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31. J. Downward, *Methods Enzymol.* **255**, 110 (1995). Briefly, for GTP-exchange assays 1 μg of the appropriate DNAs were in vitro translated using the TNT T7 Quick system (Promega). The amount of correctly synthesized CIITA was determined by SDS–polyacrylamide gel electrophoresis, with one-fifth of the translation reaction mixture. The remainder was resuspended in 0.1% Nonidet P-40 (NP-40) lysis buffer (50 mM tris-HCl, 150 mM NaCl) and immunoprecipitated (IP) with 9 μg of monoclonal antibodies to FLAG(M2) [anti-FLAG(M2)] or Ras (anti-Ras). In experiments with NF-YA, a FLAG-tagged form was used. In Fig. 1 (B and D), an anti-FLAG(M2) isotype-matched control antibody was reacted with in vitro translated CIITA as a negative control. Protein G–agarose beads (Santa Cruz) were used to isolate the antibody complexes. The IPs were washed in Ras wash buffer, resuspended in Ras exchange buffer with 5 mM EDTA, and incubated at the appropriate temperature with addition of $MgCl_2$ to 10 mM after incubation for 20 min. After 1 hour at 37°C, the IPs were washed with wash buffer [50 mM tris-HCl (pH 8.0), 100 mM NaCl, 30 mM $MgCl_2$] and bound [$^{32}$P]GTP was assayed on a scintillation counter. For GTPase assays, IPs were prepared as described above and tested for GTPase activity with CIITAs incubated at 37°C as the only modification.
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33. Supported by grants from the National Institutes of Health (NIH) (AI45580, AI41751, and AI29564 to J.P.-Y.T.; CA42978 to C.J.D.), the National Multiple Sclerosis Society (7815 to J.P.-Y.T.), and NIH training grants (D.E.C. and J.A.H.). D.E.C. is supported by an NIH postdoctoral fellowship. J.A.H. is supported by a postdoctoral fellowship from the American Cancer Society. We thank A. Cox, S. Campbell, and L. Quilliam for helpful advice.

12 April 1999; accepted 21 July 1999

# Rapid Adaptation in Visual Cortex to the Structure of Images

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**Complex cells in striate cortex of macaque showed a rapid pattern-specific adaptation. Adaptation made cells more sensitive to orientation change near the adapting orientation. It reduced correlations among the responses of populations of cells, thereby increasing the information transmitted by each action potential. These changes were brought about by brief exposures to stationary patterns, on the time scale of a single fixation. Thus, if successive fixations expose neurons' receptive fields to images with similar but not identical structure, adaptation will remove correlations and improve discriminability.**

Figure 1 shows the response of a complex cell in striate cortex (V1) to a 0.5-s presentation of a stationary grating of optimal orientation, spatial frequency, phase, and size, followed by the same pattern presented as that of two brief probes of equal contrast, separated by 1.75 s (*1*). The initial response declined quickly. This decline, which is characteristic of cortical neurons (*2*), was more rapid than is seen in responses recorded at earlier stages in the visual pathway (*3*), so a considerable part of it must arise within cortex. The initial grating presentation also left the neuron desensitized, as can be seen by comparing the responses to the first probe (sensitivity was low) and to the second (sensitivity had recovered) (*4*). Desensitization does not result from light adaptation to the stationary image: First, a 0.5-s presentation of a grating flickering at 4 Hz was as effective an adapter as a stationary one (*5*); second, were light adaptation the cause of the changes, we would expect an increased response to a probe grating of the opposite spatial phase to the adapting grating. In fact, in complex cells, adaptation almost equally reduced responses to probes of either polarity.

Sensitivity changes in cortical neurons have generally been studied after prolonged periods of adapting stimulation (*6*), although evidently brief stimuli can quickly bring about significant reductions (Fig. 1) (*7*). Contrast adaptation, known to originate in cortex (*8*), is thought to adjust the responsivity of a neuron to the prevailing levels of contrast in the image (*9*). This prevents saturation of responses to strong stimuli and maintains the

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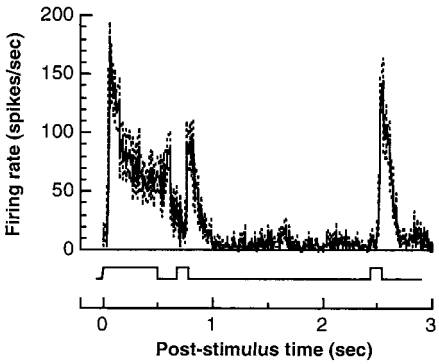


