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Inhibitory Neurotransmission, Plasticity and Aging in the Mammalian Central Auditory System

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Summary

Aging and acoustic trauma may result in partial peripheral deafferentation in the central auditory pathway of the mammalian brain. In accord with homeostatic plasticity, loss of sensory input results in a change in pre- and postsynaptic GABAergic and glycinergic inhibitory neurotransmission. As seen in development, age-related changes may be activity dependent. Age-related presynaptic changes in the cochlear nucleus include reduced glycine levels, while in the auditory midbrain and cortex, GABA synthesis and release are altered. Presumably, in response to age-related decreases in presynaptic release of inhibitory neurotransmitters, there are age-related postsynaptic subunit changes in the composition of the glycine (GlyR) and $GABA_A$ receptors ($GABA_AR$). Age-related changes in the subunit makeup of inhibitory pentameric receptor constructs result in altered pharmacological and physiological responses consistent with a net down-regulation of functional inhibition. Age-related functional changes associated with glycine neurotransmission in dorsal cochlear nucleus (DCN) include altered intensity and temporal coding by DCN projection neurons. Loss of synaptic inhibition in the superior olivary complex (SOC) and the inferior colliculus (IC) likely affect the ability of aged animals to localize sounds in their natural environment. Age-related postsynaptic $GABA_AR$ changes in IC and primary auditory cortex (A1) involve changes in the subunit makeup of $GABA_ARs$. In turn, these changes cause age-related changes in the pharmacology and response properties of neurons in IC and A1 circuits which collectively may affect temporal processing and response reliability. Findings of age-related inhibitory changes within mammalian auditory circuits are similar to age and deafferentation plasticity changes observed in other sensory systems. Although few studies have examined sensory aging in the wild, these age-related changes would likely compromise an animal's ability to avoid predation or to be a successful predator in their natural environment.

Introduction

Aging and partial damage to the peripheral sensory systems of mammals appear to result in plastic pre- and postsynaptic changes in the inhibitory neurotransmitter systems of the primary sensory pathways. The exact nature of these changes is dependent upon the anatomic location and function of the inhibitory circuits within the particular primary/lemniscal sensory system. Figure 1 shows the primary ascending auditory pathway. Coding of environmental acoustic signals occurs at all levels of the central auditory pathway. The cochlear nucleus (CN) is comprised of a dorsal and ventral division (DCN, VCN) having three functionally and anatomically segregated outputs (see Young and Oertel, 2004 for more complete review). The functions of the CN neurons are diverse, even at this early stage of auditory brainstem pathway (Kiang et al., 1965). There are at least five major CN neuronal response types (Kiang et al., 1965; Caspary, 1973; Evans and Nelson, 1973). Those in the ventral division primarily relay information about the timing and intensity of sounds from the acoustic environment (Young and Oertel, 2004). These VCN cells extract salient temporal features of communication calls, communicating time and intensity cues from both sides of the head to the superior olivary complex (SOC) (Harnischfeger et al., 1985;Frisina et al., 1990a; Frisina et al., 1990b; Frisina 2001;Irvine et al., 2001). The SOC is comprised of three main subnuclei related to the localization of sound in space (Masterton and Imig, 1984). The medial nucleus of the trapezoid body (MNTB) converts the well timed excitatory input from the VCN on one side of the head to an inhibitory projection to the lateral superior olive (LSO) (Harnischfeger et al., 1985). In the LSO, the inhibitory projection from one side is compared to an excitatory projection from the other side. This profile provides a powerful way of comparing intensity from both sides of the head (Irvine et al., 2001;Moore and Caspary, 1983). In addition, inhibitory inputs damp low frequency time-locked excitatory signals from both sides of the head as they project onto the dendrites of linearly arrayed cells in the medial superior olivary complex (MSO) (Masterton and Imig, 1984). This structure is primarily concerned with comparing arrival time of the sound from both sides of the head (Grothe and Sanes, 1994). While the functions of different neuronal types in the CN and the SOC are quite well understood, the nature of the code at the level of the inferior colliculus (IC), medial geniculate (MGB) and primary auditory cortex (A1) are less well understood. At the level of the IC, neurons are involved with refining information regarding the location of signals in the acoustic environment and providing a rate code from complex temporally modulated communication calls (Pollak et al., 2003). Neurons in the IC of specialized mammals such as bats have been shown to code echoes through specific inhibitory delay lines, a coding modality, important in determining the location of sound, echolocation and extracting information from voice and unvoiced communication signals (Carr et al., 1986;Portfors and Wenstrup, 2001).

The complex processing which occurs at the level of the MGB and the A1 is beyond the scope of the present review. Coding in the auditory cortex has been recently reviewed by Wang (2007) and also by Rauschecker (2005). As seen in the visual cortex, in the auditory cortex, acoustically complex hierarchical analysis has been described for awake behaving primates (Rauschecker, 2005; Steinschneider et al., 2007). A1 has been shown to undergo age-related plastic changes, including down-regulation of inhibitory coding, similar to that observed at lower levels of the auditory pathway and in visual cortex. Similar to age-related changes, activity dependant changes have been shown to occur in all the primary sensory systems upon selective partial deafferentation (see below).

Deafferentation Plasticity

Aging can be thought of, in part, as a slow peripheral deafferentation, which in turn can result in compensatory changes throughout the specific sensory CNS. Recent aging studies of primate and feline visual cortex show an age-related loss of orientation and directional selectivity in the responses of visual cortical neurons, including changes consistent with a selective down-regulation of GABA inhibition (Schmolesky et al., 2000; Leventhal et al., 2003; Hua et al., 2006). Similar changes have been observed in humans (Betts et al., 2007). Age-related changes of inhibitory neurotransmission occurring in ascending circuits of the mammalian central auditory system are reviewed below. Where relevant, the effects of adult peripheral deafferentation in the same circuits are described.

Homeostatic plasticity describes how, in response to activity dependent input changes in development and deafferentation, neural systems undergo pre- and postsynaptic compensatory changes to stay within a relatively narrow operating range of excitation and inhibition (Turrigiano, 2007; Rich and Wenner, 2007). Rich and Wenner (2007) describe how changes in chronic neuronal activity (over a period of days) trigger compensatory changes in synaptic activity, which in turn, contribute to a return toward original levels of neuronal activity. In this light, the sensory literature suggests that partial peripheral deafferentation of somatosensory, visual or auditory central pathways leads to a selective down-regulation of inhibition, perhaps in an effort to restore the system toward original levels of activity (D. M. Caspary, unpublished).

A few selected examples illustrate how damage to, or a blockade of, peripheral/central sensory projections results in a selective down-regulation of normal adult GABAergic function in the central target structures. Retinal lesions lead to a reduction of GABA levels in visual cortical regions receiving projections from the damaged area (Rosier et al., 1995). Blockade of peripheral visual input reversibly reduces the number of immunolabeled glutamic acid decarboxylase (GAD) (the synthetic enzyme for GABA) neurons by 50% in primary visual cortex (Hendry and Jones, 1986; Hendry and Jones, 1988; Jones, 1990). Whisker trimming in adult rats results in reversible reductions of GAD immunostaining and muscimol binding in somatosensory cortex (Akhtar and Land, 1991; Fuchs and Salazar, 1998). While in spinal cord, partial peripheral nerve injury promotes a selective functional loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord (Moore et al., 2002).

