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Synaptic morphology and the influence of auditory experience

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ABSTRACT

The auditory experience is crucial for the normal development and maturation of brain structure and the maintenance of the auditory pathways. The specific aims of this review are (i) to provide a brief background of the synaptic morphology of the endbulb of Held in hearing and deaf animals; (ii) to argue the importance of this large synaptic ending in linking neural activity along ascending pathways to environmental acoustic events; (iii) to describe how the re-introduction of electrical activity changes this synapse; and (iv) to examine how changes at the endbulb synapse initiate trans-synaptic changes in ascending auditory projections to the superior olivary complex, the inferior complex, and the auditory cortex.

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1. Introduction

Auditory experience has long been known to play a critical role in the developing mammalian auditory system. Neural activity is important for normal construction and maintenance of auditory structure and function (Parks et al., 2004; Shepherd et al., 2006; Walmsley et al., 2006; Ryugo and Limb, 2009; Sanes and Bao, 2009). It influences the refinement of the genetic blueprint for circuitry including axonal distribution, pruning, and synapse formation (Leake and Hradek, 1988; Baker et al., 2010). The absence of auditory stimulation introduces a series of pathological and atrophic changes that include more widespread distributions of axonal projections (Leake and Hradek, 1988), abnormal projections (Moore and Kitzes, 1985; Nordeen et al., 1983a,b), delayed maturation (Sanes, 1993; Kandler, 2004), and language impairments (Robbins, 2006). The effects of re-introduction of auditory activity through electrical stimulation on synaptic morphology and function have been studied using models of congenital deafness that include both hereditary deafness and chemical deafening, surgical ablation of the organ of Corti, and acoustic trauma. Collectively, these data emphasize the malleability of auditory synapses in response to variations in the acoustic environment.

In the present report, we review the evidence addressing the pathological consequences of sensory deprivation and the restorative influences brought about by the introduction of neural activity through cochlear implantation. The main focus concerns morphological plasticity observed at the level of the auditory nerve in the cochlear nucleus (CN). Not surprisingly, changes at these synapses have consequences further on up the system at the superior olivary complex (Schwartz and Higa, 1982; Russell and Moore, 1995; Kapfer et al., 2002; Sanes and Bao, 2009; Tirko et al., 2009), inferior colliculus (Snyder et al., 1995, 2000), and auditory cortex (Heid et al., 1998; Klinke et al., 1999, 2001; Kral et al., 2000, 2001). We will discuss several observations that have advanced our knowledge of synaptic plasticity and expanded our understanding of the effect that functional manipulations have on the auditory system.

Synapses are definable not only by presynaptic characteristics at the release site such as synaptic vesicle size and shape, transmitter chemicals, neuromodulators, and transporter molecules but also by the postsynaptic composition of transmitter receptor subunits, shape and curvature of the postsynaptic density (PSD), ion channels, and associated second messenger and retrograde signaling systems. Moreover, there must also be consideration of size and distribution of the terminal, target compartment (e.g., cell body, dendritic shaft, spine), and location of the cell bodies that give rise to the projection. Proper transmission of acoustic signals from neuron to neuron depends in large part on the precise spatial arrangement of these factors at the release site. The corollary to this notion is that abnormalities of synaptic structure will impair signal

Abbreviations: AVCN, Anteroventral cochlear nucleus; CN, Cochlear nucleus; IC, Inferior colliculus; ILD, Interaural level difference; ITD, Interaural time difference; LSO, Lateral superior olive; MSO, Medial superior olive; MNTB, Medial nucleus of the trapezoid body; SBC, Spherical bushy cell.

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transmission, thereby corrupting the neural representation of the acoustic stimulus.

Our ability to hear and understand sound commences with the receptor sensory organ of the ear, the cochlea. For the processing of sound, neural activity in the central nervous system must be tightly coupled to acoustic events. The hair cell receptors within the cochlea transduce sound energy into neural signals in auditory nerve fibers that are conveyed to the CN (Kiang et al., 1965). The CN receives all incoming auditory information and gives rise to the ascending auditory pathways. Different sounds are revealed by distinctive characteristics in their time-varying features. Thus, timing of neural activity within the central auditory pathways must not only be time-locked to the external sound stimuli but also to the evoked patterns of activity transmitted along the ascending pathways. Synchrony along the various parallel pathways is essential, and aberrations in these pathways will corrupt processing and disturb how sound is perceived.

Auditory nerve fibers are the major source of excitation to cells of the ventral CN (Koerber et al., 1966). In the anteroventral cochlear nucleus (AVCN), myelinated auditory nerve fibers give rise to large, axosomatic synaptic endings known as endbulbs of Held (Held, 1893; Ramón y Cajal, 1909; Lorente de Nó, 1981). Endbulbs have a calyx-like appearance where the end of the fiber is marked by the emergence of several thick, gnarled branches that divide repeatedly to form an elaborate arborization of *en passant* and terminal swellings to embrace the postsynaptic spherical bushy cell (SBC, Ryugo and Fekete, 1982). These endbulbs are among the largest synaptic endings in the brain (Lenn and Reese, 1966), and one-to-three endbulbs selectively contact a single SBC (Brawer and Morest, 1975; Cant and Morest, 1979; Ryugo and Sento, 1991; Ryugo and Fekete, 1982; Nicol and Walmsley, 2002). They contain up to 2000 release sites (Ryugo et al., 1996) and transmit activity with high fidelity to the postsynaptic SBC (Pfeiffer, 1966; Babalian et al., 2003). The size and evolutionary conservation of endbulbs among vertebrates emphasize its importance in enabling spike activity to be yoked in time to acoustic events (Fig. 1).

The endbulb synapse has been implicated in the pathway that processes the precise timing features of sound that is crucial for binaural hearing (Yin and Chan, 1990; Fitzpatrick et al., 1997). SBCs send projections from the AVCN to the superior olivary complex (Cant and Casseday, 1986). These projections terminate onto ipsilateral neurons of the lateral superior olive and bilaterally upon bipolar neurons of the medial superior olive (MSO). In the MSO, inputs from the right CN terminate on the dendrites extending to the right, whereas inputs from the left CN terminate on the dendrites extending to the left. The MSO is the first nucleus to process synaptic input from both ears (Fig. 2).