**Fig. 1.** Responses of a complex cell in V1 to presentations of a stationary sinusoidal grating (100% contrast) of optimal size, position, orientation, and spatial phase. The neuron was not directionally selective. The solid trace shows the mean discharge rate (computed from 40 stimulus presentations, in 10-ms bins), and the dotted traces show the mean ± 1 SEM. The lower trace identifies the times of onset and offset of the grating. The first (0.5 s) presentation of the grating desensitizes the cell, diminishing its response to the probe presented 200 ms later. By the time of the second probe, almost 2 s later, sensitivity has recovered. The time-constant of recovery of sensitivity measured by probing at a range of times (not all shown), was 8 s.

visual selectivity of a neuron in the face of variations in stimulus contrast (*10*). Adaptation by contrast gain control is thought to originate in signals from a pool of neurons tuned to a wide range of orientations and spatial frequencies (*11*) and is therefore distinguished from stimulus-selective adaptation, in which losses of sensitivity are greatest for stimuli like the adapting one (*12*). In this context, rapid adaptation as in Fig. 1 is of special interest, for if the loss of sensitivity is stimulus-specific we can place constraints on the properties of the underlying mechanisms.

Rapid, stimulus-specific adaptation would have other important implications. During the course of a fixation lasting perhaps a few hundred milliseconds, the image often remains nearly constant. A persisting response to an unchanging stimulus is metabolically expensive and conveys little information. Reducing the response to the persisting stimulus without diminishing a neuron's capacity to respond to a new one would be beneficial. It would save energy and could also improve the capacity to signal small differences between stimuli. This in turn might support improved perceptual discriminations (*13*).

We therefore examined the stimulus selectivity of the rapid adaptation in Fig. 1. We found that adaptation in complex cells was pattern-selective and made subsequently presented patterns more discriminable.

Figure 2, A and B, show how interleaved brief presentations of adapting gratings in different orientations brought about orientation-selective losses of sensitivity that were greatest near the orientation of the adapting grating (*14*). Adaptation to orientations other than the one initially preferred brought about a shift in orientation tuning, away from the adapting orientation. This shift was significant for the 28 complex cells on which complete measurements were made (Wilcoxon signed-ranks test, $P < 0.005$) (*15*). The tuning tended to become steeper and less variable in the neighborhood of the adapting orientation, potentially improving the neuron's capacity to discriminate orientation. We explored this by measuring how reliably neurons could distinguish two gratings that differed in orientation before and after a brief period of adaptation. We express discriminability as the percentage of trials on which the gratings could be correctly identified (*16*).

Figure 2C shows, for each of these 28 complex cells, how adaptation altered the discriminability of the two gratings. For 20 of 28 cells (those below the solid diagonal), adaptation improved the discriminability of gratings. Improvements arose from two sources: (i) the response to the grating at the adapting orientation fell substantially whereas the response to the other grating fell less or not at all; and (ii) the variability of responses was reduced. Simple cells behaved differently: Adaptation reduced responsivity in all 10 neurons that we studied exhaustively, but orientation selectivity did not depend on the orientation of the adapting stimulus.

Because the improvements in discriminability are confined to the neighborhood (in stimulus space) of the adapting stimulus, they will be valuable if successive fixations place similarly structured stimuli on a neuron's receptive field (*17*). Adaptation brings other potential benefits: By depressing the responsivity of a neuron locally in stimulus space, adaptation reduces the correlation among the responses of the population of neurons that will respond to a particular stimulus. This will increase the information transmitted by each spike (*18*). Consider how the responsiveness of a population of neurons tuned to similar orientations changes with adaptation. Figure 3A shows orientation tuning for two complex cells before and after adaptation to a grating with nominal orientation 0°. Adaptation sharply reduced both neurons' responses to gratings near the adapting orienta-

