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REVIEW

The emerging framework of mammalian auditory hindbrain development

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Abstract A defining feature of the mammalian auditory system is the extensive processing of sound information in numerous ultrafast and temporally precise circuits in the hindbrain. By exploiting the experimental advantages of mouse genetics, recent years have witnessed an impressive advance in our understanding of developmental mechanisms involved in the formation and refinement of these circuits. Here, we will summarize the progress made in four major fields: the dissection of the rhombomeric origins of auditory hindbrain nuclei; the molecular repertoire involved in circuit formation such as Hox transcription factors and the Eph-ephrin signaling system; the timeline of functional circuit assembly; and the critical role of spontaneous activity for circuit refinement. In total, this information provides a solid framework for further exploration of the factors shaping auditory hindbrain circuits and their specializations. A comprehensive understanding of the developmental pathways and instructive factors will also offer important clues to the causes and consequences of hearing-loss related disorders, which represent the most common sensory impairment in humans.

Keywords Rhombomere · Hox · Transcription factor · Activity-dependent · Refinement · Development

Abbreviations

AN	Auditory nerve
AP	Action potential
A-P	Anterior–posterior
aVCN	Anterior ventral cochlear nucleus
CNC	Cochlear nucleus complex
DCN	Dorsal cochlear nucleus
DNLL	Dorsal nucleus of the lateral lemniscus
D-V	Dorsal–ventral
E	Embryonic
INLL	Intermediate nucleus of the lateral lemniscus
LNTB	Lateral nucleus of the trapezoid body
LSO	Lateral superior olive
MNTB	Medial nucleus of the trapezoid body
P	Postnatal
pVCN	Posterior ventral cochlear nucleus
r	Rhombomere
SGN	Spiral ganglion neuron
SOC	Superior olivary complex
SPON	Superior paraolivary nucleus
VCN	Ventral cochlear nucleus
VNLL	Ventral nucleus of the lateral lemniscus
VNTB	Ventral nucleus of the trapezoid body

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Introduction

Extensive subcortical processing is an essential feature of various sensory systems. In the visual system, neural networks composed of more than 60 different cell types connected by an intricate connectome form the substrate of early image processing (Masland 2012; Marc et al. 2013). In contrast, in the auditory system, extensive processing of sensory information first takes place in numerous divergent and convergent neuronal

circuits in the hindbrain (Smith and Spirou 2002; Cant and Benson 2003; Middlebrooks and Arbor 2009). These circuits participate in a variety of tasks including signal transmission, localization of sound sources (Grothe et al. 2010) and determination of sound duration (Kopp-Scheinpflug et al. 2011). Since preservation of timing is important in these circuits, they exhibit various molecular and cellular features to ensure ultrafast and precise neurotransmission (Trussell 1997, 1999; Oertel 1997, 1999). These specializations include giant synapses and a particular repertoire of plasma membrane proteins such as fast AMPA receptors and auditory-typical voltage-gated K^+-channels (Golding 2012; Borst and van Soria 2012; Manis et al. 2012; Johnston et al. 2010; Oertel 2009; Yu and Goodrich 2014). Proper development of these circuits and their unique specializations is critical for normal hearing. Indeed, altered structure or function in the auditory hindbrain have been linked in humans to autism spectrum disorders (Kulesza et al. 2011) and dyslexia (Hornickel et al. 2012). Dysfunction of the auditory hindbrain is also thought to contribute considerably to auditory processing disorders (Tallal 2012; Chermak and Musiek 1997). Since most neuronal disorders are rooted in aberrant developmental processes, insights into the genetic, molecular and cellular mechanisms of these processes will advance basic and clinical research alike.

Development of mammalian neural circuits is a complex process, involving multiple stages (Singer et al. 1994; Pathania et al. 2010). In a first step, patterning and cell type specification has to occur. During a process of progressive subdivision, which relies on spatially restricted expression of homeotic genes such as the homeobox containing *Hox* family of transcription factors (Fig. 1), positional identity values are generated along the anterior–posterior (A-P) and dorsal–ventral (D-V) axes (Nusslein-Volhard et al. 1987; Rubenstein et al. 1998; Hunt and Krumlauf 1992; Wilkinson 1989; Pera et al. 2014). These positional values control the expression of proneural and neurogenic genes such as *neurogenin*, *NeuroD*, or members of the *atonal* gene family. The encoded transcription factors, which often display a basic helix-loop-helix-type structure, regulate the commitment of neural subtypes (Itoh et al. 2013; Pathania et al. 2010; Guillemot 2005; Bertrand et al. 2002). During commitment, cells first undergo a labile phase referred to as specification where they are capable of differentiating autonomously but where cell fate can still be altered. In a second step, the determination, cell fate becomes irreversible and independent of the cell environment. The final step during generation of specialized cell types is called differentiation, which covers all subsequent developmental steps until the end of functional maturation (Slack 1991; Gilbert 2014). In addition, proneural and neurogenic genes can promote proliferation of neural progenitors (Castro and Guillemot 2011). Commitment is followed by cell migration (Ghashghaei et al. 2007; Marin and Rubenstein 2001) and neurite outgrowth, as well as target finding (Goodman 1996; Gallo 2013) and synaptogenesis (Davis 2000). Finally, functional maturation and refinement of neural circuits takes place, which requires the interplay between genetically determined factors and neuronal activity (Katz and Shatz 1996; Spitzer 2006).

Within the last decade, an increasing number of studies have elucidated genetic and molecular mechanisms operating during development of the mammalian auditory hindbrain. Most of these investigations employed mice to take advantage of the opulent genetic tool box and the abundant stock of transgenic animal lines. These resources enable conditional gene knock-in and knock-outs on demand to probe the function of individual genes or to label genetically defined cell populations (Nagy et al. 2009; Yamamoto et al. 2001; Voncken and Hofker 2006; Branda and Dymecki 2004; Dymecki and Kim 2007; Joyner and Zervas 2006). An additional benefit from the use of mice in central auditory research came with the identification of the embryonic origin of the auditory hindbrain nuclei. This information immediately expanded the knowledge of the developmental mechanisms operating in the auditory system, as the mouse embryonic hindbrain has been intensively investigated for decades by developmental biologists. The available data, for instance, made it possible to sketch for the first time parts of the gene regulatory networks involved in building auditory hindbrain structures (Willaredt et al. 2014b). Here, we will review the current data to draft a framework of the molecular and cellular mechanisms involved in the formation of auditory hindbrain circuits. We will focus on the auditory hindbrain of the mouse. This reflects the paramount contribution of this model organism to our current knowledge. Furthermore, the restriction to a single species will provide coherence with respect to the developmental timeline, which varies between species. We will first describe the basic layouts of the mammalian auditory hindbrain and the embryonic rhombencephalon, before summarizing the current knowledge on the embryonic origins of auditory hindbrain nuclei. We then highlight important transcription factors and signaling molecules and end up with the formation of functional circuits and the role of spontaneous activity therein. The role of sound-evoked activity for maturation processes will be described in an accompanying article (Ryugo, this issue).

Layout of the mammalian auditory hindbrain

Within the central auditory system, the cochlear nucleus complex (CNC), the superior olivary complex (SOC) and the nuclei of the lateral lemniscus (NLL) share a rhombencephalic origin and are therefore part of the hindbrain (Fig. 2). Together with the mesencephalic inferior colliculus (IC), they form the auditory brainstem. All primary auditory nerve (AN) fibers, that is to say the central fibers of the spiral ganglion neurons (SGN), terminate in the CNC, where they bifurcate (Fig. 3).