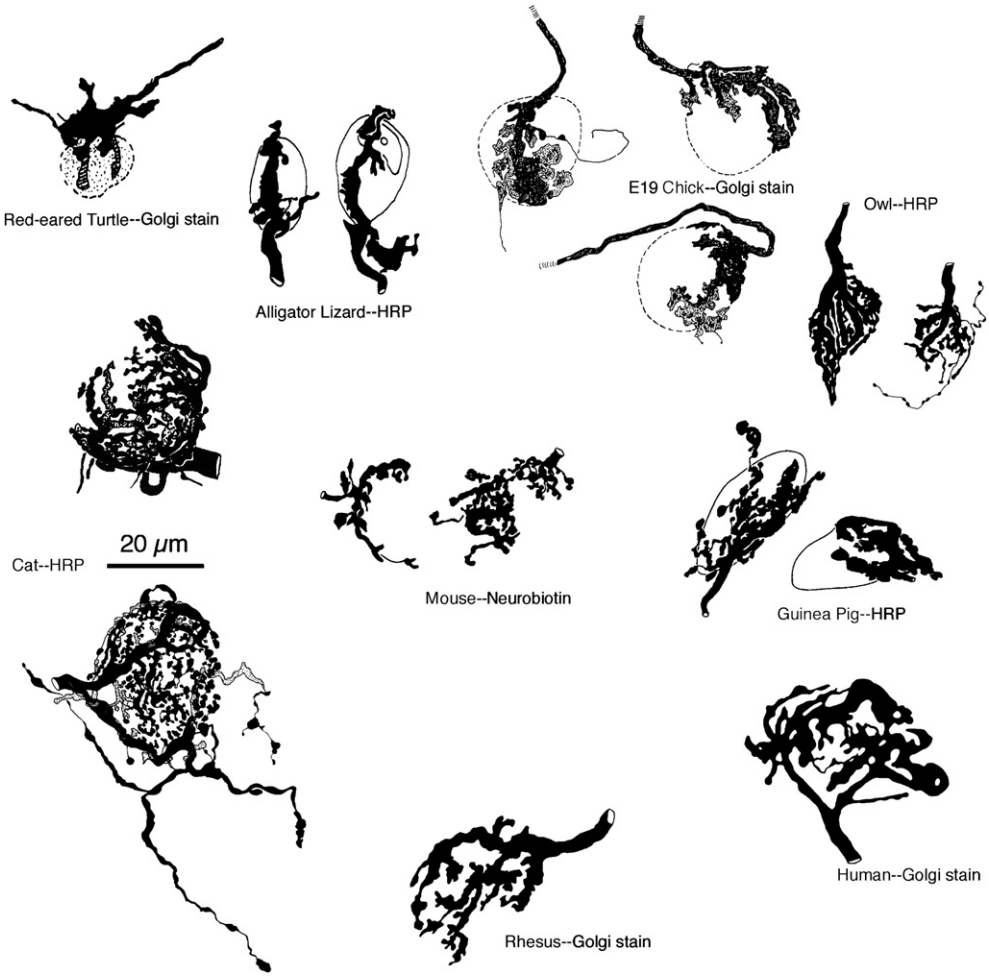

Fig. 1. Examples of endbulbs of Held from various terrestrial vertebrates. This important axosomatic terminal is found in turtles (Browner and Marbey, 1988), alligator lizards (Szpir et al., 1990), chicken (Jhaveri and Morest, 1982), barn owl (Carr and Boudreau, 1991), mouse (Limb and Ryugo, 2000), guinea pig (Tsuji and Liberman, 1997), cat (Ryugo et al., 1996, 1998), rhesus monkey (Ryugo, unpublished observations), and human (Adams, 1986). The large size and evolutionary conservation of this synaptic terminal indicates it importance in hearing. From Ryugo and Parks, 2003.

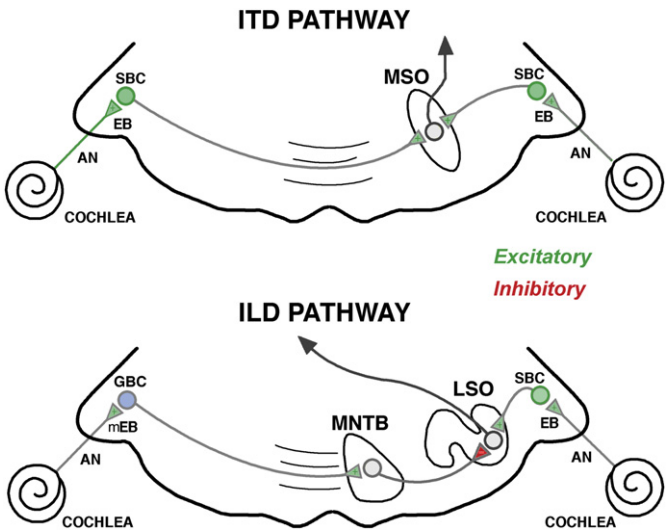

Fig. 2. Simplified schematic diagram emphasizing the timing pathway involved in binaural sound localization. The interaural timing difference (ITD) pathway relies primarily on endbulb (EB) input from the auditory nerve (AN), SBCs (green), and their projection to the MSO to achieve coincidence detection. The interaural level difference (ILD) pathway utilizes GBCs (pale blue) by way of the MNTB, and SBCs, to converge in the LSO. Abbreviations: Auditory nerve, AN; EB, endbulb; GBC, globular bushy cell; LSO, lateral superior olive; mEB, modified endbulb; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; SBC, spherical bushy cell. Green indicates excitatory action, whereas red indicates inhibitory action. Adapted from Tollin, 2003.

Interaural time differences (ITDs) are crucial for localizing sounds on the horizontal plane. The ITD pathway utilizes the difference in arrival of a sound at the two ears to place a sound source. The general concept for this binaural sensitivity is the coincidence detection model where neurons would only respond when binaural excitatory inputs converged simultaneously (Jeffress, 1948). In this model, an array of MSO neurons receives systematically arranged inputs, each with a delay line such that it would only respond if a sound source were in a particular position off the midline. Some neurons would respond when the sound was directly in front of the animal, whereas others would respond when the sound moved away from the midline. A delay line would compensate for a progressive shift in time of arrival at the two ears. The system is sensitive to differences in the range of tens of microseconds, so it is clear that precision in synaptic transmission is required (Grothe, 2000; McAlpine et al., 2001). The endbulb, therefore, is not only important for processing important timing cues for sound localization but also for time-varying cues in speech such as voice onset, stressed syllables, gaps, and amplitude modulation (Moiseff and Konishi, 1981; Blackburn and Sachs, 1990). The point of this discussion is to emphasize that endbulbs and the timing of neural activity are linked and highly important to the proper processing and perception of sound. Moreover, the endbulb is highly advantageous as a research tool because it is prominent and readily recognizable for experimental study.

2. Synaptic morphology of the endbulb

2.1. Normal hearing animals

During postnatal development, the endbulb of Held begins with the formation of a solid, spoon-shaped growth cone and culminates in a highly branched axosomatic arborization (Ryugo and Fekete, 1982). Each endbulb can form approximately 500–2000 synapses onto the postsynaptic SBC (Ryugo et al., 1996). This feature in particular suggests a highly secure synaptic interface to maintain the temporal fidelity of all incoming signals to the SBC (Romand, 1978; Oertel, 1983; Manis and Marx, 1991). The structure of this giant synaptic terminal has been extensively studied to learn about synapse formation, its target specificity, and its reaction to deafness (Gulley et al., 1977; Neises et al., 1982; Ryugo and Fekete, 1982; Carr and Boudreau, 1996; Limb and Ryugo, 2000; Ryugo et al., 1997, 1998; Oleskevich et al., 2004).

One of the most striking morphological features observed in the normal neonatal endbulb is the interdigitation of the membranes of the postsynaptic SBC and the presynaptic endbulb (Jhaveri and Morest, 1982; Neises et al., 1982; Carr and Boudreau, 1996; Ryugo et al., 2006). The abundant but transient surface contact between both endbulb and SBC has unknown function but resembles certain epithelial cell specializations (e.g., pedicel processes of the kidney, striated duct cells of the submandibular gland, or basal processes of marginal cells of the stria vascularis) where cell surface is maximized by vigorous infoldings. Such hypertrophied surface contact for endbulbs would facilitate the exchange of chemical signals involved in the stabilization of some endbulbs and elimination of others or any other developmental process yet to be determined. It is estimated that a dozen endbulbs contact a single SBC in neonatal cats but that by adulthood, this number has been reduced to two endbulbs per SBC (Ryugo et al., 2006).

