protective signalling cascade of GC-A/cGMP/PKG1/PARP may influence basic outer hair cell functions in high-frequency regions and inner hair cell synapses and integrity under challenging conditions such as acoustic trauma and ageing. This predicts that ANP regulates energy consumption and metabolism in the auditory system under metabolic demanding conditions, as suggested for cardiac systems (Kuhn, 2016).

4 | ROLE OF GC-B FOR HEARING

The membrane-bound (particulate) GC-B, (previously known as natriuretic peptide receptor 2, NPR2), is structurally similar to GC-A, but is activated in a paracrine manner by C-type natriuretic peptide (CNP) (Moyes & Hobbs, 2019). GC-B regulates various physiological functions such as bone growth (Potter, 2011), synaptic plasticity (Decker et al., 2010), axonal sprouting in dorsal root ganglion neurons (Schmidt et al., 2009) and anxiogenesis (Kellner et al., 2003). GC-B and its ligand CNP are expressed in the cochlea (Suzuki et al., 1998) and dorsally along the length of the embryonic neural tube (Schmidt et al., 2009). During development, sensory axons fail to bifurcate in the absence of GC-B. As a result, T-like branches are not formed, not in the hindbrain, not the spinal cord and also not in the nucleus cochlearis, the brainstem projection regions of the auditory nerve (Figure 3a) (Schmidt & Rathjen, 2010; Ter-Avetisyan et al., 2014). In the cochlea, GC-B expression, shown by using Npr2-lacZ reporter mice with x-gal staining (Ter-Avetisyan et al., 2014), was found in spiral ganglia and vestibular ganglion neurons, especially during embryonal stages (Whitfield, 2015; Wolter et al., 2018). It was not found in hair cells of the organ of Corti (Figure 3a,b). In the brainstem, GC-B expression was limited to the region of the vestibular nuclei and the pontine reticular nuclei (Wolter et al., 2018). While first studies of global GC-B KO mice in the auditory system pointed to a role of GC-B in the normal tonotopic organization of central auditory circuits, without affecting general, basic hearing (Lu et al., 2014), detailed analysis of the hearing of GC-B KO mice identified a mild, but significant, auditory brainstem response threshold elevation, mainly in the low- to mid-frequency range (Wolter et al., 2018). Interestingly, the mild hearing threshold elevation in GC-B KO mice could not be linked to malformations of middle ear bones (ossicles), even if the general body length was reduced, nor to differences in the phenotypes of outer hair cells or inner hair cells (Wolter et al., 2018). Rather, altered feedback control of the hair-cell output could explain the observed functional deficits in GC-B KO mice (Figure 3a). Also in mice with a conditional deletion of GC-B by expression of Cre recombinase under the Wnt promoter (GC-B<sup>Wnt<sub>Cre</sub></sup> KO mice), an elevated hearing threshold could be detected in comparison to WT mice (although as little as 7.8 dB higher thresholds than WT mice with a SD of 3.3 at 4 animals per genotype). This indicated that the threshold elevation of GC-B KO mice was likely not related to bone malformations or other global effects of GC-B deletion but is rather specific for the local loss of GC-B within the sensory cranial ganglia. GC-B<sup>Wnt<sub>Cre</sub></sup> KO mice would be a good model to answer if temporal processing is reduced in the same way as in global GC-B mice, which has to be done in future experiments. Up to now hearing functions of CNP KO mice (Chusho et al., 2001) have not yet been analysed. This should also be a continuing project for future studies.

The elevation of hearing threshold in GC-B KO mice was associated with a normal outer hair cell phenotype, as identified through normal distortion product otoacoustic emission thresholds, indicating normal electro-mechanical properties of the outer hair cells (Dallos & Harris, 1978; Rüttiger et al., 2017). In line with this, normal expression of outer hair cell marker proteins and thus normal maturation of outer hair cells was observed in GC-B KO mice (Wolter et al., 2018). Deficits in efferent feedback to outer hair cells in GC-B were shown through diminished fast neuronal output of medial olivocochlear-fferents (Wolter et al., 2018), which project to outer hair cells in the cochlea from the medial olive within the superior olivary complex in the brainstem (Warr & Guinan, 1979). In addition, reduced expression of marker proteins of efferent fibres, such as ChAT (Kitanishi et al., 2013) and the vesicle protein synaptobrevin (VAMP2; vesicle-associated membrane protein 2) (Wolter et al., 2018) was found (Figure 3c). A reduction in rapid response compression (adaptation to loud stimuli) of outer hair cell function in GC-B KO mice by medial olivocochlear efferents (Maisen et al., 2007) is expected to result in a reduced gain of the cochlea (Guinan, 2006) and strongly suggests a link between the lack of bifurcation and deficits in centrifugal auditory gain control of outer hair cells (Wolter et al., 2018).