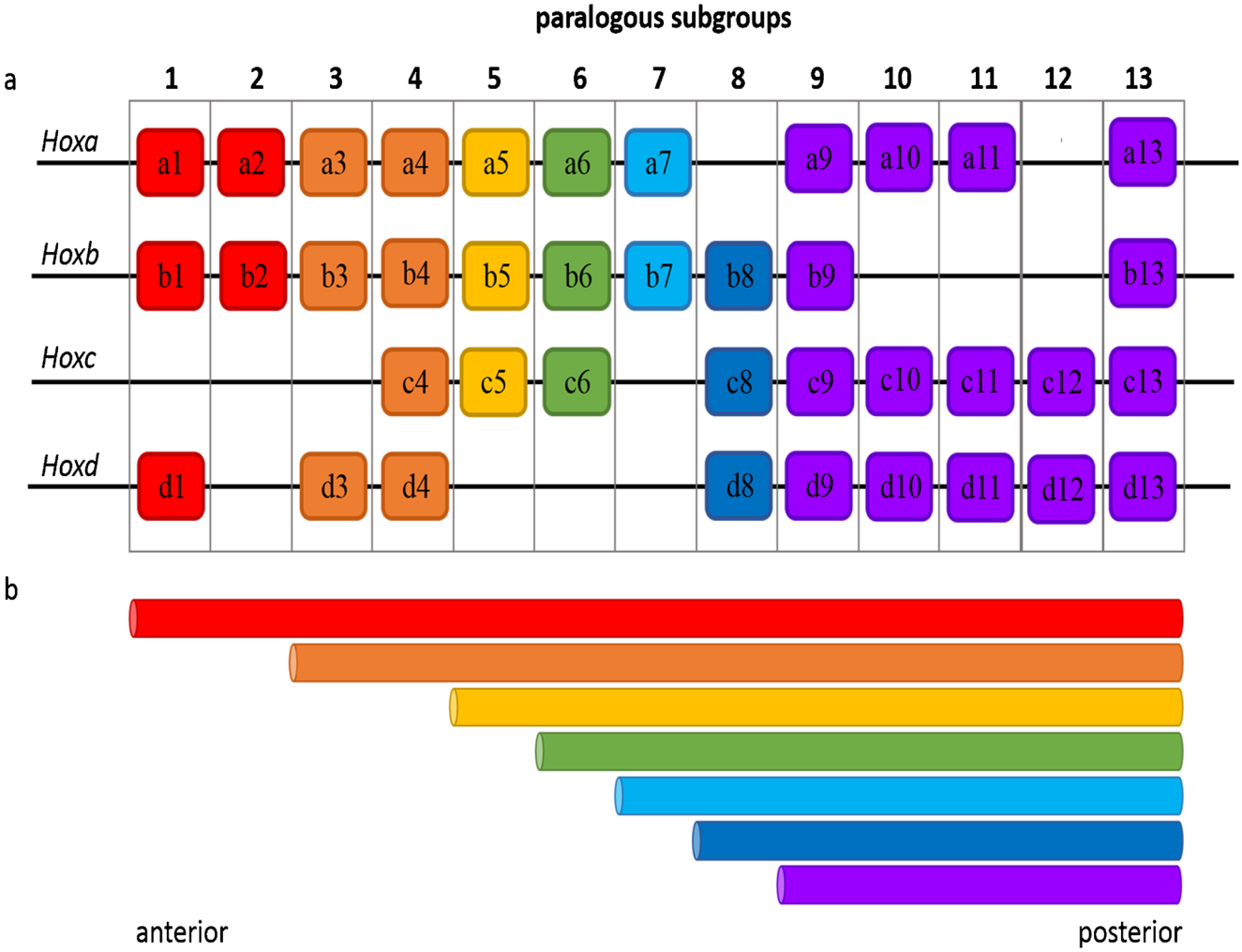

Fig. 1 *Hox* genes. *Hox* genes belong to the class of homeotic genes that regulate the identity of body regions. Mutations in homeotic genes cause the transformation of one body region or part into the likeness of another (Lewis 1978; Carroll et al. 2005). All Hox proteins contain a similar DNA-binding region of around 60 amino acids. This region, known as homeodomain, consists in a helix-turn-helix DNA binding motif. The homeodomain is encoded by the homeobox, a 180-nucleotide-long sequence (McGinnis et al. 1984a, b; Gehring 1993). *Hox* genes belong to an evolutionary ancient gene family present in all bilateria. In most vertebrates, the *Hox* genes are organized in four clusters, known as the Hox complexes, which are thought to be the product of duplications of the clusters themselves during vertebrate evolution (Tümpel et al. 2009) (**a**). A particular feature of *Hox* clusters is that the order of the genes from 3′ to 5′ in the DNA is the order of their spatial and temporal expression along the anterior-posterior axis (Gehring 1993; Tümpel et al. 2009). This principle is called colinearity as the genes in the clusters are expressed in a temporal and spatial order that reflects their order on the chromosome. Thus, the gene lying most 3′ in a cluster is expressed earliest and in the most anterior position (**b**). This property results in the generation of overlapping or nested patterns of *Hox* gene expression, which provide a combinatorial code for specifying unique regional identities. In general, the neural expression of each *Hox* gene is initiated in a posterior region and expands in an anterior direction to form a sharp and distinct anterior boundary (Deschamps and Wijgerde 1993; Murphy and Hill 1991; Murphy et al. 1989; Wilkinson 1989). Genes that have arisen by duplication and subsequent divergence within a species are called paralogs (Fitch 1970, 2000) and the corresponding genes in the different clusters (e.g., *Hoxa4*, *Hoxb4*, *Hoxc4* and *Hoxd4*) are known as paralagous subgroups. In mouse and man, 13 paralogous subgroups exist, providing ample combinatorial possibilities for the Hox code

An ascending branch projects to the anterior ventral cochlear nucleus (aVCN), whereas a descending branch innervates the posterior ventral cochlear nucleus (pVCN) and the dorsal cochlear nucleus (DCN) (Middlebrooks and Arbor 2009). The CNC distributes the incoming auditory information to distinct ascending pathways in the brainstem (Fig. 3). Major projections of the DCN innervate the contralateral nuclei of the LL and the IC (Cant and Benson 2003). The VCN projects mainly into the region of the ipsilateral and contralateral SOC. This auditory structure comprises several third-order nuclei including the lateral superior olive (LSO), the medial superior olive (MSO), the superior paraolivary nucleus (SPON) as well as the ventral, medial and lateral nuclei of the trapezoid body (VNTB, MNTB, LNTB, respectively) (Thompson and Schofield 2000; Moore 1991). The major ascending projections of the SOC innervate the dorsal nuclei of the LL (DNLL)