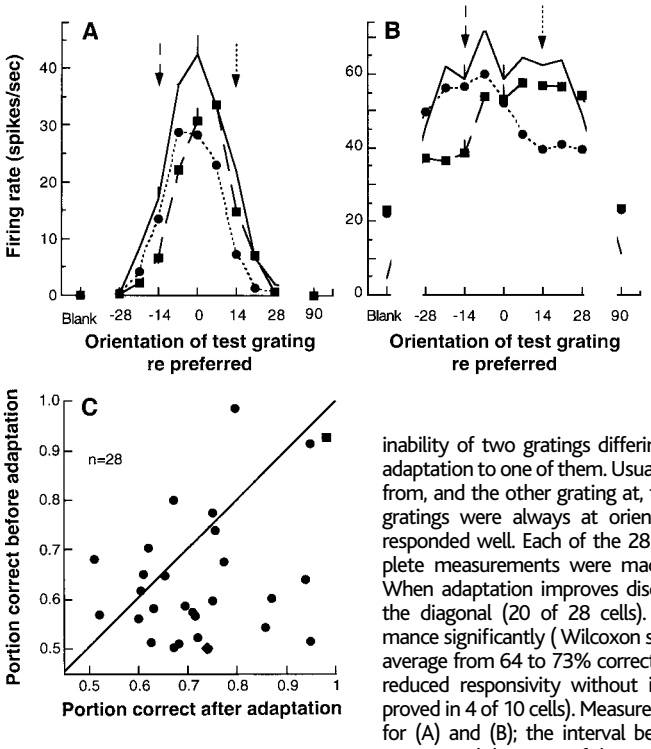


**Fig. 2.** (**A** and **B**) Orientation tuning of two V1 complex cells, measured with stationary gratings, before (solid line) and after adaptation to each of two stationary gratings, at −14° (■) or +14° (●) relative to the neuron's (initial) preferred orientation; adapting orientations are indicated by arrows. Occasional vertical bars show +1 SEM. As adaptation reduced response, it also reduced standard error of response, in (A) by 30 to 50%, in (B) by up to 30%. (**C**) Change in the discriminability of two gratings differing in orientation by 14°, after adaptation to one of them. Usually the adapting grating lay 14° from, and the other grating at, the preferred orientation; both gratings were always at orientations to which the neuron responded well. Each of the 28 complex cells on which complete measurements were made is represented by a point. When adaptation improves discriminability, points fall below the diagonal (20 of 28 cells). Adaptation improved performance significantly (Wilcoxon signed-ranks test, $P < 0.01$), on average from 64 to 73% correct. Adaptation in 10 simple cells reduced responsivity without improving discrimination (improved in 4 of 10 cells). Measurements were made as described for (A) and (B); the interval between offset of the adapting pattern and the onset of the probe varied between 13 and 215 ms. For four cells that were unusually narrowly or broadly tuned, the orientations of the adapting stimuli were separated less, or more, than the standard 14°. (■) The neuron in (A); (◆) the neuron in (B).

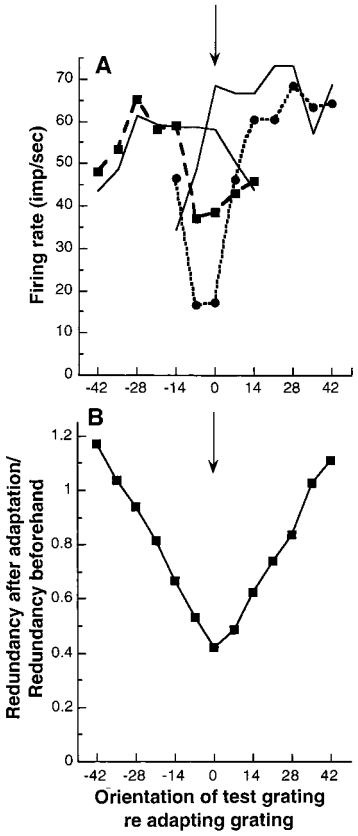


**Fig. 3.** Adaptation reduces the correlation among responses of a population of neurons that all respond to the adapting pattern, but have different preferred orientations. (**A**) Tuning curves for two complex cells before (solid line) and after (■, ●) adaptation at orientation 0° (arrow). (**B**) The reduction brought about by adaptation in the redundancy among responses of a group of 28 complex cells to probe gratings at different orientations around the adapting orientation. Redundancy is most reduced when the orientation of the probe is near the adapting orientation.

tion. Insofar as multiple neurons respond simultaneously to a grating at a particular location in the visual field, reduced responsiveness makes responses less redundant.

