Presbyacusis and the Auditory Brainstem Response

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Age-related hearing loss (ARHL or presbyacusis) is an increasingly common form of sensorineural hearing loss (SNHL) as a result of changing demographics, and the auditory brainstem response (ABR) is a common experimental and clinical tool in audiology and neurology. Some of the changes that occur in the aging auditory system may significantly influence the interpretation of the ABR in comparison to the ABRs of younger adults. The approach of this review will be to integrate physiological and histopathological data from human and animal studies to provide a better understanding of the array of age-related changes in the ABR and to determine how age-related changes in the auditory system may influence how the ABR should be interpreted in presbyacusis. Data will be described in terms of thresholds, latencies, and amplitudes, as well as more complex auditory functions such as masking and temporal processing. Included in the review of data will be an attempt to differentiate between age-related effects that may strictly be due to threshold elevation from those that may be due to the aging process.

KEY WORDS: presbyacusis, aging, age-related hearing loss, auditory brainstem response, evoked potentials (auditory)

Age-related hearing loss (ARHL), or presbyacusis, is a complex phenomenon consisting of an elevation of hearing levels as well as changes in auditory processing. The purpose of this review is to describe recent studies regarding age-related effects on the auditory brainstem response (ABR), an electrophysiologic technique commonly used to measure peripheral auditory sensitivity, differentiate between cochlear and retrocochlear hearing loss, monitor the auditory system during surgery, and evaluate the neurologic intactness of the brainstem (Møller, 1999). The main supposition of this review is that pathophysiological and histopathological changes that occur in the aging auditory system may significantly influence interpretation of the ABR in older compared to younger individuals. The discussion will progress from those ABR measures in common clinical use to more experimental uses of the ABR.

Aging and Threshold Elevation

A major difficulty in studying the effects of aging on the ABR is the interaction of age with threshold elevation. Some investigators suggest that understanding the effects of age itself requires that the sensitivity of the aged system be normal—not normal for age-matched control participants, but normal compared to a young control participant (Boettcher, Mills, & Norton, 1993; Dubno & Schaefer, 1995). Others have attempted

to minimize the effects of threshold elevation by comparing young and older participants with hearing impairment but with similar thresholds (Kelly-Ballweber & Dobie, 1984) or by comparing older, hearing-impaired participants with young participants tested in the presence of a masker that elevates the young participants' thresholds to levels that are equivalent to those of the older participants with hearing loss (e.g., Dubno & Schaefer, 1992). In contrast, Martin, Ellsworth, and Cranford (1991) posited that choosing participants with normal thresholds compared to young participants results in data that are not representative of the older population. This review takes the position that it is critical to understand the role of threshold elevation on age-related changes in presbyacusis in order to determine what changes are truly age related.

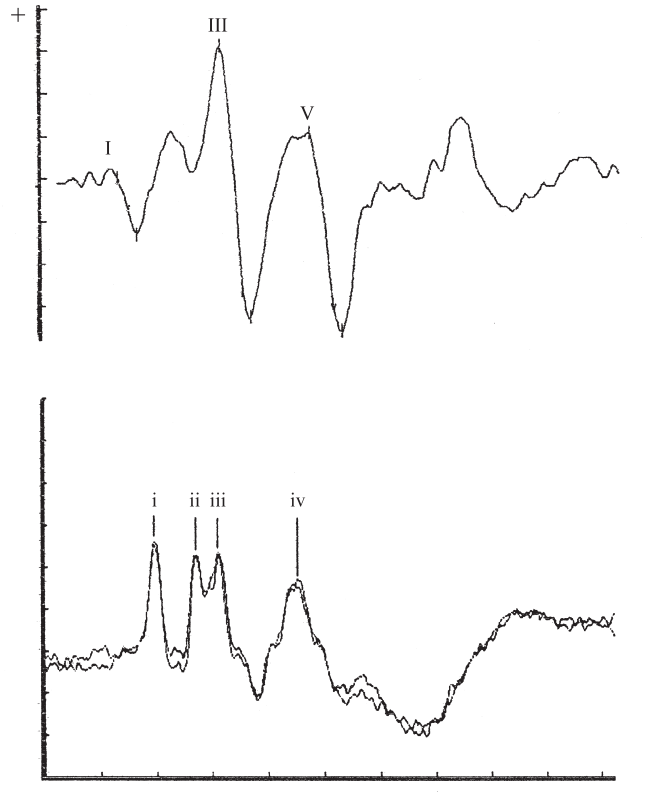
Characteristics of the ABR

The ABR consists of a series of waveforms occurring approximately 1–7 ms following a moderate-level transient stimulus. The most common terminology to describe the waveforms is to refer to them relative to their absolute latencies following a moderate-level transient stimulus. Typically, five to seven waves are observed in a human scalp recording, with the most prominent being Waves I, III, and V. There are variations to this nomenclature scheme, and latencies of the responses will vary with stimulus parameters; these issues are beyond the scope of this review and the reader is referred to Hall (1992).

Figure 1 shows ABRs recorded from a young human (upper waveform) and gerbil (lower waveform). The most prominent waves in the human ABR, namely I, III, and V, are apparent in the figure. The gerbil ABR is included for comparison, as much work on presbyacusis and the ABR has been performed in this species (see below). The waves are marked based on Burkard, Boettcher, Voigt, and Mills (1993). Wave i in the gerbil is homologous to wave I in the human, wave ii-iii (which is often a merged wave) is homologous to wave III in the human, and wave iv is homologous to wave V in the human. This terminology will be used throughout the paper when referring to the gerbil.