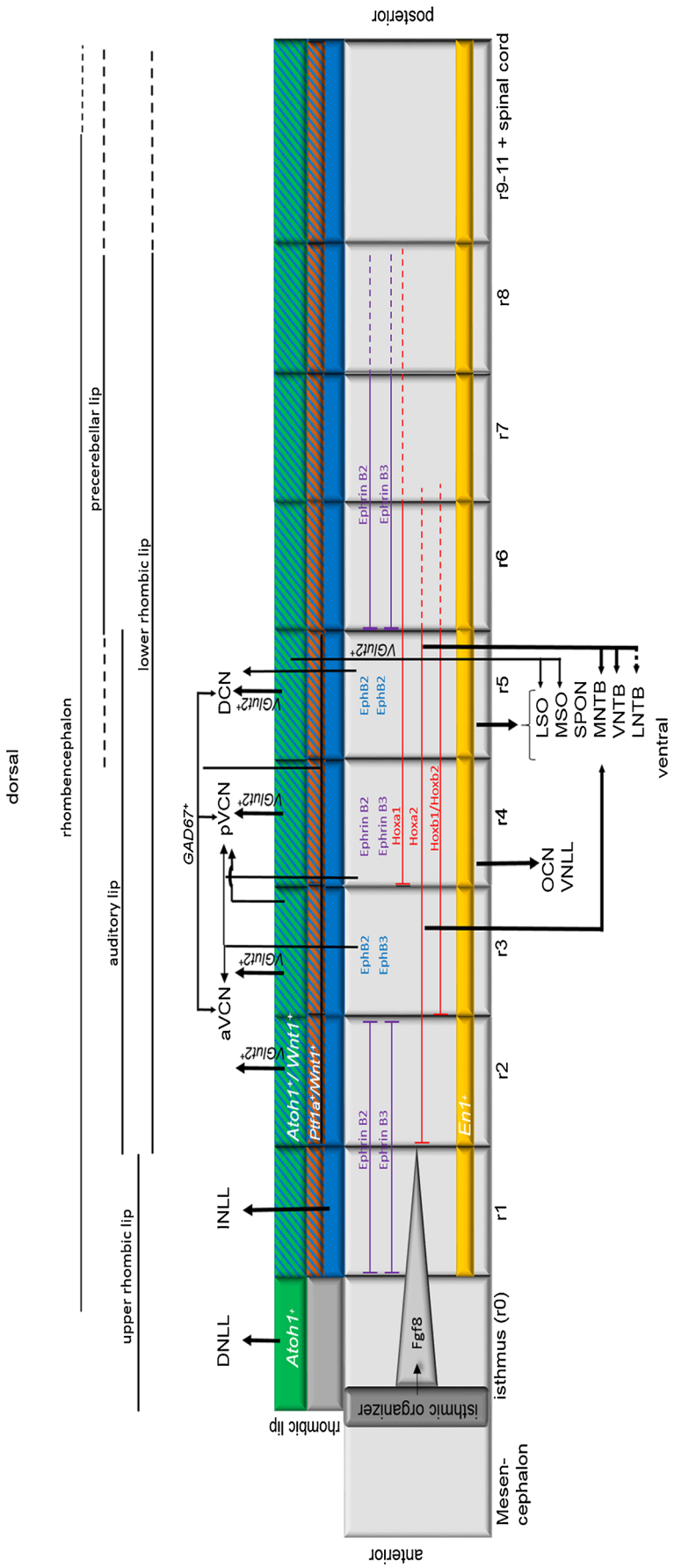

Fig. 2 Origin of mammalian auditory hindbrain nuclei. The developing mammalian hindbrain is transversally segmented into rhombomeres, which represent developmental compartments. The dorsal part of the rhombomeres consists in the rhombic lip that can be further subdivided into anatomical and functional areas. The origin of auditory brainstem nuclei is indicated by *arrows*. Note that most auditory nuclei represent composite populations with neurons originating from different rhombomeres and/or different areas within rhombomeres. Only expression of selected *Hox* genes is indicated. For details, see text. *aVCN* anterior ventral cochlear nucleus, *DCN* dorsal cochlear nucleus, *DNLL* dorsal nucleus of the lateral lemniscus, *INLL* intermediate nucleus of the lateral lemniscus, *LNTB* lateral nucleus of the trapezoid body, *LSO* lateral superior olive, *MNTB* medial nucleus of the trapezoid body, *pVCN* posterior ventral cochlear nucleus, *r* rhombomere, *SOC* superior olivary complex, *VNLL* ventral nucleus of the lateral lemniscus, *VNTB* ventral nucleus of the trapezoid body