Behavioral Evidence of Age-related Auditory Dysfunction

In humans, age-related hearing loss is associated with both peripheral and central processing deficits that combine to make it difficult for the elderly to process speech and other acoustic signals in noisy or complex environments (Bergman et al., 1976; Willott, 1991; Divenyi and Haupt 1997a; Divenyi and Haupt, 1997b). A common complaint of older adults is difficulty understanding communication signals and speech, in complex acoustic environments (Gordon-Salant and Fitzgibbons, 1993; Dubno et al., 1997; Snell, 1997; Strouse et al., 1998). A decreased ability to temporally process acoustic signals may underpin difficulties processing environmental sounds (Gordon-Salant and Fitzgibbons, 1993; Strouse et al., 1998). The impact of aging on temporal processing has been behaviorally assessed in humans and in laboratory animals by varying the width of a silent gap embedded in a continuous acoustic background (Schneider et al., 1994; Snell, 1997; Schneider et al., 1998; Schneider et al., 1999; He et al., 1999; Lister et al., 2002; Barsz et al., 2002; Ison and Allen, 2003; Roberts et al., 2004; Turner et al., 2005c). In addition, human studies show age-related decline in the ability to extract visual signals from a cluttered visual background (Cremer and Zeef, 1987).

Age-related Changes in Mammalian Central Auditory Pathways

Inhibitory circuits throughout the auditory neuraxis are responsible for important survival functions. These include coding the localization of sound in space, as well as extraction and coding of salient communication signals. Processing environmental sounds is necessary for successful predation or avoiding predation. Certain species of Chiropterans (bats) use many of these same circuits for echo location to navigate their environment and locate insects (Pollak et al., 1977; Simmons, 1989; Portfors and Sinex, 2003; Vater et al., 2003; Portfors and Sinex, 2005). For example, behavioral studies in bats, kangaroo rats, insects and fish show the importance of the auditory system for survival in the wild. This, in turn, suggests that an age-related degradation of acoustic signal processing (sensory function) could play as important a role as motor decline in loss of normal adult behavioral success within an animal’s natural habitat (Webster and Webster, 1971; Cumming, 1996; Anderson et al., 1998; Sisneros and Bass, 2005; Hollen and Manser, 2006). Increasingly, recent studies suggest that a selective loss of normal adult inhibitory neurotransmission may subserve this loss of sensory function. This review is focused on aging in inhibitory neurotransmitter systems; however, it is important to understand that age-related changes occur in other neurotransmitter systems including serotonergic (Tadros et al., 2007a), cholinergic (Caspary et al., 1990) and excitant amino acids (Banay-Schwartz et al., 1989a; Banay-Schwartz et al., 1989b; Tadros et al., 2007b).

Accurate temporal processing depends on the ability of inhibitory circuits to sharpen responses to rapidly time-varying signals (Walton et al., 1997; Walton et al., 1998; Krishna and Semple, 2000; Frisina, 2001; Caspary et al., 2002; Liang et al., 2002). Rapidly time-varying signals play an important role in communication and socialization among mammals. For either predator or prey, the loss of these abilities would prove detrimental to survival. The present review will focus on age-related changes in inhibitory neurotransmission involved in circuits within the CN, the SOC, the IC and the A1 (Fig. 1). Major age-related pre- and postsynaptic changes and age-related functional changes in these structures are summarized in Table 1. Age-related changes are reviewed in the context of coding salient species-specific sounds, localization cues and echo location. Neurochemical and functional literature reviewed below is primarily from two rat strains (Fischer-344 [F344]; Fischer Brown-Norway F1 hybrid [FBN]) unless otherwise noted. The two strains differ in the nature of their age-related loss of cochlear inner and outer hair cells with the FBN strain approximating the pattern of hair cell loss seen for the wild-type, Brown Norway rat (Fig. 2A) (Keithley et al., 1992; Turner and Caspary, 2005). Figure 2 displays the modest age-related inner hair cell changes for both strains while outer hair cell changes are more extensive (Fig. 2A), and likely subserve the 20–30 dB parallel age-related shift in functional threshold measures using the auditory brainstem-evoked response (Fig. 2B). The two strains differ in hearing sensitivity (Fig. 2B) and their 50% mortality rate (F344 at 24mos. and FBN at 32mos.). Central age-related hearing changes have also been extensively studied in mice, whose upper frequency of hearing is higher compared to rats with cut-off frequencies listed up into the 60 kHz range for some strains of mice (Ehret, 1975; Kulig and Willott, 1984).

Cochlear Nuclei and Superior Olivary Complex

The first central auditory “relay stations” are the DCN and VCN (for review see Young and Oertel, 2004). In young adult animals, the VCN codes both time and intensity features of sound (Rhode and Smith, 1986a) sending projections to the second major group of nuclei on the auditory neuraxis, the SOC (Warr, 1966). As with all lemniscal auditory structures (primary ascending auditory pathway), these structures are tonotopically arranged. Low frequency sounds may be coded by a firing pattern that approximates the frequency of the acoustic signal, phase-locking, while higher frequencies are coded spatially (Sullivan, 1985; Rhode and Smith, 1986a; Pollak et al., 2002). Response properties of many neurons code both the fine structure and the envelope of communication signals and environmental sounds. Accurate temporal representations of environmental sounds are required for accurate localization of both low and high frequency sounds (Joris and Yin, 2007). Localization of sounds in the horizontal plane is necessary to avoid predation or to successfully localize prey. Localization of high frequency sounds is thought to involve left vs. right comparison of interaural intensity differences, which primarily occurs in the LSO (Batra et al., 1997; Tollin and Yin, 2002). Neurons which compare low frequency sounds from both sides of the head are mostly located in the MSO. The relative size and importance of the LSO and MSO cell groups are directly related to the frequency range of particular species and their particular diurnal habitats (Warr, 1982). In order to minimize temporal jitter in the SOC system, projection neurons in VCN receive both intrinsic and extrinsic inputs, primarily from glycinergic neurons, which dampen excitatory responses and allow VCN neurons to accurately follow small latency shifts and code rapidly time-varying signals over a wide range of signal intensities (Frisina et al., 1990a).

