This Week in The Journal

Distorted Tonotopy after Noise-Induced Hearing Loss

Satyabrata Parida and Michael G. Heinz

(see pages 1477–1490)

Sounds entering the ear vibrate the cochlear basilar membrane, activating inner hair cells, which excite auditory nerve fibers. Different sound frequencies (pitches) cause maximal vibration at different locations along the basilar membrane, producing a tonotopic map in which auditory nerves innervating different locations respond most strongly to a particular sound frequency, called their characteristic frequency. Importantly, natural sounds comprise multiple frequencies, and thus vibrate multiple points along the basilar membrane.

Outer hair cells amplify local vibration of the basilar membrane, increasing sensitivity to quiet sounds, while dampening nearby vibrations and sharpening frequency tuning of auditory fibers. Exposure to loud noise or certain toxins damages outer hair cells, increasing auditory thresholds, broadening tuning curves, and altering cross-frequency interactions. Hearing aids can compensate for increased thresholds but not for changes in tuning, and hearing-aid wearers typically continue to have difficulty understanding speech in noisy environments (Lesica, 2018, *Trends Neurosci* 41:174). This indicates that speech comprehension in noise relies on factors other than auditory threshold. Remarkably, however, few studies examining how hearing loss affects sound encoding have used natural speech in noise as the auditory stimulus. By using such stimuli, Parida and Heinz discovered that gross distortion of tonotopy is the most important contributor to impaired encoding of speech in noise in chinchillas with noise-induced hearing loss.

Noise exposure greatly altered responses of auditory fibers to both vowels and consonants in a spoken sentence. Normally, auditory fibers are driven most strongly by stimulus features with frequencies closest to the fiber's characteristic frequency. In noise-exposed chinchillas, however, low-frequency features were overrepresented,

even by fibers with much higher characteristic frequencies. Meanwhile, high-frequency features, which are most informative for speech comprehension, were underrepresented. These effects were exacerbated in the presence of speech-shaped noise.

Importantly, linear mixed-effects modeling revealed that reduction in the ratio between fiber responses at the characteristic frequency and at much lower frequencies—a measure of distorted tonotopy—was the major factor contributing to degraded neural representations of speech. In contrast, broadening of tuning curves had minimal effect on speech representation. Therefore, distorted tonotopy may be a major cause of speech comprehension deficits in individuals with noise-induced hearing loss.

Loss of presenilin (top) causes ApoE (red) to accumulate in the nucleus (cyan) of fibroblasts. Normal cytosolic expression is rescued by reintroducing wild-type presenilin (middle), but not by expressing an AD-linked mutant form of presenilin (bottom). See Islam et al. for details.

Interaction between Two Genes Linked to Alzheimer's Disease

Sadequl Islam, Yang Sun, Yuan Gao, Tomohisa Nakamura, Arshad Ali Noorani, et al.

(see pages 1574–1586)

Alzheimer's disease (AD) is characterized by cognitive decline accompanied by extracellular accumulation of β -amyloid ($A\beta$) peptides in the brain. $A\beta$ is generated by sequential cleavage of amyloid precursor protein (APP) by β - and γ -secretases. Notably, mutations in APP or presenilin, a

component of the γ -secretase complex, cause autosomal dominant forms of AD. But, the vast majority of AD cases are sporadic, and the strongest genetic risk factor for sporadic AD is possession of the $\epsilon 4$ allele of apolipoprotein E (ApoE). ApoE is the primary carrier of lipids in the brain, and it is essential for transferring cholesterol from astrocytes to neurons for use in maintaining synaptic structure. In addition to altering cholesterol transport, the ApoE4 allele has been proposed to increase AD risk by impairing glucose metabolism, disrupting the blood–brain barrier, promoting neuroinflammation, and reducing the clearance of $A\beta$. The fact that ApoE4 and mutant forms of presenilin and APP all increase accumulation of $A\beta$ is consistent with the hypothesis that $A\beta$ accumulation causes AD. But work by Islam et al. indicates that the overlapping effects of AD-linked genes may extend far beyond $A\beta$ accumulation.

Intracellular ApoE is normally localized predominantly in the cytoplasm, but some is present in the nucleus, where it modulates transcription. In presenilin-deficient mouse embryonic fibroblasts, however, intracellular ApoE was largely restricted to the nucleus, and secretion of ApoE was greatly reduced. Importantly, reintroducing wild-type presenilin after presenilin knockout fully reversed nuclear accumulation and restored secretion of ApoE, whereas expressing AD-linked forms of presenilin only partially rescued these effects. Inhibiting γ -secretase activity also increased nuclear accumulation and reduced secretion of ApoE in fibroblasts, and it produced similar effects in primary astrocytes. Moreover, inhibiting γ -secretase *in vivo* decreased levels of ApoE in CSF. Finally, plasma levels of ApoE were lower in AD patients carrying mutant presenilin than in healthy control subjects.

These results suggest that mutations in presenilin may promote AD in part by causing ApoE to accumulate in the nucleus, which may lead to aberrant transcriptional regulation, and by reducing ApoE secretion, which may impair delivery of cholesterol from astrocytes to neurons. Further elucidation of pathways affected by altering ApoE trafficking may suggest new approaches for treating both sporadic and familial AD.

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