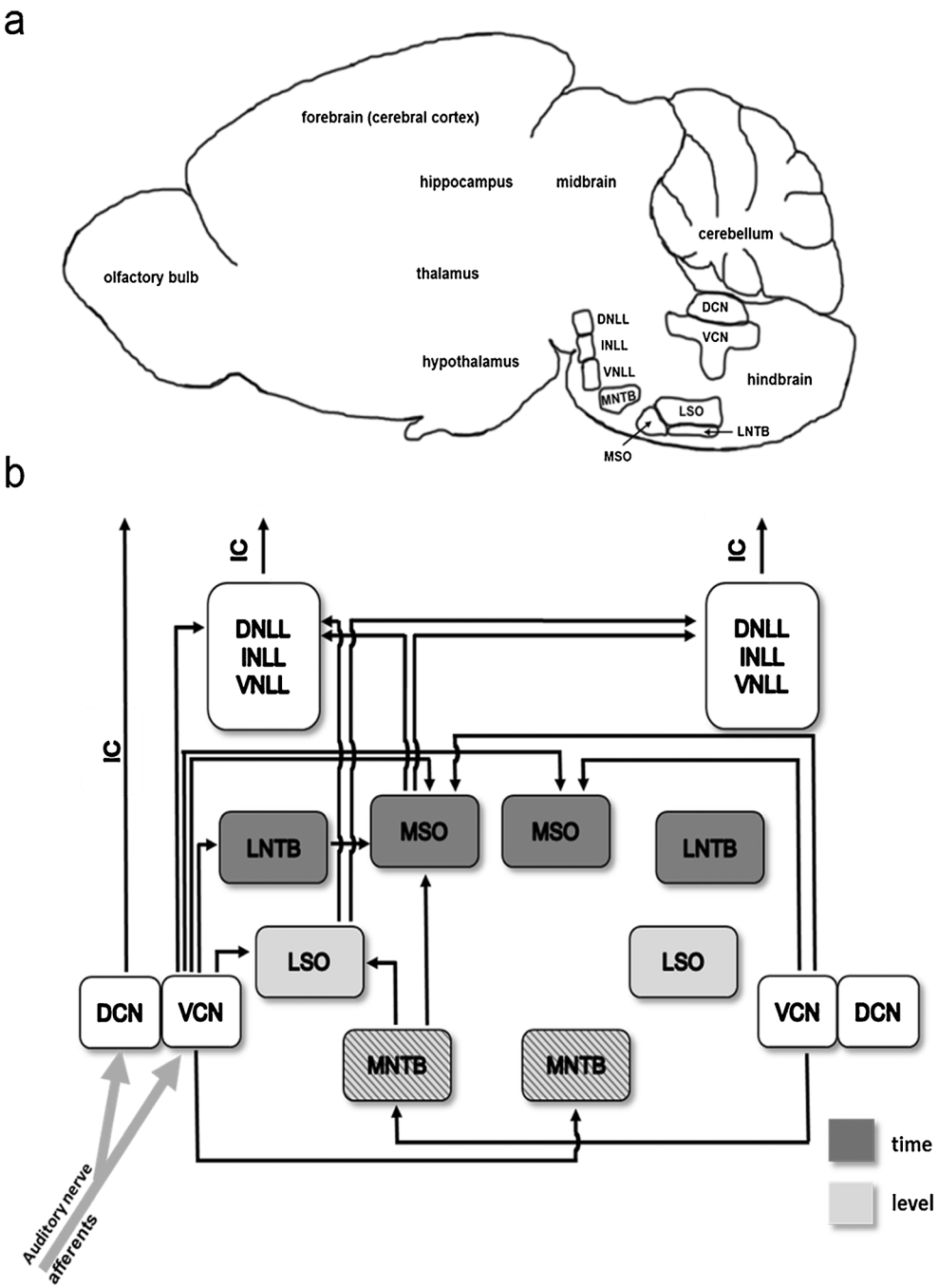

Fig. 3 Anatomical organization of the mouse auditory hindbrain. **a** Anatomical location of auditory hindbrain centers in a sagittal view of the mouse brain. **b** Major projections within the mammalian auditory hindbrain. The auditory nerve bifurcates and innervates both the dorsal cochlear nucleus (*DCN*) and the ventral cochlear nucleus (*VCN*). Neurons of the DCN innervate the inferior colliculus (*IC*), whereas the VCN innervates multiple nuclei within the superior olivary complex (*SOC*) such as the lateral superior olive (LSO), the medial superior olive (*MSO*), the medial nucleus of the trapezoid body (*MNTB*) and the lateral nucleus of the trapezoid body (*LNTB*). These circuits are involved in processing of interaural time and level differences. SOC neurons have major projections to the ventral, intermediate and dorsal nucleus of the lateral lemniscus (*VNLL*, *INLL*, and *DNLL*, respectively). Note that not all nuclei and projections in the auditory hindbrain are shown

and the IC (Fig. 3). In addition, the olivocochlear neurons (OCN), an important feedback system to the cochlea, are located in the SOC (Guinan et al. 1983; Simmons 2002). Along the ascending auditory pathway, information of the CNC and the SOC is carried to the three nuclei of the LL, i.e., the dorsal, intermediate and ventral nucleus (DNLL, INLL, VNLL, respectively) (Fig. 3). All projections of hindbrain auditory nuclei terminate in the IC, which acts as an important hub and

integration center (Middlebrooks and Arbor 2009). From there, information is passed to the medial geniculate body (MGN), a thalamic area in the forebrain, before reaching the auditory cortex.

Most data concerning the anatomy of the auditory pathway have been obtained in mammalian model systems such as rodents or cats. With respect to hearing disorders, it is important to notice that the basic layout is conserved in humans. Differences have only been reported in fine structure. The human DCN shows a laminar organization with only two layers instead of the typical three found in most mammals (Baizer et al. 2014). Furthermore, two cell types were described based on location, morphology and immunoreactivity against non-phosphorylated neurofilament protein and neuronal nitric oxide synthetase, which lack counterparts in non-primates (Baizer et al. 2014). Within the SOC, the human MSO appears as a very prominent nucleus, while the LSO is rather small (Kulesza 2007; Moore 1987; Strominger and Hurwitz 1976). Compared to other mammals, the human MNTB seems to be reduced and was even questioned to exist (Moore 2000; Hilbig et al. 2009; Bazwinsky et al. 2003). However, recent anatomical and immunohistochemical analyses clearly demonstrated the presence of this auditory relay nucleus (Kulesza 2014; see Grothe et al. 2010 for further discussion).

Organizational principles of the embryonic rhombencephalon

Toward the end of gastrulation, the neural plate begins to fold and to form the neural tube, which becomes regionalized along the A-P axis. This regionalization is most obvious in the rhombencephalon that is segmented into transversal swellings called rhombomeres (r) (Fig. 2) (Birgbauer and Fraser 1994; McKay et al. 1996). Currently, 12 rhombomeres are proposed: the isthmus (r0) (Vieira et al. 2010) and r1–r11, next to the rhombo-spinal junction (Marín et al. 2008; Alonso et al. 2013). Between r1 and r7, clear boundaries are visible and the segmental character can be demonstrated by clonal analysis (Fraser et al. 1990). Cells derived from a single labeled progenitor will cross between rhombomeres only at an early stage (Lumsden and Keynes 1989; Fraser et al. 1990). This clonal restriction is due to the alternating expression of Eph receptors and their ephrin ligands in the individual rhombomeres (Figs. 2 and 4) (Xu et al. 1999; Tümpel et al. 2009). Several Eph receptors such as EphA4 are found in the odd-numbered rhombomeres 3 and 5, while ephrin ligands such as ephrin B1 are present in the even-numbered rhombomeres 2, 4 and 6 (Cooke and Moens 2002; Lumsden and Krumlauf 1996; Tümpel et al. 2009). Thus, Eph-ephrin interfaces coincide with all boundaries from r2 to r6 and the repulsion between the two cell groups causes boundary formation (Fig. 2). Accordingly, expression of a dominant negative Eph prevents this segmentation, as evidenced by ectopic expression of r3 and r5 markers in the adjacent even-numbered segments (Xu et al. 1995, 1999). Once the rhombomere boundaries are formed, the character of the rhombomeres can no longer be re-specified by transplantation (Kuratani and Eichele 1993). These rhombomeres are thus compartments that serve to segregate cell populations with similar potential, enabling them to respond to signals in a different manner. This allows each rhombomere to gain a distinct identity, which ultimately results in the generation of diverse neuronal

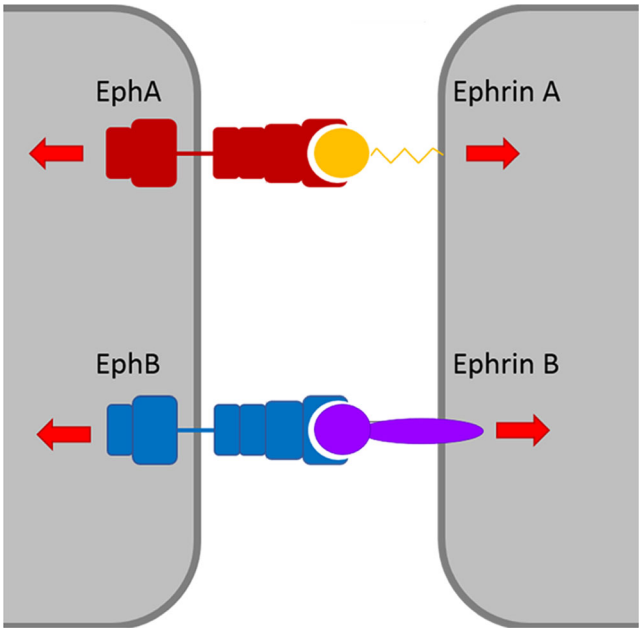

Fig. 4 Eph receptors and their ephrin ligands. Eph receptors and their ephrin ligands are transmembrane proteins that act through direct cell–cell contact (Klein 2009; Klein and Kania 2014). Their signaling thus occurs at small distances. Eph receptors are the largest family of receptor tyrosine kinases in vertebrates and fall into two structural classes: EphAs and EphBs. Mammalian genomes encode 10 EphA receptors (EphA1–A10) and 6 EphB receptors (EphB1–B6). Ephrins similarly can be classified into ephrin As and ephrin Bs. Ephrin A proteins (A1–A6) bind to all of the EphA receptors and are tethered to the plasma membrane via a glycosylphosphatidylinositol (GPI) anchor. Ephrin B proteins (B1–B3) bind to all the EphB receptors and are integral membrane proteins with a transmembrane domain. The broad binding properties within each class provide considerable redundancy and several family members are often co-expressed in populations of cells (Klein and Kania 2014). Furthermore, exceptions to these binding restrictions result in crosstalk between the A and B families. EphA4 can bind to both ephrin A and ephrin B ligands and EphB2 can bind to ephrin A5. The association of both Eph receptors and ephrins with cell membranes facilitates bidirectional signaling. In addition to forward signaling via Eph receptors, reverse signaling also occurs, whereby the binding of ephrins by their receptor activates cell signaling events in the cell expressing the ephrins. Activated Eph receptors are arranged as a tetramer with two ephrin molecules and two Eph receptors. The main targets of Eph receptor–ephrin signaling are small Rho family members GTPases such as RhoA, Rac1, and Cdc42, which in turn regulate the cytoskeleton (Klein and Kania 2014). Although Eph receptor-ephrin contact can generate both repulsive and adhesive interactions between cells, the interaction is best known for producing repulsion between the interacting cells, as at the interface between different rhombomeres. Eph receptor–ephrin signaling furthermore partakes in cell segregation and positioning, tissue segmentation, cell migration, axon guidance, topographic mapping and morphogenesis

components essential for organization and function of the hindbrain.

