Deaf mice have nearly normal inner ear function until ear canal opens

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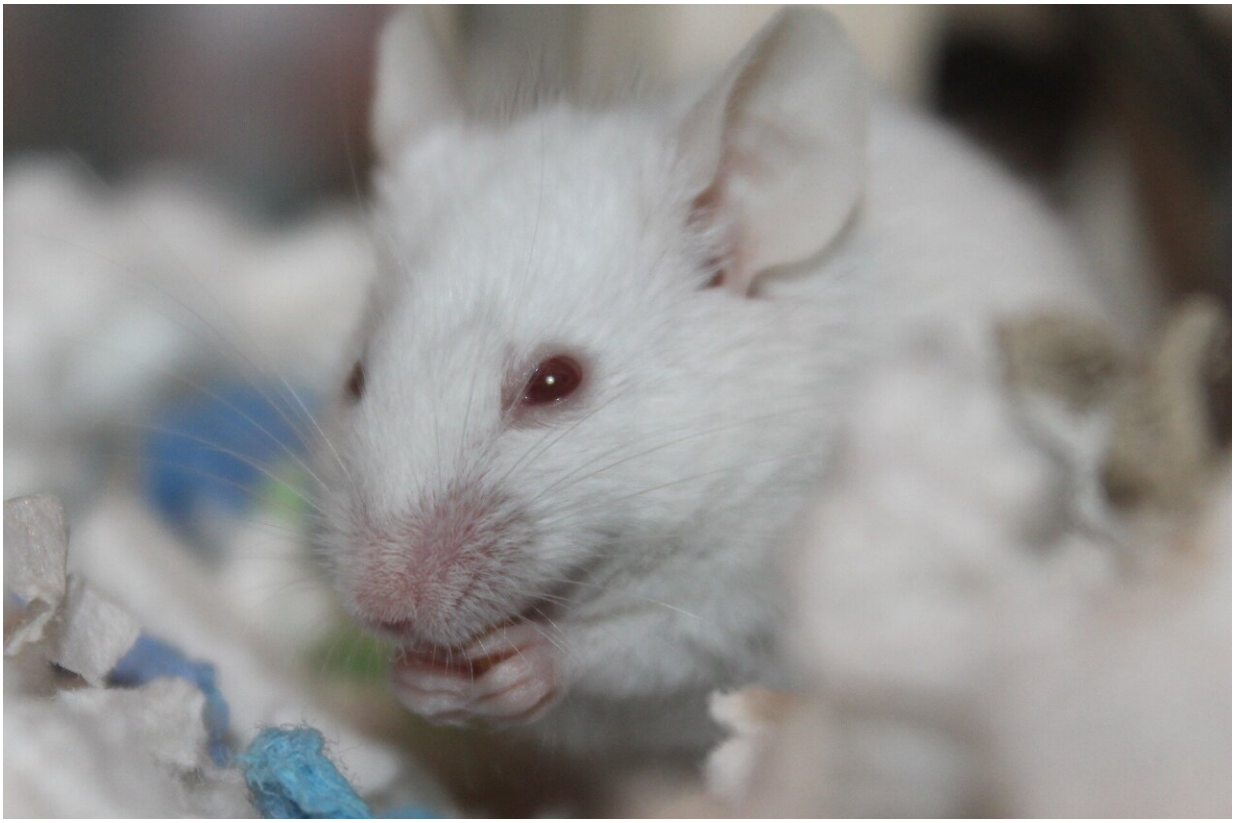

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For the first two weeks of life, mice with a hereditary form of deafness have nearly normal neural activity in the auditory system, according to a new study by Johns Hopkins Medicine scientists. Their previous studies

indicate that this early auditory activity—before the onset of hearing—provides a kind of training to prepare the brain to process sound when hearing begins. The findings are published June 27 in *PLOS Biology*.

Mutations in Gjb2 cause more than a quarter of all hereditary forms of hearing loss at birth in people, according to some estimates. The connexin 26 protein coded by the gene is in a family of proteins known as GAP junctions, because these proteins span the tiny gap between cells and form a kind of tube that connects two cells to trade ions, metabolites and other molecules that communicate or maintain an equilibrium.