A useful information-theoretic measure of redundancy is the pairwise cross-correlation between the response rates of the population of neurons, weighted according to the probability of a stimulus of each orientation (*19*). Figure 3B shows, for 28 complex cells, the average reduction in redundancy due to each orientation. This makes clear that redundancy is most reduced locally around the adapting orientation. If the responses of the population of neurons were statistically independent, the correlation measure would be reduced to zero. It is most reduced when the orientation of the stimulus is near the adapting orientation. The greater the likelihood that successive fixations of a natural scene present complex cells with patterns of similar orientation, the more adaptation will reduce the redundancy among their responses. Rapid adaptation also reduced the redundancy among responses of simple cells, but because adaptation does not change simple cells' orientation tuning, the reduction in the redundancy is not orientation-selective.

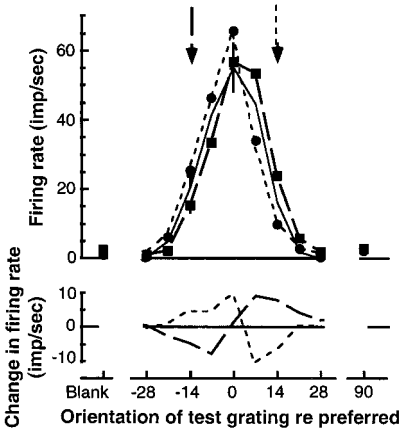


**Fig. 4.** Orientation tuning of the complex cell of Fig. 2A, measured with a stationary grating of optimal spatial frequency, size, and position, at 100% contrast. (**Top**) Different curves show tuning for the probe grating presented alone (solid curve) and in the presence of a moving surrounding grating oriented at −14° (■) or 14° (●) (arrows) that enclosed but did not intrude upon the receptive field. A surround grating presented alone elicited no response, but depressed sensitivity disproportionately for orientations near its own and increased sensitivity at other orientations. (**Bottom**) The change in response to the probe grating brought about by surround gratings at −14° (dashed line) and +14° (dotted line). The discriminability (*16*) of two gratings differing in orientation by 14° is increased from 91% correct to 98% correct (*28*). Twenty-two measurements contributed to each point. In each trial lasting 2 s, test and surround gratings were displayed simultaneously for 1.25 s; we analyzed the initial 100 ms of response. In control trials, the probe grating or the surround grating or both were absent, in which case the appropriate region was uniformly lit at the space average luminance. In successive trials, presentations of the different patterns and controls were randomly interleaved.

Rapid adaptation helps to remove correlations among, and improves the discriminability of, signals arising from successively viewed images of similar structure. Adjacent regions of natural images tend to have similar structure (*20*). Do mechanisms also exist to remove correlations between, and improve discriminability of, signals arising from spatially adjacent regions? The receptive fields of many V1 neurons are enclosed by regions in which a visual stimulus alone evokes no response, but can powerfully modulate the response to a concurrently presented stimulus in the receptive field (*21*). These surrounding regions might act to sharpen the neuron's selectivity for orientation (*22*) or spatial frequency (*23*). We found that a grating surrounding the receptive field had much the same effect on orientation selectivity as a briefly presented adapting grating on the receptive field.

Figure 4 shows (for the neuron of Fig. 2A) two orientation tuning curves, measured with gratings well-matched to the receptive field. Each curve was obtained in the presence of a surrounding grating of a different orientation, under conditions formally analogous to those used for studying adaptation. A surrounding grating whose orientation differed from the neuron's preferred orientation changed the shape of the curve, decreasing the sensitivity for orientations near that of the surround and increasing sensitivity to other orientations. The orientation tuning curve became steeper near the orientation of the surrounding grating, improving the neuron's capacity to signal differences in orientation. This improvement resulted from both a greater difference between the responses to the two gratings and, despite increases in absolute discharge rate, lower variance.

Adaptation in cortical neurons has been described before (*6–8*, *12*) but has not been induced with brief, stationary stimulation of the sort to which neurons will be exposed through normal fixations. Rapidly induced improvements in discrimination of the kind we have shown here will be particularly beneficial if successive fixations result in a receptive field being exposed to images of similar structure. Available evidence on this is suggestive, though incomplete: Adjacent regions of images tend to have similar structure (*20*), and the distribution of saccade sizes in free viewing is skewed toward small values (*24*). Our finding that lateral interactions arising from stimuli surrounding the receptive field (*21–23*) can also improve the discriminability of similar stimuli falling on the receptive field, encourages us to think of lateral interaction as a phenomenon that complements rapid adaptation; both remove local correlations from neuronal signals, one in time, the other in space.

