An earful of physiology

G.D. Housley, Department of Physiology, and Translational Neuroscience Facility, School of Medical Sciences, UNSW, NSW 2052, Australia.

The field of inner ear physiology is a cornerstone of otology, audiology and vestibular therapy, biotech development of auditory prostheses, and hearing therapeutics. My perspective has been gained from engagement with comparative electrophysiology to resolve modulation of neurotransmission of the hearing and balance organs, and studies leveraging molecular physiology to elucidate processes driving neurodevelopment of the cochlea and establishment of electrochemical homeostasis which maintains hearing across a lifetime. Study of purinergic signalling at the cellular level opened a window into how the cochlea safely sustains hearing at high sound levels. This work benefitted from broad collaborations and use of transgenic mouse models. The observation that the $P2X_2$ receptor knockout mouse fails to develop temporary threshold shifts when exposed to moderate noise for many minutes to hours, led to a paradigm shift, where, evidently, the normally seen reversible loss of hearing following noise reflects not pathophysiology, but rather an intrinsic physiological process where noise-evoked release of ATP by the cochlear tissues activates $P2X_2$ receptor type ATP-gated ion channels in cochlear epithelial cells, including hair cells, that suppresses sound transduction (Housley *et al.*, 2013). It is likely that this extends to the dynamics of human hearing with noise exposure. In the absence of purinergic adaptation, the cochlea is vulnerable to damage from sustained environmental noise, and the P2X2 knockout mice, and humans with loss of function single nucleotide polymorphisms in the *P2rX2* gene encoding these ion channels, show accelerated hearing loss with aging (Yan *et al.*, 2013). This purinergic adaptation beautifully complements the rapid dynamic adaptation of sound transduction mediated by the brainstem - derived olivocochlear efferent innervation of the cochlear outer hair cells. This efferent feedback circuit enables binaural balancing of hearing that is central to unmasking sounds in noise, sound localization, and protection of sound transduction. Insight into the sensory drive for this feedback control has come from analysis of the peripherin knockout mouse. Here, the absence of expression of the type III intermediate filament peripherin by the type II spiral ganglion neurons which exclusively innervate the outer hair cells, produces a phenotype where these type II sensory fibres are disrupted and contralateral suppression is absent; that is, noise presented to one ear fails to reduce sound transduction by the outer hair cells in the opposite ear (Froud *et al.*, 2015). This model can inform how the brain is able to dynamically filter the auditory coding from the cochlea. Clinical translation stemming from developmental neurobiology research has engaged with neuro-engineering, leading to development of Bionic array Directed Gene Electrotransfer (*BaDGE*™) for targeted cochlear expression of naked DNA gene constructs encoding neurotrophins. This drives regrowth of the spiral ganglion neurites towards cochlear implant electrodes; closing the ‘neural gap’ and enhancing the ‘Bionic Ear’ (Pinyon *et al.*, 2014).

Froud, K., Wong, A., Cederholm, J., Klugmann, M., Sandow, S., Julien, J.P., Ryan, A. and Housley, G. (2015). Type II spiral ganglion afferent neurons drive medial olivocochlear reflex suppression of the cochlear amplifier. *Nat Commun*, **6,** 7115.

Housley, G., Morton-Jones, R., Vlajkovic S., Telang, R., Paramananthasivam, Y., Snguanwongchai, P., Khakh, B., Cockayne, D., Thorne, P. and Ryan, A. (2013). ATP-gated ion channels mediate adaptation to elevated sound levels. *Proc Natl Acad Sci U S A*, **110,** 7494-9.

Pinyon, J., Tadros, S., Froud, K., Wong, A., Tompson I., Crawford E., Ko, M., Morris, R., Klugmann, M. and Housley, G. (2014). Close-field electroporation gene delivery using the cochlear implant electrode array enhances the bionic ear. *Sci Transl Med*, **6,** 233ra54.

Yan, D., Zhu, Y., Walsh, T., Xei, D., Yan, H., Simaci, A., Fujikawa, T., Wong, A., Loh, T., Du, L., Grati, M., Vlajkovoic, S., Blanton, S., Ryan, A., Chen, Z., Thorne, P., Kachar, B., Tekin, M., Zhao, H., Housley, G., King, M. and Liu, X. (2013). Mutation of the ATP-gated $P2X_2$ receptor leads to progressive hearing loss and increased susceptibility to noise. *Proc Natl Acad Sci U S A*, **110,** 2228-33.

---

* *BaDGE*™ is a registered trademark of UNSW Innovations and is linked to patent filings around somatic cell gene delivery using array-based electric field focusing.