This unexpected finding, according to investigators, suggests a molecular mechanism for the observation that people with this hereditary mutation respond well to cochlear implants, the electronic devices that are designed to mimic sound conduction in the inner ear and can improve hearing in those with severe hearing loss. According to the National Institutes of Health, about 118,100 cochlear implants were implanted in adults and 65,000 in children between December 2019 and March 2021.

The connexin 26 protein in the cochlea, the spiral-like structure in the inner ear, is highly enriched in supportive cells, which, like their name implies, provide structural and nutritional help to surrounding hair cells and auditory neurons.

Previous studies have shown that, without connexin 26, the cochlea fails to develop its normal shape and is incapable of amplifying sound-induced vibrations necessary for efficient sound detection. Despite this disruption to the cochlear structure, this research shows the cochlea is still capable of producing the "spontaneous" activity needed to shape brain development.

"Supportive cells are extremely important for tissues and organs," says

neuroscientist Dwight Bergles, Ph.D., the Diana Sylvestre and Charles Homcy Professor at the Johns Hopkins University School of Medicine. "The new study shows how critical they are for training the auditory system and getting it ready to process sound."

For the study, Bergles and Calvin Kersbergen, an M.D./Ph.D. candidate in Johns Hopkins' Medical Scientist Training Program, created a mouse model that lacked connexin 26 specifically in supportive cells in the cochlea.

By using external electrodes to measure electrical responses in the auditory nerve in response to tones or clicks, they found that mice lacking connexin 26 only in supportive cells of the cochlea were, indeed, deaf, demonstrating the crucial role of these intercellular channels in hearing.

However, Bergles and Kersbergen wondered if this change in supportive cells and shape of the cochlea would also disrupt spontaneous activity in younger mice, less than two weeks old, before their ear canal opens.

The researchers found that mice without connexin 26 still exhibit bursts of electrical activity in auditory neurons at nearly the same levels as young mice with intact connexin 26. Further investigation revealed that spontaneous activity in supportive cells was able to activate sensory hair cells in the inner ear, leading to normal neuronal activity in sound-processing areas of the brain.

"Even in the absence of connexin 26, we still find robust spontaneous activity in the cochlea in these young mice," says Bergles.

Bergles says there is now evidence that the role of supportive cells in this early period is to "train" the auditory system to respond to sound at certain frequencies. Since the ear canal isn't open yet, supportive cells

generate their own activity spontaneously to stimulate the mechanically sensitive hair cells in the fluid-filled cochlea.

"It's as if the cochlea is producing its own 'sounds' at this stage of development," Bergles says. "This practice may help the auditory neurons and circuits in the brain mature before the ear canal opens."

"It's like a baseball player in a batting cage, learning the basics of their swing and preparing to face the unpredictability of a real pitcher," says Bergles.

Finally, the researchers found that spontaneous activity in supportive cells of deaf mice halts once the ear canal opens. At the same time, because the mice can't process sound, their auditory neurons actually increase their sensitivity to sound.

This hypersensitivity to sound is similar to the phenomenon of hyperacusis, in which normal levels of sound can be painful. In humans, this hearing loss-induced hypersensitivity can also lead to constant ringing of the ears, called tinnitus.

Bergles says the research also suggests a molecular mechanism for why people with this hereditary mutation who receive cochlear implants early on tend to do better than those who receive them later.

"Spontaneous activity in supportive cells in the cochlea may provide the molecular evidence for empirical data showing better outcomes among people who have cochlear implants placed earlier in life," says Bergles.

The research team plans to study whether they can tap into the spontaneous activity pathway in supportive cells to treat tinnitus and other auditory conditions. Scientists Travis Babola and Patrick Kanold also contributed to this research.

More information: Kersbergen CJ, Babola TA, Kanold PO, Bergles DE Preservation of developmental spontaneous activity enables early auditory system maturation in deaf mice, *PLoS Biology* (2023). DOI: 10.1371/journal.pbio.3002160. journals.plos.org/plosbiology/ … journal.pbio.3002160

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