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## Age-Related Plasticity in Central Auditory Structures

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An increasing number of studies suggest that damage to the acoustic periphery caused by trauma or aging results in altered inhibitory neurotransmitter function at several levels of the central auditory pathway. Age-related and sound-induced insults to the cochlea result in changes to glycinergic circuits in the cochlear nucleus. Age-related pre- and post-synaptic GABA neurotransmission is altered in the inferior colliculus and is reflected by altered function and pharmacology in aged subjects. Insults to the auditory periphery have been shown to induce plastic changes at the level of auditory cortex. The present studies examined age-related, layer selective, changes in the GABAergic circuitry of rat primary auditory cortex (A1). Neurochemical changes indicate layer specific down-regulation of the GABA synthetic enzyme glutamic acid decarboxylase (GAD<sub>67</sub>) likely leading to an age-related decrease in GABA release. Postsynaptically, the subunit construct of the GABA<sub>A</sub> receptor in A1 appears altered by aging. A selective down regulation of the  $\alpha 1$  subunit message and protein was observed throughout A1 of aged rats. The GABA<sub>A</sub>  $\alpha 3$  subunit displayed an age-related, layer selective, up-regulation in both message and protein. Together these data indicate an age-related change in the subunit makeup of the GABA<sub>A</sub> receptor suggesting altered pharmacology and function in the aged animal. If findings in a rat aging model are confirmed in human studies, these novel GABA receptor constructs could provide a unique target for the development of future agents for treatment of certain forms of age-related hearing loss.

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## Age-related Changes in the Subunit Makeup of the GABA<sub>A</sub> Receptor in Rat Primary Auditory Cortex

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GABA has been shown to have a key role in processing of complex acoustic signals at many levels of the auditory neuroaxis. Primary auditory cortex (A1) is endowed with a rich network of GABAergic neurons and extrinsic GABA inputs throughout its layers. Normal adult inhibitory processing appears affected by altered peripheral input to the auditory pathway. Damage to the adult cochlea results in an increase in the amplitude of superthreshold cortical-evoked potentials. Aging, which results in a slow peripheral degradation of the auditory input into the brain, alters GABA and glycinergic systems in auditory brainstem. The present study examined age-related changes in the heteromeric layers of the rat A1. Results of Western blots of punches from A1 found an age-related decrease in the level of the  $\alpha 1$  subunit protein throughout A1. Cellular level *in situ* hybridization techniques and immunocytochemistry were used to determine mRNA and protein levels for three  $\alpha$  subunits (1-3) of the GABA<sub>A</sub> receptor. All layers showed a significant age-related decrease in  $\alpha 1$  mRNA levels, while protein  $\alpha 1$  levels showed a significant decrease in all layers except layer 5. Layers 3 and 6 showed significant age-related loss of  $\alpha 1$  mRNA; modest reductions in  $\alpha 1$  mRNA were seen in layers 2, 4 and 5. Age-related changes in  $\alpha 2$  expression levels were modest and mixed throughout the layers of A1. Age-related increases in  $\alpha 3$  mRNA levels were found in layers 3, 5 and 6 with modest increases in layers 2.  $\alpha 3$  protein levels were increased in layers 4 and 5 with modest changes in layer 2. These preliminary data are suggestive of age-related layer-specific subunit switches within the primary auditory cortex. Age-related layer-specific changes in GABA<sub>A</sub> receptor composition are suggestive of altered coding of acoustic signals and altered pharmacology in the A1 of elderly individuals.

Keywords: Auditory, Cortex, GABA<sub>A</sub>, Aging