The hindbrain regions posterior to the r6/r7 boundary lack visible inter-rhombomeric boundaries. Yet, they feature a molecular regionalization mainly based on differential expression of *Hox* genes from paralogus groups 3–7 (Fig. 1) (Cambronero and Puelles 2000; Marín et al. 2008; Lorente-Cánovas et al. 2012). Since the boundaries in the isthmic domain and between r7 to r11 are not morphologically visible, these areas of the rhombencephalon were proposed to represent crypto-rhombomeres (Alonso et al. 2013). Whether these rhombomeres display cell lineage restriction and unique characteristics, similar to r2 to r7, remains to be determined.

Within each rhombomere, inductive signals and specific combinations of transcription factors provide positional information along the A-P and D-V axis. The resulting positional value instructs subpopulations of progenitors and specifies the neuronal fate of differentiating neurons (Jessell 2000; Machold and Fishell 2005; Tümpel et al. 2009; Jacob et al. 2007; Pattyn et al. 2003; Di Bonito et al. 2013a; Fujiyama et al. 2009; Wolpert 2011). Single rhombomeres can therefore contribute to distinct neuronal systems. On the other hand, neuronal groups can be composed of cells, originating from different rhombomeres (Tan and Le Douarin 1991; Marin and Puelles 1995; Cramer et al. 2000; Farago et al. 2006; Di Bonito et al. 2013b; Pasqualetti et al. 2007) (Fig. 2).

In addition to this transversal segmentation, longitudinal organizational principles are present. Over 100 years ago, Wilhelm His defined a highly proliferative region along the dorsal edge of the fourth ventricle of 2-month-old human embryos as the rhombic lip ("Rautenlippe") (Fig. 5) (His 1891). The rhombic lip is positioned between the roof plate and the neural tube and represents the dorsalmost territory of the hindbrain proliferative neuroepithelium (Wingate 2001). The dorsal border of the rhombic lip represents the dorsal edge of the hindbrain, where the rhombic lip gives way to the roof plate. The precise ventral border has yet to be defined (Dun 2012). The rhombic lip is classically divided into two parts. The upper rhombic lip, also called the cerebellar rhombic lip, spans r0 and r1 and the lower rhombic lip, also called the hindbrain rhombic lip (Altman and Bayer 1997), starts at r2 and extends posteriorly (Fig. 2). Alternatively, the rhombic lip can be parceled according to the expression domains of different transcription factors like *Wnt1* (Landsberg et al. 2005), *Atoh1* (also known as *Math1*) (Wang et al. 2005) and *Olig3* (Liu et al. 2008). Yet, this genetic definition is of limited use, since the transcription factors exhibit varying ventral boundaries.

Embryonic origin of the auditory hindbrain

Fate-mapping studies have revealed significant contributions of the rhombic lip to the auditory hindbrain. The upper rhombic lip likely contributes to the LL, whereas the complete CNC as well as a subpopulation of excitatory (glutamatergic) neurons of the SOC are descended from the lower rhombic lip of r2 to r5 (Farago et al. 2006; Nichols and Bruce 2006; Rose et al. 2009). This area of the lower rhombic lip is therefore also termed the auditory lip, whereas the lower rhombic lip from r6 to r8 (possibly until r11) is called the precerebellar lip (Farago et al. 2006; Ray and Dymecki 2009) (Fig. 2). According to the genetic definition, the auditory lip lies within the $Wnt1^+$ territory. $Wnt1^+$ cells substantially contribute to all three subdivisions of the CNC (Farago et al. 2006). Within the $Wnt1^+$ territory, an $Atoh1^+$ domain is present, which contributes strongly to the aVCN and pVCN and marginally to the DCN (Landsberg et al. 2005; Wang et al. 2005; Farago et al. 2006). These data suggest that a $Wnt1^+$;$Atoh1^+$ domain gives rise to the VCN, whereas two different subdomains, a $Wnt1^+$;$Atoh1^+$ and a $Wnt1^+$;$Atoh1^-$ region, generate the DCN (Farago et al. 2006). Fate mapping of

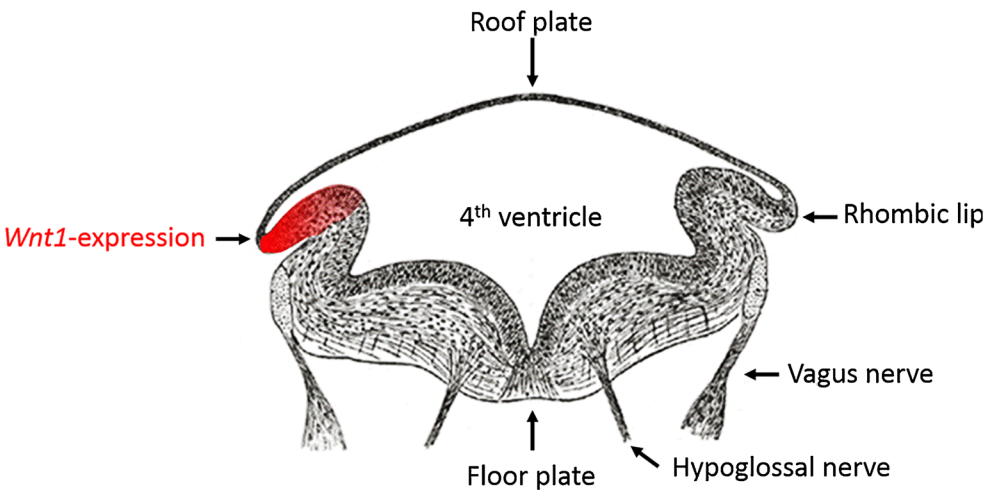

Fig. 5 A schematic drawing of the rhombic lip, as originally defined by His (1891). Modified from Gray (1918). The dorsal part of the rhombic lip is characterized by high expression of *Wnt1*, the ventral part by low expression of *Wnt1* (Landsberg et al. 2005; Farago et al. 2006)

cellular subtypes suggests that the *Wnt1*$^{+}$;*Atoh1*$^{+}$ domain contributes the excitatory giant, fusiform, granule and unipolar brush cells in the DCN, as well as octopus, globular and spherical bushy cells in the VCN (Fujiyama et al. 2009). In contrast, the glycinergic/GABAergic cartwheel, Golgi and ML-stellate cells in the DCN and glycinergic D-stellate cells in the VCN are derived from a *Ptf1a*$^{+}$ lineage (Fujiyama et al. 2009). These data were corroborated by the observation that the number of *VGlut2*$^{+}$ cells was considerably reduced in the CNC of *Atoh1*$^{-/-}$ at E18.5, whereas GABA staining was unchanged (Fujiyama et al. 2009). With respect to the anatomical definition, the aVCN and the associated shell are essentially generated from r2 and r3, the pVCN is mainly derived from r4 and the DCN is primarily descended from r5 with some input from r3 and r4 (Fig. 2) (Farago et al. 2006; Di Bonito et al. 2013b; Renier et al. 2010).