In GC-B KO mice the phenotype and function of inner hair cells was also normal, as confirmed through normal amplitudes and latencies of the summating potential from the sensory cells (inner hair cells) in the cochlea in GC-B KO mice (Wolter et al., 2018). The summating potential, measured from the first deflection in the auditory brainstem response waveform fine structure, is generated by the receptor potentials of inner hair cell ensembles (Durrant et al., 1998) and can provide information about intact mechanoelectrical transduction channel currents in inner hair cells (Patuzzi et al., 1989; Rüttiger et al., 2017). Furthermore, expression in inner hair cells of normal levels of the synaptic-ribbon protein CtBP2/RIBEYE, the inner hair
cell synaptic vesicle protein otoferlin (Roux et al., 2006), the vesicular glutamate transporter 3 (VGLUT3) (Seal et al., 2008) and of voltage-activated potassium (BK) channels (Rüttiger et al., 2004) indicated a normal inner hair cell phenotype of GC-B KO mice (Wolter et al., 2018). On the other hand, auditory brainstem response wave I, II, III and IV amplitudes were elevated in GC-B KO mice, but delayed in latency and thus linked to diminished temporal coding of sound, particularly for low sound levels (Wolter et al., 2018) (Figure 3c).

This GC-B KO phenotype was best explained through deficient axo-dendritic efferent innervation of the type I afferents from inner hair cells. The efferents from the lateral superior olive project to the cochlea and strongly influence activity patterns (Darrow et al., 2007;
The elevated auditory brainstem response wave I–IV amplitudes of GC-B KO mice point to a disinhibition of auditory nerve fibres by reduced activity in the inhibitory efferents (Darrow et al., 2007). Prolonged latencies of auditory brainstem response wave I–IV and temporal processing deficits to low sound levels in GC-B KO mice therefore suggest inappropriate efferent shaping of the activity of auditory fibres that have high spontaneous rate firing fibres and define detection thresholds and response latencies along the entire auditory tract (Heil et al., 2008; Maison et al., 2007; Meddis, 2006; Ruel et al., 2001). As the deficits in GC-B KO mice also include the efferent marker protein VAMP2 found below inner hair cell synapses (Wolter et al., 2018), bifurcation deficits in GC-B were suggested not only to result in deficits in centrifugal auditory gain control of outer hair cells, but also of inner hair cell afferent output activity (Figure 3a,c).

We conclude that the GC-B KO phenotype—although affecting auditory nerve bifurcation before hearing onset in embryonal stages (Ter-Avetisyan et al., 2014), nevertheless allowed the development of a robust, basic hearing function. The consequences of the loss of bifurcation became evident only after hearing onset, when auditory experience drives auditory acuity through feed-forward and feed-back control of auditory sensation (see next chapter). Accordingly, we hypothesize that the deficits in embryonal development in GC-B KO mice influence the mature hearing of the mice mutants through deficits in centrifugal efferent control that shape auditory nerve fibre responses (Liberman, 1990; Puel et al., 2002; Simmons, 2002) and ascending auditory circuits (Blackwell et al., 2020; Suga, 2020) mainly after hearing onset, explaining the nearly normal basal hearing function in GC-B KO mice.

5 ROLE OF CGMP SIGNALLING IN CENTRAL AUDITORY PLASTICITY RESPONSES

Considering that the analysis of hearing function following the deletion of sGC, GC-A and GC-B does not indicate an impact on gross basal hearing function (see above, Sections 1–3), we can assume that cGMP signalling influences central auditory processing after the onset of hearing during the maturation of fast auditory processing, which in rodents develops with the first auditory experience between P10 to P14 (de Villers-Sidani et al., 2007). In humans, it appears between the 27th embryonic week and the 6th to 12th month after birth (de Villers-Sidani et al., 2007; Knipper et al., 2020; Sharma et al., 2016). A proper maturation of high-spontaneous firing rate fibres and fast auditory processing is a prerequisite for the sharpening of cortical receptive fields at the end of the critical period after hearing onset (Xu et al., 2010). Sharpening of receptive fields depends on the integration of inhibitory networks in functional fronto-striatal circuits, thereby establishing improved auditory perception (Irvine, 2018; Knipper et al., 2020; Kraus & White-Schwoch, 2015; Weinberger, 2015). With the sharpening of receptive fields in the auditory cortex, narrower bandwidth responses and mature sound-discrimination capacity matures through brain-derived neurotrophic factor (BDNF)-driven implementation of inhibitory feed-back circuits.

