An investigation into cochlear HPA-like signalling

Professor Douglas Vetter and his group at the University of Mississippi Medical Centre are challenging the status quo of cochlear protection systems in the ear. Their research provides novel insights into the mechanisms underlying cochlear protection against noise-induced hearing loss and the associated structural damage by suggesting the presence of an endogenous ‘cocktail stress axis’.

It is currently unknown how the inner ear protects itself from day to day acoustic insults. This is an important problem because mammalian cochlear hair cells (the sensory cells which convert acoustic pressure variations into electrical impulses used by the nervous system) can be lost following exposure to, for example, intense sound. Because they do not regenerate in mammals (including humans), this can lead to permanent hearing loss.

Hearing loss can be congenital, related to ageing, or acquired. The work of Douglas Vetter and colleagues focuses on the latter. Acquired hearing loss most commonly arises from noise exposures, viruses, reactions to chemicals or drugs and can be classified into three categories based on how hearing sensitivity, measured as threshold of hearing, is affected.

Threshold shifts

Perhaps the most well-known form of hearing loss is a permanent loss of hearing that manifests as a permanent threshold shift (PTS). This can be a loss of hearing sensitivity to a specific range of frequencies, possibly caused by exposure to specific sounds, or loss of overall sensitivity, often caused by exposure to certain chemicals or drugs.

In contrast, temporary threshold shifts (TTS) result in recovery of all or some hearing ability. There are two types of TTS; the first is a temporary reduction of hearing sensitivity which then returns over time. The best example of this is buzzing ears experienced after a loud concert, which is usually back to normal the next day. The second form of TTS was only recently identified in animal models of hearing loss and is a much more serious issue. This is TTS with synaptopathy (damage to the nerve fibres) or ‘hidden hearing loss’ as recently described by Sharon Kujawa and Charlie Liberman of the Mass. Eye and Ear Infirmary. TTS with synaptopathy may first present as typical TTS, but the ability of the inner ear to process more intense sounds is compromised.

The reason for this can be explained by examining the different types of auditory nerves that contact the sensory hair cells of the cochlea. One type of nerve fibre is easily turned on. Their connections with hair cells detect low intensity sounds that we respond to. They therefore, transmit “threshold” information, detection of very faint sounds, to the brain. They are also spontaneously very active and are therefore termed ‘high spontaneous rate low threshold fibres’. However, as sound intensity increases, the low threshold fibres slowly lose their ability to increase activity and transmit neural codes of ever-increasing intensity to the brain. This is where the second fibre type comes in. The second type of nerve fibre is the ‘low spontaneous rate of high threshold fibres’. These are not turned on by the first hint of sound but are activated by a more intense sound. They add information to the low threshold fibres output of the cochlea headed to the brain by signalling that higher intensity sounds are being detected beyond the levels that can be signalled by the low threshold fibres. By working together, these two types of nerve fibre allow the ear to detect sounds ranging from 0dB (threshold) to 120dB (pain-inducing sound), equivalent to detecting sounds 1012 times more intense than threshold, or from near-total silence to the sound of a jet engine at close range. However, in hidden hearing loss, the high threshold fibres permanently loose connection with the hair cells, thus compromising our ability to hear louder sounds. With the loss of contact between the hair cells and the high threshold fibres, there is an inability to distinguish sounds in the presence of a noisy background. In people, this could also translate to degradation of speech intelligibility.

The current work of Douglas Vetter’s group is to look at TTS without synaptopathy, and ask the question “what protects the inner ear from always losing the high threshold fibres; what prevents non-synaptopathic TTS from progressing to TTS with synaptopathy?”

Existing theories

In order to appreciate the paradigm shift which Prof Vetter suggests may underlie cochlear protection, it is important to examine the existing knowledge on protection from noise-induced hearing loss. While a number of models of cochlear protection have been described, two main mechanisms have historically been proposed. The first is the olivocochlear system (a component of the auditory system involved in controlling the mechanical state of the cochlea) provides protection against acoustic injury. The second is the hypothalamic-pituitary-adrenal (HPA) axis, which is most well known as being the central stress response system, linking the central nervous and endocrine (hormone) systems together. However, the efficacy of these mechanisms in protecting the cochlea remains controversial.

There is a local inflammatory signalling system in the ear. Previous work has shown that immune responses occur in the inner ear following noise exposure to intense sound. A cochlear protective signalling system should act in an anti-inflammatory manner to regulate these responses that, unchecked, can damage cellular elements of the inner ear much as inflammatory can damage nerve cells and their processes in diseases such as Multiple Sclerosis.

New discoveries

Vetter’s team has described a family of proteins that represent a previously unknown cochlear signalling system. This system uses corticotropin releasing factor (CRF) that Vetter’s team identified to be in the cochlea, as the initial signal which ultimately results in the release of steroid hormones from cells within the cochlea. Interestingly, this includes cochlear expression of all the major stress-response proteins that are involved in the in vivo stress response.

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Vetter and colleagues have shown that ablation of the CRF receptor CRFR1 in mice produces a mouse with elevated baseline hearing thresholds—a PTS. Ablation of a related CRF receptor, the CRFR2 receptor, produces a mouse with vastly greater hearing loss resulting from noise exposure. This suggests that CRF plays a role in protecting the cochlea from insult. Additionally, exploring cochlear CRF signalling highlights a potential role for cochlear support cells, an understudied, enigmatic set of cells that far outnumber sensory hair cells and neurons.

Moving away from the current models of cochlear protection, which are focused on the cochlea itself, which takes time to respond to a challenge, is where Vetter's idea of CRF-based signalling comes in, which seemingly occurs between the support cells of the cochlea, rather than focusing only on the hair cells and auditory neurons. In this way, the cochlea acts as an organ and not simply as a collection of specialised sensory cells. If this is the case, then the cochlear CRF-based system, equivalent to the HPA-axis, may be critical to protecting the cochlea from insult. Exploring cochlear CRF signalling highlights a potential role for cochlear support cells, an understudied, enigmatic set of cells that far outnumber sensory hair cells and neurons.