Age–related Changes in Cochlear Nuclei

Age-related changes in the cochlear nuclei are suggestive of a compensatory down-regulation of inhibition following an age-related loss of peripheral input (Turner and Caspary, 2005) and have been recently reviewed by Frisina and Walton (2001). These age-related changes include reduction of glycine levels in both DCN and VCN (Banay-Schwartz et al., 1989b) along with changes in the subunit make-up of the pentameric, heteromeric glycine receptor (GlyR) (Krenning et al., 1998; Caspary et al., 2002). Age-related GlyR subunit changes in VCN are suggestive of an age-related return to a more developmental form of the GlyRs with a down-regulation of the α_1 and up-regulation of the l aα_2 subunit (Krenning et al., 1998). Age-related subunit mRNA changes are found throughout the cochlear nuclei, resulting in the loss of strychnine binding observed in the DCN of both aged rats and mice (Milbrandt and Caspary, 1995; Willott et al., 1997). Functionally, the DCN appears to have a role in the extraction of signals in noise (Gibson et al., 1985), while also coding spectral notches to locate sounds in the vertical plane (Nelken and Young, 1996). Similar to communication sounds, the envelope of amplitude and frequency modulated signals are coded by DCN projection neurons (Frisina et al., 1994; Nelken and Young, 1996; Imig et al., 2000). Many of the major response types within the cochlear nuclei receive intrinsic glycinergic endings from vertical and cartwheel cells in the DCN and D-stellate cells in the VCN (see Oertel and Young, 2004 for review). Strychnine blockade of GlyRs within DCN and VCN increases discharge rate, primarily, within the excitatory response area and reduces synchrony of temporal coded events (Wickesberg and Oertel, 1990; Caspary et al., 1994; Backoff et al., 1999). Response properties recorded from aged DCN projection neurons resemble responses observed in young adult animals from the same DCN neurons with their GlyRs blocked. Fusiform cells display age-related increases in maximum discharge rate and changes in temporal responses, consistent with a loss of glycinergic inhibition (Caspary et al., 2005). The reduced damping seen in the response properties of aged DCN fusiform cells would likely affect the ability to extract salient signals from a cluttered acoustic environment and degrade envelope coding of communication signals. Since DCN output neurons project to the contralateral IC, age-related changes would be reflected in the responses of the fusiform cell projection targets in the IC (Ramachandran et al., 1999; Frisina and Walton, 2001).

Age-related Changes in the Superior Olivary Complex

As noted above, the subnuclei of the superior olivary complex are highly specialized for the localization of sound in space. For the most part, environmental high-frequency sounds are coded by interaural intensity differences. Circuits leading from the VCN on one side enter the LSO directly, while inputs from the contralateral side, synapse first in the medial nucleus of the trapezoid body, which converts the excitatory glutamatergic message into an inhibitory glycinergic message at a short latency, high fidelity synapse known as the endbulb of Held (Moore and Caspary, 1983). Glycinergic inputs impinge on LSO neurons completing a circuit that is exquisitely suited for spatial localization using interaural intensity (Finalayson and Caspary, 1991). Relatively few aging studies have been carried out in the SOC. A selective loss of inhibitory input from the MNTB to the LSO would hamper localization in the ipsilateral hemifield. Casey and Feldman (1982; 1988) found that MNTB neurons were selectively lost in two strains of aged rat. However, functional studies found only small changes in the slope of interaural intensity difference functions in the F344 rat (Finlayson and Caspary, 1993). Two additional aging studies in mouse and gerbil also found relatively small age-related changes in the SOC (O’Neill et al., 1997; Frisina, 2001; Gleich et al., 2004). SOC studies do show age-related changes in potassium channels and calcium binding proteins in cells of origin of a descending pathway from the SOC to the cochlea (Zettle et al., 2007).

Inferior Colliculus

The IC is a mandatory relay-station on the ascending auditory pathway (Oliver and Heurta 1992; Pollak et al., 2002; Malmierca, 2003; Morest and Oliver, 1984). Age-related changes of inhibition within the IC would likely impair the ability of the animal to further refine the localization of an environmental sound source from information received from the SOC, nuclei of the lateral lemnisci, and DCN (Litovsky and Delgutte, 2002; Escabi et al., 2003; Pecka et al., 2007; Palmer et al., 2007). In addition, inhibition plays a role in processing acoustic delay information as well as strict temporal processing (Pollak et al., 2002). Delay coding is critical for echo location in bats and may play a role in processing periodic vs. aperiodic segments in communication signals. IC circuits utilizing both GABAergic and glycinergic inhibition have been shown to be important in coding selective communication calls in animals and are critically involved in delay circuits in bats (Yan and Suga, 1996; Portfors and Wenstrup, 2001; Klug et al., 2002). The IC receives excitatory glutamatergic inputs directly from the DCN as well as a major ascending projection from the SOC (see Kelly and Caspary, 2005 for review). Extrinsic GABAergic projections to the IC arise bilaterally from the dorsal nuclei of the lateral lemniscus, while glycinergic inputs originate from the ventral nucleus of the lateral lemniscus and the LSO. In addition, intrinsic GABAergic neurons are located throughout both the central nucleus and the shell nuclei of the IC. IC neurons also receive a major excitatory descending projection from the auditory cortex (Winer et al., 1998; Winer et al., 2002; Winer, 2006).

As is the case for age-related changes described below, it is not known whether age-related inhibitory changes in IC are the result of *de novo* aging changes within the central nervous system or are the direct result of a gradual loss of peripheral input or both. In response to superthreshold acoustic stimulation, noise-exposed animals (modest damage to the auditory periphery) show altered evoked responses in the IC and auditory cortex, providing a functional picture suggestive of hyperexcitability (Willott and Lu, 1982; Popelar et al., 1987; Salvi et al., 1990; Gerken et al., 1991; Syka et al., 1994; Szczepaniak and Møller, 1995; Wang et al., 1996; Syka and Rybalko, 2000; Aizawa and Eggermont, 2007). Neurochemical findings in support of these functional changes reveal that damage to the auditory periphery results in a selective down-regulation of normal adult inhibitory GABAergic function in the IC. Surface-recorded evoked potentials from the IC of noise-exposed rats show reduced sensitivity to bicuculline blockade (Szczepaniak and Møller, 1995). Bledsoe et al. (1995) found that deafness resulted in decreased GABA release *in vivo* and decreased numbers of IC neurons showing electrically evoked suppression of unit activity. IC GAD levels were reduced 2–30 days following noise exposure (Abbott et al., 1999; Milbrandt et al., 2000). GABA uptake and release following ossicle removal or cochlear ablation resulted in complex long-term changes in GABA and glycine neurochemistry (Suneja et al., 1998). Collectively, these studies suggest that decreased acoustic input at the auditory periphery results in significant changes in GABA neurotransmission in normal adult IC.

Age–related Changes in Inferior Colliculus

Single unit recordings from the IC of aged rats show a significant decrease in the level of inhibition within the excitatory response area, an increase in the breadth of the excitatory response area at 30 dB above threshold, and less precise temporal processing of modulated sounds (Palombi and Caspary, 1996a; Palombi and Caspary, 1996b; Palombi and Caspary, 1996c; Shaddock-Palombi et al., 2001). Similar physiological changes occur in C57 and CBA mice (Willott, 1986; Willott et al., 1988; Willott et al., 1991; McFadden and Willott, 1994; Walton et al., 1998; Walton et al., 2002; Simon et al., 2004).