The ABR represents the synchronized activity of the auditory nerve and brainstem. Although there is fairly uniform agreement that fiber tracts generate potentials that can be recorded with scalp electrodes, there is not as yet strong evidence that neurons within auditory nuclei elicit responses in a synchronized fashion such that they can be recorded with far-field electrodes (Møller, 1999). Nevertheless, although the precise generators of the human ABR are not known, recent studies by several groups give an excellent approximation of the loci of generation of the ABR. Based on comparisons of the ABR and the electrocochleogram (Ecog) recorded in the ear canal, Wave I is clearly generated in the peripheral portion of the auditory nerve (Chiappa, 1997). By comparing the responses recorded directly from the auditory nerve in the human during intraoperative monitoring with the ABR, several groups have concluded that Wave II is generated by the central, or intracranial, portion of the auditory nerve (Hashimoto, Ishiyama, Yoshimoto, & Nemoto, 1981; Møller & Janetta, 1981; Møller, Janetta, & Møller, 1981; Pratt, Martin, Schwegler, Rosenwasser, & Rosenberg, 1992; see also Møller, 1999). Human studies using intraoperative monitoring techniques suggest that Wave III is generated in the cochlear nucleus (Møller & Janetta, 1983); although the precise location within the nucleus is not known in the human, the homologous wave is generated in the anteroventral cochlear nucleus (AVCN) and posteroventral cochlear nucleus (PVCN) in the cat (Melcher, Guinan, Knudson, & Kiang, 1996; Melcher & Kiang, 1996). Wave IV is likely to arise in the superior olivary complex (SOC) (Møller & Janetta, 1982; Møller, Jho, Yokoto, & Janetta, 1994). Wave V in the human is likely to be generated in the tracts of the lateral lemniscus, particularly those contralateral to the stimulated ear (Hashimoto, 1989; Hashimoto et al., 1981; Møller, 1999; Møller & Janetta,

Figure 1. ABR waveforms from a young adult human (upper wave) and gerbil (lower wave). Waves I, III, and V are labeled on the human waveform. The gerbil waveform is labeled as described in Burkard et al. (1993) and includes waves i, ii-iii, and iv.



1982, 1983). In the cat, a complex consisting of waves P4, N4, and P5 is generated by two sources: the AVCN as well as the ipsilateral and contralateral SOC. This complex may be homologous to Wave V of the human ABR, again suggesting that portions of the ABR are generated by parallel pathways (Melcher et al., 1996). Possible roles for parallel pathways in generation of the ABR are described in detail in Møller (1999).

The ABR is used for estimating auditory sensitivity and to examine neural processing at the suprathreshold level in the central auditory system. Although in no way exhaustive, a list of the applications of the ABR includes estimation of auditory thresholds in difficult-to-test patients as well as laboratory animals, site-of-lesion studies (i.e., to identify acoustic neuromas), examination of neural transmission times (as in studies of neurologic diseases), and the study of changes that may occur in the auditory brainstem independently of changes in the cochlea (such as in auditory neuropathy and possibly in presbyacusis). Thus, the ABR is a valuable tool in the standard clinical test battery in both audiology and neurology as well as an important experimental technique in understanding the auditory brainstem. However, at times, the ABR must be viewed with caution because changes may occur at both peripheral and central regions of the auditory system that may influence the interpretation of results of an ABR examination. This review will focus on changes in the aging auditory system that may influence ABR interpretation.

Histopathological Changes in the Aging Auditory System

Throughout the following review, results of clinical and laboratory studies on human participants will be compared to those in animal studies. Ideally, the focus would be on data from human studies, but for both ethical and practical reasons few such data are available. A large database of human temporal bones exists, but there are crucial limitations as to what can be learned regarding mechanisms of presbyacusis and, in turn, the relationship of presbyacusis to ABRs. Human temporal bones must be processed quickly after death for preservation of tissue, which is rarely done (Schulte, personal communication, 1999; Vincent, Gratton, Smyth, & Schulte, 1995). Furthermore, temporal bones are often gathered from persons with little or no audiometric histories, making it particularly difficult to examine the relationship between structure and function in aging. Thus, much of the following discussion will focus on controlled studies of ARHL with animals, linking the work to the few well-controlled studies in humans to demonstrate that certain animal models are good models for the study of human presbyacusis at the histopathological level.

Much of the work will focus on data from our laboratories using the Mongolian gerbil. The gerbil is an excellent model for presbyacusis because (a) it lives approximately 3 years and thus hearing can be monitored across the life span of a subject; (b) the histopathology of presbyacusis is well understood in the gerbil and is similar to that found in the human; and (c) the species is resistant to middle ear disease, such as otitis media, and thus hearing loss observed in gerbils is typically sensorineural without the complicating factor of conductive loss. Several other animal models of presbyacusis have been used and will be described where appropriate. Another popular model in studying presbyacusis is the chinchilla, in part because it has an audiogram similar to the human and because many aspects of chinchilla hearing, both behavioral and physiological, have been examined in detail. A drawback of the chinchilla as a model of presbyacusis is the species' relatively long life (up to 20 years), making studies over the life span of a subject difficult, as is true for studies of primates. Furthermore, a series of mouse models of ARHL have been examined; for various reasons described below, such models may not be ideal for studies of human presbyacusis. In summary, several species have been used to a great extent in studying presbyacusis; for multiple reasons, the Mongolian gerbil may be the most useful model explored at this time.

Categories of Presbyacusis

Schuknecht (1974) described four categories of presbyacusis in the human: (a) sensory, referring to loss of hair cells; (b) neural, referring to loss of nerve fibers and neural elements; (c) metabolic or strial, referring to loss of blood supply to the cochlea; and (d) cochlear conductive (for which there is no evidence and which will not be discussed). These categories of presbyacusis, particularly sensory presbyacusis, have become nearly doctrinal over time despite strong evidence of support for the metabolic and neural categories and poor support for the remaining categories. Indeed, in one of Schuknecht's final studies, he stated that "sensory cell losses are the least important cause of hearing loss in the aged" and that the predominant form of ARHL appears to be metabolic presbyacusis (Schuknecht & Gacek, 1993). Recent data from human and animal studies will, it is hoped, allow the field to move beyond the antiquated categories of ARHL to a better understanding of how aging can affect the auditory system.

