Unravelling the cochlea to understand hearing loss

Our sense of sound is central to how we understand and interact with the world around us, and its loss has profound effects on quality of life. Mark A. Rutherford, Assistant Professor in the Department of Otolaryngology, Division of Biology and Biomedical Sciences at Washington University in St. Louis is using pioneering tools to understand how we process sound at nanoscale levels. His work on the chemical glutamate sheds light not only on how we perceive sound, but also on how scientists could develop ways to prevent or reverse hearing loss.

Sound plays a major role in our interaction with the world around us. Our hearing ability enables us to make meaningful connections with other people through speech, allows us to experience rousing music and warns us of imminent dangers such as an approaching car or a burning building.

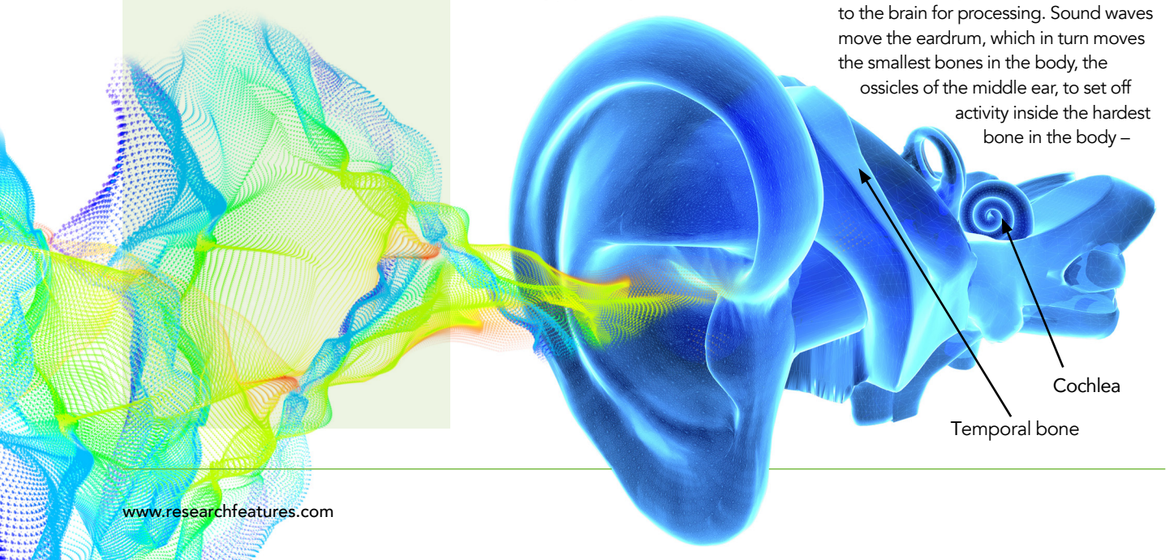
The World Health Organization estimates that 466 million people – including 34 million children – live with disabling hearing loss worldwide, a figure that is expected to rise to over 900 million by 2050. Around one third of people over 65 years old lives with disabling hearing loss, a condition that also disproportionately affects those living in low and middle-income countries.

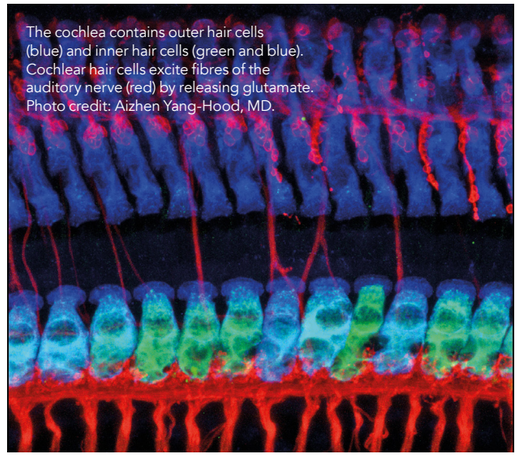
Whilst many deaf people live full and meaningful lives, some are isolated from everyday life, with their hearing loss affecting their ability to work and having a profound emotional and social impact. Deaf people are also more likely to be abused, but less likely to report abuse, due to struggles with communication and reliance on other people. Compounding this, people with hearing loss often struggle to access key support, including psychological services.