A number of measures of presynaptic GABA neurotransmission show age-related changes in the mammalian IC. GABA levels, GABA immunostaining, GAD activity and $GABA_A$ and $GABA_B$ receptor binding all decrease in the aged rodent IC (Banay-Schwartz et al., 1989a; Banay-Schwartz et al., 1989b; Caspary et al., 1990; Gutiérrez et al., 1994; Raza et al., 1994; Milbrandt et al., 1994; Milbrandt et al., 1996;). The IC neuropil shows an age-related rearrangement of synaptic endings onto soma and proximal dendrites (Helfert et al., 1999).

Possibly in response to age-related presynaptic changes, age-related postsynaptic changes occur in the mammalian IC $GABA_A$ receptor. The $GABA_A$ receptor is a heterogeneous family of ligand-gated Cl^- ion channel receptors, which receive input from GABA-releasing inhibitory circuits. $GABA_A$ receptors exist as pentameric subunit complexes made up of combinations of 19 possible $GABA_A$ receptor subunits, which can be activated/allosterically modulated by numerous pharmacological agents (Sieghart, 1992a; Sieghart, 1992b; Wafford et al., 1993; Sieghart, 1995; Rabow et al. 1995; Mohler et al., 2002). Thus, changes in the make-up of the $GABA_A$ receptor would alter the function of sensory coding in the aged IC. In the IC, both $GABA_A$ receptor subunit message and protein levels show age-related changes with a significant down-regulation of the adult α_1 subunit in favor of an up-regulation of the α_3 $GABA_A$ receptor subunit (Gutierrez et al., 1994; Milbrandt et al., 1997; Caspary et al., 1999). *In situ* hybridization and western blot studies show significant age-related up-regulation of the γ_1 subunit (Fig. 3) suggestive of a compensatory age-related increase in the affinity for GABA (Milbrandt et al., 1997; Caspary et al., 1999). Coexpression of the γ_1 subunit with al $_1$ and β_2 subunits in oocytes produces a $GABA_A$ receptor complex, which fluxes more Cl^- ions per millimole of GABA than wild-type γ_2 subunit containing receptor constructs (Ducic et al., 1995). Receptor binding studies found significant age-related enhancement of GABA's ability to modulate binding at the picrotoxin $GABA_A$ receptor site (Fig. 4) (Milbrandt et al., 1996). Modulation of $GABA_A$ receptor binding at this site using bath-application of GABA resulted in an age-related, dose-dependent shift to the left in the GABA modulation curve (Fig. 4) (Milbrandt et al., 1996). This dose-response shift in the binding assay further supports the observed age-related subunit changes.

In addition, a direct measure of age-related subunit efficacy was obtained by examining the ability of GABA to flux Cl^- ions into microsac/synaptosome preparations from rat IC. GABA influx was significantly increased in samples from aged rat IC, confirming oocyte expression studies noted above (Caspary et al., 1999). These findings differ with previous whole brain synaptosome chloride uptake studies, which found reduced Cl^- uptake with aging (Concas et al., 1988). Age-related $GABA_A$ receptor changes may reflect a partial postsynaptic compensation for the significant age-related loss in presynaptic GABA release.

Taken together, these changes suggest a net down-regulation from normal levels of adult inhibitory function in the aged animals leading to a degradation of temporal and binaural coding in the aged IC.

Primary Auditory Cortex

Primary auditory cortex (A1) is generally considered necessary for perception and interpretation of the stimulus. Acoustic information reaching A1 has been extensively processed/coded at lower levels of the auditory neuraxis and generally no longer directly resembles the acoustic stimulus in time, intensity, or spatial relationship when observed in the discharge properties of A1 neurons (Schreiner et al., 2000; Nelken, 2004). A1 receives its major ascending projection from the medial geniculate body (MGB) projecting to A1 layer IV (Brodal, 1981; Winer and Lee, 2007). Inputs from the contralateral auditory cortex and nonauditory inputs impinge on layers II and VI with descending and intracortical outputs from layer V (Winer et al., 1998; Winer, 2006).

Functionally, A1 has a tonotopic map of the cochlea and a map of binaural properties with excitation and inhibition from the different hemifields represented on orthogonal stripes (Purves et al., 2007). Different regions of primary auditory cortex may be specialized for processing frequency combinations or may selectively code frequency or amplitude modulations (Schreiner et al., 2000). Acoustic processing in non-primary auditory cortex is not well understood, but is likely involved in higher-order processing of scenes and communication signals (Esser et al., 1997; Nelkin, 2004). Specifically, the ability to process temporal sequences of sound, similar to those found in communication signals, is lost following ablation of auditory cortex in cats and primates (Neff, 1977; Hupfer et al., 1977). Thus, without the auditory cortex, primates cannot discriminate conspecific communication sounds from each other (Hupfer et al., 1977). Increased neural noise in the aged cortex due to loss of GABAergic inhibition would likely impair normal adult coding functions.

Age-related Changes in Primary Auditory Cortex

Aging in mice with high frequency hearing loss showed tonotopic reorganization of A1 similar to that observed with small lesions of the cochlea in adult animals (Willott et al., 1993; Irvine et al., 2000). In rats, aging was associated with deterioration of temporal processing speed in A1 neurons, which was not present in lower structures such as the inferior colliculus and auditory thalamus (Mendelson and Ricketts, 2001; Lee et al., 2002; Mendelson and Lui, 2004). These electrophysiological studies suggest that aging is associated with degraded spectral and temporal properties of the auditory cortex, which might play a role in accurate processing of communication signals.

In a recent aging study in rat A1, Turner et al. (2005a) found that aging was associated with a number of changes in response properties. First, the distribution of receptive field shapes was altered in aging. A percentage of classic V/U-shaped, receptive fields (Fig. 5A), more commonly seen in young A1 neurons were replaced by more complex receptive fields (Fig. 5B) seen in aged A1 neurons. Second, more on-stimulus firing was seen for Complex receptive fields, which were generally associated with inhibited firing in young-adult Complex neurons. Third, receptive field maps from aged rats, regardless of shape, were less reliable across three successive repetitions of the same stimulus. Fourth, aging in Complex receptive field maps, but not V/U maps, was associated with an increased discharge rate in response to extracellular current pulse stimulation (Fig. 5C).

The two major divergent receptive field shapes clearly code sounds differently and are thought to convey different stimulus information (Turner et al., 2005a; Turner et al., 2005b), and are likely to have distinctly different projection patterns (Hefti and Smith, 2000; Hefti and Smith, 2003). V/U-shaped receptive field neurons are more closely associated with larger pyramidal cells that form the descending projections to the brainstem (Games and Winer, 1988; Winer et al., 1998; Winer and Prieto, 2001; Turner et al., 2005a). In contrast, neurons with the Complex maps are associated with smaller layer V pyramidal neurons thought to exhibit an intracortical projection pattern and are more likely to receive direct inhibitory inputs (Hefti and Smith, 2000; Hefti and Smith, 2003; Turner et al., 2005a; Turner et al., 2005b).