In contrast to the CNC, the *Wnt1*$^{+}$ territory of the auditory lip contributes poorly to the SOC (Fig. 2). Only a subpopulation of LSO and MSO neurons and none of the other SOC nuclei are addressed by a *Wnt1*::*Cre* mouse line (Marrs et al. 2013). A divergent result was obtained by Fu et al. (2011). They reported labeled cells in the LSO, VNTB and LNTB, when using a *Wnt1*::Cre driver line. This interpretation, however, was based on parasagittal sections, where auditory nuclei can easily be mistaken. Furthermore, this labeling is difficult to reconcile with data obtained for the *Atoh1*$^{+}$ lineage, which resides within the *Wnt1*$^{+}$ territory in the lower rhombic lip. The *Atoh1*$^{+}$ lineage labeled a subpopulation of LSO and MSO neurons (Maricich et al. 2009), similar to the *Wnt1*::*Cre* mouse line used by Marrs et al. (2013). With respect to the MSO labeling, it should be noted that this nucleus is difficult to identify in the mouse at E18.5, the stage used for defining the *Atoh1*$^{+}$ lineage. Independent of this caveat, the *Atoh1*$^{+}$ lineage likely expresses *VGlut2*, as the number of *VGlut2*$^{+}$ cells was drastically reduced in the SOC of mice lacking *Atoh1* in r3 and r5 (Maricich et al. 2009). In total, these data suggest that a subpopulation of LSO and MSO neurons is derived from a *Wnt1*$^{+}$;*Atoh1*$^{+}$ domain, whereas all other SOC neurons are generated outside the *Wnt1*$^{+}$ territory. Of note, the basic leucine zipper TF MafB is also mainly expressed in LSO and MSO neurons at P0 (the only other *MafB*$^{+}$ structure is the ventral part of the LNTB) (Marrs et al. 2013). This shared expression of *MafB*, *Wnt1* and *Atoh1* hints to a common origin of high-frequency (LSO) and low-frequency (MSO) processing binaural neurons that use rather different strategies for sound localization (Grothe et al. 2010).

Note, however, that the VGlut2 neurons of LSO and MSO show different projection patterns. Whereas the ascending MSO projections remain largely ipsilateral (Thompson and Schofield 2000), the excitatory LSO projections cross the midline (Glendenning et al. 1992).

A similar overlap of *Wnt1*-, *Atoh1*- and *MafB*-expressing cells is observed for the VCN, which provides the excitatory input to the MSO and LSO (Fujiyama et al. 2009; Maricich et al. 2009; Farago et al. 2006; Landsberg et al. 2005; Howell et al. 2007). It will be interesting to study the implications of this shared genetic program for the evolution of sound localization circuits (Christensen-Dalsgaard and Carr 2008; Grothe and Pecka 2014). Further fate-mapping of SOC neurons revealed that the LNTB, MNTB and VNTB are all derived from an *En1*$^{+}$ progenitor pool (Fig. 2) (Marrs et al. 2013). Lack of this transcription factor in r3 and r5 disrupts MNTB and VNTB formation, whereas the LNTB is preserved (Jalabi et al. 2013). The SPON is neither derived from a *Wnt1*$^{+}$ nor an *En1*$^{+}$ progenitor pool (Marrs et al. 2013). According to the rhombomeric origin, the main part of the SOC is derived from r5, with r3 contributing to the MNTB (Fig. 2) (Maricich et al. 2009; Rosengauer et al. 2012; Marrs et al. 2013). The OCNs, which reside within the SOC, are derived from r4 (Fig. 2) (Di Bonito et al. 2013b; Bruce et al. 1997; Rosengauer et al. 2012). A contribution of r4 to *VGlut2*$^{+}$ neurons to the LSO was also reported (Di Bonito et al. 2013b). This observation is currently difficult to reconcile with the reported loss of these neuronal subtypes after ablation of *Atoh1* specifically in r3 and r5 (Maricich et al. 2009).

The DNLL originates primarily in the isthmic *Atoh1*$^{+}$ lineage (Wang et al. 2005; Rose et al. 2009; Machold and Fishell 2005) (Fig. 2). The INLL is derived from the alar plate of r1 (Moreno-Bravo et al. 2014) and the VNLL from r4 (Fig. 2) (Di Bonito et al. 2013b). Most auditory brainstem centers as well as the thalamic medial geniculate body are prominently addressed by a *Wnt3a*::*Cre* driver mouse (Louvi et al. 2007). Intensive labeling was observed in the VCN, DCN, LSO, MSO, MNTB, DNLL and the MGN and moderate labeling was seen in the VNLL and the IC. As the embryonic *Wnt3a*$^{+}$ domain is rather broad (Louvi et al. 2007; Parr et al. 1993), this labeling, however, provides poor spatial information concerning the origin of auditory brainstem neurons.

Hox genes, associated gene regulatory networks and the auditory hindbrain

Hox genes and their associated gene regulatory networks are crucial components for proper formation of the auditory hindbrain (Willaredt et al. 2014a, 2014b; Di Bonito et al. 2013a). They are required for A-P and D-V patterning in most parts of the rhombencephalon, starting from the r1/2 boundary (Tümpel et al. 2009; Di Bonito et al. 2013a, b; Alexander et al. 2009; Davenne et al. 1999; Prin et al. 2014). The domain anterior to the r1/2 boundary does not express *Hox* genes. Instead, this domain seems to rely mainly on FGF8 signaling from the isthmic organizer (Echevarria et al. 2005; Aroca and Puelles 2005), which is positioned anterior to r0 (Martínez 2001; Wurst and Bally-Cuif 2001). *Hox* genes are thus involved in the development of most auditory hindbrain nuclei, the only exception being the INLL and DNLL (Fig. 2).

Hoxa1 and *Hoxb1* are the first *Hox* genes expressed in the hindbrain and show an anterior limit of expression at the

presumptive r3/r4 border (Tümpel et al. 2007). Their ablation in mice entails severe alterations in the auditory hindbrain. Lack of *Hoxa1* disrupts formation of the SOC, which originates from r3 and r5 (Chisaka et al. 1992). In contrast, *Hoxb1* is required for establishing the regional identity of ventral and dorsal r4 by differentially regulating the expression of *Hoxa2* and *Hoxb2* (Maconochie et al. 1997; Tümpel et al. 2007; Di Bonito et al. 2013b). Its elimination in r4 results in up-regulation of *Hoxa2* and down-regulation of *Hoxb2* (Di Bonito et al. 2013b). As a result, r4 adopts an r3 identity and r4-derived auditory nuclei (pVCN, VNLL, OCN) are lost, whereas r3-derived auditory nuclei (aVCN, cochlear granule cells) are ectopically induced (Studer et al. 1996; Di Bonito et al. 2013a, b). This repatterning is indicated by the expanded expression domain of *Atoh7*, a marker of glutamatergic bushy cells (Saul et al. 2008) in the area of the pVCN and the projection of neurons in this area to the contralateral MNTB as if these neurons were aVCN neurons (Di Bonito et al. 2013b). This identity shift of the pVCN is likely due to an increased $Atoh1^{+}$ expression domain in r4 in the absence of Hoxb1 (Di Bonito et al. 2013b). Along the ascending auditory pathway, the VNLL was reduced by almost 90 % in $Hoxb1^{-/-}$ mice, which was mainly due to the lack of GABAergic/glycinergic cells (Di Bonito et al. 2013b). Thus, deletion of *Hoxb1* in r4 results in an increase of $Atoh1^{+}$-lineage derived excitatory cell types and an accompanying decrease of inhibitory cell types in r4. In agreement with the altered projection pattern in $Hoxb1^{-/-}$ mice, where *Hoxb2* is down-regulated, $Hoxb2^{-/-}$ mice make ectopic projections from the pVCN area to the MNTB (Di Bonito et al. 2013b). Finally, a genetic network, involving *Hoxa1*, *Hoxb1*, *Hoxa2* and *Hoxb2*, regulates the expression of r4 target genes like *EphA2* (Chen and Ruley 1998; Willaredt et al. 2014b), *Phox2b* (Samad et al. 2004; Willaredt et al. 2014b), *Gata2* (Pata et al. 1999; Willaredt et al. 2014b) and the LIM-homeodomain transcription factors *Lhx5* and *Lhx9* (Bami et al. 2011; Willaredt et al. 2014b).

