Loudness-Coding Mechanisms Inferred from Electric Stimulation of the Human Auditory System

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Two distinct physiological mechanisms underlying loudness sensation were inferred from electric stimulation of the human auditory nerve and brainstem. In contrast to a power function relating loudness and stimulus intensity in acoustic hearing, loudness in electric stimulation of the auditory nerve depends on stimulus frequency. Loudness is an exponential function of electric amplitude for high frequencies and is a power function for low frequencies. A frequency-dependent, two-stage model is suggested to explain the loudness function, in which the first stage of processing is performed by a mechanical mechanism in the cochlea for high-frequency stimuli and by a neural mechanism in the cochlear nucleus for low-frequency stimuli.

A fundamental relation in perception is Stevens's power law, in which sensation magnitude is a power function of stimulus intensity (*1*). In vision and hearing, the small (<1) exponents of the power function reflect the fact that the light or sound dynamic range must be compressed as much as 1,000,000:1 for processing by the brain. The physiological mechanisms underlying Stevens's law are not clear. The power function may simply reflect the compressive characteristics of the peripheral transducer, with the central nervous system performing only linear processing (*2*). Alternatively, a two-stage hypothesis suggests that no single stage performs a power law transformation; instead, a logarithmic peripheral transducer coupled with an exponential central transformation produces the power function (*3*).

The development of implantable auditory prostheses in the 1980s not only has restored partial hearing sensation to deaf patients but also has provided an opportunity to examine physiological mechanisms underlying loudness sensation. In cochlear implant listeners, electric signals bypass the peripheral transducer (the cochlea) and stimulate the auditory nerve directly (*4, 5*). The auditory brainstem implant bypasses the auditory nerve and stimulates the human cochlear nucleus, the first information-processing structure in the central auditory system (*6*). Therefore, we can infer the contributions of the cochlea, the peripheral nervous system, and the central nervous system to loudness sensation by quantitatively comparing loudness functions in acoustic stimulation of the cochlea and in electric stimulation of the auditory nerve and cochlear nucleus.

Eight adults (five males and three females) with Ineraid cochlear implants and three adults with auditory brainstem implants (one male and two females) participated in this study (*7*). Several electrical waveforms were presented at different repetition rates to the implant subjects. Each waveform was balanced in loudness against a 1000-Hz sinusoidal standard, for which Zeng and Shannon (*8*) showed that loudness is an exponential function of the electric amplitude. If the exponential model were to apply for all electric stimuli, we would expect to observe a linear loudness balance function between the standard and all comparison stimuli. To balance the loudness, the subjects moved a pointer up and down along a touch-sensitive pad to make the comparison stimulus first louder, then softer, and finally equally as loud as the 1000-Hz sinusoidal standard (*9*). Three to five such measures were repeated for each condition. No feedback was provided to the subjects. Five levels of the 1000-Hz sine standard were chosen for each subject to represent approximately 10, 30, 50, 70, and 90% of the dynamic range in microamperes (*10*).

A linear loudness balance function was obtained for the comparison stimuli of the 3000-Hz sinusoid, the 300-Hz sinusoid, and the 1000-Hz pulse (Figs. 1A and 2, A to C), indicating that the exponential loudness function holds for stimuli with frequencies above 300 Hz. However, for the 100-Hz sinusoid and the 100-Hz pulse comparison stimuli, the logarithmic scale on the y axis (Fig. 1B) and the best fit functions (Fig. 2, D to E) indicate a logarithmic loudness balance function. Thus, the exponential loudness model fails for these low-frequency stimuli.

Nevertheless, the loudness function can be derived for low-frequency electric stimuli. Suppose that the 1000-Hz standard stimulus has an exponential loudness function (*8*)

$$L = 10^{E_{1000}} \quad (1)$$

where L is loudness magnitude and E_{1000} is the amplitude of the 1000-Hz standard. Also suppose that the loudness balance function is logarithmic between the amplitude of the 1000-Hz standard and the amplitude of the 100-Hz stimulus

$$E_{1000} = \theta \log E_{100} \quad (2)$$

where E_{100} is the amplitude of the 100-Hz stimulus and θ is a constant. A combination of Eqs. 1 and 2 gives a power function for the 100-Hz stimuli

$$L = 10^{\theta \log E_{100}} = E_{100}{}^{\theta} \quad (3)$$

The similarity in the loudness balance functions for the 100-Hz sine and the 100-Hz pulse is of interest because these two stimuli share no common electric properties except for frequency. Compared with the 100-Hz pulse, the 100-Hz sinusoid produces a much lower threshold, smaller dynamic range in linear microampere units, and longer distribution of charge within the period of the stimulus. These characteristics suggest that stimulus frequency, rather than threshold, dynamic range, or charge distribution, is the important factor determining the form of the loudness function in cochlear implant subjects.

