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Review

Central auditory function of deafness genes

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ABSTRACT

The highly variable benefit of hearing devices is a serious challenge in auditory rehabilitation. Various factors contribute to this phenomenon such as the diversity in ear defects, the different extent of auditory nerve hypoplasia, the age of intervention, and cognitive abilities. Recent analyses indicate that, in addition, central auditory functions of deafness genes have to be considered in this context. Since reduced neuronal activity acts as the common denominator in deafness, it is widely assumed that peripheral deafness influences development and function of the central auditory system in a stereotypical manner. However, functional characterization of transgenic mice with mutated deafness genes demonstrated gene-specific abnormalities in the central auditory system as well. A frequent function of deafness genes in the central auditory system is supported by a genome-wide expression study that revealed significant enrichment of these genes in the transcriptome of the auditory brainstem compared to the entire brain. Here, we will summarize current knowledge of the diverse central auditory functions of deafness genes. We furthermore propose the intimately interwoven gene regulatory networks governing development of the otic placode and the hindbrain as a mechanistic explanation for the widespread expression of these genes beyond the cochlea. We conclude that better knowledge of central auditory dysfunction caused by genetic alterations in deafness genes is required. In combination with improved genetic diagnostics becoming currently available through novel sequencing technologies, this information will likely contribute to better outcome prediction of hearing devices.

1. Introduction

Perception of sensory information results from signal transduction in the sensory endorgan and processing of this information in the central nervous system. Proper formation and function of both components is therefore necessary to achieve optimal performance. It is now well recognized that a combination of genetically encoded programs and neural activity are prerequisites for the development and maintenance of sensory systems (reviewed in Flavell and Greenberg, 2008; Loebrich and Nedivi, 2009; Wolfram and Baines, 2013). The importance of genetic information in sensory perception is demonstrated by the many genes that are involved in sensory impairments. Currently, mutations in more than 60 genes are known to cause hearing loss (reviewed in Brown et al., 2008; Lenz and Avraham, 2011; Angeli et al., 2012) and more than 180 genes are involved in visual impairment (reviewed in Hamel, 2013; Daiger, 2006). Similarly, dysfunctions in other sensory systems such as those for nociception (Mogil et al., 2000; Akopian, 2013), taste (Drayna, 2005), and olfaction (Karstensen and Tommerup, 2012) have a genetic background, albeit much less is currently known about the underlying genetic programs.

Neuronal activity plays a key role in shaping and maintaining sensory circuits after their initial formation and establishing the terminal gene batteries (reviewed in Reid, 2012; Johnston et al., 2005; Hobert, 2011; Fishell and Heintz, 2013; Wolfram and Baines, 2013). The importance of neuronal activity in development was first analyzed in great detail in the visual system, in which eye closure during critical periods leads to anatomical and physical alterations (reviewed in Hubel and Wiesel, 1964, 1965, 2005). Similar observations were later reported for other senses

Abbreviations: ABR, auditory brainstem response; AVCN, anterior ventral cochlear nucleus; CNC, cochlear nucleus complex; DCN, dorsal cochlear nucleus; IHC, inner hair cell; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; OHC, outer hair cell; PVCN, posterior ventral cochlear nucleus; r, rhombomere; SOC, superior olivary complex; SPN, spiral ganglion neuron; TF, transcription factor

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as well (reviewed in Kirkby et al., 2013; Blankenship and Feller, 2010; Katz and Shatz, 1996). In fact, a study of Rita Levi-Montalcini in the auditory system was amongst the first to describe the dependence of central sensory systems on input from the periphery (Levi-Montalcini, 1949). Her experiments in the auditory brainstem of chicken revealed that extirpation of the otic placode resulted in strong hypotrophy of cochlear nuclei. This ground-breaking work was followed by an impressive wealth of data, demonstrating the importance of both spontaneous and experience-driven activity for normal maturation and function of the auditory system (reviewed in Friauf and Lohmann, 1999; Walmsley et al., 2006; Tollin, 2010; Rubel et al., 2004; Kral, 2013). As most forms of deafness result in reduced synaptic input to the auditory nerve, central auditory consequences of hearing impairment were often assumed to be stereotyped, simply reflecting the lack of activity. However, recent analyses mainly from transgenic mice suggest that genetically caused deafness is associated with a larger variety of central auditory defects than previously thought. Here, we will summarize current knowledge on the diverse central auditory functions of deafness genes, provide a mechanistic explanation for a shared genetic program between the peripheral and central auditory system, and discuss the implications of the data for auditory rehabilitation.