Hoxa2 is strongly expressed in r3 and required for proper development of auditory nuclei derived from this segment (Gavalas et al. 1997). Its constitutive ablation disrupts CNC formation (likely affecting formation of the aVCN) (Gavalas et al. 1997). Its spatially restricted ablation in the $Wnt1^{+}$ lineage of the rhombic lip results in the innervation of the ipsilateral MNTB by aVCN neurons, which normally project to the contralateral MNTB (Di Bonito et al. 2013b). This abnormal circuitry is caused by down-regulation of the Slit receptor Robo3 (Di Bonito et al. 2013b), known to control midline crossing by commissural axons in the hindbrain (Renier et al. 2010). In addition, *Hoxa2* is the only *Hox* gene expressed in r2, where it participates in transcriptional activation of *EphA7* (Taneja et al. 1996). In summary, these data show that Hoxa2 is involved in the formation of the r2/3-derived aVCN, whereas Hoxb1 and Hoxb2 are required for specification of the r4-derived pVCN by imposing an r4-specific identity during auditory development.

The expression of *Hox* genes is sustained in the CNC, VNLL and SOC up to postnatal stages (Narita and Rijli 2009; Di Bonito et al. 2013b). In postmitotic neurons, these transcription factors were shown to participate in the regulation of neuronal migration and axon pathfinding, including topographic connectivity mapping (Oury et al. 2006; Geisen et al. 2008; Di Meglio et al. 2013). Such as role is supported by the above-mentioned finding that Hoxa2 upregulates the expression of the axon guidance molecule Robo3 (Di Bonito et al. 2013a). In addition, Hox function might involve regulation of the expression of *Eph* receptors and *ephrins* (Salsi and Zappavigna 2006). The Eph-ephrin system does not only play a role in rhombomere boundary formation but also in the establishment of auditory hindbrain circuits (Cramer and Gabriele 2014). Ephrin B2 and EphA4 seem to be needed for the formation of appropriately restricted tonotopic maps in the DCN and MNTB, as altered frequency maps were observed in mice without EphA4 or with reduced levels of ephrin B2 (Miko et al. 2007). The VCN–MNTB projection is normally strictly contralateral but the number of ipsilateral terminations significantly increases, when either *ephrin B2*, or *EphB2* together with *EphB3* are eliminated in mice (Hsieh et al. 2010; Nakamura and Cramer 2011). These ipsilateral projections make calyceal terminations that form coincidentally with the contralateral connections and are not eliminated at later stages.

Circuit formation of the auditory hindbrain and the role of spontanous activity

Most auditory hindbrain neurons in the mouse are born between E9 and E14 (DCN, E9–E17; VCN, E11–E14; LSO, E9–E14; MSO, E9–E12, MNTB, E11–12; LNTB, E9–E12, VNTB, E10–12), as judged by timed radioactive ^{3}H-thymidine labeling of DNA (Pierce 1967, 1973). For comparison, hair cells are born between E11.5 and 14.5 (Matei et al. 2005) and can be distinguished in the inner ear starting from E15, using Myo7a as a marker (Koundakjian et al. 2007), whereas SGNs are generated between E9–E14 (Ruben 1967; Koundakjian et al. 2007). Thus, there is no peripheral-to-central developmental pattern nor are second-order hindbrain nuclei (CNC) generated prior to third-order nuclei (SOC) (Hoffpauir et al. 2009). This raises the question of the temporal sequence of circuit assembly in the auditory system.

After birth, auditory hindbrain neurons first migrate to their final destinations, where they become discernable between E12.5 (CNC) and E17 (SOC) (Howell et al. 2007; Hoffpauir et al. 2010). The functional connectivity between these nuclei and the innervation by the SGNs was analyzed by using a whole head slice preparation containing the cochlea, SGNs, CNC and the SOC (Hoffpauir et al. 2010; Marrs and Spirou 2012). Stimulating AN fibers identified the first stimulus-

matched responses in the VCN at E15, using Ca^{2+} imaging (Marrs and Spirou 2012). This agrees with the presence of AN fibers in the presumptive VCN area as early as E12.5 (Karis et al. 2001). Electrophysiological recordings from responding cells revealed robust spiking of VCN neurons at E16, with almost 90 % of stimulation events resulting in action potential (AP) generation (Marrs and Spirou 2012). Functional assessment of SGNs demonstrated that consistently 15 % of these cells demonstrated spontaneous APs between E14 and the day of birth (P0) (Marrs and Spirou 2012). Thus, some kind of spontaneous activity is present in the central auditory system from a very early time point onward (see also Wang and Bergles, this issue).

VCN neurons project to several third-order nuclei of the SOC and to the LL (Thompson and Schofield 2000; Moore 1991; Webster 1992). At E13, first VCN axons elongate towards the SOC area, crossing the midline and reaching the prospective location of the contralateral MNTB at E13.5 (Howell et al. 2007). This projection extends further and reaches the remaining region of the contralateral SOC at E14.5. Collaterals to the ipsilateral SOC area and to the LL are first observed at E15.5, while at E16.5 VCN projections reach the IC. Functionally, MNTB neurons can be driven by VCN neurons (Hoffpauir et al. 2010) or by stimulation of AN fibers at E17 (Marrs and Spirou 2012) Thus, several auditory hindbrain circuits are already functional 1–2 days before birth (between E18 and E19 in mice) and spontaneous activity of SGNs can therefore activate the auditory pathway at embryonic stages. The observation that functional innervation of the VCN by SGNs precedes that of the MNTB by VCN neurons suggests a sequential development of functional connectivity along the central auditory pathway in the hindbrain, despite similar birth times (Marrs and Spirou 2012). Another conclusion emerging from these studies is that initial circuit formation is independent of spontaneous activity from the periphery. Only 15 % of SGNs are spontaneously active between E14 and P0 (Marrs and Spirou 2012), the time period of auditory circuit formation in the hindbrain. Activity-independent formation of neuronal circuits is in agreement with results from mice, which lack Munc13. This presynaptic protein is essential for neurotransmitter secretion and its lack abolishes synaptic transmission but does not impair initial synaptic formation in cell culture and in several regions of the brain (Verhage et al. 2000; Varoqueaux et al. 2002).

