

Hearing Through the Din Receptors embedded in the ear's hair cells might explain mammals' selective hearing.

A CHICKEN WAITING TO CROSS A NOISY ROAD CAN'T BE blamed if it doesn't hear the fox sneaking up behind it. Chickens—and a host of other vertebrates—don't have as sophisticated hearing systems as mammals.

One protein makes the difference, says HHMI international research scholar A. Belén Elgoyhen. It's a component of a receptor in a part of the auditory system of mammals, called the efferent pathway, that modulates whether sounds reach the brain or are filtered out.

Basic sound detection is a one-way process that begins when sound waves strike the eardrum and jiggle hair cells in the cochlea of the inner ear. That jiggling generates neural signals that speed to the brain's auditory center, where they register as sound.

But really sophisticated sound processing in mammals also depends on efferent signals that travel in reverse, from the brain back to the cochlea. These signals control specialized, adjustable outer hair cells that can modulate sound signals traveling to the brain. The exact function of this feedback system largely remains a mystery. But researchers believe it enables mammals, including humans, to filter background noise so they can

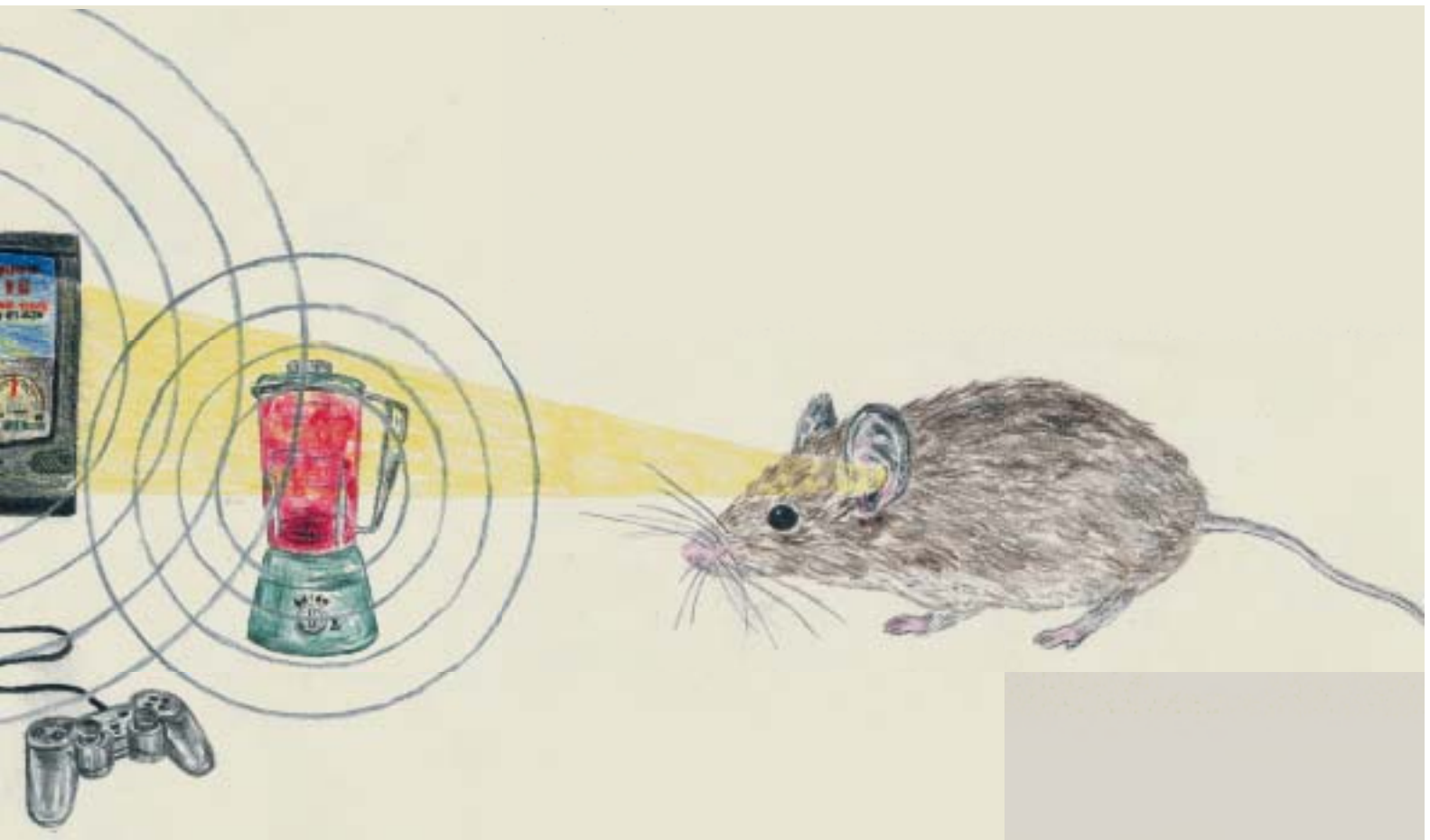
concentrate on relevant sounds such as hearing a knock at the door over the sound of music. The efferent system also may dampen loud sounds to protect ears from injury.