2. Central auditory function of deafness genes

2.1. Transcription factors

Mutations in multiple transcription factors (TFs) have been associated with hearing impairment (Dror and Avraham, 2010). Among them, several TFs were reported to function as well in the central auditory system. Mutations in the homeodomain TF HOXA1[1] are associated with the autosomal recessive Athabaskan brain dysgenesis syndrome (ABDS), observed in some Native American tribes, and the Bosley-Salih-Alorainy syndrome (BSAS), reported in Saudi Arabian and Turkish families (Tischfield et al., 2005; Bosley et al., 2008). Both syndromes are characterized by horizontal gaze restriction, delayed motor development, and sensorineural deafness due to aplasia of the cochlea. Ablation of *Hoxa1* in mice resulted in severe abnormalities throughout the ear, including lack of middle ear ossicles and the cochlea (Chisaka et al., 1992; Lufkin et al., 1991). Beyond the ear, the auditory nerve was absent and the superior olivary complex (SOC), the first binaural processing center in the auditory brainstem, was not visible in coronal sections at embryonic day (E)18 (Chisaka et al., 1992) (Table 1). In contrast, the cochlear nucleus complex (CNC) appeared normal (Chisaka et al., 1992). *Hoxa1* is expressed in the developing hindbrain in rhombomeres (r)4 to r7 (Carpenter et al., 1993; Lufkin et al., 1991), which give rise to the posterior ventral cochlear nucleus (PVCN), the dorsal cochlear nucleus (DVCN) (Farago et al., 2006), and large parts of the SOC (Maricich et al., 2009; Rosengauer et al., 2012; Marrs et al., 2013) (Fig. 1). The expression pattern of *Hoxa1* is thus in agreement with a disrupted SOC in *Hoxa1* null mice. Quantitative alterations in the CNC might have escaped detection, as *Hoxa1* null mice die at birth (Chisaka et al., 1992; Lufkin et al., 1991). This renders quantitative analysis of auditory brainstem structures difficult, since they become visible just shortly before birth (Hoffpauir et al., 2009, 2010).

[1] Research in humans is indicated by italicized gene symbols with all letters in uppercase. Mouse research is indicated by italicized gene symbols with only the first letter in uppercase and the remaining letters in lowercase. Protein symbols are not italicized and all letters are uppercase for both species.

Missense or nonsense mutations in the related gene *HOXA2* results in an another autosomal-recessive disorder characterized by microtia, hearing impairment, and cleft palate (Alasti et al., 2008; Brown et al., 2013). Ears in these persons are characterized by small, malformed external ears and variable abnormalities of the ossicular chain, such as absence of the anterior crus of the stapes and the stapedial tendon, or the presence of a rigid ossicular chain. Similar observations were made in constitutive *Hoxa2* null mice. These animals lacked the pinna, the tubotympanic recess, and the stapes; instead they showed a duplication of the malleus and tympanic bones, and a hyperplastic tympanic ring with altered ossification (Gendron-Maguire et al., 1993). These homeotic transformations likely reflect the replacement of skeletal elements from the second branchial arch by those of the first branchial arch (Gendron-Maguire et al., 1993). In the brainstem, the CNC was considerably reduced at birth (Gavalas et al., 1997), presumably due to disturbed r2 and r3 identities (Gavalas et al., 1997) (Table 1). These two rhombomeres give rise to the anteroventral cochlear nucleus (AVCN) (Farago et al., 2006; Maricich et al., 2009; Rosengauer et al., 2012). In addition, lack of *Hoxa2* resulted in the innervation of the ipsilateral instead of the contralateral medial nucleus of the trapezoid body (MNTB) by AVCN neurons (Di Bonito et al., 2013) (Table 1). This abnormal circuitry is presumably caused by down-regulation of the Rig1 axon guidance receptor (Di Bonito et al., 2013). Postnatal alterations of auditory structures could not be analyzed, as the transgenic mice used in these studies die perinatally (Rijli et al., 1993; Di Bonito et al., 2013; Gendron-Maguire et al., 1993).

Within the context of *HOX* genes and their importance for the auditory system, it is of note that another family member, *Hoxb2*, is expressed both in the hindbrain and the inner ear (Szeto et al., 2009). In the hindbrain, *Hoxb2* null mice experience ectopic projections from the PVCN to the MNTB (Table 1). This is likely due to a transformation of the molecular identity of the PVCN to that of the AVCN, as indicated by the increased expression of *Atoh7* in PVCN neurons (Di Bonito et al., 2013). So far, functional consequences of *Hoxb2* mutations for development of the inner ear have not been investigated.

Another TF important for the auditory system is the zinc finger protein GATA3. Mutations in the corresponding gene cause the autosomal-dominant human HDR syndrome (aka Barakat syndrome), characterized by hypoparathyroidism (H), congenital sensorineural deafness (D), and renal insufficiency (R) (van Esch et al., 2000; Nesbit et al., 2004; Muroya et al., 2001). Heterozygote $Gata3^{+/-}$ mice showed a progressive 30 dB shift in hearing thresholds caused by the degeneration of hair cells and supporting cells in the cochlea (van der Wees et al., 2004). Homozygous deletion of *Gata3* affected early inner ear morphogenesis (Karis et al., 2001; Haugas et al., 2012) by causing massive cell death during development of the cochlear duct (Luo et al., 2013). Furthermore, formation of the prosensory domain, which gives rise to the organ of Corti, is disturbed (Luo et al., 2013). Beyond the cochlea, lack of GATA3 caused significantly increased loss of spiral ganglion neurons (SGNs) between embryonic days (E) 12.5 and 14.5 (Luo et al., 2013). In a $Bhlhb5::Cre;Gata3^{fl/fl}$ mouse line with specific ablation of *Gata3* in the SGNs, peripheral projections made highly aberrant trajectories to hair cells in the cochlea, whereas projections to the CNC were normal (Appler et al., 2013) (Table 1). The TF GATA3 thus plays an important role for survival and peripheral wiring of SGNs. *Gata3* is also expressed throughout the central auditory brainstem from the CNC up to the inferior colliculus (Zhao et al., 2008; Karis et al., 2001). Detailed characterization of the projections of the efferent olivocochlear bundle, a feedback system running from the SOC back to the cochlea, revealed that GATA3 is essential for innervation of the inner ear. In the absence of GATA3,