Metabolic Presbyacusis

The stria vascularis is critical for maintenance of the endolymphatic potential (EP), the difference in potential between the scala media (containing endolymph)

and surrounding tissue. This potential is critical in maintaining exquisite sensitivity of sensory cells in the cochlea. In most young mammals, the EP is at least +80 mV, whereas a hair cell has an intracellular potential of approximately –70 mV relative to other tissue. The combination of the +80 mV potential of the EP plus the –70 mV intracellular potential of the hair cell results in a potential of at least 150 mV across the apical end of the hair cell. Reductions in the EP result in a loss of the electrical driving force across the hair cells and a concomitant loss in sensitivity. The EP is reduced in many older gerbils (Schmiedt, 1996; Schulte & Schmiedt, 1992) and appears to be related to reduced amplitudes of distortion-product otoacoustic emissions (DPOAEs) in older gerbils (Boettcher, Gratton, & Schmiedt, 1995). Age-related changes in EP are not completely understood but are a result of several changes in the lateral wall of the cochlea. The area of the stria vascularis and its capillaries (forming the blood supply) is reduced in older gerbils (Gratton & Schulte, 1995). Age-related changes in the stria include a thickening of the basement membrane of the vessels, ultimately leading to occlusion of the capillaries and loss of the blood supply to the stria (Thomopoulos, Spicer, Gratton, & Schulte, 1997).

Spiral Ganglion Degeneration

The second major type of histopathology related to presbyacusis is degeneration of the spiral ganglion (SG), which consists of the cell bodies of auditory nerve fibers. Primary degeneration of the SG, that is, a loss of fibers without concomitant loss of inner hair cells, has been observed in older humans and animals. Primary degeneration of the SG contrasts with secondary degeneration of the SG, in which fibers degenerate following a loss of inner hair cells (IHCs). Primary SG degeneration has been observed in the aging human at the electron-microscopic level from the region of IHCs through to the SG (Felder & Schrott-Fischer, 1995; Felix, Johnsson, Gleeson, & Pollack, 1990). Such degeneration has also been observed in the Mongolian gerbil (Adams & Schulte, 1997; Keithley, Ryan, & Woolf, 1989).

Hair Cell Loss

A minimal loss of hair cells occurs in presbyacusis, at least in individuals without exposure to other ototrauma (such as noise or ototoxic drugs). The hair cell loss typically observed in presbyacusis is restricted to the extreme apical (low-frequency) and basal (high-frequency) regions of the cochlea (Johnsson, Felix, Gleeson, & Pollack, 1990). Animal studies have also shown that hair cell loss is restricted to the extreme apical and basal regions of the cochleas of older gerbils (Adams & Schulte, 1997; Tarnowski, Schmiedt, Hellstrom, Lee, & Adams, 1991), chinchillas (Bohne, Gruner, & Harding, 1990; McFadden, Campo, Quaranta, & Henderson, 1997), and rats (Keithley & Feldman, 1982). Several mouse strains, such as the C57, show an early and progressive loss of hair cells (Spongr, Flood, Frisina, & Salvi, 1997) and though described by some as a model of presbyacusis (see Willott, 1991), the early loss of hearing and hair cell loss by definition rules out the C57 and related strains as appropriate models of human presbyacusis. In summary, the vast majority of evidence suggests that hair cell loss is *not* a major factor in presbyacusis.

Central Auditory System

Whereas the vast majority of information on the histopathologic bases of presbyacusis is focused on the auditory periphery, there is some evidence that age-related histopathology may occur in the central auditory system. The volume of the cochlear nucleus in the older human is reduced due to a loss of myelin surrounding axons (Konigsmark & Murphy, 1972). An array of structural and neurochemical changes has been observed in the aging central auditory system, primarily in the inferior colliculus (IC) of the Fisher 344 rat. Studies have primarily focused on gamma-amino butyric acid (GABA), an inhibitory neurotransmitter important in coding for sound localization at the level of the IC. In older Fisher-344 rats, the number of neurons (Caspary, Milbrandt, & Helfert, 1995) and synapses affected by GABA (Helfert, Sommer, Meeks, Hofstetter, & Hughes, 1999) are reduced, as is the overall level of GABA (Banay-Schwartz, Palkovits, & Lajtha, 1993).

Presbyacusis and ABR Thresholds

Thresholds measured behaviorally and electrophysiologically in young individuals are highly correlated. There is an expected elevation in ABR thresholds compared to behavioral thresholds, primarily due to temporal integration. ABR stimuli are typically 1–2 ms in duration, and stimuli used to elicit behavioral responses are approximately 200–2,000 ms in duration. Differences between ABR and behavioral thresholds vary depending on stimulus frequency, typically ranging from several decibels at high frequencies to as much as 15–20 dB at lower frequencies (Davis, Hirsh, Turpin, & Peacock, 1985; Gorga, Beauchaine, Reiland, Worthington, & Javel, 1984; Purdy, Houghton, Keith, & Greville, 1989; Stapells, Picton, Durieux-Smith, Edwards, & Moran, 1990). For example, Stapells et al. (1990) reported that the average difference between ABRs elicited with tone pips in notched noise and behavioral thresholds ranged from 2.5 dB at 4 kHz to 16.7 dB at

0.5 kHz in participants with normal hearing. Approximately 91% of ABR and behavioral thresholds were within 20 dB of each other. In participants with sensorineural hearing loss, differences between ABR and behavioral thresholds were smaller, ranging from 1 to 7 dB, presumably due, at least in part, to the lack of temporal integration in sensorineural hearing loss (Stapells et al., 1990). Similarly, mean differences between ABR and behavioral thresholds of approximately 1.4 to 5.2 dB were reported for persons with sensorineural hearing loss by Munnerly, Greville, Purdy, and Keith (1991). However, a standard deviation of 8.3 dB and a range of 41 dB between behavioral and ABR threshold measures was observed; both were larger than those observed by Purdy et al. (1989) for participants with normal hearing.