The molecular mechanisms involved in target finding have recently started to be unveiled. Next to the Eph-ephrin system, netrin-1, DCC and the Robo3 receptor have been implicated. Embryonic analysis demonstrated presence of the axon guidance receptors DCC, Robo-2 and Robo-3 in VCN neurons and their ligands netrin-1 and slit-1 at the brainstem midline (Howell et al. 2007). Functional analysis of the DCC-netrin system by using mice with constitutive ablation of either *DCC* or *netrin-1* revealed that VCN axons did not reach the midline (Howell et al. 2007). Deletion of *Robo-3* in r3 and r5 resulted in the projection of aVCN neurons to the ipsilateral MNTB in lieu of the normally innervated contralateral MNTB. Of note, calyces still formed (Renier et al. 2010). Electrophysiological analyses, however, revealed strong transmission defects, indicating that axonal midline crossing is required for proper maturation of this giant synapse (Renier et al. 2010; Michalski et al. 2013).

Since the pioneering work of Rita Levi-Montalcini in chick embryo, neuronal activity is known to play an important role for proper formation of the auditory brainstem. Removal of the otocyst on one side of the embryo resulted in drastically reduced auditory brainstem nuclei (Levi-Montalcini 1949). Subsequent studies revealed that cochlear removal causes widespread cell death in second-order auditory hindbrain nuclei, as evidenced in chicken and mammals (reviewed in Rubel et al. 2004; Harris and Rubel 2006; see also Ryugo, this issue). In contrast, survival of the third-order SOC seems be less dependent on peripheral activity. Ablation of *Slc17a8*, encoding the vesicular glutamate transporter VGlut3, causes peripheral deafness, due to the lack of glutamate release at the inner hair cell synapse. This lack of cochlea-driven activity results in significant reduction of the CNC volume at P10 (Seal et al. 2008), whereas the SOC appears normal (Noh et al. 2010). Increased survival of SOC neurons is thought to reflect compensatory neuronal activity in auditory hindbrain nuclei (Marrs and Spirou 2012), as increased non-auditory input to the VCN has been observed after auditory deprivation (Zeng et al. 2012; Trune and Morgan 1988). Although these studies analyzed adult animals after postnatal deafening, similar processes might occur in congenital deaf animals. Such a view is supported by the spontaneous activity recorded at P14 in the VCN of a genetically deafened *dn*/*dn* mouse with a mutation in the transmembrane cochlea-expressed gene 1 (Youssoufian et al. 2008; note, however, that only one out of two mice showed this activity). The dependence of SOC nuclei on spontaneous activity was finally shown in mice lacking the voltage-gated L-type $Ca_v1.3$. (Hirtz et al. 2011; Satheesh et al. 2012). This channel acts as an important postsynaptic signal transducer of neuronal activity and its absence causes altered anatomy of SOC nuclei as early as P4 (Hirtz et al. 2011; Satheesh et al. 2012).

In addition to its requirement for neuronal survival, spontaneous activity was shown to be essential for maturation of both excitatory and inhibitory circuits. Here, we focus on those results obtained within the first two postnatal weeks in order to eliminate any influence of sound-deprivation on the observed outcomes (this topic is reviewed by Ryugo, this issue). Most studies concerning the maturation of excitatory circuits have been performed in the *dn*/*dn* mouse, which lacks spontaneous and acoustically driven cochlear activity due to hair cell dysfunction (Bock et al. 1982; Leao et al. 2006; Durham et al. 1989; Steel and Bock 1980). Electrophysiological analyses

demonstrated a panoply of changes in biophysical properties such as increased amplitude of evoked excitatory postsynaptic potentials, increased synaptic depression and impaired calcium buffering at the calyceal synapse between AN fibers and bushy cells of the aVCN (Oleskevich and Walmsley 2002). In MNTB neurons, enhanced excitability, changes in Na^+ and K^+ currents and alterations in tonotopic gradients of ionic currents were reported (Leao et al. 2004a; Leao et al. 2005; Leao et al. 2006). A comparison between aVCN, MNTB and LSO neurons indicates that each neuronal population is differentially affected by the lack of spontaneous activity (Walmsley et al. 2006; Couchman et al. 2011). With respect to synaptic inhibition, MNTB neurons of *dn*/*dn* mice show altered amplitude, time course and frequency of miniature inhibitory postsynaptic currents as well as an increase of discrete gephyrin clusters (Leao et al. 2004b).

A frequently used model system to study maturation of inhibitory projections is the MNTB–LSO pathway (Kandler 2004). During the first two postnatal weeks, normalized MNTB input areas into LSO neurons decrease by about 75 %, which is paralleled by a roughly 12-fold increase in synaptic conductance generated by individual MNTB axons (Kim and Kandler 2003). Remarkably, during early postnatal stages, MNTB neurons are positive for VGlut3 and release glutamate in addition to glycine and GABA (Blaesse et al. 2005; Gillespie et al. 2005). This glutamate release is required for refinement as this process fails in *VGlut3*$^{-/-}$ mice (Noh et al. 2010). Finally, analysis of a *Chrna9*$^{-/-}$ mouse line, lacking the α9 acetylcholine receptor, demonstrated that refinement is crucially depending on the precise temporal pattern of spontaneous activity (Clause et al. 2014). The postsynaptic signaling pathways underlying sharpening of the MNTB-LSO projections are poorly known. Likely, $Ca_v1.3$-mediated signaling in the SOC is required, as constitutive ablation of this channel causes impaired refinement (Hirtz et al. 2012). This failure is likely not due to the absence of cochlea-generated activity in this mouse model (Platzer et al. 2000), as refinement is undisturbed in *Otof*$^{-/-}$ mice (Noh et al. 2010), which also lack glutamate release from hair cells (Roux et al. 2006; Beurg et al. 2008; Longo-Guess et al. 2007).

Summary

The last decade has been a time of substantial progress in our knowledge of the developmental mechanisms building up the auditory hindbrain. Much of this information is owed to the strength of mouse genetics, which allows region-specific ablation of genes or labeling of genetically defined cell populations. Altogether, the data provide an excellent framework to further explore the genetic, molecular and cellular mechanisms. We have already witnessed excellent examples on how to combine available information and genetic techniques in order to solve important topics. Cases in point are the deployment of intersectional fate mapping strategies (Farago et al. 2006) or the generation of new *Cre* driver lines using genetic information about rhombomere specific enhancers (Di Bonito et al. 2013b). This advance in knowledge and techniques will greatly facilitate filling in the many remaining gaps. We still lack a comprehensive picture of the gene regulatory networks resulting ultimately in the many different cell types in the auditory hindbrain. We are also ignorant of the precise axon guidance mechanisms involved in the initial establishment of crude tonotopic maps, as well as of the molecular pathways partaking in synaptogenesis, maturation and refinement. Though it should be noted that valuable progress has already been made in these fields as well. Examples are the unveiling of the critical role of bone morphogenic protein signaling for maturation of giant synapses (Xiao et al. 2013), or the identification of candidate transcription factors for differentiation processes by transcriptome (Ehmann et al. 2013) and single gene expression analysis (Marrs et al. 2013).

Improved insight into the mechanisms building up the auditory hindbrain will bear important implications for clinical research. All genetic factors involved in the development of the auditory system are promising candidates for auditory processing disorders (Chermak and Musiek 1997). Furthermore, a comprehensive picture of the gene regulatory networks operating in the central auditory system will allow better prediction of functional consequences associated with mutations in hearing-related genes. A recent survey has identified central auditory functions for several peripheral deafness genes (Willaredt et al. 2014a) and their number will likely increase. This type of knowledge will open avenues for better tailored auditory rehabilitation by addressing mutation-specific central auditory deficiencies as well. Thus, both basic and clinically orientated research will benefit from in-depth knowledge of the developmental processes operating in the auditory system.

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