The relative reduction of V/U-shaped maps and increase in Complex maps could have significant implications for auditory processing in aged animals. The loss of the tips of the tuning curves with aging and hearing loss, in combination with a reduction in the more finely-tuned V/U-shaped receptive fields, would impact descending pathways. Similarly, the relative increase in the poorly tuned Complex receptive fields, as well as their reduced inhibitory response to sound, might serve to introduce more noise into A1 and cortical coding of sound in general. Together, receptive field changes observed in the two major types of aged auditory cortex neurons could translate into degraded coding of acoustic signals, especially in complex acoustic environments. The degree to which these electrophysiological changes seen in aging are associated with specific neurochemical changes related to GABA neurotransmission has been addressed in a series of studies. As noted above, age-related changes within the auditory brainstem included pre- and postsynaptic changes in the neurochemistry of the inhibitory neurotransmitters, GABA and glycine. As was the case for the inferior colliculus, there were significant age-related reductions in the level of both the message and protein for GAD in the rat A1 (Ling et al., 2005). The largest age-related changes in GAD message were found in A1 layer II (GAD_{67}: -40%, Ling et al., 2005). Although GAD message changes related to aging have been observed in other cortical regions, including hippocampus, protein changes in parietal cortex were small when compared to GAD protein changes in A1 (Fig. 6) (Stanley and Shetty, 2004; Ling et al., 2005). Taken together, the findings from A1 suggest a systematic age-related disruption in GABA neurotransmission that is associated with specific changes in how neurons in A1 code sensory signals.

Overview and Future Research

A search of the background literature for this review quickly revealed that little systematic neuroethological research has examined age-related hearing loss and its impact on survival in the wild. While the importance of auditory and visual acuity has been shown to have great survival value for a number of different species (Webster and Webster, 1971; Cumming, 1996; Anderson et al., 1998; Sisneros and Bass, 2005; Hollen and Manser, 2006), the impact of sensory aging on predator/prey relationships in a natural habitat has not been well studied. Many years ago, Webster and Webster (1971) demonstrated that altering the nature of the middle ear of the kangaroo rat changed hearing sensitivity in such a way that the adult kangaroo rats were more susceptible to predation by snakes in a restricted natural habitat. Similar studies designed to examine the impact of aging in the wild have not been carried out. Studies designed to examine the impact of aging, in species which survive into old age in the wild, are sorely needed. Additional sensory studies might investigate how compensatory plastic changes at one brain nucleus within a circuit would impact on other nuclei, and how homeostatic plasticity of aging might differentially affect changes in temporal reliability relative to changes in the place code. Future studies will need to model the impact of age-related changes across the entire ascending and descending auditory pathways mapping the plastic adjustments with both positive and negative consequences throughout the system. It is generally assumed that many mammalian species don’t survive into old age in the wild. However, few systematic aging studies have been done for most species in the wild. The present studies suggest that it is important to consider the impact of age-related sensory dysfunction on survival, rather than simply focus on the impact of aging on normal adult motor function.

Conclusions

Studies reviewed above suggest there is an age-related net down-regulation of glycinergic and GABAergic inhibition throughout the auditory central nervous system. Behavioral studies in humans and animals suggest 1) an age-related loss of GAP detection, a measure of temporal processing (Barsz et al., 2002); 2) an age-related loss of localization of sound in space (Warren et al., 1978; Brown, 1984) and 3) an age-related loss in the ability to discriminate complex communication signals (Gordon-Salant and Fitzgibbons, 1993; Frisina and Frisina, 1997; Gordon-Salant and Fitzgibbons, 2001; Hamann et al., 2004; He et al., 2007). Diminished dampening due to a decrease of tonic inhibition, reduced accuracy of binaural cues due to a loss of time-locked inhibition, and an increase in neural noise due to a loss of tonic inhibition, all observed in aged populations at different levels of the central auditory process, or help explain the significant auditory deficits observed in aged animals.

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List of Abbreviations

A1	primary auditory cortex
CN	cochlear nucleus
DCN	dorsal cochlear nucleus

GABA	gamma amino butyric acid
$GABA_A$R	$GABA_A$ receptor
GAD	glutamic acid decarboxylase
GlyR	glycine receptor (strychnine sensitive)
IC	inferior colliculus
LSO	lateral superior olivary nucleus
MGB	medial geniculate body
MNTB	medial nucleus of the trapezoid body
MSO	medial superior olivary nucleus
SOC	superior olivary complex
VCN	ventral cochlear nucleus

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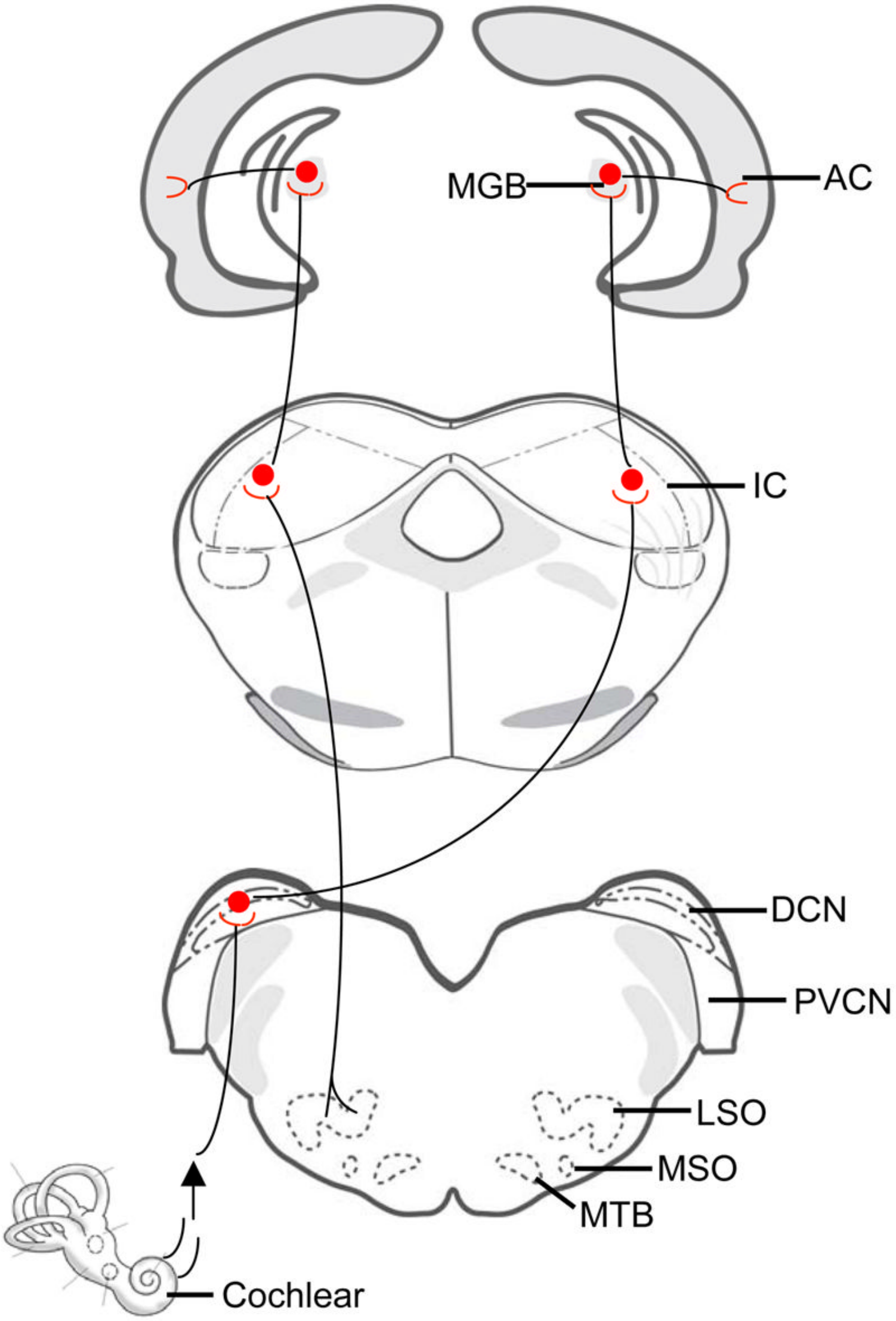