In normal hearing cats the endbulb arborization onto the SBC has been shown to vary systematically with respect to the average level of spike discharges received from auditory nerve fibers having low or high levels of activity (Ryugo et al., 1996). Endbulbs from fibers having high levels of activity (e.g., high (>18 s/s) spontaneous discharge rates and low thresholds for evoked responses) exhibit modest levels of branching with relatively large *en passant* and terminal swellings. In contrast, endbulbs from fibers having relatively low levels of activity (e.g., low (<18 s/s) spontaneous discharge rates and high thresholds for evoked responses) exhibit highly elaborate branching with relatively small *en passant* and terminal swellings. The differences in branching complexity were confirmed by statistically significant differences in fractal values. Moreover, the larger swellings on the highly active endbulbs resembled the swollen endings of overactive terminals where it was speculated that the swelling was caused by the fusion of synaptic vesicles (Heuser and Reese, 1973; Boyne et al., 1975; Burwen and Satir, 1977). Using electron microscopy to study synaptic ultrastructure, endbulbs receiving relatively low levels of spike discharges were associated with larger PSDs, whereas those exhibiting high rates of spike discharges exhibited smaller PSDs (Ryugo et al., 1996). These data are consistent with observations from rats exposed to repetitive tones or silence; stimulated animals exhibited endbulbs with smaller PSDs compared to those of animals exposed to silence (Rees et al., 1985). The synapse structure of endbulbs is clearly plastic and subject to activity-related change.

2.2. Congenitally deaf animals

The endbulb synapse has been studied in congenitally deaf white cats to determine the extent to which sound influences its growth (Ryugo et al., 1997, 1998). Due to the elaborate form of the endbulb, changes in morphology should be evident and quantitative. Moreover, given that variations in endbulb morphology were already apparent in normal hearing cats where differences could be attributed to disparities in spike discharge rates, we predicted that in the extreme case of congenital deafness, there should be definable and obvious abnormalities.

Single unit recordings in the auditory nerve of congenitally deaf white cats revealed several important features (Ryugo et al., 1998).

First, in completely deaf cats, there was virtually no spontaneous activity and no evoked activity. Second, in hard of hearing cats (thresholds >60 dB), there was spontaneous activity, but elevated in distribution. Spontaneous activity in general was similar to that of normal hearing cats, but the upper range of spontaneous activity was extended (>150 s/s). In some auditory nerve fibers, spontaneous discharges exceeded 180 s/s. These data on activity were consistent with inner ear histology: deaf animals exhibited no organ of Corti, whereas hard of hearing animals exhibited a full complement of hair cells but showed signs of hydrops with an outward bulging Reissner's membrane (Ryugo et al., 1998).

The most obvious structural correlate in the CN was that the endbulbs contact significantly smaller postsynaptic SBCs (Saada et al., 1996; O'Neil et al., 2010; Ryugo et al., 2010). Second, the degree of endbulb arborization was graded in arborization complexity with respect to hearing threshold. In completely deaf cats, the extent and complexity of endbulb branching were much less and there were significantly fewer swellings (Ryugo et al., 1997, 1998). These features were quantified by fractal analysis and counts, respectively (Fig. 3). The graded nature of this effect was revealed by the intermediate position of endbulbs from cats with some but diminished hearing. Cats with elevated thresholds exhibited statistically different fractal values from completely deaf cats and normal hearing cats. Normal hearing cats displayed the most elaborate and complex endbulb arborizations.

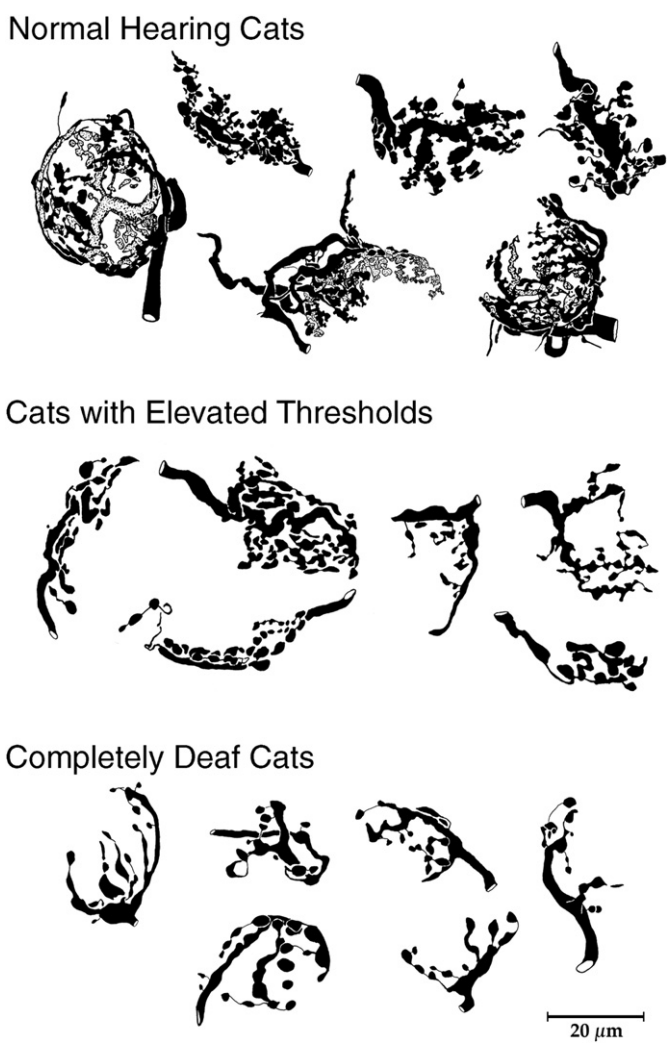

Fig. 3. Light microscopic drawing tube reconstructions of HRP-labeled endbulbs collected from cats. Note how the branching complexity is positively correlated to hearing status. From Ryugo et al., 1998.

When these endbulbs were examined at greater resolution with an electron microscope, additional features are shown to be affected by hearing loss (Ryugo et al., 1997, 1998). In normal hearing cats, endbulbs give rise to numerous punctate, dome-shaped PSDs (Fig. 4A). Surrounding the PSD were accumulations of round, clear synaptic vesicles. In contrast, endbulbs of congenitally deaf white cats exhibited a flattening and hypertrophy of the PSDs (Fig. 4B). Moreover, there was a striking increase in synaptic vesicle density near the release site (Baker et al., 2010). The endbulb synapses from cats that were not deaf but suffering from hearing loss exhibited features that were intermediate between those of normal hearing and completely deaf cats (Ryugo et al., 1998). That is, the PSDs were intermediate in size and curvature.

Deafness and hearing loss caused abnormalities in endbulb branching, soma size, and synapse morphology that were statistically different between cohorts (Ryugo et al., 1998; Redd et al., 2000). Abnormalities in synaptic transmission do not just occur with complete deafness. There have been transmission abnormalities reported in DBA/2J mice with hearing loss (Wang and Manis, 2005, 2006). These changes reveal that auditory synapses are highly sensitive to the quantity and quality of simulation. The presence of transmission irregularities from the presynaptic endbulb to the postsynaptic SBC could introduce jitter or perhaps even transmission failure. Such interruptions would diminish the precise processing of timing information. The implication is that even hearing loss will produce difficulties beyond elevated thresholds.