It was suggested that fast high spontaneous rate firing auditory processing is the critical driving force for BDNF release from cortical pyramidal neurons, which in turn triggers synaptogenesis of a complex network of fast-spiking parvalbumin-expressing GABAergic interneurons (Knipper et al., 2020). Activated parvalbumin-interneuron contact cortical pyramidal neurons through perisomatic and dendritic inhibition (Hong et al., 2008; Lehmann et al., 2012; Xu et al., 2010). This implementation of inhibitory microcircuits is the prerequisite for feed-forward and feed-back inhibitory circuits, high-frequency network oscillations and pattern separation (Hu et al., 2014, 2018), which enable memory-dependent central auditory adjustment processes following altered auditory input (Knipper et al., 2020; Matt et al., 2018). These adjustment processes can be monitored through altered levels of excitatory (activity-regulated cytoskeleton-associated protein) and inhibitory parvalbumin marker proteins in the auditory cortex and hippocampus. Furthermore, these molecular changes were correlated with changes in LTP in hippocampal CA1 pyramidal neurons (Marchetta, Savitska, et al., 2020; Matt et al., 2018). Therefore, sound-induced adjustment processes are likely to be reflected in altered plasticity changes, not only in central auditory nuclei, but also in associated brain regions like the hippocampus. Therefore, the role of cGMP signalling for central auditory processing needs to be analysed in greater detail.

5.1 sGC in the central auditory system

Knowledge about the role of cGMP signalling in central auditory processes is still limited and mainly covers NO-triggered cGMP cascades. The first studies analysing NOS during age-dependent hearing loss were controversial. While some studies described decreased levels of NOS (Druga & Syka, 2001; Sanchez-Zuriaga et al., 2007) others found NOS levels to increase with age (Reuss et al., 2000; Suzuki et al., 1998) or were distributed in a region-specific manner (Sanchez-Zuriaga et al., 2007). When reconsidering the normal basic hearing threshold shown in sGC KO mice (Möhre et al., 2017), sGC signal cascades may show their major function after hearing onset. Within this context, we hypothesize a specific role of sGC/cGMP signalling, particularly for central haemodynamic responses during fast auditory processing that develop after hearing onset (Knipper et al., 2020). As outlined above, fast auditory processing is the likely prerequisite for maturation of BDNF-dependent synaptogenesis of a complex, fast-spiking parvalbumin-interneuron microcircuit with sensory experience (see above and Knipper et al., 2020). This is the prerequisite for feed-forward and feed-back inhibitory circuits that are critical for generating γ-(feed-forward inhibition) and β-frequency oscillations (feed-back inhibition) (Cardin et al., 2009; Chen et al., 2017; Sohal et al., 2009). These are possibly disturbed in hearing disorders such as, for example, tinnitus (Knipper et al., 2020). In the brain, nNOS-derived NO has been suggested to be released not only from pyramidal cells, but particularly from inhibitory nNOS-expressing GABAergic interneurons.
that have direct contact to parenchymal arterioles and thereby regulate nearby arteriolar diameter (Cauli et al., 2004; Kocharyan et al., 2008). Thus, only after hearing onset and with maturation of proper parvalbumin-interneuron positive feed-forward and feed-back circuits, can a stimulus-induced activation of NO-release from nNOS-positive GABAergic interneurons drive haemodynamic changes that are required to meet metabolic demands during learning and memory-dependent processes.

Stressful conditions, such as strong acoustic trauma, has previously been shown to diminish central auditory processing and memory-dependent auditory adjustment processes (Matt et al., 2018), an observation that has to be reconsidered in the context of failed sGC activation. Thus, chronic stress was suggested to lead to diminished neurovascular function through decreased NO-release from GABAergic interneurons (Han et al., 2019). Correspondingly, functional haemodynamic changes are elicited during sensory stimulation when nNOS-specific blockers are used, or experiments are performed in nNOS KO mice (Han et al., 2019; Lee et al., 2015; Stefanovic et al., 2007). The various observations that demonstrate how nNOS-derived NO modulates physiological functions, such as synaptic plasticity, learning, memory and neurogenesis (Kourosh-Arami et al., 2020), need to be reconsidered in the context of a specific function of nNOS-expressing inhibitory GABAergic interneurons on haemodynamic responses. The integral role that cGMP signalling is suggested to have in vascular function (Feil et al., 2003; Kemp-Harper & Schmidt, 2009) may be reconsidered in the context of neurovascular coupling processes in the brain (Han et al., 2020; Olthof et al., 2019). For the auditory system, NO-related druggable targets may be of particular interest in overcoming hearing disorders linked to fast-auditory processing deficits. This includes, for example, neurodevelopmental disorders in children that are suggested to be linked to deficits in fast auditory processing, a deficit that not only impedes initial language development, but ultimately has implications for higher-order processes, including social learning (Fitch & Tallal, 2003; Ramus, 2003; Rendall et al., 2017). Deficits in fast auditory processing also influence hearing loss during acoustic trauma (Matt et al., 2018) or with age (Wolter et al., 2018), resulting in a reduction of memory-dependent adjustment processes (Marchetta, Savitska, et al., 2020; Matt et al., 2018).