The expected correlation between behavioral and ABR thresholds is not observed in presbyacusis. Even when temporal integration effects between behavioral and ABR thresholds are accounted for, older participants have unexpectedly elevated ABR thresholds. Mills, Dubno, Boettcher, Matthews, and Ahlstrom (2001a) reported that the difference between behavioral and ABR thresholds was much larger in older individuals than in young participants. The differences between ABR and behavioral thresholds were approximately 12, 7.5, and 8 dB for 1.0, 2.0, and 4.0 kHz (tone pips, 1.8-ms duration with 0.7-ms rise-fall times), respectively, for young (17- to 37-year-old) human participants. In contrast, older participants (65–74 years old) had ABR-behavioral threshold differences of 17.5, 18, and 21 dB at the three frequencies, respectively. Thus, older participants had approximately 5.5 to 13 dB larger differences between ABR and behavioral thresholds than did young participants.

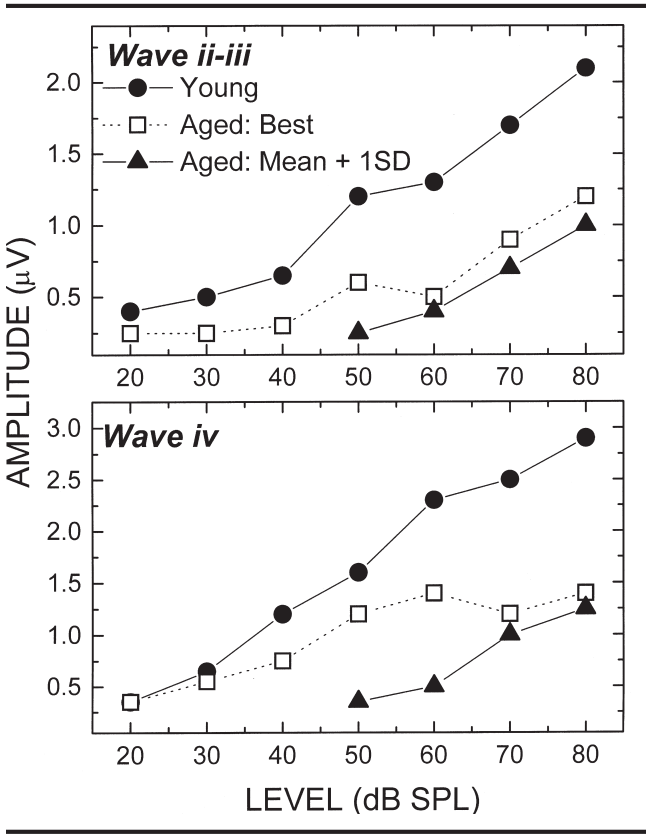
Age-related differences in ABR and behavioral thresholds are probably based on a reduction in the number of spiral ganglion fibers in older participants (Adams & Schulte, 1997; Felder & Schrott-Fischer, 1995; Felix et al., 1990; Keithley et al., 1989) and reduced synchrony among elements contributing to generation of the ABR (Mills et al., 2001a). Although not routinely used in estimating sensitivity in older individuals, the ABR may be used in some older persons, such as those unable to respond behaviorally. Thus, the clinical import of such findings is that an ABR may overestimate the behavioral sensitivity of an older individual, even when a correction factor based on simple temporal integration is incorporated.

Presbyacusis and ABR Amplitudes

Most, if not all, studies of the effects of aging on ABR amplitudes in humans demonstrate reductions in amplitudes as a function of age (Beagley & Sheldrake, 1978; Costa, Benna, Bianco, Ferrero, & Bergamasco, 1990; Harkins, 1981; Kjaer, 1980; Psatta & Matei, 1988; Sand, 1991). Even when threshold elevation is accounted for, most studies suggest a reduction in ABR amplitudes in older participants. Typically, the amplitude of Wave I or the electrocochleogram is more affected by age than Wave V (Costa et al., 1990; Psatta & Matei, 1988; Sand, 1990).

Animal studies support the thesis that ABR amplitudes vary with age, at least in part independently of hearing loss. Figure 2 shows two waves from the gerbil ABR: wave ii-iii (homologous to Wave III in the human) and wave iv (homologous to Wave V in the human). The older gerbils were divided into several groups based on hearing loss. All older gerbils, regardless of the degree of threshold elevation, had reduced ABR amplitudes. The reductions were particularly apparent at higher stimulus levels. Indeed, even gerbils with no threshold elevations had approximately 50% reductions in wave iv amplitudes at stimulus levels of 60 dB SPL and greater.

Figure 2. ABR amplitudes as a function of stimulus level for young gerbils, older gerbils with no threshold elevation ("Best"), and older gerbils with threshold elevations one standard deviation above the mean for 36-month-old subjects ("Mean + 1SD"). Data are shown for waves ii-iii and iv of the gerbil ABR (homologous to Waves III and V of the human ABR) (adapted from Boettcher, Mills, & Norton, 1993).



This was observed for waves ii-iii and iv in the gerbil ABR (Boettcher, Mills, & Norton, 1993) as well as for the compound action potential (CAP; homologous to Wave I) of the gerbil (Hellstrom & Schmiedt, 1990). Some effect of threshold elevation was observed, however, as the greater the hearing loss, the more reduction in amplitude occurred (Boettcher, Mills, Norton, & Schmiedt, 1993). Similarly, Torre and Fowler (2000) reported that peak I, II, and IV amplitudes were larger in young than older monkeys. Analysis of covariance suggested that age-related changes in amplitudes for peaks II and IV were not simply due to the reductions in peak I. Changes in peak IV were approximately 50%, consistent with the gerbil and human changes (Torre & Fowler, 2000).