Light and electron microscopic analyses were conducted on the synaptic inputs to the somata of SBCs from congenitally deaf and normal hearing cats and mice. Normally, approximately 40% of axosomatic terminals appear to be inhibitory because they exhibit non-round synaptic vesicles or they stain for the inhibitory neurotransmitters, GABA or glycine (Adams and Mugnaini, 1987; Kolston et al., 1992). Based on the changes in endbulb structure and size as a result of deafness, it might be predicted that non-auditory nerve endings would expand into the territory vacated by shrinking auditory nerve endings. Instead, there is a selective loss of inhibitory terminals (Asako et al., 2005). This change in the composition of endings on SBCs in profoundly deaf animals is expected to have a significant effect on auditory processing of information transmitted through hearing aids or cochlear implants. The loss of inhibitory endings could also lead to increased excitability caused by a "release" of inhibition, a phenomenon that might underlie some forms of tinnitus.

The congenitally deaf white cat model used in these studies manifests a type of cochleosaccular degeneration that causes sensorineural hearing loss, mimicking the Scheibe deformity in humans. That is, the deafness is apparently caused by a collapse of Reissner's membrane, which obliterates the scala media and the organ of Corti (Scheibe, 1882, 1885; Bosher and Hallpike, 1965, 1967; Deol, 1970; Suga and Hattler, 1970; Mair, 1973; Brighton et al., 1991). The question could be asked whether the synaptic changes observed in these deaf cats are due to loss of neural activity in the auditory nerve, or whether they are part of the genetic syndrome and unrelated to spike activity. Several arguments can be presented to counter this concern. First, ototoxic deafening produces a similar flattening and hypertrophy of the PSD (Ryugo et al., 2010). Second, in *Shaker-2* mice whose deafness is caused by a mutation of the myosin 15 gene that leads to loss of hair cell stereocilia, changes in endbulb form (Limb and Ryugo, 2000) and synaptic structure (Lee et al., 2003) resemble those of the congenitally deaf white cat. Third, similar pathologic changes in endbulb morphology have been inferred in the congenitally deaf

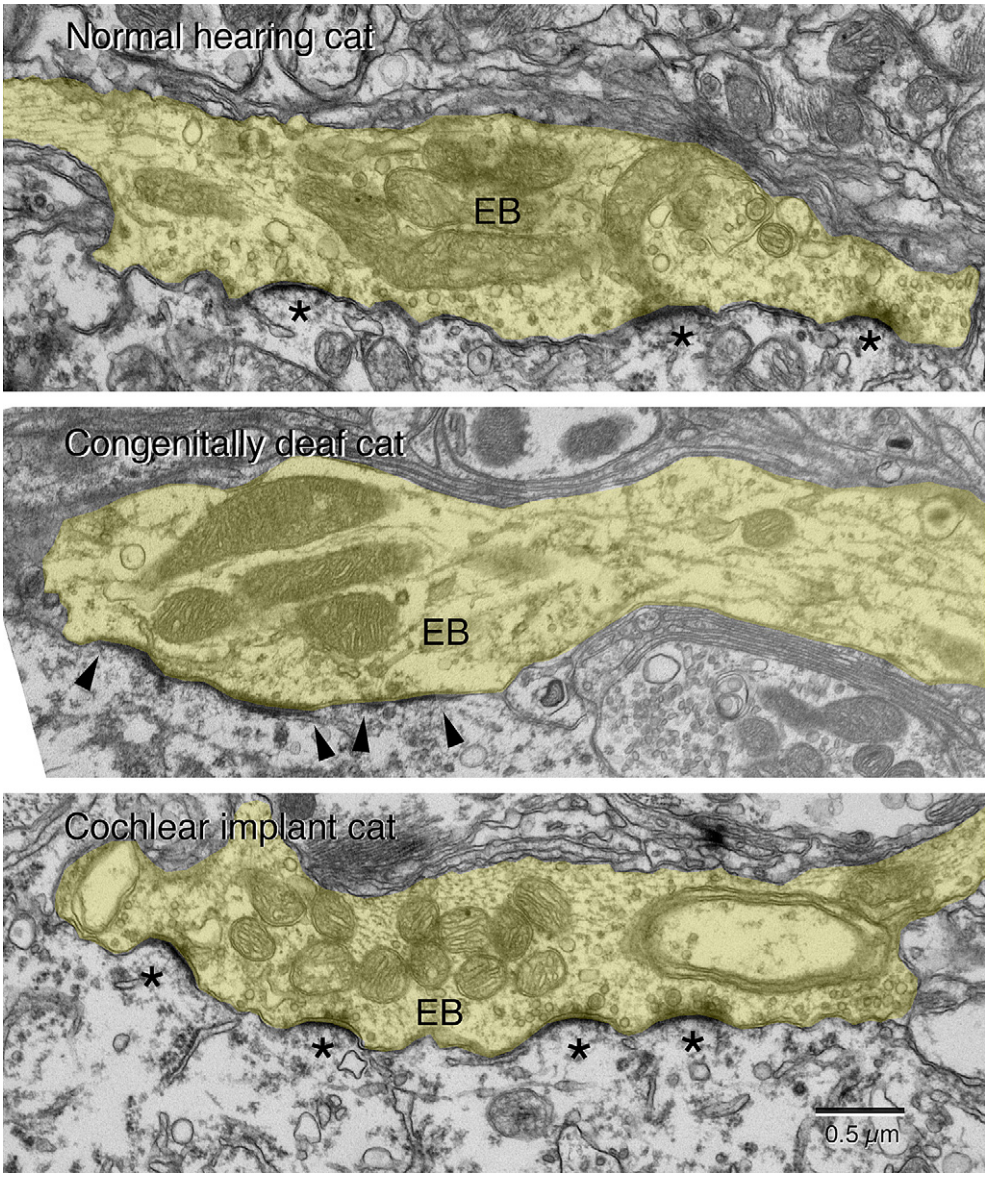

Fig. 4. Representative electron micrographs of endbulbs (EB, tinted yellow) taken from a normal hearing cat, a congenitally deaf cat, and a congenitally deaf cat stimulated electrically through a cochlear implant. The cats are matched in age. This series of micrographs illustrate that stimulation of the auditory nerve via a cochlear implant restores the structure of the synapse, specifically with respect to the size and curvature of the postsynaptic density (*) and the return of synaptic vesicle density adjacent to the synapse. From Ryugo et al., 2005.

guinea pig (Gulley et al., 1978). Because non-feline animals with deafness caused by independent means and cats of normal genetics but deafened by drugs all show these same synaptic anomalies, we can attribute the synaptic pathology, at least in part, to the lack of auditory nerve activity.

Congenital deafness does not restrict its effects to the auditory nerve and CN (Mair, 1973; Rebillard et al., 1981a,b; West and Harrison, 1973; Larsen and Kirchhoff, 1992; Saada et al., 1996). Alterations in cell size and number, receptive field properties, and laminar organization are expressed at higher nuclei of the auditory system including the superior olivary complex (Schwartz and Higa, 1982), inferior colliculus (Snyder et al., 1995, 2000; Heid et al., 1997), and auditory cortex (Heid et al., 1998; Klinke et al., 1999, 2001; Kral et al., 2000, 2001). Thus, alterations and plasticity at the endbulb synapse are reflections of a wider range of possible change throughout the central auditory system initiated by hearing loss and deafness.