5.3 | GC-B in the central auditory system

We next considered GC-B and its ligand CNP in the context of central auditory processing, as CNP and GC-B are widely expressed in the CNS (Cao & Yang, 2008). In rodents there is an early expression peak around P1 and a decline maximally towards P14 (Muller et al., 2009), the end of the critical time period of the auditory system (de Villers-Sidani et al., 2007). From this early time of expression and the observation that GC-B KO mice exhibit nearly normal hearing thresholds (Wolter et al., 2018) (see above), we can already conclude that the consequences of bifurcation deficits in GC-B KO mice mainly affect auditory fibres with low spontaneous firing rate and high activation thresholds, as these are the only auditory fibre types functional at around hearing onset at P10/P12 (Glowatzki & Fuchs, 2002; Grant et al., 2010). It is conceivable that GC-B control of bifurcation of early (low spontaneous firing rate) high-threshold auditory fibres prior to hearing onset, through their influence on second-order neurons, produce subsequent deficits in feed-back loops to the cochlea that finally also cause deficits in the proper maturation of the 60% of auditory fibres that develop only after hearing onset and that generate high spontaneous rate firing fibres with low activation thresholds (Glowatzki & Fuchs, 2002; Grant et al., 2010). Indeed, it has been speculated that the firing properties of high spontaneous rate firing, low-threshold fibres are influenced by normal efferent gain control that may shape the spontaneous firing properties of auditory fibres (Knipper et al., 2020; Ruel et al., 2001). While this is to date hypothetical, the slightly elevated hearing thresholds and prolonged latencies of central auditory brainstem response waves in GC-B KO mice (Wolter et al., 2018) can best be

5.2 | GC-A in the central auditory system

The expression profile of GC-A and its ligands, natriuretic peptides ANP and BNP, rises only briefly before hearing onset, in rodents from P7 onwards, reaching saturation at around P28 (Muller et al., 2009), the time of mature hearing (Starr et al., 1991). Besides CNP, ANP and GC-A are also widely distributed in the CNS (Cao & Yang, 2008). Preliminary insight into a role for GC-A in central auditory processing came from observations documenting reduced sound-evoked late auditory brainstem response wave responses in GC-A KO mice in aged animals or after acoustic trauma (Marchetta, Möhrle, et al., 2020). Regarding lifetime noise exposure as one of the major contributors to hearing loss with age in human civilizations (Wu et al., 2019), ANP and BNP peptide analogues or GC-A must be considered as a protective or counteracting therapeutic approach. Within the context of the sustained, fast auditory processing essential for memory-linked central adjustments (Knipper et al., 2020), previous suggestions of a role of GC-A in neurogenesis (Muller et al., 2009) and angiogenesis (Kuhn et al., 2009) are of particular interest. Both neurogenesis and angiogenesis are likely essential to proper memory-dependent processes (Anacker & Hen, 2017) and for brain recovery (Xiong et al., 2010). They are, therefore, also expected to play a role in progressing hearing loss over age or through acoustic trauma. It is moreover interesting in this context that GC-A deletion in pericytes was shown to lead to retarded physiological retinal vascularization and enhanced cell apoptosis of the retina (Spiranec Spes et al., 2020). Pericytes are suggested to regulate not only blood–brain barrier permeability but also angiogenesis and capillary haemodynamic responses (Sweeney et al., 2016), suggesting that GC-A in pericytes may play a role in hearing under challenging situations in which proper central memory-dependent auditory adjustment processes are vital for recovery from noise- and age-dependent hearing loss (Liu et al., 2016; Marchetta, Möhrle, et al., 2020; Matt et al., 2018).
explained through the immaturity of fast (high spontaneous rate firing) auditory fibres, as these low threshold fibres are responsible for the low perceptual thresholds and shortened latencies of sound responses along the ascending auditory pathway (Heil et al., 2008; Meddis, 2006).

Considering that GC-B KO mice exhibit reduced fast (high spontaneous rate firing) auditory processing, as concluded here from phenotype characteristics of GC-B KO mice (Wolter et al., 2018), we would expect reduced parvalbumin-interneuron expression levels, which would normally develop with sensory experience in auditory subcortical and cortical projections (Chumak et al., 2016; Lohmann & Friauf, 1996). When reduced, parvalbumin-inhibition, which includes tonic and phasic activity, fails to adjust the increased synchronization of spontaneous activity across a broad frequency range, leading to increased baseline spontaneous $\gamma$ power and occlusion of changes in evoked $\gamma$ power (Chen et al., 2017). Interestingly, increased baseline spontaneous $\gamma$ power linked with reduced evoked $\gamma$ power was observed in children with deficits in fast auditory processing and an autism-like phenotype (Mamashli et al., 2017), emphasizing the current need to reinvestigate GC-B KO mice for possible cognitive consequences of deficits in fast auditory processing.

### 6 | OUTLOOK AND ENVISIONED PHARMACOLOGY APPROACHES

As an overall finding, we conclude that neither sGC, nor GC-A or GC-B have a profound impact on basal hearing function.