Fig. 1.

A schematic drawing of the ascending auditory pathway in rat. The auditory nerve carries signals from hair cells of cochlea into cochlear nucleus, where acoustic information projects to other brainstem auditory nuclei. Signals from ventral cochlear nucleus (VCN) travel to the superior olivary complex (SOC) which is comprised of three important subgroups (LSO, MSO, MNTB) involved in the localization of sound in space. The SOC sends projections primarily to the inferior colliculus (IC), while information from dorsal cochlear nucleus (DCN) projects directly to IC. From IC, auditory messages proceed to medial geniculate body (MGB, a subregion of thalamus), which in turn projects to primary auditory cortex (A1), located in the temporal lobe of cerebrum.

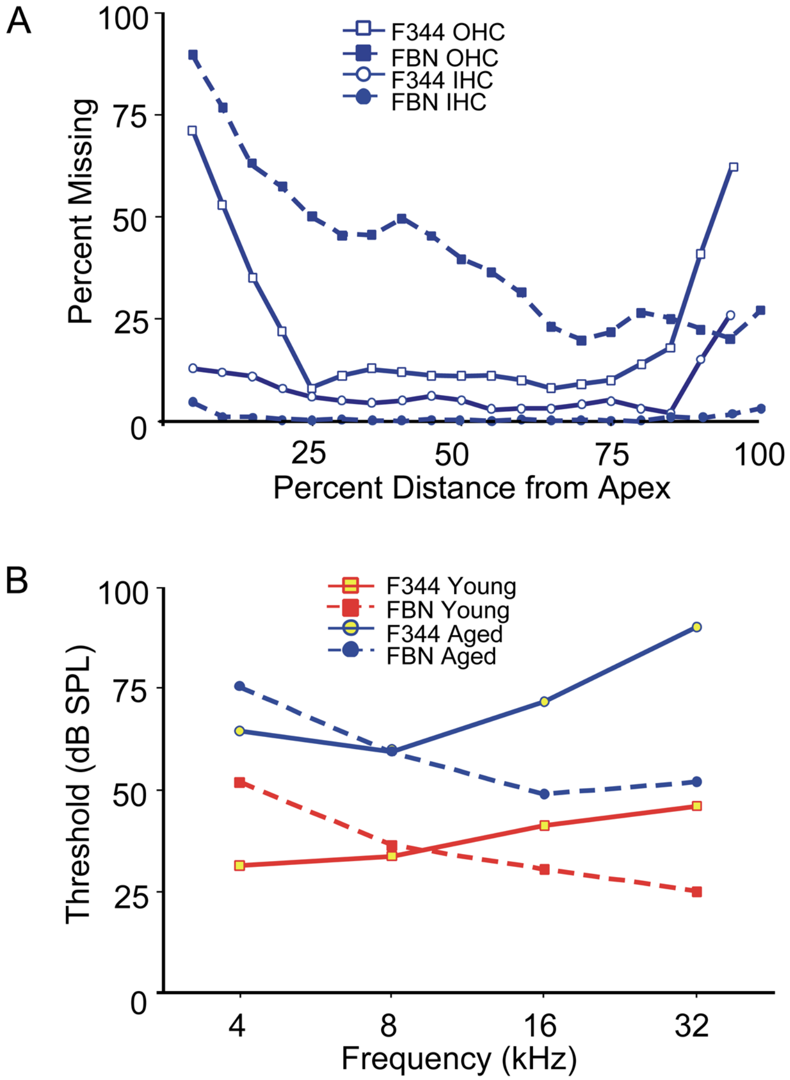

Fig. 2.

Comparison of age-related haircell loss and changes in auditory brainstem response (ABR) thresholds of FBN and F344 rats. (A) Cochleograms of aged F344 (24mos, n = 8) and aged FBN (32mos, n = 7) rats showing percent hair cells relative to young rats. The pattern of age-related hair cell loss was different between the two strains. Aged FBN rats lost few IHCs, while aged F344 rats displayed small IHC losses (< 10%) throughout the cochlea with pronounced increase in IHC loss near the basal end. F344 exhibited U-shaped loss of OHCs with the greatest losses (as high as 70%) confined to apical and basal turns. Low levels of OHC losses were observed throughout the F344 cochlea. FBN rats had significant OHC losses starting at the apex, which tapered to moderate losses in the basal regions. The pattern of OHC loss resembles those described by Keithley and colleagues (1992) for Brown Norway spiral ganglion cells. (B) ABR thresholds for young and aged F344 (3mos, n = 28; 24mos, n = 18) and FBN rats (4mos, n = 11; 32mos, n = 10) are shown. F344 rat thresholds were lower at 4 and 8 kHz than 16 and 24 kHz. FBN rats displayed a significantly different threshold pattern, with the lowest thresholds at higher frequencies (ANOVA, *$p < 0.01$). Aging affected both strains similarly with near parallel upward threshold shifts. For the FBN strains, age-related threshold shifts did not correlate with the apical pattern of hair cell loss. *Adapted from* Turner and Caspary, 2005.