Little existing physiology bears upon the mechanism of rapid adaptation. Intracellular recordings from cortical neurons show that a major component of long-term adaptation is a tonic hyperpolarization that raises a neuron's threshold for discharging action potentials (*25*), but this comes about too slowly to explain the changes in sensitivity that we have found (*26*). Rapid depression of excitatory synapses (*27*) provides an attractive alternative account. The different behaviors of simple and complex cells can be accommodated by supposing that whatever changes are brought about by adaptation occur in simple cells, and a group of simple cells in turn drives a complex cell.

Perceptual benefits of adaptation, explored in studies that use long induction times, have not been easy to find (*13*). Our results suggest that it might be worth looking for larger benefits in psychophysical experiments that probe the aftereffects of very brief adapting exposures to stationary stimuli.

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1. Responses of single units were recorded from *Macaca fascicularis*, anesthetized with sufentanil citrate, and with eyes immobilized with vecuronimum bromide, as described [P. Lennie, J. Krauskopf, G. Sclar, *J. Neurosci.* **10**, 649 (1990); M. J. M. Lankheet, P. Lennie, J. Krauskopf, *Vis. Neurosci.* **15**, 37 (1998)]. Each neuron was stimulated with an achromatic sinusoidal grating of optimal size and spatial frequency, displayed on the screen of a calibrated NEC P750 monitor, controlled by a Macintosh computer. The screen subtended between 4.9° (170 pixels/°) and 14.5° (57 pixels/°) depending on viewing distance; its space-time average luminance was 54 cd/m$^2$, and the display was refreshed at 75 Hz. Action potentials from isolated single units were recorded with 0.1-ms accuracy. All receptive fields lay within 3° of the center of the fovea. Simple and complex cells were distinguished by their responses to moving gratings.
2. A rapidly decaying response to a step stimulus implies low sensitivity to low temporal frequencies of stimulation, and this is found [M. J. Hawken, R. M. Shapley, D. H. Grosof, *Vis. Neurosci.* **13**, 477 (1996)]. Nonlinearities in the behavior of cortical neurons make the decay of responses to steps even more rapid than would be expected from the temporal modulation transfer function [D. J. Tolhurst, N. S. Walker, I. D. Thompson, A. F. Dean, *Exp. Brain Res.* **38**, 431 (1980); F. S. Chance, S. B. Nelson, L. F. Abbott, *J. Neurosci.* **18**, 4785 (1998)].
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4. The median time-constant of recovery of sensitivity in our sample of cells was 6 s. The median time-constant of desensitization was less than 100 ms.
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14. At the beginning of each trial lasting 1.75 s, an adapting grating (or a blank field) was presented for 0.5 s. This was followed after 215 ms (Fig. 2A) or 27 ms (Fig. 2B) by a 94-ms presentation of a test grating at one of 10 orientations (0°, ±7°, ±14°, ±21°, ±28°, or +90°), or by nothing. Discharge rate was calculated from the whole response to the test grating. Gratings had optimal spatial frequency, size, and position, and 100% contrast. In successive trials the different adapting and test grating pairs were randomly interleaved, and each such trial was repeated 40 times. When no grating was visible, the screen displayed a spatially uniform field of the average luminance.
15. Orientation tuning before adaptation was similar whether measured with stationary or moving gratings. Orientation tuning before and after adaptation was summarized by the center-of-mass $\sum_i R_i$ of the responses to stimuli with orientations $i \in \{0°, \pm7°, \pm14°, \pm21°, \pm28°\}$. For sharply (and symmetrically) tuned neurons with half-width <28° this is exactly the preferred orientation. For all neurons it increases monotonically with preferred orientation. The average neuron's center-of-mass changed by 1.5°.
16. To estimate the discriminability of two gratings we measured a series of responses to each, and for the resulting distributions of response amplitudes computed the means ± SDs. We treated the distributions as normal and calculated the difference between their means divided by the root-mean-square standard deviation $d' = \frac{\mu_1 - \mu_2}{\sqrt{(\sigma_1^2 + \sigma_1^2)/2}}$ [D. M. Green and J. A. Swets, *Signal Detection Theory and Psychophysics* (Wiley, New York, 1966)]. The percentage of correct responses was then obtained from the normal distribution function, $\Phi(d') = \frac{1}{\sqrt{2\pi}} \sum_{-\infty}^{d'} e^{-\frac{1}{2}x^2}\, dx$. This measure characterizes the performance of an ideal observer.
17. Not much is known about this, but successive fixations are often close together [A. L. Yarbus, *Eye Movements and Vision* (Plenum, New York, 1967); A. T. Bahill, D. Adler, L. Stark, *Invest. Ophthalmol.* **14**, 468 (1975)], and nearby image patches have correlated orientation and spatial frequency [E. P. Simoncelli and O. Schwartz, in *Advances in Neural Information Processing Systems 11*, M. S. Kearns, S. A. Solla, D. A. Cohn, Eds. (MIT Press, Cambridge, MA, 1999)].
18. Barlow [H. B. Barlow, in *Vision: Coding and Efficiency*, C. Blakemore, Ed. (Cambridge Univ. Press, Cambridge, 1990), p. 363.] first drew attention to this consequence of adaptation.
19. We define redundancy in the population's response ($\Psi$) due to each probe orientation ($\theta$) relative to the adapting orientation by
$$\psi(\theta) = \sum_{\text{All cells}} \frac{\text{Resp(cell A,}\theta\text{)}\cdot\text{Resp(cell B,}\theta\text{)}}{\text{Number of cell pairs}}$$
the average, unnormalized, point-by-point product of the responses of all pairs of neurons. This is an intermediate stage in the calculation of the cross-correlation. To establish how adaptation reduces the redundancy among responses, we calculate $\psi$ before and after adaptation, for probes at a range of orientations. We treat every neuron as if it had been adapted to the pattern at orientation 0°.
20. E. P. Simoncelli and O. Schwartz, in *Advances in Neural Information Processing Systems 11*, M. S. Kearns, S. A. Solla, D. A. Cohn, Eds. (MIT Press, Cambridge, MA, 1999).
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23. L. Maffei and A. Fiorentini [*Vision Res.* **16**, 1131 (1976)] suggested that adaptation sharpens spatial frequency tuning.
24. See, for example, A. T. Bahill, D. Adler, L. Stark, *Invest. Ophthalmol.* **14**, 468 (1975). The distribution of saccade sizes is heavily task-dependent [for example, M. F. Land and S. Furneaux, *Philos. Trans. R. Soc. London Ser. B* **352**, 1231 (1997)].
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28. A surrounding grating brought about significant changes in orientation tuning in almost half of the complex cells we studied.
29. All animal procedures were approved by the University of Rochester committee for the care and use of laboratory animals. Funded by NIH grants EY04440, EY01319, EY06638, and EY07125.