#### 6.1 | Targeting sGC for hearing disorders

The deletion of sGCisoforms (GC1 and GC2) points to a differential role of sGC. sGC stimulation that is potentially protective in young animals when sGC downstream targets such as PARP exhibit pro-survival activity (Figure 1c, upper panel). It may become deleterious when presumptive sGC-induced facilitated opening of postsynaptic NMDA receptors in auditory nerve fibres coincide with a presumptive pathological decline of pro-survival signalling as PARP (Figure 1c, lower panel). Regarding the crucial importance played by memory-dependent plasticity changes in auditory adjustment and fast auditory processing and vice versa [see above, (Marchetta, Savitska, et al., 2020)] an additional function of sGC in central auditory processing may be envisioned. Here, the previous findings that an NO cascade rescues synaptic and memory dysfunctions (Acquarone et al., 2019), and may control neurovascular coupling (Han et al., 2019), should motivate timely preclinical trials involving trauma-induced hearing deficits. Moreover, the recent discoveries of compounds that stimulate or activate sGC independently of NO-release may allow this venerable pharmacological target to be approached from a completely different perspective, features that may be particularly valuable for sGC based strategies for hearing disorders. Thus, NO-independent but haem-dependent stimulators of sGC, as well as NO- and haem-independent sGC activators, are emerging as valuable tools that could help to elucidate the physiology and pathophysiology of the NO/sGC/cGMP pathway in more detail and that may allow modulating the activity of sGC in a highly selective, NO-independent manner (Evgenov et al., 2006; Stasch et al., 2002). In this context, tetrahydrobiopterin (BH4), previously only shown to counteract aversive memory (Latini et al., 2018), may also be of particular interest to counteract central auditory processing deficits. This may be essential, since when treated at young ages, activators of sGC signalling have a potential to prevent noise-induced cochlear inner hair cell synaptopathy, while when administered to aged animals, they worsen effects (Möhrle et al., 2017) (Figure 1c). Even if challenging, more research on the differential pharmaceutical modulation of either GC1 or GC2 would be interesting to specifically address effects of individual isoforms on hearing.

#### 6.2 | Targeting GC-A for hearing disorders

Future pharmaceutical targeting of GC-A should be considered for overcoming age-dependent, acoustic-trauma-induced or hidden hearing loss, all devastating diseases with an increasing prevalence due to demographic changes and altered leisure behaviour (Keithley, 2020; Lee et al., 2019). Stimulation of GC-A through the ligand ANP may be particularly promising because (i) ANP levels in endolymph are two orders of magnitude higher than in plasma (Yoon et al., 2012); (ii) the ANP-producing serine protease corin is expressed in the cochlea, indicating that cochlear cells are capable of converting proANP to ANP (Fitzakerley & Trachte, 2018) and (iii) preliminary studies pointed to a transient improvement in hearing thresholds following systemic ANP administration (Yoon et al., 2015). Alternatively, since BNP expression is found in hair cells and spiral ganglia of the adult murine cochlea (Marchetta, Möhrle, et al., 2020), stimulation with the GC-A ligand BNP may be considered as a future therapeutic target. Based on these findings, as an alternative to PDE5 inhibitors, that were previously suggested as potential drugs to overcome hearing deficits (Jaumann et al., 2012), the cGMP-degrading enzyme PDE9a might be a drug target. PDE9a expression is not only found in the cochlea (Marchetta, Möhrle, et al., 2020), it also increases cGMP pools that are predominantly controlled by ANP/GC-A (Lee et al., 2015). Also PDE2a, which is expressed in the cochlea (Fitzakerley & Trachte, 2018) and the CNS (Ruan et al., 2019), would be an interesting target to improve hearing deficits.

Finally, inhibition of the natriuretic peptide-degrading enzymes, for example, membrane metalloendopeptidase (MME) (also called nephrilysin or neutral endopeptidase), which typically reduce cGMP production through GC-A, should be considered. Indeed, MME mRNA was found to be expressed in hair cells and possibly in spiral ganglia (Fitzakerley & Trachte, 2018; Shen et al., 2015), but the protective potential of MME inhibition against acoustic trauma or age-dependent hearing loss has not yet been tested.
6.3 | Targeting GC-B for hearing disorders

Since GC-B was found to be possibly crucial for temporal sound coding, pharmaceutical targeting of GC-B may be also considered in the future. Indeed, it is still unclear which contribution and consequences impaired auditory nerve fibre bifurcation might have for hereditary kinds of hearing deficits, nor what impact bifurcation deficits might have on the death of cochlear neurons and for the therapeutic restoration of hearing using cochlear implants (Wilkerson et al., 2017). Moreover, a genetic mutation of Npr2 is expected to lead mainly to a developmental phenotype, suggesting pharmacological interventions in adult organisms may be limited in their effects. For children with cochlear implants, moreover, dysfunction of GC-B needs to be considered as a profound limitation for cochlea implant outcomes. This can be assessed from the severe temporal deficits of auditory processing in GC-B KO mice (Wolter et al., 2018) and the prerequisite of proper temporal coding of auditory information that remains an indispensable element underlying good speech perception (He et al., 2008; Shannon et al., 1995). However, if in humans hereditary GC-B defects may contribute to hearing deficits, a therapeutic effect could be reached with pharmacological treatments at an embryonic stage to overcome deficits in brainstem bifurcation. Appropriate research and studies of side-effects are required on the application methods and the dosage, as GC-B influences many physiological development steps, such as bone growth.