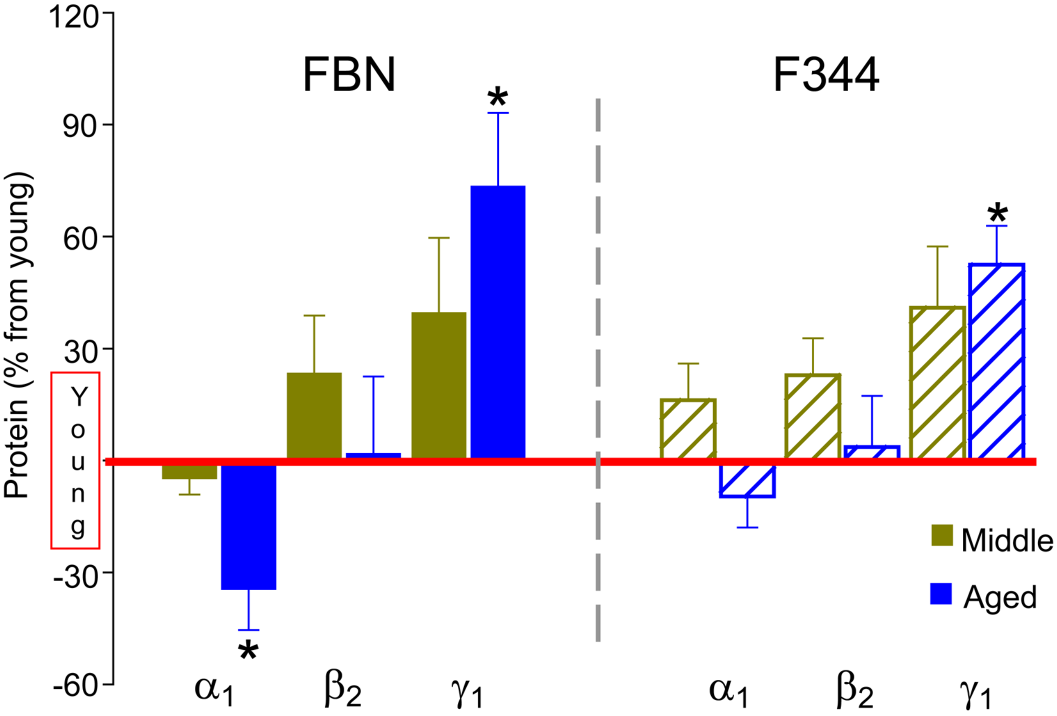

Fig. 3.

The effects of aging on protein levels of GABA$_A$ receptor subunit α$_1$, β$_2$ and γ$_1$ in the IC of FBN and F344 rats. The y-axis represents subunit protein percentage difference from young adult animals (3–4mos) of middle aged (18–20mos) and aged (28–32mos) in rat IC. Note that GABA$_A$ receptor γ$_1$ subunit protein significantly increased in aged rats of both FBN and F344. While significantly decreased α$_1$ subunit protein was found in the IC of aged FBN rats, it was not found in aged F344 rats (*$p < 0.05$). *Modified from* Caspary et al., 1999.

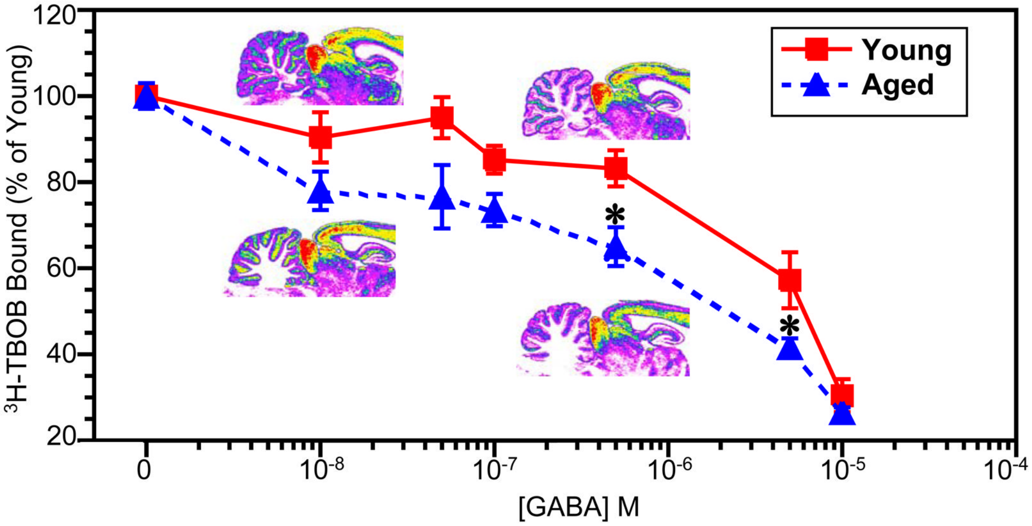

Fig. 4.

GABA (10nM - 10μM) modulation of ^{3}[H]-TBOB binding in the CIC of young and aged F344 rats. The dose-response curve is shifted to the left. These data have functional implications since the aged $GABA_A$ receptor must be more sensitive to GABA than the young $GABA_A$ receptor for the channel to be open allowing TBOB to bind to the picrotoxin binding site. *Modified from* Milbrandt et al., 1996.

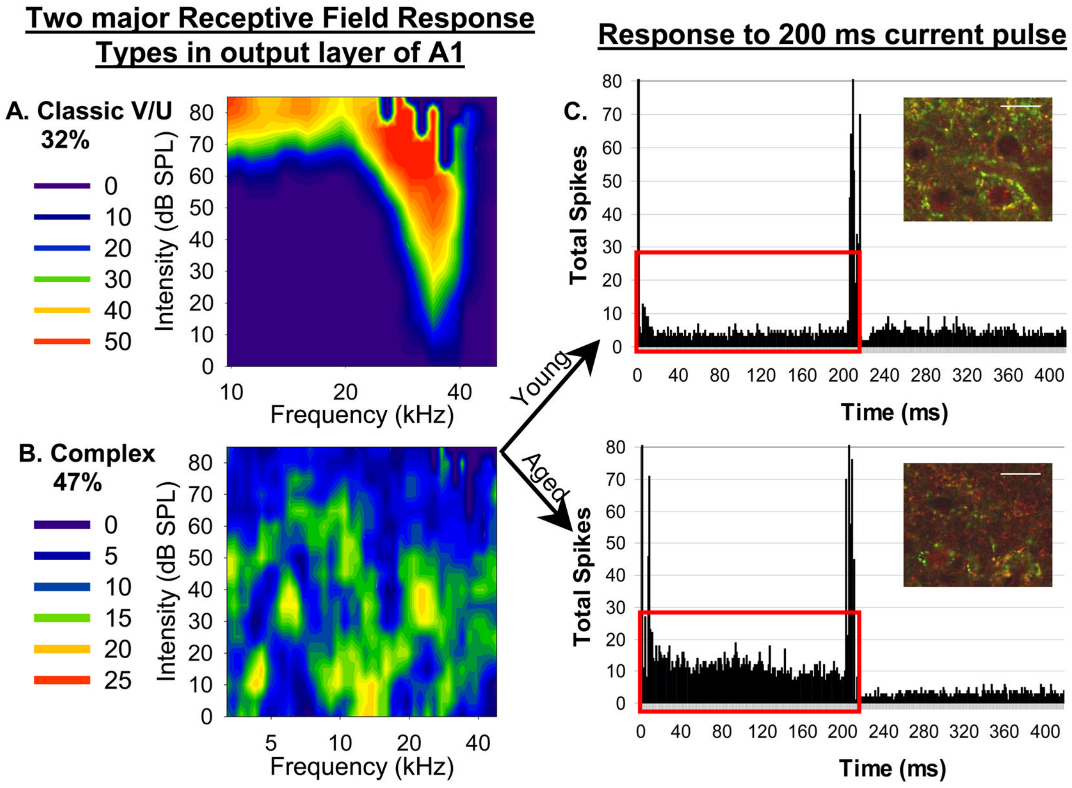

Fig. 5.