3 May 1999; accepted 26 July 1999

# Altered Cochlear Fibrocytes in a Mouse Model of DFN3 Nonsyndromic Deafness

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**DFN3, an X chromosome-linked nonsyndromic mixed deafness, is caused by mutations in the *BRN-4* gene, which encodes a POU transcription factor. Brn-4-deficient mice were created and found to exhibit profound deafness. No gross morphological changes were observed in the conductive ossicles or cochlea, although there was a dramatic reduction in endocochlear potential. Electron microscopy revealed severe ultrastructural alterations in cochlear spiral ligament fibrocytes. The findings suggest that these fibrocytes, which are mesenchymal in origin and for which a role in potassium ion homeostasis has been postulated, may play a critical role in auditory function.**

Hereditary deafness affects about 1 in 2000 children and 70% of the cases occur nonsyndromically (in the absence of other associated clinical features). DFN3, an X chromosome-linked nonsyndromic deafness, is clinically characterized by a conductive hearing loss, a flow of perilymph during the opening of the stapes footplate, and progressive sensorineural deafness (*1*). Genetic studies have shown that DFN3 is caused by mutations in *BRN-4*/*RHS2*/*POU3F4*, which encodes a POU transcription factor (*2*). The role of Brn-4 in the development of auditory function, however, remains unclear. Mutations in *BRN-3.1*/*BRN-3c*, which encodes another POU factor, are responsible for hereditary nonsyndromic deafness, DFNA15, and targeted mutagenesis in mice has suggested that the protein plays a critical role in differentiation of hair cells in the inner ear (*3*). During development, Brn-4 is expressed throughout the inner ear in the mesenchyme of both the cochlear and vestibular aspects but not in tissues derived from neuroepithelial or neuronal cells (*4*).

To analyze Brn-4 function in vivo and to elucidate possible mechanisms underlying DFN3, we generated Brn-4-deficient mice by

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