7 | OVERALL CONCLUSION

Based on the general assumption that deficits in sGC, GC-A and GC-B might not primarily influence gross basal hearing function (see above), we here suggest reconsidering a crucial role of cGMP signalling on central (fast) high spontaneous rate firing fibre dependent auditory processing that only develops at hearing onset. Fast action potential sequences for high-frequency activity and fast temporal precise transmission is a characteristic feature of fast parvalbumin synapses (Hu et al., 2018), what may render this fast processing most vulnerable to limits in the total action potential-related energy budget under, for example, ischaemic conditions or reduced vascular metabolic supply (Kann, 2016). The integral role of cGMP signalling in vascular function (Feil et al., 2003; Kemp-Harper & Schmidt, 2009) needs to be considered in this context. Furthermore, an orchestrated differential function of sGC and GC-A for neurovascular coupling in the brain may also be involved and should be addressed in future studies.

We propose the particular value of delivering cGMP level influencing drugs locally to the round window in the inner ear, especially if these drugs do not cross the blood–brain barrier or will generate side effects when applied systemically. We suggest that GC-A and sGC pathway stimulating drugs may overcome or prevent noise-induced hearing loss. The devastating consequences of noise exposure as a major contributor to hearing loss with age in human civilization (Wu et al., 2019), the dramatic impact hearing loss has as a risk factor for cognitive decline and dementia (Liu et al., 2020; Livingston et al., 2017) and first indications that not hearing loss per se but perhaps fast auditory processing may be the link to cognition (Knipper et al., 2020; Marchetta, Savitska, et al., 2020; Matt et al., 2018), emphasize the need to consider cGMP signalling cascades in contemporary clinical trials of hearing disorders.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Christopoulos, et al., 2019; Alexander et al., 2019b; Alexander, Kelly, et al., 2019; Alexander, Mathie, et al., 2019).

ACKNOWLEDGEMENTS

This work was funded by Deutsche Forschungsgemeinschaft FOR 2060 project RU 713/3-2, GRK 2381, SPP 1608 RU 316/12-1 and KN 316/12-1 and the British Heart Foundation (RG/16/7/32357). English language services provided by stels-ol.de.

AUTHOR CONTRIBUTIONS

M.K., L.R.: Conceptualization. P.M., L.R., A.J.H., W.S., M.K.: Writing of the manuscript. P.M., W.S.: Creating of the figures.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