The amplitude of the ABR is a direct function of the number of neurons and the synchrony of the neurons contributing to the response, as well as the value of the EP. This would suggest that age-related changes in ABR amplitudes are a combination of (a) a reduction in the number of neurons available to respond to a given signal, (b) a reduction in the synchronized activity of neurons responding to a given signal, and/or (c) a reduction in the EP. There is abundant evidence that the number of SG neurons is reduced in presbyacusis, resulting in decreased ABR amplitudes. Direct measures of synchrony across neurons contributing to the ABR are difficult, but an indirect measure has been used, namely changes in responses across stimulus presentation rates. These studies have mixed conclusions, as described in the section below regarding stimulus presentation rate. In summary, ABR amplitudes are reduced in aging, to a large degree independently of threshold elevation.

Presbyacusis and Masking of the ABR

Presbyacusis is associated with overmasking of the ABR. Overmasking refers to the phenomenon in which the behavioral or physiological threshold is elevated to a greater extent by a concurrent noise or tone than would be predicted based on the participant's thresholds measured in quiet. Overmasking has been observed in both human and animal participants and occurs both with normal and elevated quiet thresholds. Behavioral results have been mixed. For example, Klein, Mills, and Adkins (1990) reported that thresholds, measured in the presence of a low-pass noise, were similar for young and older listeners. In contrast, Margolis and Goldberg (1980) reported that patients with presbyacusis had poorer detection of tones in low-pass noise than did adults with normal hearing.

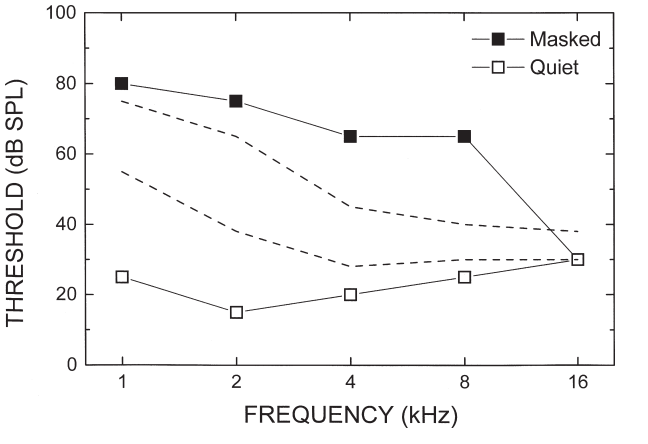
Mills et al. (2001a) reported that masked ABR thresholds were higher in older participants than would be predicted from behavioral thresholds. However, the differences between ABR and behavioral thresholds were not as great as those observed for quiet thresholds (see above and Mills et al., 2001a). Furthermore, the disparity between electrophysiological and behavioral thresholds decreased as the masker level was increased.

McFadden, Quaranta, and Henderson (1997) reported that older chinchillas show overmasking for the evoked potential recorded from the region of the inferior colliculus. Thresholds were determined for tone pips at 0.5, 1, and 2 kHz in quiet and in the presence of a noise centered at 3 kHz. Older participants had excess masking at 1 and 2 kHz.

Figure 3 shows masking data from an older gerbil with no age-related threshold elevation. The masker was a low-pass noise with a cut-off frequency of 1 kHz. The open squares represent the thresholds measured in quiet, the area between the dashed lines represents the predicted range (mean ± 1 standard deviation) of masked thresholds based on data from young gerbils with normal hearing, and the filled squares represent thresholds collected in the presence of the low-frequency masker. Thresholds for frequencies both within and above the masker were elevated relative to the predicted thresholds. Overmasking occurred in 24 of 28 older gerbils for a low-pass masker but in only 4 of 25 for a high-pass masker (Boettcher, Mills, Dubno, & Schmiedt, 1995).

The basis of overmasking of the ABR in presbyacusis is postulated to be the same as that for overestimation

Figure 3. ABR thresholds measured in quiet (open squares) and in the presence of a low-pass noise (closed squares) for a 36-month-old gerbil. Dashed lines represent the predicted range of masked thresholds (±1 *SD*) for this subject, based on models of the additivity of masking (Humes, Espinoza-Varas, &Watson, 1988; Humes & Jesteadt, 1989). The model incorporates data from young, subjects with normal hearing and the quiet thresholds from this older subject (data adapted from Boettcher, Mills, et al., 1995). In this example, the observed masked thresholds were higher than the predicted masked thresholds, as was true in the vast majority of older gerbils.



of thresholds, namely low amplitudes of the ABR (Boettcher, Mills, et al., 1995; Mills, Dubno, Boettcher, Matthews, & Ahlstrom, 2001b). Estimating auditory thresholds with the ABR by presenting tone pips in the presence of notched noise (noise with energy above and below the frequency of the tone) is currently of experimental and clinical utility (Beattie, Thielen, & Franzone, 1994; Munnerly et al., 1991; Oates & Purdy, 2001; Sininger, Cone-Wesson, & Abdala, 1998; Stapells et al., 1990). The new technique of stacked derived-band ABRs (Don, Masuda, Nelson, & Brackmann, 1997), used primarily to detect small acoustic neuromas, may also be influenced by presbyacusis. In this technique, high-pass noise is used to mask the amplitude of Wave V of the ABR. Overmasking, as observed in presbyacusis, might lead to a false impression of a neuroma. In summary, the implications of overmasking in presbyacusis are that older individuals may be more susceptible to masking and thus the use of masking techniques may require adjustments of noise levels for appropriate masking.