FBN rat layer V neurons exhibit two major types of receptive field maps; (A) 32% showed the classic V/U-shape with young and aged neurons showing similar responses to current pulse stimulation (not shown). (B) 47% of pyramidal neurons demonstrated a more Complex, dynamic response map. Aged complex receptive field neurons responded more vigorously than young neurons to 200ms current pulses, suggesting altered inhibitory control. Such increased excitability to current would be consistent with reduced GAD_{67} immunostaining around layer V (LV) somata (see insets, scale bar = 15 μm). *Modified from* Turner et al., 2005c.

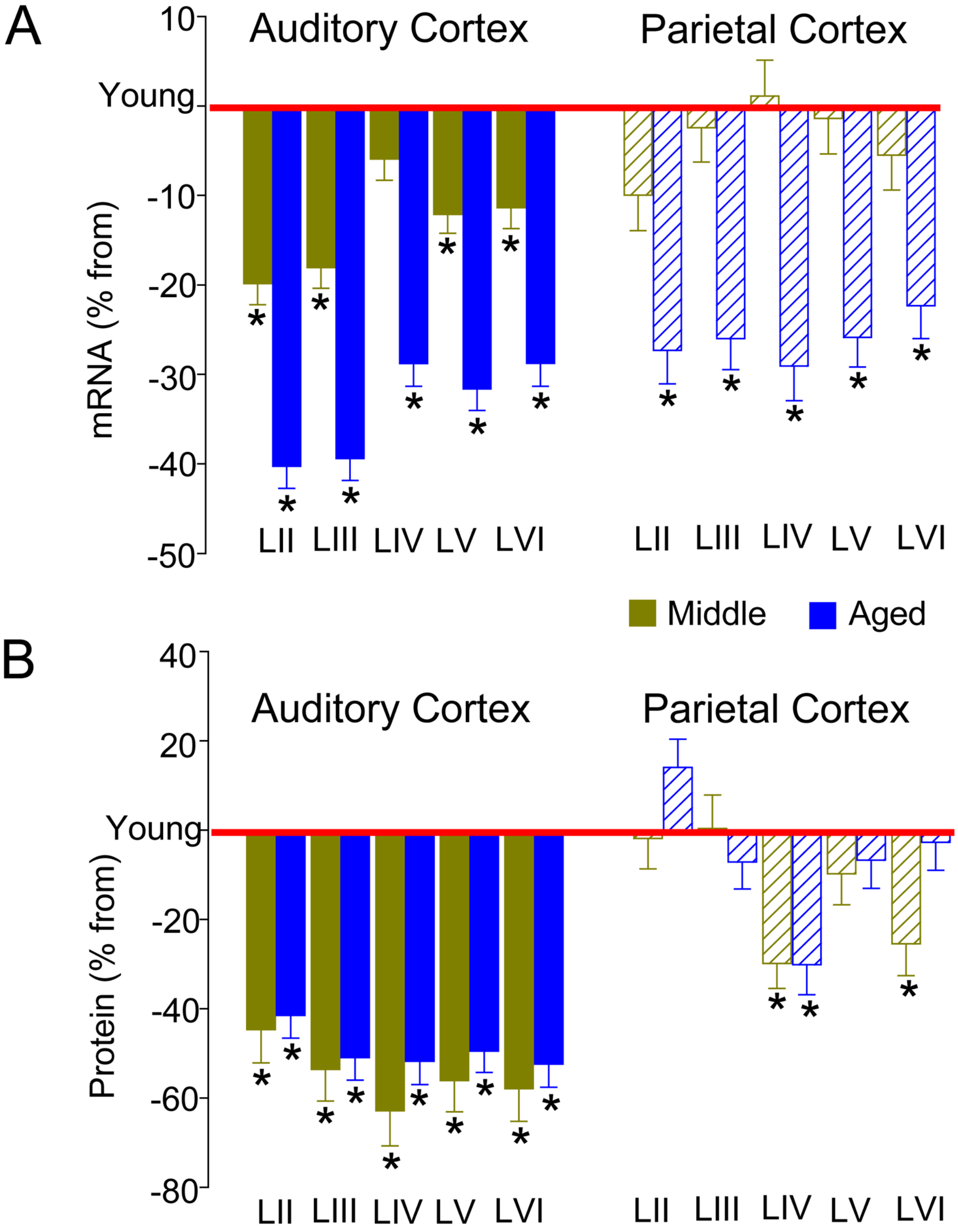

Fig. 6.

Age-related changes of GAD_{67} message and protein levels in A1 and parietal cortex (PtA) of middle- and aged FBN rats compared to young adult rats. Significant age-related changes in GAD_{67} message levels were seen across all layers of A1 in middle- and aged FBN rats (except layer IV of middle-aged A1). Significant GAD_{67} message decreases within PtA occurred only in the aged group (A). Whereas all layers of middle-aged and aged A1 showed significant age-related decreases in GAD_{67} protein, in PtA GAD_{67} protein levels showed no age-related decreases except in layer IV of middle-aged and aged, and in middle-aged layer VI (B; $*p < 0.05$). *Modified from* Ling et al. 2005.

Table 1

Age-Related inhibitory Changes in Central Auditory Systems

Structure	Function	Response	Reference
Cochlear Nucleus	Presynaptic	Lower Glycine Levels.	Banay-Schwartz et al., 1989a; Banay-Schwartz et al., 1989b Willot et al., 1997
	Postsynaptic	Altered glycine receptor subunit composition; Loss of Strychnine binding.	Krenning et al., 1998; Caspary et al., 2001; Milbrandt and Caspary., 1995; Willot et al., 1997
	Physiology	Loss of on-CF inhibition; Altered temporal responses.	Caspary et al., 2005; Caspary et al., 2006
Inferior Colliculus	Presynaptic	Reduced GAD level and its activity; Reduced GAB$_A$ level and its release.	McGeer& McGeer, 1975; Caspary et al., 1990; Gutierrez et al., 1994; Milbrandt et al., 1994; Raza et al. 1994; Milbrandt et al 2000
	Postsynaptic	Altered GABA$_A$ receptor subunit composition and quantitative receptor binding.	Gutierrez et al., 1994; Milbrandt et al., 1996; Milbrandt et al., 1997; Caspary et al., 1999
	Physiology	Loss of on-CF inhibition, altered SAM responses. Increased spontaneous activity.	Palombi and Caspary, 1996a; Palombi and Caspary, 1996b; Palombi and Caspary, 1996c; Shddock-Palombi et al.,2001; Walton et al., 1997; Walton et al., 1998; Willott et al., 1988
Auditory Cortex	Presynaptic	Reduced GAD levels (message and protein).	Ling et al., 2005
	Postsynaptic	Altered GABA$_A$ receptor subunit composition.	Ling et al., 2004
	Physiology	Altered response maps; Reduced reproducibility of response maps; Increased ability to drive complex units with current.	Turner et al., 2005a; Turner et al., 2005b; Mendelson & Ricketts, 2001