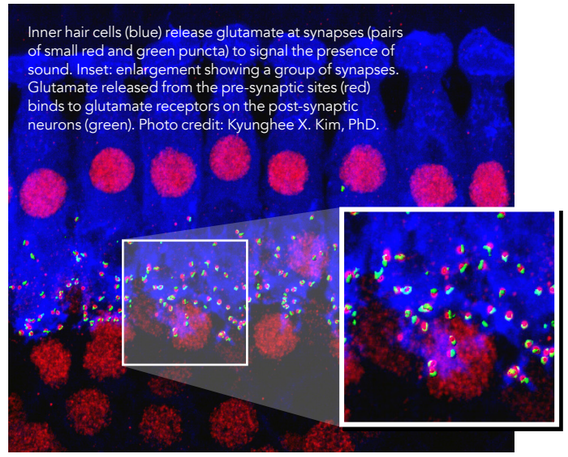
Hearing loss can occur as a result of age, genetics, or damage to the ear due to overexposure to sound. As life expectancy rises across the globe and our society ages, understanding the causes of age-related hearing loss becomes more pressing. Our modern world produces sounds with which our species did not evolve. Long-term exposure to even moderately loud sounds that are not immediately deafening may accelerate age-related hearing loss. Despite the profound importance of this sense, the cellular processes that underlie hearing are still not fully known, making it difficult to design treatments to help patients. Professor Mark Rutherford, an auditory neurobiologist in the Department of Otolaryngology at Washington University School of Medicine in St Louis, is an expert in the molecular processes that govern our sense of hearing; he studies the effects of age and excess noise on the intricate workings of the inner ear.

THE STRUCTURE OF THE INNER EAR

The human ear is made up of three parts, namely, the outer, middle and inner ear. The inner ear is central to regulating balance and is the site where sound is transformed into electrochemical signals, allowing sensory information to be sent to the brain for processing. Sound waves move the eardrum, which in turn moves the smallest bones in the body, the ossicles of the middle ear, to set off activity inside the hardest bone in the body – the temporal bone of the skull – where specialist cells of the inner ear known as hair cells reside. Hair cells are the primary sensory receptors in mammalian ears. They endow mechanical sensitivity to the vestibular organs (utricle, saccule, and canal) and the cochlea, a tiny structure named from the Greek for 'snail shell'. Each cochlear hair cell connects to 10–20 auditory neurons, each of which has a different sensitivity to sound. Central to the transmission of sensory information to the brain are the synapses that connect hair cells to auditory neurons. These tiny junctions allow electrochemical information to flow between hair cells and neurons, and they are at the heart of all we experience in our auditory lives. Each cochlea contains thousands of these synapses and auditory neurons. When an individual synapse is lost, the brain loses one line of information about sound. Humans are born with a given set and, unfortunately, like the hair cells and neurons that comprise them, these synapses do not spontaneously regenerate.




The cochlea contains outer hair cells (blue) and inner hair cells (green and blue). Cochlear hair cells excite fibres of the auditory nerve (red) by releasing glutamate. Photo credit: Aizhen Yang-Hood, MD.


Inner hair cells (blue) release glutamate at synapses (pairs of small red and green puncta) to signal the presence of sound. Inset: enlargement showing a group of synapses. Glutamate released from the pre-synaptic sites (red) binds to glutamate receptors on the post-synaptic neurons (green). Photo credit: Kyunghee X. Kim, PhD.

Ageing and excessive noise are linked to damage of hair cell synapses, leading to degeneration of neurons and hearing loss, but the mechanism of how this occurs is still unknown. Professor Rutherford's research is focused on characterising how sound is transduced by the cochlea and encoded as electrical signals transmitted to the brain in the auditory nerve, centring on the pivotal role of the neurotransmitter glutamate. The aim of this research is to discover how glutamate regulates the synapse under normal conditions and damages the synapse in the case of overexposure, so that researchers might learn how to protect cells from a type of damage associated with glutamate excitotoxicity.

GLUTAMATE

Glutamate is the predominant excitatory neurotransmitter in the nervous system, a chemical messenger that allows electrical signals to be translated across synapses from one neuron to another. Central to the work in the Rutherford laboratory is understanding how glutamate excites auditory neurons to send a signal to the brain, a digital signal known as a spike. Without glutamate there are no spikes, no information from ear to brain.