3. Synaptic plasticity: implications for cochlear implants

3.1. Restoration of the endbulb synapse

Cochlear implants are electronic neural prostheses that are able to restore functional hearing to most individuals who are profoundly deaf or severely hard of hearing. Cochlear implants achieve their effects through bypassing the nonfunctioning auditory receptors of the inner ear and directly stimulating the auditory nerve (Rauschecker and Shannon, 2002). It is estimated that over 188,000 people worldwide benefit from cochlear implantation (http://www.nidcd.nih.gov/health/hearing/coch.asp). Individuals who lose hearing after developing speech and congenitally deaf children who receive implants early in life are the best candidates for cochlear implants, although the level of benefit varies widely from one individual to the next. Young children under the age of 2 years who exhibit nonsyndromic sensorineural deafness are also

excellent candidates (Waltzman et al., 1994, 1997). Because children who receive implants at progressively older ages tend to perform more poorly, it is hypothesized that uncorrected congenital deafness lead to irreversible abnormalities throughout the central auditory system.

The synaptic changes in auditory nerve endings associated with congenital deafness present an interesting test for thinking about sensory deprivation and brain plasticity. Could the synaptic abnormalities in the CN represent the key to disrupting auditory processing throughout the central auditory system? Would the reintroduction of spike discharges in the auditory nerve serve to reverse or prevent the synaptic abnormalities?

Miniaturized cochlear implants (Clarion II implants donated by Advanced Bionics Corporation) were implanted into 3-month old, congenitally deaf white kittens. The implants utilized a 6-electrode array. After a short period of recovery, each kitten was stimulated 7 h a day, 5 days a week for 2–3 months. The device utilized a speech processor identical to that used with human patients (Kretzmer et al., 2004). During the period of stimulation animals learned to approach their food bowl in response to a specific "call" showing that the animals were processing signals of biological relevance. Synapse restoration was evident on the side of stimulation where the small size and dome-shaped curvature of the PSD returned (Ryugo et al., 2005).

The plasticity of the endbulb-SBC synapse is notably different from that of the modified endbulb – globular bushy cell (GBC) synapse (Redd et al., 2000). Deafness induced an assortment of synaptic abnormalities that included a reduction in the size but not branching complexity of the modified endbulbs, reduction in GBC size, a flattening and slight but statistically significant hypertrophy of PSDs, and loss of extracellular cisternae between pre- and postsynaptic structures. The same stimulation parameters that restored endbulb synapses on SBCs had surprisingly different effects on modified endbulb synapses: synapses of the electrically stimulated ipsilateral auditory nerve showed no recovery (O'Neil et al., 2011).

The differential effects of deafness and electrical stimulation on the synapses of spherical and globular bushy cells emphasize biological variability even within the CN. Auditory stimulation with a unilateral cochlear implant restores the structure of the ITD pathway but does not restore the initial stages of the interaural level difference (ILD) pathway. This observation raises intriguing questions about the specific mechanisms by which cochlear implants mediate hearing. Even with the apparent restoration of endbulb synapses, individuals with bilateral cochlear implants have trouble processing interaural time differences, whereas paradoxically, they are able to utilize interaural level differences (van Hoesel, 2004, 2007). There remains a discrepancy between clinical observations and the differential restoration of binaural pathways by electrical stimulation through cochlear implantation.

Glutamate is the major excitatory neurotransmitter of the central synapses of myelinated auditory nerve fibers mediating rapid transmission (Hunter et al., 1993; Safieddine and Wenthold, 1997; Hollmann and Heinemann, 1994; Hackney et al., 1996; Wang et al., 1998; Petralia et al., 2000; Ryugo and Parks, 2003). Vesicular glutamate transporter 1 (Vglut1) functions to package glutamate into synaptic vesicles (Wojcik et al., 2004; Zhou et al., 2007) and is a marker for excitatory projections (Altschuler et al., 1984; Martin, 1985; Schweitzer et al., 1991; Zhou et al., 2007). Within the CN, auditory nerve terminals immunostain predominantly for Vglut1, whereas the distribution of Vglut1 after unilateral deafening was decreased in the side ipsilateral to that which was deafened (Zeng et al., 2009). The appearance of nests of swellings around SBC somata (Fig. 5) was reminiscent of HRP-labeled endbulbs (Ryugo and Fekete, 1982; Ryugo et al., 1997, 1998; Tsuji and Liberman, 1997).

Antibodies directed against Vglut1 were used to identify endbulbs in the AVCN of cats. Endbulb morphology was analyzed from cats having normal hearing, congenital deafness, or congenital deafness and electrical stimulation by way of a unilateral cochlear implant. The goal was to assess to what extent electrical stimulation restored the morphology of these prominent terminal endings. Because the tissue was counterstained using cresyl violet, the cells could be identified by their axosomatic embrace of swellings and by cytologic criteria (Osen, 1969; Cant and Morest, 1979). Aggregates of boutons completely surrounding the equator of the SBC were analyzed (Fig. 5). Those from normal hearing cats contained on average 17.2 ± 4.45 boutons with an average size of 7.76 ± 4.0 μm^2. In contrast, those of congenitally deaf cats contained an average of 12.44 ± 2.9 boutons with an average size of 5.0 ± 2.35 μm^2. Electrical stimulation of the auditory nerve fibers via cochlear implants resulted in a restoration of bouton number (mean, 17.6 ± 2.4) but not bouton size (mean, 5.25 ± 1.2 μm^2). These data imply that activity also restores endbulb arborization complexity (Fig. 7).

It seems intuitive that the benefits derived from cochlear implants should be mediated by the health of the spiral ganglion cells because cochlear implants could not function without the presence of some surviving cells. The structural restoration of

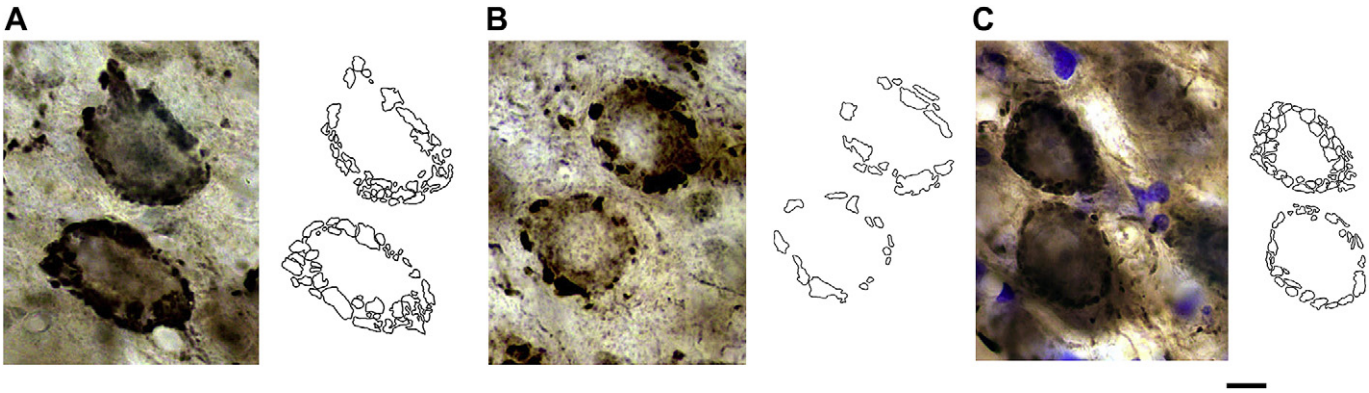

Fig. 5. Photomicrographs of endbulbs of cats stained by antibodies directed against the vesicular glutamate transporter (Vglut1), alongside corresponding drawings to illustrate the individual swellings that were drawn and measured. (A) Representative endbulbs from a normal hearing cat. Note the high density of small swellings that encircle the equator of the cell body. (B) Typical staining from a congenitally deaf cat, where the number of swellings around the cell body is greatly reduced. These images of Vglut1-stained endbulbs resemble those of HRP-labeled endbulbs illustrated in Fig. 3. (C) Usual images of endbulbs from congenitally deaf cat that received 2–3 months of electrical stimulation through a cochlear implant. The increased number of swellings around the cell body implies that activity restored the endbulb arborization. Scale bar equals 10 μm.

