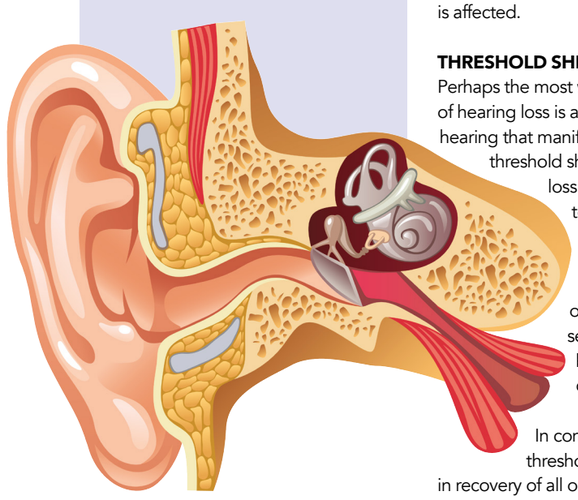
An investigation into cochlear HPA-like signalling

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 'cochlea 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 the 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 fibre'. 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 fibre 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 10^{12} 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 that 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.

CLASSICAL HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

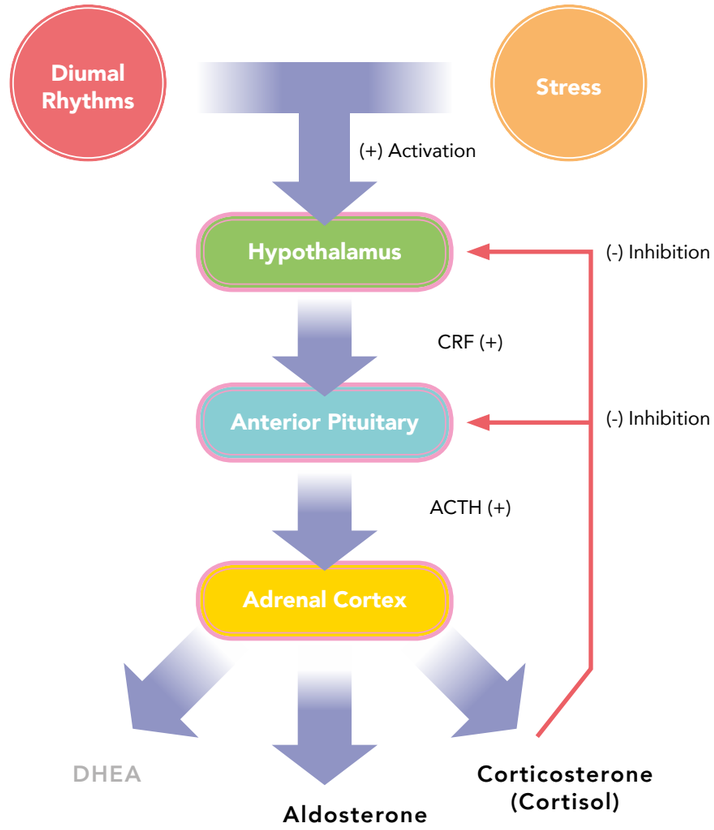


FIGURE 1: The classic hypothalamic-pituitary-adrenal (HPA) axis is a distributed system that requires the coordinated function of numerous organs. HPA signalling originates with various activities in the brain signalling to the CRF neurons of the hypothalamus. These cells in turn signal cells in the pituitary that cleave a precursor molecule into numerous bioactive molecules, one of which is adrenocorticotropic hormone (ACTH). ACTH is released into the blood system and activates its receptor (MC2R) in the adrenal cortex, where it induces production and release of corticosterone (in rodents, cortisol in humans). Corticosterone is secreted into the blood supply for distribution throughout the body. Other steroid hormones produced by the adrenal gland include aldosterone and dehydroepiandrosterone (DHEA, although this is not produced in the rodent adrenals and is therefore greyed out).

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 inflammation can damage nerve cells and their processes in diseases such as Multiple Sclerosis.

Vetter suggests that the cochlea should be thought of first as an organ like any other, but with a specialisation being the ability to encode sound.

