

DECEMBER 18, 2007

Mammalian Protein Helps Calibrate Hearing

Researchers have established how a molecule in the inner ear of mammals helps fine-tune auditory perception. Their findings help explain how the brain communicates with the inner ear, reducing its response to sound in loud or distracting environments. Damage by loud noise or drugs underlies the most widespread form of sensorineural hearing loss as well as tinnitus, the debilitating perception of sound in the absence of an external source.

The findings were reported December 18, 2007, in the print edition of the *Proceedings of the National Academy of Sciences (PNAS)*, by a research team that included Howard Hughes Medical Institute international research scholar Belén Elgoyhen. The article was also published as an advance online publication in *PNAS* on December 12, 2007. Elgoyhen is at the Institute for Research on Genetic Engineering and Molecular Biology, CONICET, in Buenos Aires, Argentina. Other co-authors were from Tufts University, the University of Buenos Aires, the Massachusetts Eye and Ear Infirmary and the University of California at Los Angeles.

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— A. Belén Elgoyhen

Tiny hair cells in the cochlea of the inner ear transform the mechanical vibrations of sound into neural impulses that travel to the auditory center of the brain. However, nerve impulses can also travel in reverse, from the auditory center to specific types of hair cells called outer hair cells that fine-tune the machinery of the inner ear. This type of signaling makes up the cochlear efferent system, and inhibits sound response in the inner ear. Researchers suspect the system may serve several purposes, such as helping to improve signal detection in noisy environments, protecting the inner ear from noise damage, or decreasing auditory input when attention must be focused elsewhere.

Neurons in the cochlear efferent system communicate with the sensory hair cells by releasing the chemical acetylcholine. Specific receptors on the hair cells, known as the nicotinic cholinergic receptors, recognize acetylcholine.

When triggered, the acetylcholine receptors swing open to allow calcium to flow into the cell, thereby triggering changes in membrane resting potential. Elgoyhen and her colleagues have been exploring the structural composition of these receptors. Each receptor is composed of different structural modules, called subunits.

The receptors in each sensory system deal with different kinds of energy—electromagnetic, mechanical, or chemical. The receptor cells look different from one another, and they exhibit different receptor proteins. But they all do the same job: converting a stimulus from the environment into an electrochemical nerve impulse, which is the common language of the brain.

In earlier studies, researchers found that two main subunits, alpha-9 and alpha-10, make up the nicotinic acetylcholine receptor of hair cells. A central question, said Elgoyhen, was what was the role of the alpha-10 subunit? Test-tube experiments had shown that receptors composed of only alpha-9 subunits functioned perfectly well.

To explore the role of the alpha-10 subunit *in vivo*, Elgoyhen and her colleagues knocked out the gene for the subunit in mice and studied the effects on the structure and function of hair cells. Their analyses indicated abnormalities in both the electrophysiological function of the efferent system neurons and in cochlear function in the mice. Although the genetically altered mice hear normally, said Elgoyhen, they have deficits in processing sound that reflect specific defects in the outer hair cell efferent system. The researchers also saw abnormalities in the structure of the efferent synapses to the cochlea that hinted that these receptors may help ensure that synapses develop normally, she said.

With these experiments, we have demonstrated that the receptor really needs the alpha-10 subunit to drive inhibition of outer hair cell activity. So, this finding helps us better define the structure of this receptor.

Based on evolutionary analysis we propose that the alpha-10 subunit uniquely evolved a special role in mammals, even though the gene for alpha-10 exists in the genomes of all vertebrates, she said. So, this finding tells us that the alpha-10 subunit represents a special structure that is key to the abilities of the mammalian auditory system. In further studies, Elgoyhen and her colleagues are comparing the structure of the acetylcholine receptors in mammals and non-mammals, such as chickens, to understand differences in the properties of the receptor in diverse animals.