As life expectancy rises and our modern environments become increasingly noisy, understanding the interactions between noise-induced and age-related hearing loss becomes more pressing

The balance of glutamate is extremely important to normal hearing. Excessively loud sounds excite hair cells to release toxic amounts of glutamate, resulting in synapse loss and hearing loss in a process known as excitotoxicity. Interestingly, a sustained lack of glutamate as a result of genetic disorders can also lead to synapse loss. Rutherford and colleagues are studying the cellular and molecular processes that govern this glutamate-mediated balance between synapse survival and damage, focusing on how different glutamate-binding molecules (glutamate receptors) mediate cellular responses to high levels of glutamate, such as from loud noise, to cause damage.

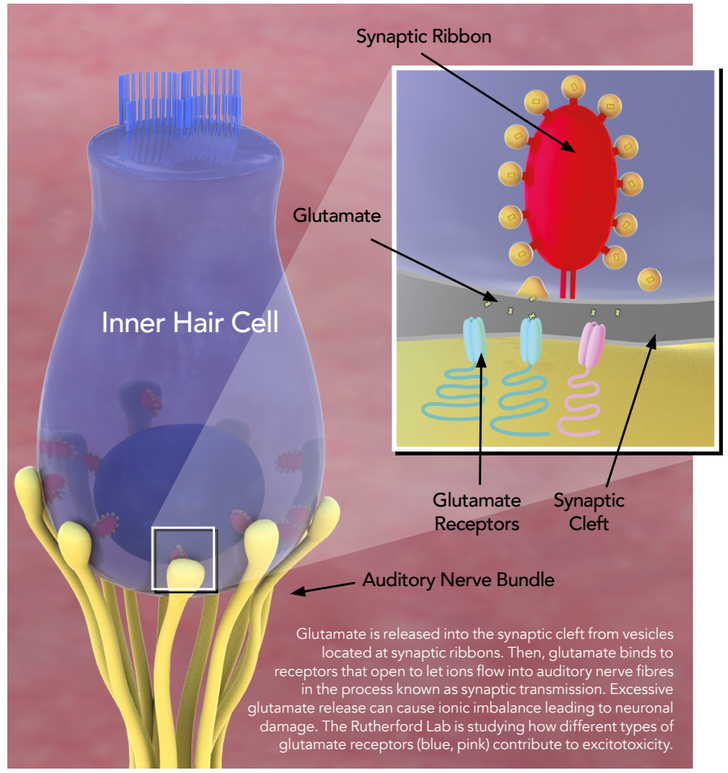
Professor Rutherford recently co-authored a study that offers fresh insights into how cochlear neurons degenerate. The study, published in the Journal of Neuroscience, identifies specific subtypes of glutamate receptors that mediate glutamate transmission at the hair cell synapse. Blocking these receptors, a type of calcium-permeable glutamate receptor, prevents cell swelling and synapse loss during an experiment that would normally be excitotoxic. This suggests that these receptors are key mediators of synaptic damage caused by excess glutamate. Together, the findings – made by studying zebrafish, bull frogs and rats – could help scientists develop approaches to protect the cochlea from excitotoxicity and resulting degeneration.

SHEDDING LIGHT ON SOUND CELLS

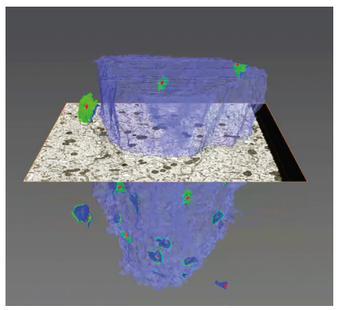
Professor Rutherford and colleagues

employ several pioneering techniques, including electrophysiology and immunohistochemistry, to study molecular processes underlying hearing and deafness. A recent project using laser scanning confocal microscopy allowed the team to characterise the molecular anatomy of ion channels in the auditory nerve as the mammalian cochlea acquired its sensitivity to sound during development.

Working with colleagues in the groups of Tobias Moser, MD and Stefan Hell, PhD at the Max Plank Institute for Biophysical Chemistry in Göttingen, Germany, the team has employed an exciting new form of light microscopy known as stimulation emission depletion (STED) to study the anatomy of synapses. Synapses are thought to be the smallest functional units in the nervous system. Indeed, they are smaller structures than can be resolved by conventional light microscopy. STED is a powerful technique that allows researchers to see even smaller structures, such as the individual components from which synapses are made. Professor Rutherford and colleagues have used this cutting-edge approach to study the structure and function of cochlear synapses in minute detail. In collaboration with Adish Dani, PhD at Washington University and now at the Tata Institute of Fundamental Research, Centre for Interdisciplinary Sciences in India, Professor Rutherford is employing another super-resolution microscopy technique for the first time in the inner ear called Stochastic Optical Reconstruction Microscopy (STORM). As science seeks answers to more complex questions, the need for technical specialisation across disciplines places value on national and international collaborations between investigators in different laboratory settings.