Presbyacusis and ABR Latencies

The latency of an auditory evoked potential is influenced directly both by the point of maximum motion of the basilar membrane and by synchrony of neurons contributing to the response (Møller, 1985). In the case of high-frequency loss, the peak of basilar membrane motion may occur at a point of hair cell loss. Thus, hair cells located apically to the peak of membrane motion respond to the signal, resulting in an increase in response latency. Furthermore, primary degeneration of spiral ganglion cells may alter the probability of a response in a central auditory neuron because of the reduction in the number of auditory nerve fibers that innervate the neuron in question. Changes in interpeak intervals (IPIs—the time difference between two wave peaks) reflect changes in neural conduction time in the auditory system and are used diagnostically in cases of acoustic neuromas and demyelinating diseases. They have been studied in detail in presbyacusis to identify possible changes in the auditory brainstem that may occur independently of changes in the auditory periphery.

Absolute latencies of ABR waves tend to increase in older adults (Allison, Hume, Wood, & Goff, 1984; Allison, Wood, & Goff, 1983; Jerger & Hall, 1980; Martini, Comacchio, & Magnavita, 1991; Ottaviani, Maurizi, D'Alatri, & Almadori, 1991; Otto & McCandless, 1982; Rowe, 1978). IPIs may also increase in the aging human (Allison et al., 1983; Oku & Hasegewa, 1997; Rosenhall, Pedersen, & Dovetall, 1986; Rowe, 1978), although not all studies have found evidence for age-related increases in IPIs (Beagley & Sheldrake, 1978; Costa et al., 1990; Harkins, 1981; Martini et al., 1991; Ottaviani et al., 1991; Otto & McCandless, 1982).

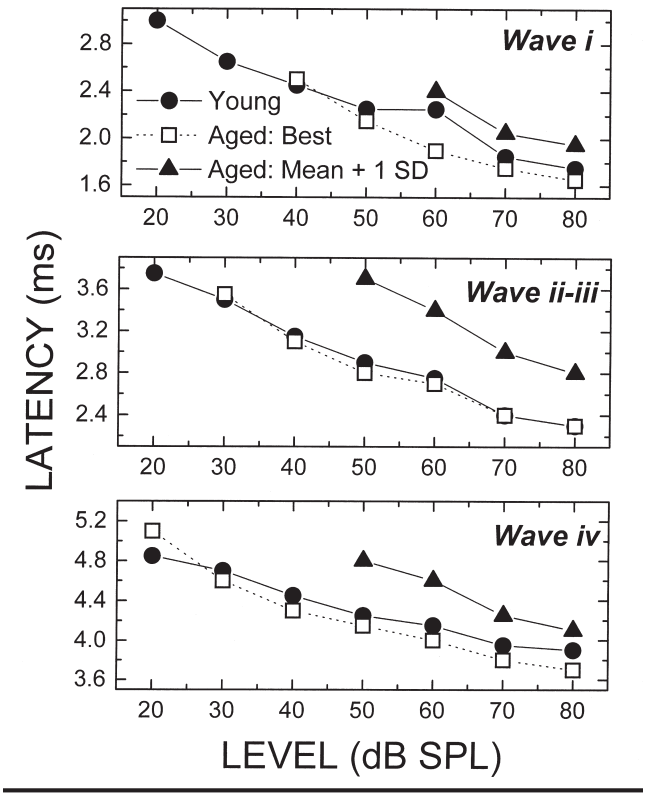
In many studies of presbyacusis, hearing levels of young and older participants are not always closely matched, making it difficult to determine if purported aging effects may simply be a result of threshold differences between groups. Stimuli are often presented at high sensation levels (SLs) to overcome differences in hearing levels between young and older groups (cf. Allison et al., 1983, 1984), but such techniques can lead to misinterpretation of results. In others, only certain frequencies have been matched between groups. Rowe (1978) reported that all ABR waves had increased latencies in older adults (51–74 years old) compared to young adults (17–33 years old). Wave I-III IPI increased in the older participants, but the III-V interval did not. Participants' hearing levels were matched based on click thresholds; significant hearing loss may have occurred at specific frequencies despite normal click thresholds. Oku and Hasegewa (1997) compared the ABR and Ecog in young and older participants (50–89 years old). Older participants had normal pure tone averages (PTAs) at 0.5–2 kHz, but their thresholds ranged from 35 to 72 dB HL at 4–8 kHz. The latencies of Waves I, III, and V showed a progressive delay in the older participants, but again because of the increased high-frequency thresholds in all older participants, it is difficult to rule out an effect of threshold elevation on the latency effects.

In contrast with studies suggesting that age has a direct effect on ABR latencies and IPIs, other studies suggest that threshold elevation is more of a factor. Beagley and Sheldrake (1978) did not find latency abnormalities in older adults with normal hearing. Harkins (1981) recorded ABRs in young (19–32 years old) and older (63–79 years old) women. The older participants had slightly poorer hearing (by 17 dB) at 4 kHz than the young participants. Absolute latencies were prolonged for the older group, with no differences in IPIs. The results suggest that the changes in latency were a result of the threshold elevation and that no sign of central pathology was present (Harkins, 1981). Otto and McCandless (1982) compared ABR latencies in young and older participants with similar degrees of high-frequency hearing loss. No differences were found between groups, although participant selection may have influenced the data, according to Kelly-Ballweber and Dobie (1984). Martini et al. (1991) reported that older adults (mean age of 67 years old) with normal PTAs (0.25–2 kHz), but mild high frequency loss at 4 kHz and above, had increased latencies for Waves I, III, and V compared to young participants with normal sensitivity. The differences were considered to be due to the mild hearing loss at 4 kHz and not specifically to aging. The Wave I-V IPI did not increase in the older participants (Martini et al., 1991). Ottaviani et al. (1991) examined ABR latencies in

adults 60–80 years old (divided into four age groups and three groups based on the PTA at 0.5–4 kHz). The latencies of Waves III and V were significantly prolonged relative to control participants in each age group. However, Waves III and V were significantly prolonged only for the groups with PTAs of greater than 30 dB HL. Similarly, participants 60–80 years old had significant increases in the I-V IPI, but when the participants were regrouped by hearing levels, no significant changes were observed in the IPIs. The authors thus concluded that age-related changes in the absolute latencies and IPIs were due to threshold changes rather than aging per se (Ottaviani et al., 1991).