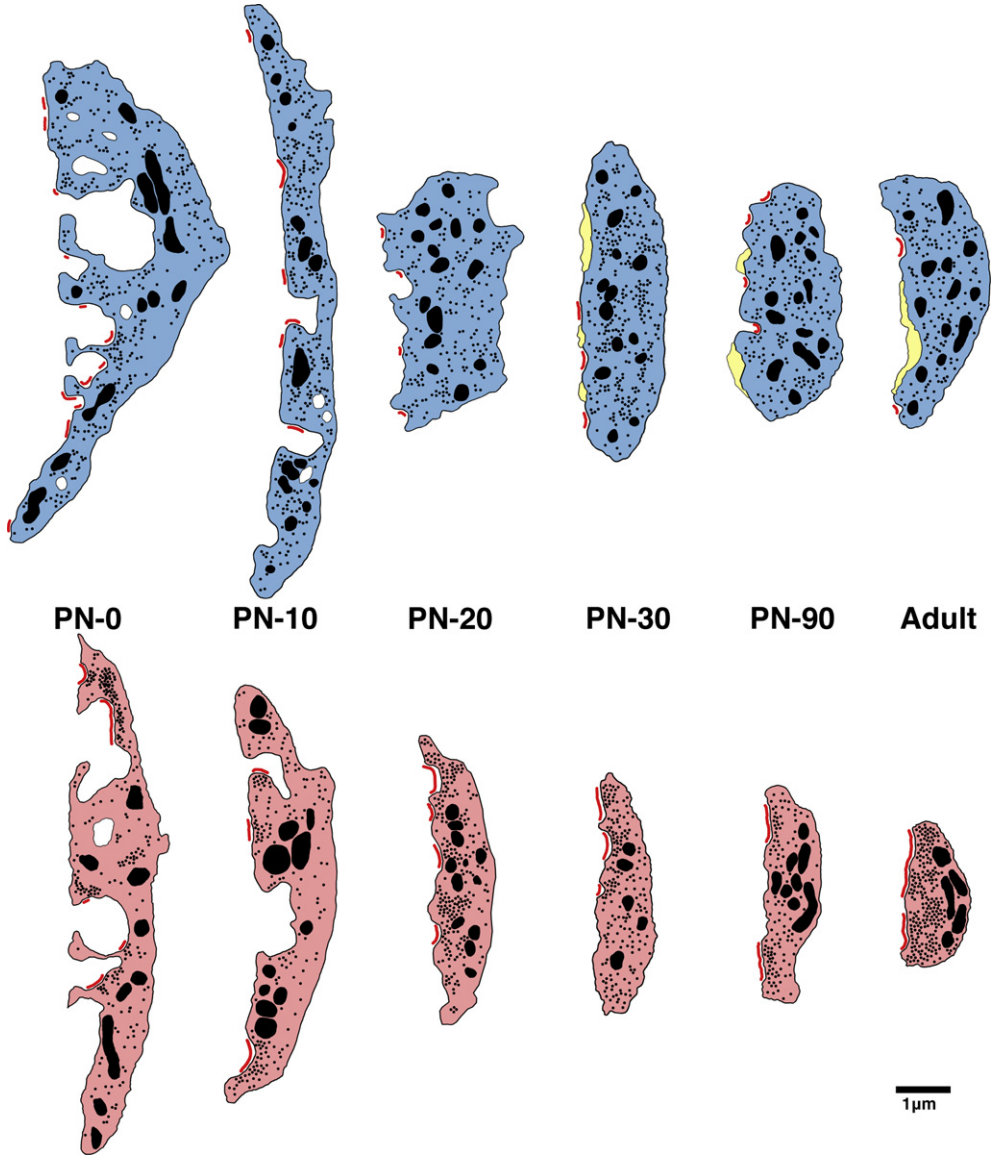

Fig. 6. Schematic of endbulb development in normal hearing (top) and deaf (bottom) cats. At birth, endbulb profiles have a highly convoluted membrane abutting the SBC, which gradually becomes smoother with age. Endbulbs of deaf animals are on average smaller than those found in age-matched normal hearing cats. The number of PSDs (red) at birth in deaf animals is less than half that of normal. Mature endbulbs of both deaf and normal animals have the same number of PSDs, the PSDs of deaf animals are longer and flatter than the normal convex PSDs. Deaf endbulbs exhibit an increase in synaptic vesicle (black dots) density near the PSDs. No differences were seen with respect to mitochondria (large black) size or volume fraction between the two groups. Endbulbs of normal cats begin to develop intermembraneous cisternae (yellow) around postnatal day 10, whereas endbulbs from deaf cats rarely develop them. From Baker et al., 2010.

endbulb synapses, however, was not related to ganglion cell number (26,130–48,192) or mean ganglion cell size (112.6–244.4 μm^2). The most important variable was the age at onset of ipsilateral electrical stimulation: stimulation commencing at three months of age had a positive effect on synapse recovery, whereas stimulation commencing at six months of age had no effect (Chen et al., 2010). Variables that influence implant success (e.g., open speech recognition) include cause of deafness and duration of deafness (Nadol et al., 1989; Moore et al., 1997; Linthicum and Fayad, 2009). Other possible variables are the degree of auditory nerve myelination, peripheral process survival, proximity of stimulating electrodes to spiral ganglion neurons, amount of scar tissue produced by surgical trauma and cochlear implantation, and blood supply to spiral ganglion neurons. The issue of how many neurons are required to produce maximum benefit from a cochlear implant remains an open question.

3.2. Bilateral effects of unilateral implantation

Restoration of auditory activity by unilateral electrical stimulation in deaf cats resulted in improvements in temporal processing at the level of the cortex (Klinke et al., 1999), the inferior colliculus (Vollmer et al., 2005) and the CN (Ryugo et al., 2005). In a separate study, three- and six-month old congenitally deaf cats received unilateral cochlear implants and were stimulated for 10–19 weeks. Animals learned to approach their food bowl for a food reward in response to a specific acoustic stimulus (a bugle playing *Adjutant's Call*). The cats ignored other bugle calls. Upon examination of the endbulb synapse, restoration was seen in animals implanted at 3 months of age but not at 6 months of age (Fig. 4C). The endbulb synapses of the contralateral CN in the 3-month old implanted cats also exhibited synapses with more normal structural features demonstrating that electrical stimulation with a cochlear implant