ORCID

Adrian J. Hobbs https://orcid.org/0000-0002-3589-7108

REFERENCES

Acquarone, E., Argyrousi, E. K., van den Berg, M., Gulisano, W., Fa, M., Staniszewski, A., Calcagno, E., Zuccarello, E., D’Adamo, L., Deng, S. X., Puzzo, D., & Fiorito, J. (2019). Synaptic and memory dysfunction induced by tau oligomers is rescued by up-regulation of the nitric oxide cascade. Molecular Neurodegeneration, 14, 26. https://doi.org/10.1186/s13024-019-0326-4
Alexander, S. P. H., Christopoulos, A., Davenport, A. P., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., & Collaborators C. (2019). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: G protein–coupled receptors. British Journal of Pharmacology, 176(Suppl 1), S21–S141.
Alexander, S. P. H., Fabbro, D., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Sharman, J. L., & Collaborators C. (2019a). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Catalytic receptors. British Journal of Pharmacology, 176(Suppl 1), S527–S529.
Alexander, S. P. H., Fabbro, D., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Sharman, J. L., & Collaborators C. (2019b). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Enzymes. British Journal of Pharmacology, 176(Suppl 1), S297–S396.
Alexander, S. P. H., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J.,
neuronal coherence and neurovascular coupling under acute stress. The Journal of Neuroscience, 40, 9148–9162.
Han, K., Min, J., Lee, M., Kang, B. M., Park, T., Hahn, J., Yei, J., Lee, J., Woo, J., Lee, C. J., & Suh, M. (2019). Neurovascular coupling under chronic stress is modified by altered GABAergic interneuron activity. The Journal of Neuroscience, 39, 10081–10095. https://doi.org/10.1523/JNEUROSCI.1257-19.2019
He, N. J., Mills, J. H., Ahlström, J. B., & Dubno, J. R. (2008). Age-related differences in the temporal modulation transfer function with pure-tone carriers. The Journal of the Acoustical Society of America, 124, 3841–3849.
Heil, P., Neubauer, H., Brown, M., & Irvine, D. R. (2008). Towards a unifying basis of auditory thresholds: Distributions of the first-spoke latencies of auditory-nerve fibers. Hearing Research, 238, 25–38.
Heinrich, U., Maurer, J., Koesling, D., Mann, W., & Förstermann, U. (2000). Immuno-electron microscopic localization of the α4 and β1-subunits of soluble guanylyl cyclase in the Guinea pig organ of corti. Brain Research, 885, 6–13.
Heinrich, U. R., Maurer, J., Gosepath, K., & Mann, W. (1998). Immunoelectron microscopic localization of nitric oxide synthase III in the Guinea pig organ of Corti. European Archives of Oto-Rhino-Laryngology; Official Journal of the European Federation of Oto-Rhino-Laryngological Societies, 255, 483–490.
Hong, E. J., McCord, A. E., & Greenberg, M. E. (2008). A biological function for the neuronal activity-dependent component of BDNF transcription in the development of cortical inhibition. Neuron, 60, 610–624.
Hu, H., Gan, J., & Jonas, D. (2014). Interneurons. Fast-spiking, parvalbumin+ GABAergic interneurons: From cellular design to microcircuit function. Trends in Neurosciences, 37, 60–66.
Hu, H., Roth, F. C., Vandael, D., & Jonas, P. (2018). Complementary tuning of Na+ and K+ channel gating underlies fast and energy-efficient action potentials in GABAergic interneuron axons. Neuron, 98, 156–165 e156.
Irvine, D. R. F. (2018). Plasticity in the auditory system. Hearing Research, 362, 61–73.
Ishizuka, Y. Y. M., Ambe, K., Sasaki, J., Sugihara, N., & Watanabe, H. (2019). Expression profiles of iNOS isoforms in dental pulp and odontoblasts in nNOS knockout mice. The Bulletin of Tokyo Dental College, 60(4), 261–266.
Jaumann, M., Dettling, J., Gubelt, M., Zimmermann, U., Gerling, A., Dettling, J., Feil, S., Wolpert, S., Franz, C., Varakina, K., Xiong, H., Brandt, N., Kuhn, S., Geisler, H.-S., Rohbock, K., Ruth, P., Schlossmann, J., Hütter, J., Sandner, P., ... Rüttiger, L. (2012). cGMP-PKG signaling and Pde5 inhibition shelter cochlear hair cells and hearing function. Nature Medicine, 18, 252–259.
Kann, O. (2016). The interneuron energy hypothesis: Implications for brain disease. Neurobiology of Disease, 90, 75–85.
Keithley, E. M. (2020). Pathology and mechanisms of cochlear aging. Journal of Neuroscience Research, 98(9), 1674–1684. https://doi.org/10.1002/jnr.24439
Kellner, M., Jahn, H., & Wiedemann, K. (2003). Natriuretic peptides and Keithley, E. M. (2020). Pathology and mechanisms of cochlear aging. Journal of Neuroscience Research, 98, 6740–6747. https://doi.org/10.1523/JNEUROSCI.19-16-06740.1999
Kitanishi, T., Aimi, Y., Kitano, H., Suzuki, M., Kimura, H., Saito, A., Shimizu, T., & Tooyama, I. (2013). Distinct localization of peripheral and central types of choline acetyltransferase in the rat cochlea. Acta Histochemica et Cytochemica, 46, 145–152.
Knipper, M., van Dijk, P., Schulze, H., Mazurek, B., Krauss, P., Scheper, V., Warnecke, A., Schlee, W., Schwabe, K., Singer, W., & Ruttiger, L. (2020). The neural bases of tinnitus: Lessons from deafness and Cochlear implants. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 40, 7190–7202. https://doi.org/10.1523/JNEUROSCI.1314-19.2020
Kocharyan, A., Fernandes, P., Tong, X. K., Vacher, E., & Hamel, E. (2008). Specific subtypes of cortical GABA interneurons contribute to the neurovascular coupling response to basal forebrain stimulation. Journal of Cerebral Blood Flow and Metabolism, 28, 221–231.
Koesling, D., Mergia, E., & Russwurm, M. (2016). Physiological functions of NO-sensitive guanylyl cyclase isoforms. Current Medicinal Chemistry, 23, 2653–2665.
Koesling, D., Russwurm, M., Mergia, E., Müllershausen, F., & Friebe, A. (2004). Nitric oxide-sensitive guanylyl cyclase: Structure and regulation. Neurochemistry International, 43, 813–819.
Kopp-Scheinpflug, C., Pigott, B. M., & Forsythe, I. D. (2015). Nitric oxide selectively suppresses IH currents mediated by HCN1-containing channels. The Journal of Physiology, 593, 1685–1700.
Kourouch-Arami, M., Hossein, N., Molsenmadeg, M., Komaki, A., & Jhogataei, M. T. (2020). Neurophysiologic implications of neuronal nitric oxide synthase. Reviews in the Neurosciences, 31, 617–636.
Kraus, N., & White-Schwoch, T. (2015). Unraveling the biology of auditory learning: A cognitive-sensorimotor-reward framework. Trends in Cognitive Sciences, 19, 642–654.
Kuhn, M. (2005). Cardiac and intestinal natriuretic peptides: Insights from genetically modified mice. Peptides, 26(6), 1078–1085.
Kuhn, M. (2016). Molecular physiology of membrane guanylyl cyclase receptors. Physiological Reviews, 96, 751–804.
Kuhn, M., Volker, K., Schwarz, K., Carabajo-Lozoya, J., Flogel, U., Jacoby, C., Stypmann, J., Van Eickels, M., Gambaryan, S., & Baba, H. A. (2009). The natriuretic peptide/guanylyl cyclase–A system functions as a stress-responsive regulator of angiogenesis in mice. The Journal of Clinical Investigation, 119, 2019–2030. https://doi.org/10.1172/JCI37430
Kujawa, S. G., & Liberman, M. C. (2015). Synaptopathy in the noise-exposed and aging cochlea: Primary neural degeneration in acquired sensorineural hearing loss. Hearing Research, 330, 191–199.
Lateri, A., de Bortoli da Silva, L., da Luz Scheffer, D., Pires, A. C. S., de Matos, F. J., Nesi, R. T., Ghisoni, K., de Paula Martins, R. de Oliveira, P. A., Prediger, R. D., & Aguiar, A. S. (2018). Tetrahydrobiopterin improves hippocampal nitric oxide-linked long-term memory. Molecular Genetics and Metabolism, 125, 104–111. https://doi.org/10.1016/j.ymgme.2018.06.003
Le Prell, C. G., Shore, S. E., Hughes, L. F., & Bledsoe, S. C. Jr. (2003). Disruption of lateral efferent pathways: Functional changes in auditory evoked responses. Journal of the Association for Research in Otologyngology, 4, 276–290.
Lee, J. H., Kang, M., Park, S., Perez-Flores, M. C., Zhang, X. D., Wang, W., Gratto, M. A., Chiamvimonvat, N., & Yamoah, E. N. (2019). The local translation of KNAs in dendritic projections of auditory neurons and the roles of KNAs in the transition from hidden to overt hearing loss. Aging, 11, 11541–11564.
Lee, S., Kang, B. M., Shin, M. K., Min, J., Heo, C., Lee, Y., Baeg, E., & Suh, M. (2015). Chronic stress decreases cerebrovascular responses during rat hindlimb electrical stimulation. Frontiers in Neuroscience, 9, 462.
mitochondrial abnormality. Free Radical Biology and Medicine, 87, 181–192.