The effects of aging on ABR latencies and IPIs have also been examined extensively in animal studies, in which there is more opportunity to control for environmental effects on hearing throughout the lifetime of subjects. Results using gerbils suggest that ABR latencies and IPIs are influenced by threshold elevation, but not directly by aging (Boettcher, Mills, Norton, & Schmiedt, 1993). Older (36-month) subjects were divided into groups based on hearing levels. Figure 4 shows latencies of waves i, ii, and iv of the gerbil ABR (corresponding to Waves I, III, and V in the human ABR) for (a) young subjects, (b) older subjects with no hearing loss, and (c) older subjects with hearing loss approximately equal to one standard deviation above the mean loss in 36-month-old gerbils. Older subjects with no loss had slight reductions in ABR latencies, whereas subjects with significant threshold elevation had longer latencies than control subjects. IPIs tended not to vary systematically with age, although older animals with no threshold elevation had slightly reduced i-iv interpeak intervals in comparison to young animals (Boettcher, Mills, Norton, & Schmiedt, 1993). Reduced latencies in the subjects with normal sensitivity have not yet been adequately explained, but they are consistent with data suggesting that the central auditory systems of some older subjects have losses of inhibitory neurotransmitters (see above, Caspary et al., 1995), which in turn might lead to shorter evoked response latencies. Such a hypothesis is tenuous at best and requires more correlation between physiology and histopathology. It is also plausible that IPIs are reduced in older subjects if Wave I is prolonged but Wave V is normal.

Figure 4. ABR latencies as a function of stimulus level for young gerbils, older gerbils with no threshold elevation ("Best"), and older gerbils with threshold elevations one standard deviation above the mean for 36-month-old subjects ("Mean + 1 SD"). Data are shown for waves i, ii-iii, and iv of the gerbil ABR (adapted from Boettcher, Mills, Norton, & Schmiedt, 1993).



Several other common laboratory species have been used to examine presbyacusis and ABR latencies. Older Fisher-344 rats (20–25 months old, equivalent to 80–100% of the life span) with significant threshold elevation show prolongations of latency for waves I and IV (homologous to the human Wave V) compared to young rats when equal-level stimuli are presented, but not when stimuli of equal sensation level (SL) are used (Backoff & Caspary, 1994; Cooper, Coleman, & Newton, 1990; Simpson, Knight, Brailowsky, Prospero-Garcia, & Scabini, 1985). IPIs are also prolonged in the older rats, suggesting the possibility of age-related changes in the auditory brainstem, although the significant threshold elevations prevent a definitive determination of a strict age-related change (Backoff & Caspary, 1994; Cooper et al., 1990). Torre and Fowler (2000) compared ABR latencies in young (approximately 10.5 years old) and older (approximately 26 years old) rhesus monkeys. The data were not examined in terms of threshold, making independent evaluations of threshold and aging difficult. Latencies for peaks II and IV (homologous to Waves III and V) increased in the older individuals, although the latency for peak I did not; thus, the I-IV IPI was prolonged, suggesting possible increases in neural transmission time.

In summary, results from human and animal studies on the effects of age on ABR latencies and IPIs are equivocal due to the complicating factor of threshold elevation in many studies. There is little question that threshold elevation, often associated with age, has a direct effect on ABR latencies and IPIs. In most studies that have closely controlled for threshold elevation, the conclusions have been that age-related prolongations

of ABR latencies and IPIs are caused by threshold elevation rather than aging itself. Thus, in contrast with observations suggesting that aging alters interpretation of threshold and amplitude information, the implications regarding latency are that an increase in latency would only be expected if thresholds are elevated, and that there is nothing to suggest that aging per se influences the interpretation of latency information in the ABR.

Presbyacusis and Presentation Rates

A method for measuring adaptation and possibly synchrony in an evoked response is to examine the effect of different stimulus presentation rates on the response. As the stimulus presentation rate increases, ABR latencies typically become longer and amplitudes decrease. For the human ABR, the latency of Wave V tends to increase more than that of Wave I (Picton, Stapells, & Campbell, 1981), whereas the amplitude of Wave I decreases more than that of Wave V (Harkins, 1981; Picton et al., 1981). Experimental data suggest minimal influence of age on rate effects. Harkins (1981) reported that Wave I latency was reduced in older participants (but only at a presentation rate of 10/s), as was Wave V latency (but only at a rate of 20/s). Boettcher, White, Mills, and Schmiedt (1995) examined amplitudes of the gerbil ABR for tone bursts presented at 11–91/s. The relative change in amplitude (i.e., the amplitude measured at 91/s divided by that measured at 11/s) was similar in young and older gerbils, suggesting that age did not influence rate effects. Thus, the influence of neural synchrony on reduced ABR amplitudes in presbyacusis, although theoretically important, has yet to be demonstrated in a definitive manner.