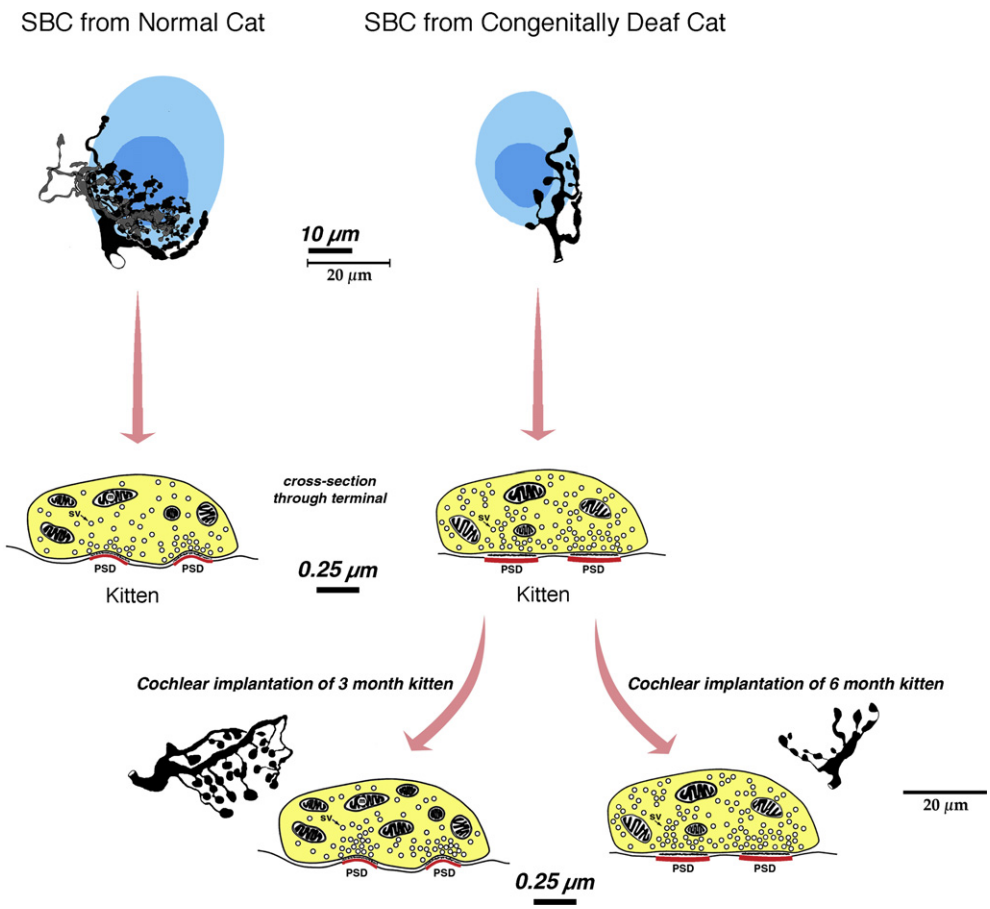

Fig. 7. Summary diagram illustrating endbulb plasticity under conditions of normal hearing, congenital deafness, and congenital deafness with cochlear implantation. Deafness results in a reduction in terminal arborization. The endbulb synapses of deaf animals lose their dome shape and hypertrophy, and synaptic vesicle density increases. Electrical stimulation through a cochlear implant in young but not older cats restores synaptic morphology. Synapses regain their dome shape and punctate distribution, and synaptic vesicle density over the release site returns to normal. The endbulb itself does not regain its highly branched arborization, nor do the swellings return to the small size typical of those in hearing cats.

can help preserve central auditory synapses through direct and indirect pathways. Because newborn kittens destined to be deaf (e.g., histologic verification of an absent organ of Corti) already exhibit statistically significant hypertrophy of PSDs (Fig. 6), we can safely use the term "restore" when referring to the effect of cochlear implantation on synaptic structure (Baker et al., 2010).

3.3. Critical periods

The concept of the critical period has been applied to explain biological phenomena that occur or are most severely affected over a brief period of time during development. Examples of such developmental events are exemplified by "imprinting" (Lorenz, 1935), cortical barrel plasticity (Van der Loos and Woolsey, 1973; Weller and Johnson, 1975), birdsong acquisition (Konishi, 1985), and functional maturation of auditory cortex (Chang and Merzenich, 2003; Zhou et al., 2008). Reports that young children receiving cochlear implants gained far superior benefit compared to that of older children and adults also hinted strongly at a critical period (Quittner and Steck, 1991; Waltzman et al., 1993; Gantz et al., 1994; Tyler and Summerfield, 1996). In congenitally deaf cats, electrical stimulation was reported to recruit auditory cortical responses contingent upon its commencement before 6 months of age (Klinke et al., 2001; Kral et al., 2002). The structural foundation for these observations may be attributable to the fact that 3-month old cochlear implant recipient exhibited somewhat restored auditory nerve synapses, whereas 6-month old cochlear implant recipients did not. The developmental period preceding puberty (cats reach puberty at six months of age) appears most favorable for implant-induced synaptic plasticity, and the restoration of endbulb synapses is hypothesized to have facilitated the proper delivery of afferent signals to the forebrain in a timely, coherent, and synchronized way.

3.4. Chemical deafening and cochlear implantation

Ototoxically deafened animals in comparison to congenitally deaf animals exhibited the characteristically hypertrophied PSDs (Ryugo et al., 2010). After electrical stimulation for a period of up to twelve months the auditory nerve synapse demonstrated recovery with a size that was statistically identical to that of normal hearing animals. However, other aspects of synapse morphology were dissimilar to that seen in heredity deafened and stimulated animals (Ryugo et al., 2010). Some studies that used ototoxic deafening have reported small but positive effects of electrical stimulation on CN cell size (Lustig et al., 1994; Leake et al., 1999; Stakhovskaya et al., 2008), whereas others using similar methods (and often from the same lab) showed no effects (Hultcrantz et al., 1991; Ni et al., 1993; Coco et al., 2007). Electrical stimulation of auditory nerve fibers via cochlear implants had no effect on the size of the SBC neurons in deaf white cats (O'Neil et al., 2010). In summary, the two models of

congenital deafness—hereditary versus ototoxic—are not identical and are associated with different morphological consequences.

4. Trans-synaptic changes in the auditory pathway

Electrical stimulation of the auditory nerve via cochlear implantation rescued many of the synaptic abnormalities associated with congenital deafness, including PSD size, distribution, and curvature, and synaptic vesicle density. The restored synapses, however, were not completely normal because intermembraneous cisternae that tend to flank release sites did not return (O'Neil et al., 2010), and restoration was not uniform across all cell types in the CN (O'Neil et al., 2011). Accordingly, electrically evoked ABRs differed from those in normal cats. Evoked peaks in the ABR waveform whose height and sharpness are indicative of synchronous ascending volleys, while more prominent in implanted cats compared to that of unstimulated congenitally deaf cats, were nonetheless delayed and flattened. These defects in the ABR waveform suggest a reduction of synchrony in the evoked responses, perhaps caused by transmission jitter or transmission failure along the ascending pathways (e.g., the ITD and ILD circuits).