Viana, L. M., O'Malley, J. T., Burgess, B. J., Jones, D. D., Oliveira, C. A., Santos, F., Merchant, S. N., Liberman, L. D., & Liberman, M. C. (2015). Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue. Hearing Research, 327, 78–88.

Warr, W. B., & Guinan, J. J. Jr. (1979). Efferent innervation of the organ of corti: Two separate systems. Brain Research, 173, 152–155.

Weinberger, N. M. (2015). New perspectives on the auditory cortex: Learning and memory. Handbook of Clinical Neurology, 129, 117–147.

Whitfield, T. T. (2015). Development of the inner ear. Current Opinion in Genetics & Development, 32, 112–118.

Wilkerson, B. J., Porps, S. F., & Babu, S. C. (2017). The impact of comorbidities in the aging population on Cochlear implant outcomes. Otology & Neurotology, 38, e285–e288.

Wolter, S., Mohrle, D., Schmidt, H., Pfeiffer, S., Zelle, D., Eckert, P., Krämer, M., Feil, R., Pilz, P. K. D., Knipper, M., & Ruttiger, L. (2018). GC-B deficient mice with axon bifurcation loss exhibit compromised auditory processing. Frontiers in Neural Circuits, 12, 65.

Wu, P. Z., Liberman, L. D., Bennett, K., de Gruttola, V., O'Malley, J. T., & Liberman, M. C. (2019). Primary neural degeneration in the human cochlea: Evidence for hidden hearing loss in the aging ear. Neuroscience, 407, 8–20.

Wu, P. Z., Liberman, L. D., Bennett, K., de Gruttola, V., O'Malley, J. T., & Liberman, M. C. (2019). Primary neural degeneration in the human cochlea: Evidence for hidden hearing loss in the aging ear. Neuroscience, 407, 8–20.

Xiong, Y., Mahmood, A., & Chopp, M. (2010). Angiogenesis, neurogenesis and brain recovery of function following injury. Current Opinion in Investigational Drugs, 11, 298–308.

Xu, H., Kotak, V. C., & Sanes, D. H. (2010). Normal hearing is required for the emergence of long-lasting inhibitory potentiation in cortex. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 30, 331–341.

Yoon, Y. J., Lee, E. J., Hellstrom, S., & Kim, J. S. (2015). Atrial natriuretic peptide modulates auditory brainstem response of rat. Acta Oto-Laryngologica, 135, 1293–1297.

Yoon, Y. J., Lee, E. J., & Kim, S. H. (2012). Synthesis of atrial natriuretic peptide in the rabbit inner ear. The Laryngoscope, 122, 1605–1608.

How to cite this article: Marchetta P, Rüttiger L, Hobbs AJ, Singer W, Knipper M. The role of cGMP signalling in auditory processing in health and disease. Br J Pharmacol. 2021;1–16. https://doi.org/10.1111/bph.15455