The efferent system's neurons control outer hair cells by launching bursts of the neurotransmitter acetylcholine at receptors embedded in the surface of these hair cells. These receptors latch onto the acetylcholine, which triggers a gush of calcium into the outer hair cell, inhibiting the cells' ability to modulate auditory output and dampen sound signals. So by adjusting the amount of acetylcholine it pumps out, the efferent system can change how the outer hair cells function, and how much they dampen sound.

In earlier work, Elgoyhen discovered that these “nicotinic acetylcholine receptors” are built of two basic protein components, the alpha-9 subunit and the alpha-10 subunit, which differ subtly in structure.

“We know these receptor subunits exist in all vertebrates; however, only the mammalian cochlea has this fine-tuning of outer hair cells,” says Elgoyhen, who is at the Institute for Research on Genetic Engineering and Molecular Biology, CONICET, in Buenos Aires, Argentina. “We believe that

Alex Robbins



mammals and nonmammals may have slightly different alpha-10 subunits that enables this tuning in mammals.”

In their latest study, Elgoyhen and her colleagues tackled the key question of whether the alpha-10 subunit is really critical to the receptor’s function. To their puzzlement, earlier test-tube studies had revealed the opposite—that even without the alpha-10 subunit, the receptor appeared to function normally.

So the researchers explored what would happen when they created “knockout” mice that had no alpha-10 subunit. They reported their findings in the December 18, 2007, *Proceedings of the National Academy of Sciences*.

Their first measurements of the physiological functioning of the basic machinery of the animals’ auditory system indicated that it functioned perfectly well. Then they conducted more subtle physiological tests that specifically measured whether the animals’ efferent auditory systems were working properly. To determine how the ears of the mice responded to different sound frequencies, the researchers inserted electrodes into the auditory nerves of the mice and placed delicate microphones next to the outer hair cells. Those tests revealed that, although the animals’ basic hearing was intact, the efferent systems in the

mice lacking the alpha-10 subunit were not fully functional at the electrophysiological level. The outer hair cells in those mice did not respond normally to bursts of acetylcholine from efferent neurons.

Establishing the physiological role of the alpha-10 subunit represents only the beginning of their explorations into its function, says Elgoyhen. Her lab has already started cloning the chicken versions of the alpha-10 and alpha-9 subunits.

“We are comparing the properties of the chicken receptor to the mammalian receptor,” she says, “to see if there is some functional difference between them that can tell us why this alpha-10 subunit uniquely evolved a special role in mammals compared with nonmammalian vertebrates.” What’s more, Elgoyhen and her colleagues plan to explore the more subtle hearing consequences of loss of the alpha-10 subunit and thus a fully functional efferent system.

“So far, we only know that without the subunit, the efferent system does not work,” she says. “Now, we are investigating the consequences at the level of behavior—whether the knockout mice show a difference in protection from sound injury or in attentional behavior.” ■ —DENNIS MEREDITH