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

Paracrine CRF signalling could release hormones

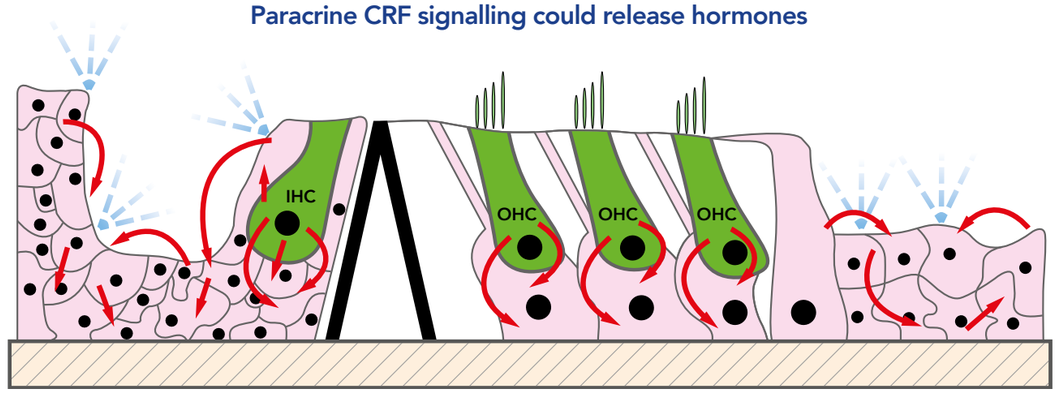


FIGURE 2: Unlike the HPA axis, the cochlear HPA-equivalent signalling system is wholly contained within the cochlea itself. Support cells (pink) that surround the hair cells (green) express both CRF and the CRF receptors required to detect CRF release. The support cells are actually composed of numerous different cell types, but all of them seem to serve the same function as the full HPA axis, as indicated by their pink colour corresponding to the pink outline of the individual HPA axis elements represented as boxes in Fig. 1.

signalling molecules of the HPA axis, suggesting that there is a system in the cochlea molecularly and functionally equivalent to the HPA-axis. This isn't unique to the cochlea. There have also been HPA-like systems described in the skin and retina.

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 than normal hearing sensitivity, but which is also much more susceptible to noise-induced hearing loss. This suggests that CRF signalling through the two receptors acts as a complementary mechanism to ensure a balance is maintained between good hearing and protection against hearing loss resulting from noise exposure.

In cochlear CRF signalling, hair cells express CRF, whilst the majority of support cells express both CRF and these CRF receptors, suggesting that the target for CRF-mediated signalling from hair cells is support cells, which then activate neighbouring support cells much as a relay runner passes the baton to the next runner. The advantage of this proposed 'cochlear stress axis' is that because it is contained within the cochlea itself, there would be no delay between encountering an excessively loud noise, and the activation of protective mechanisms that could include anti-inflammatory signalling. This is in contrast to the previous theories discussed above, which focuses on feedback mechanisms outside the cochlea itself, which takes time to respond to a challenge.

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.

IMPACT

The cochlea must have an innate ability to protect itself, ideally without waiting for feedback from the brain or HPA axis, and to prevent sound, chemical, age-related or trauma-related hearing loss. Vetter and colleagues suggest that the cochlea should be thought of as any other typical organ, but with a specialisation being the ability to encode sound. This 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. 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 cochlea protection is required to not only advance understanding of natural modes of protection but also to potentially uncover novel therapeutic targets which could be useful in alleviating some forms of cochlear dysfunction or damage caused by noise exposure.

Behind the Research

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Research Objectives

Professor Vetter and his collaborators' research explores a newly discovered biological system that may protect the inner ear against noise-induced damage with the expectation that a complete knowledge of this system may reveal new drug targets for future therapeutic treatments against cochlear injury.

Detail

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Bio

Douglas Vetter received his PhD in Biobehavioural Sciences (neuromorphology) from the University of Connecticut, Storrs in 1992. His research interests include the mechanisms by which synapses form and undergo structural plasticity, what role early maturational processes such as peripheral spontaneous activity play in setting up mature CNS pathways, and mechanisms underlying endogenous systems of protection involved in maintaining synapses in the face of challenge (metabolic, physical injury, etc.).

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Collaborators/Mentors

- Graduate School Mentor – Enrico Mugnaini, Univ. Connecticut
- Postdoctoral Mentor – Steve Heinemann, The Salk Institute for Biological Studies
- Kathleen T. Yee, Assist. Prof., Univ. Mississippi Medical Center
- Christine Graham, Vidya Murthy, Sevin Turcan, Julian Taranda, students in the Vetter lab, Tufts Univ. School of Medicine, and Johnvesley Basappa, a postdoctoral fellow in the Vetter lab, Tufts Univ. School of Medicine

References

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http://www.douglasvetter.com/

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Personal Response

What is the advantage of the cochlea locally releasing steroid hormones if they are already being released by the HPA-axis?

"Systemic steroids play a role in cellular-level time-keeping. In tissues outside the adrenal gland (the source of systemic steroid release) that produce their own steroid hormones, systemically delivered steroids reset the clock of their cells every 24 hours. We believe that this reset of the clock in the cochlea is the main role of systemic steroids. It is already known that the time of day of noise exposure can have significant impacts on the severity of noise-induced damage. We also think that endogenous cochlear release of steroids is vital for modulating inflammatory responses following intense noise exposure. Thus, the ability to mount a coordinated, fast response is made possible first by the clock reset, but once reset, the cochlear stress-response system is left to function autonomously until the next reset. With exposure to loud sounds, the systemic release of new steroids is useful for adding to the protection of the cochlea, but it is the cochlear-based steroid signal that initiates the protective signalling cascade."