4.1. Medial superior olive (MSO)

Excitatory inputs to MSO neurons are segregated such that ipsilateral input innervates lateral dendrites and contralateral inputs innervate medial dendrites (Smith et al., 1993; Russell and Moore, 1995; Kapfer et al., 2002). These neurons function as a "coincidence detector" for processing ITDs (Grothe and Sanes, 1994; Brand et al., 2002; Carr and Koppl, 2004). In addition, inhibitory inputs tend to be confined to the MSO cell bodies of mammals specialized for low frequency hearing (e.g., gerbil, cat, chinchilla) that are thought to "fine tune" the timing of inputs from the separate ears (Werthat et al., 2008; Couchman et al., 2010). This topographical arrangement differs in MSO cells of mammals specialized for high frequency hearing (e.g., rat, opossum, bat, juvenile gerbil) where there is an equal excitatory–inhibitory synapse distribution on both cell somata and dendrites. Inhibitory input to the MSO arises from the medial and lateral nucleus of the trapezoid body (MNTB, LNTB, Cant and Hyson, 1992; Kuwabara and Zook, 1992; Grothe and Sanes, 1993) and functions to adjust the output signal of MSO neurons (Brand et al., 2002; Pecka et al., 2008). The spatial distribution of these excitatory and inhibitory inputs is sensitive to developmental abnormalities within the acoustic environment.

Deafness causes a bilateral disruption in the spatially segregated inputs to the MSO principal neurons as seen in mammals with low-frequency hearing. In congenitally deaf animals, inhibitory input at the cell somata is significantly less than what is observed in hearing controls (Kapfer et al., 2002; Tirko et al., 2009). This change in axosomatic inhibition was inferred by a loss of staining for gephyrin, an anchoring protein for the glycine receptor (Kapfer et al., 2002) and the migration of terminals containing flattened and pleomorphic synaptic vesicles (indicative of inhibitory synapses) away from the cell body and out onto the dendrites (Tirko et al., 2009). Cochlear implantation of the congenitally deaf cat and 2–3 months of stimulation resulted in a restoration of inhibitory input onto the cell somata and a return of excitatory inputs to the dendrites (Tirko et al., 2009).

4.2. Lateral superior olive (LSO)

The LSO is involved in the processing of ILDs (Tollin, 2003). The ILD circuit measures the difference in sound level or intensity between the two ears, since the ear further from the sound source receives a relatively softer sound due to the "shadow" effect of the head. This binaural nucleus also plays a central role in sound localization, specifically in the processing of high frequency sounds. ILDs are encoded by integrating both excitatory and inhibitory input. The LSO receives excitatory input from ipsilateral SBCs and inhibitory input from the ipsilateral MNTB that is excited by input from the contralateral globular bushy cells (Boudreau and Tsuchitani, 1968; Moore and Caspary, 1983; Sanes et al., 1987; Sanes and Rubel, 1988; Sanes, 1990; Wu and Kelly, 1994; Kandler et al., 2009).

Inputs to the LSO are tonotopically organized and aligned so that a single neuron is excited and inhibited by the same sound frequency (Kandler et al., 2009). Within the LSO, there is a remarkable degree of synaptic reorganization involving experience dependent plasticity that is important for normal auditory development (Sanes and Takacs, 1993; Kandler and Friauf, 1995; Sanes and Friauf, 2000; Kapfer et al., 2002; Kim and Kandler, 2003). In gerbils, development of the MNTB-LSO pathway begins with synaptic pruning of MNTB axon terminals in the LSO and a decrease in the spread of LSO dendrites occurring after hearing onset (Sanes and Siverls, 1991; Sanes et al., 1992; Rietzel and Friauf, 1998; Kandler et al., 2009).Pruning depends in large part on auditory experience where GABA and glycinergic synapses are essential for the formation of precise tonotopic maps (Kim and Kandler, 2003; Gillespie et al., 2005; Kandler et al., 2009).

Deafness-associated synaptic alterations occur throughout the auditory brain stem and an imbalance of excitation and inhibition are reflected in neuronal response profiles (Bledsoe et al., 1995; Francis and Manis, 2000; Kaltenbach and Afman, 2000; Mossop et al., 2000; Syka et al., 2000). The types of change vary with respect to cell type as well as cause and extent of deafness. A decrease in excitatory transmission to the LSO may be a result of a change in total synaptic contacts, distribution of the inputs, presynaptic release, postsynaptic cell response, or any combination above (Buras et al., 2006). The fact is that any change in one location can result in widespread trans-synaptic change elsewhere.

4.3. Inferior colliculus (IC)

The IC is a large midbrain structure that has three principal subdivisions and a complex organization. There is a dorsal and lateral cortex that forms a "rind" around a central nucleus that forms the core (Morest and Oliver, 1984; Winer, 2005). The rind receives inputs from auditory as well as nonauditory sources (Robards, 1979; Ryugo et al., 1981). The central nucleus is tonotopically organized and receives ascending auditory inputs from many sources including cochlear nuclei, superior olivary complex, and nuclei of the lateral lemniscus as well as descending inputs from the auditory cortex and superior colliculus (Roth et al., 1978; Adams, 1979; Andersen et al., 1980). It is the main brain stem station through which nearly all ascending projections must pass before reaching the auditory forebrain. A rudimentary tonotopic organization within the IC has been shown to exist in long-term deafened animals (Snyder et al., 1990; Shepherd and Javel, 1999). This organization is established and maintained in the absence of auditory input (e.g., deafness) revealing the power of the genetic blueprint (Young and Rubel, 1986; Friauf and Kandler, 1990). Acute deafness did not increase temporal dispersion in spike timing to electric pulse trains in the auditory nerve nor impair ITD sensitivity (Shepherd and Javel, 1997; Sly et al., 2007; Hancock et al., 2010). Congenital deafness, however, did reduce ITD sensitivity in the responses of IC units. Single unit data in the IC showed that half as many neurons in the congenitally deaf cat showed ITD sensitivity to low pulse trains when compared to the acutely deafened animals. In neurons that showed ITD tuning, the tuning was found to be

broader and more variable (Hancock et al., 2010). These findings reveal that ITD sensitivity is seriously affected by congenital deafness.

4.4. Auditory cortex (AC)

Deafness leads to structural and functional change throughout the central auditory system (Ferrara and Halnan, 1983; McMullen and Glaser, 1988; McMullen et al., 1988; Kral et al., 2000, 2001). In congenitally deaf cats, the AC does not receive any sound evoked input but it does display some rudimentary representation of cochleotopy and ITDs (Hartmann et al., 1997; Tillein et al., 2010). Investigations on the functional deficits of the auditory cortex in adult deaf cats were conducted where electrically evoked synaptic currents in cortical layers were compared between congenitally deaf and normal hearing animals (Kral et al., 2000). Marked functional deficits were found in the AC of the congenitally deaf cat attributed to result from abnormalities of the corticocortical and thalamocortical projections. Auditory experience through electrical stimulation was found to be necessary for recruitment and maturation of the AC, and such experiences expanded the functional area of AC over that of animals who did not receive meaningful stimulation (Klinke et al., 1999, 2001). Successful restoration of auditory synapses depended on early intervention in the life of the deaf animal and reflected the kinds of beneficial clinical outcomes in humans that reinforced the idea of a critical period in development (Busby et al., 1992, 1993; Tyler et al., 1997; Busby and Clark, 1999) as well as cats (Klinke et al., 2001; O'Neil et al., 2010).

5. Concluding remarks

Auditory experience has been shown to influence the structure and function of the central auditory system from birth to adulthood. Neural activity in the form of spike discharges is necessary for the initial formation of precise synaptic structure, tonotopic organization, and proper distribution of terminals in the ascending auditory pathway. Abnormalities in the organization of both excitatory and inhibitory connections are produced by deafness, hearing loss, and/or abnormal auditory environments. The pathologic changes in the developing organism become permanent unless normal activity is restored within an age-dependent critical period. The reestablishment of activity in the auditory system through electrical stimulation results in a remarkable recovery of the involved synapses and circuit organization.

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