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BRAIN RESEARCH

Review

Mechanisms and genes in human strial presbycusis from animal models☆

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ABSTRACT

Schuknecht proposed a discrete form of presbycusis in which hearing loss results principally from degeneration of cochlear stria vascularis and decline of the endocochlear potential (EP). This form was asserted to be genetically linked, and to arise independently from age-related pathology of either the organ of Corti or cochlear neurons. Although extensive strial degeneration in humans coincides with hearing loss, EPs have never been measured in humans, and age-related EP reduction has never been verified. No human genes that promote strial presbycusis have been identified, nor is its pathophysiology well understood. Effective application of animal models to this issue requires models demonstrating EP decline, and preferably, genetically distinct strains that vary in patterns of EP decline and its cellular correlates. Until recently, only two models, Mongolian gerbils and *Tyrp1*$^{B\text{-}lt}$ mice, were known to undergo age-associated EP reduction. Detailed studies of seven inbred mouse strains have now revealed three strains (C57BL/6J, B6.CAST-*Cdh23*^{CAST}, CBA/J) showing essentially no EP decline with age, and four strains ranging from modest to severe EP reduction (C57BL/6-*Tyr*$^{c\text{-}2J}$, BALB/cJ, CBA/CaJ, NOD.NON-*H2*^{nbl}/LtJ). Collectively, animal models support five basic principles regarding a strial form of presbycusis: 1) Progressive EP decline from initially normal levels as a defining characteristic; 2) Non-universality, not all age-associated hearing loss involves EP decline; 3) A clear genetic basis; 4) Modulation by environment or stochastic events; and 5) Independent strial, organ of Corti, and neural pathology. Shared features between human strial presbycusis, gerbils, and BALB/cJ and C57BL/6-*Tyr*$^{c\text{-}2J}$ mice further suggest this condition frequently begins with strial marginal cell dysfunction and loss. By contrast, NOD.NON-*H2*^{nbl} mice may model a sequence more closely associated with strial microvascular disease. Additional studies of these and other inbred mouse and rat models should reveal candidate processes and genes that promote EP decline in humans.

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1. Introduction

Age-related strial degeneration and subsequent endocochlear potential (EP) decline are taken to be the hallmarks of a form of presbycusis Schuknecht termed *metabolic* or *strial* (Schuknecht, 1993; Schuknecht and Gacek, 1993; Schuknecht et al., 1974). Compared to other posited forms, strial presbycusis was asserted to show the earliest onset (as early as the third decade of life), and to show the clearest genetic influence. Causally distinct pathology of the stria vascularis certainly seems plausible. The cellular processes that give rise to progressive hair cell and neural loss are often spatially and biochemically distinct from those in the stria, and examples of 'pure' and delimited strial pathology have been demonstrated in temporal bones. Yet EP decline has never been demonstrated in humans. While the incidence of strial presbycusis has been estimated to range from ~30% (Schuknecht and Gacek, 1993) of cases to 100% of 'true' presbycusis cases (Gates and Mills, 2005; Schmiedt et al., 2002), there are no universally accepted diagnostic criteria, so it is hard to be sure how frequently it occurs. Diagnosis is difficult both in living subjects, in whom the shape of the audiogram is of questionable value (Nelson and Hinojosa, 2003), and post-mortem, when the extent of strial dysfunction is difficult to infer from tissue samples. Presently, there are no verified mechanisms and no known predisposing genes.

1.1. *Strial presbycusis as a distinct aging pathology*

From the foregoing, the first question one might formulate about strial presbycusis is 'Does it exist?' Is it more nearly universal or mythical unicorn? And if there are no specific treatments, do we care which? Underneath some spoken or written discourses on the importance of presbycusis research, there is latent cynicism about the value of dissecting out its causes and forms. Most temporal bones studied–and indeed most animal models–indicate multiform aging cochlear pathology and multiple contributors to hearing loss. This is not surprising, given that all major cochlear cell types decrease in number with age (Ohlemiller and Frisina, 2008). The mechanisms driving this cell loss are probably those underlying most cellular aging, and may include oxidative stress, mitochondrial damage, calcium dysregulation, and loss of progenitor cells. If most aging cochleas are subject to loss of both sensory and strial cells, are potentially minor differences in *why* they die really important enough to study? We (Ohlemiller and Frisina, 2008) recently distinguished two general classes of age-related cochlear pathology, somewhat ponderously termed 'biological-age synchronous' (BAS) and 'biological-age accelerated' (BAA). Given a hypothetical set of biomarkers to establish the 'true biological age' of an individual, BAS aging of the cochlea will mirror the biological age. The quality of life will be impinged by multiple ailments, one of which ultimately becomes fatal. In such an individual, there will be hearing loss, but it will not stand out among other limitations, and any biologic fixes will probably overlap those for treating other tissues and organs. By contrast, BAA aging of the cochlea is taken to far outpace overall biological age, and to singularly interfere with quality of life. Rather than reflect broad cellular aging mechanisms, it will reflect processes and vulnerabilities specific to the cochlea. It may also primarily impact a specific cochlear cell population and give rise to a distinct form of presbycusis. Regardless of how it arises, presbycusis merits study. But it is the latter scenario that generates the most urgency. If strial presbycusis can be established, and its dissimilarity to noise injury is confirmed, it may emerge as the clearest example of biological-age accelerated cochlear aging. That said, we do not subscribe to the view that strial presbycusis is the only true form. This view originates from evidence that sensory and neural presbycusis often have an injury component, and the propensity for these will reflect gene/environment interactions (Ohlemiller and Frisina, 2008). Evidence presented here argues that strial presbycusis is no different in this regard.

Animal models offer the best strategy for linking specific patterns of strial pathology to EP reduction and uncovering related genes. Yet despite the fact that the EP is not difficult to measure, few animal studies have included this fundamental metric. Until recently, all direct evidence for age-related EP decline came from a single model, the Mongolian gerbil. Now