Presbyacusis and Temporal Processing

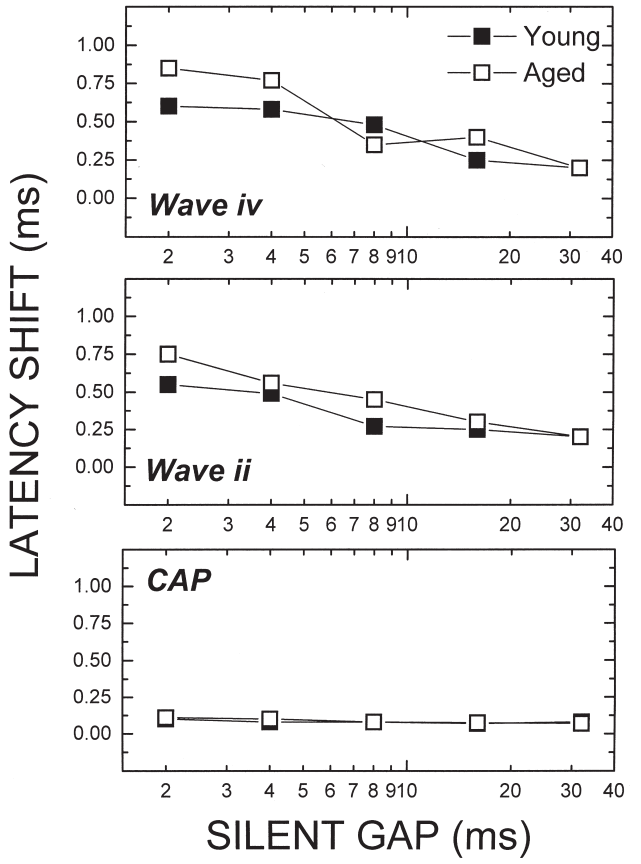
Temporal processing refers to the ability of the auditory system to resolve rapid changes in stimulus intensity. It is a key component in speech processing, and abnormal temporal processing has been shown to occur behaviorally in older adults, including those with little or no hearing loss (Fitzgibbons & Gordon-Salant, 1996). A number of paradigms have been used to quantify temporal resolution, including recovery from forward masking and detection of a silent gap in an ongoing signal ("gap detection").

Walton, Orlando, and Burkard (1999) examined forward masking in the ABRs of young and older human participants with normal sensitivity through 8 kHz. The response to a short tone burst (1, 4, or 8 kHz; "probe") was determined in the absence and presence of a preceding masker of identical frequency to the probe. The offset of the masker to the onset of the probe ("ΔT") varied from 2 to 64 ms. Masking was quantified as the difference in latency of Wave V to the probe between the masked and unmasked condition (termed the "latency shift"). Young and older participants had similar latency shifts as a function of ΔT for 1-kHz probes, but older participants had larger shifts for 4- and 8-kHz probe frequencies. Because the groups had similar sensitivity, the differences are not related to a threshold effect. However, because Wave I data were not available, it is not known if the effect was related to changes in the auditory periphery or brainstem in the older participants (Walton et al., 1999).

Results consistent with Walton et al. (1999) have been described by Poth, Mills, Dubno, and Boettcher (2001). The ABRs for young (19–32 years old) and older (60–72 years old) adults were recorded in response to two 50-ms broadband noise bursts separated by ΔTs of 4–64 ms. Thresholds in both groups were 30 dB HL or less at 0.25–8 kHz. Whereas all young participants (n = 8) had responses to ΔTs of 8 ms or greater and 7 of 8 to a ΔT of 4 ms, only 5 of 8 older participants had responses at ΔTs of 4 and 8 ms. These results suggest that a portion of the older participants had reduced temporal processing ability, despite minimal or no threshold elevation.

Several animal studies have also shown deficits in temporal processing in older subjects. Walton, Frisina, and O'Neill (1998) reported that mice with no peripheral threshold elevation have deficits in coding of silent gaps in noise, both at the single neuron and the evoked response levels. In our lab, ABRs were recorded in young and older gerbils in response to paired broadband noises, separated by ΔTs of 2–32 ms. Large differences were observed in the latency shift (see description above) between young and older subjects, as shown in Figure 5. The latency shifts were approximately equal at each ΔT for the CAP (wave i), but at short ΔTs, the latency shift was much larger for the older subjects than the young subjects for more central waves (iii and iv). The older gerbils had mild threshold shifts (15–20 dB) relative to the young gerbils. It is possible that the threshold shift influenced the results, yet the CAP did not show abnormalities in temporal processing; thus, the differences between groups may be a result of age-related changes in the central auditory system of the older subjects (Boettcher, Mills, Swerdloff, & Holley, 1996). In contrast, McFadden, Quaranta, et al. (1997) reported that young and older chinchillas had similar forward masking recovery functions for the evoked potential from the inferior colliculus (probably equivalent to Wave V). However, because the thresholds were elevated in the older subjects, the results did not address

Figure 5. ABR latency shifts as a function of gap duration for young and older gerbils. The latency shift was defined as the latency to the second burst of a pair of noises minus the latency to the first burst of noise. Data are shown for the compound action potential (CAP), wave ii, and wave iv of the gerbil ABR, collected with 80-dB SPL noise (adapted from Boettcher et al., 1996).



the issue of threshold elevation versus aging. It is possible that for equal SPLs, the young subjects may have required higher masker levels to mask the probe, suggesting greater resistance to masking.

Summary

A better understanding of the effects of aging and presbyacusis on the ABR has begun to emerge, partially through the use of animals models in which excellent control over extrinsic variables is possible. Furthermore, advances in the identification of histopathologic changes associated with presbyacusis have allowed correlation of structural changes with functional changes. The difference between behavioral and ABR thresholds is larger in older than in young individuals, potentially leading to overestimation of hearing loss in older persons when the ABR is used. Aging itself does not appear to influence ABR latencies or IPIs if no threshold elevation occurs. There is as yet no evidence of changes in the effects of stimulus presentation rates as a result of presbyacusis. ABR measures of temporal processing may be influenced by age and not only threshold elevation and may suggest reduced ability to resolve rapid fluctuations in stimulus characteristics in older individuals. Changes that occur primarily as a function of threshold elevation are probably related to reductions in the EP and degeneration of the stria vascularis, whereas changes in the ABR unrelated to threshold elevation may be more closely related to degeneration of the spiral ganglion. Furthermore, changes in temporal processing may reflect changes in the auditory system that occur independently of degeneration of the auditory periphery.

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