Glutamate is released into the synaptic cleft from vesicles located at synaptic ribbons. Then, glutamate binds to receptors that open to let ions flow into auditory nerve fibres in the process known as synaptic transmission. Excessive glutamate release can cause ionic imbalance leading to neuronal damage. The Rutherford Lab is studying how different types of glutamate receptors (blue, pink) contribute to excitotoxicity.



With James Fitzpatrick, PhD, and Matt Joens. PhD, at the Washington University Center for Cellular Imaging (WUCCI), the Rutherford Lab is using advanced three-dimensional electron microscopy techniques to reconstruct hair cell synapses. Photo credit: Shelby Payne, BS.

Professor Rutherford's work on glutamate excitotoxicity in the cochlea could open avenues for prevention of excitotoxicity, or for hearing loss therapies.

Auditory neurons have different levels of excitability, which allows us to recognise different levels of sound, to distinguish between the auditory signal and the background noise. As we age, we lose hair cells and auditory nerve cells, leading to permanent hearing problems and eventual loss that cannot be repaired, as these cells do not regenerate. However, under some conditions when the cells themselves are not fully lost, the synapses that link hair cells to auditory neurons may have the ability to regenerate after damage. By studying the conditions that lead to either irrevocable damage or damage that could be restored, the Rutherford lab is elucidating mechanisms by which synapses may be damaged, but also regained, before leading to permanent hearing loss.

FUTURE DIRECTIONS

Ultimately, Professor Rutherford's work to highlight glutamate excitotoxicity in the cochlea benefits not only our basic understanding of our hearing sense but could also help to open avenues for prevention of excitotoxicity, or for therapies for people who have experienced hearing loss. Key to this will be explaining why some neurons appear to be more sensitive to loud noises and glutamatergic damage than others. By understanding how age and excess noise impact on the inner ear, scientists will be in a better position to protect against and reverse impairment.

Behind the Bench

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Bio

From home in St. Louis to the Oregon trail, then to the Fatherland and back home again: Born in St. Louis, MO; College in Columbia, MO (University of Missouri), BA Nutritional Sciences; Graduate School at University of Oregon (Eugene, OR) with William M. Roberts in the Institute of Neuroscience (PhD, Biology); Postdoc with Tobias Moser in Goettingen, Germany; Faculty in Dept. of Otolaryngology at Washington University in St. Louis.

Research Objectives

Professor Rutherford aims to reveal the mechanisms of glutamate excitotoxicity in the cochlea that underlie noise-induced hearing loss.

Funding

- Dept. of Otolaryngology at Washington University
- Washington University Center for Cellular Imaging, Children's Discovery Institute
- National Institutes of Health, National Institute on Deafness and Communication Disorders
- Action on Hearing Loss
- McDonnell Center for Cellular and Molecular Neurobiology

Mentors

William M. Roberts, PhD (University of Oregon, Eugene) and Tobias Moser, MD (University of Goettingen, Germany).

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Personal Response

How might work on glutamate excitotoxicity inform the design of better quality hearing aids or cochlear implants?

When the ear is not working well, hearing aids can help by amplifying sounds. When the ear is no longer sensitive to sound, a cochlear implant can partly restore hearing function by direct electrical stimulation of the auditory nerve. In the case of a hearing aid, the amplified sound evokes glutamate transmission between hair cells and neurons. Work on glutamate excitotoxicity may help us preserve the working synapses for stimulation by the hearing aid. In the case of a cochlear implant, glutamate transmission is bypassed because that stage of signal transduction is defective. However, defective hearing function in one part of the cochlea (the high-frequency region in the basal cochlea) can be accompanied by intact hearing in the low-frequency region in the apical cochlea. In these cases where residual acoustic hearing co-exists in the same ear with a cochlear implant, it is critical to understand how cochlear implants might be prevented from evoking excitotoxicity at the remaining intact synapses. With Dr Craig Buchman, MD, chair of the Department of Otolaryngology at Washington University in St. Louis, we are trying to understand how to prevent degradation of residual acoustic hearing in cochlear implant recipients.