A linear loudness balance function between the 1000-Hz standard and a 100-Hz pulse (*11*) stimulus was observed for three brainstem implant subjects (Fig. 2F). The linear balance function indicates an exponential loudness function for the 100-Hz stimulus in brainstem implant subjects. The difference in loudness functions between the cochlear and brainstem implant sub-

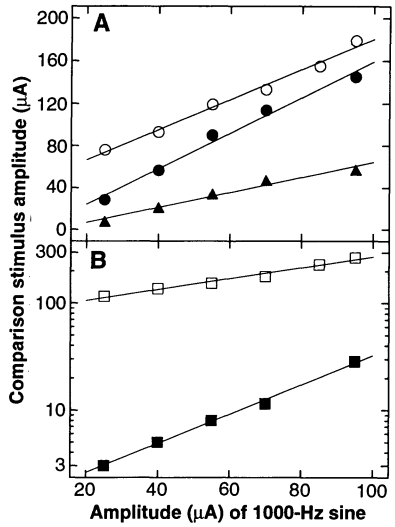

Fig. 1. Loudness balance functions for cochlear implant subject BO. Solid lines represent the best fit functions to the data. The standard deviations for each measurement are about the size of the symbols. (**A**) Loudness balance functions between the 1000-Hz sinusoidal standard and the comparison 3000-Hz sinusoid (●), 300-Hz sinusoid (▲), and 1000-Hz biphasic pulse (○). Both the *x* axis and the *y* axis are linear scales. (**B**) Loudness balance functions for the 100-Hz sinusoid (■) and biphasic pulse (□). Note the logarithmic scale on the *y* axis.

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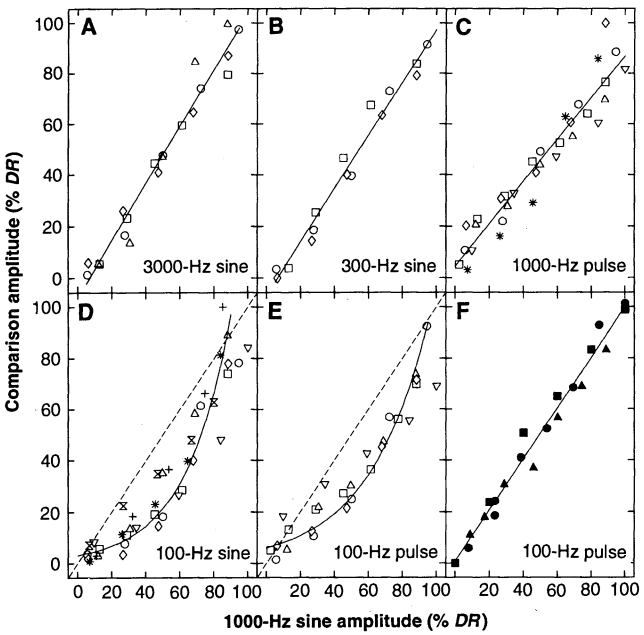

Fig. 2. (A to E) Normalized loudness balance functions for eight cochlear implant subjects. The electric amplitude (E) was normalized according to each subject's dynamic range (DR): percent $DR(E) = 100(E - TH)/(ULL - TH)$, where TH and ULL were the subject's threshold and uncomfortable level in microamperes. Symbols for subjects are as follows: BO (□), DC (○), JB (△), JP (▽), KM (◇), MM (⧖), MP (✳), and RM (+). The x axis in all panels represents the percent DR of the 1000-Hz sinusoid. The y axis represents the percent DR of the comparison stimuli. Solid lines represent the best fit functions to the data. (**A**) For 3000-Hz sinusoid comparison, the coefficient of the linear regression $r = 0.98$. (**B**) For 300-Hz sinusoid, $r = 0.99$. (**C**) For 1000-Hz biphasic pulse, $r = 0.96$. (**D**) For 100-Hz sinusoid, $r = 0.93$ after the logarithmic transformation of the 100-Hz sinusoid amplitude. The dashed line represents an ideal linear balance function. (**E**) For 100-Hz biphasic pulse, $r = 0.90$ after the logarithmic transformation on the 100-Hz pulse amplitude. The dashed line represents an ideal linear balance function. (**F**) Normalized loudness balance function for three auditory brainstem implant subjects: CB (■), JP (●), and KM (▲). For 100-Hz biphasic pulse, $r = 0.99$.

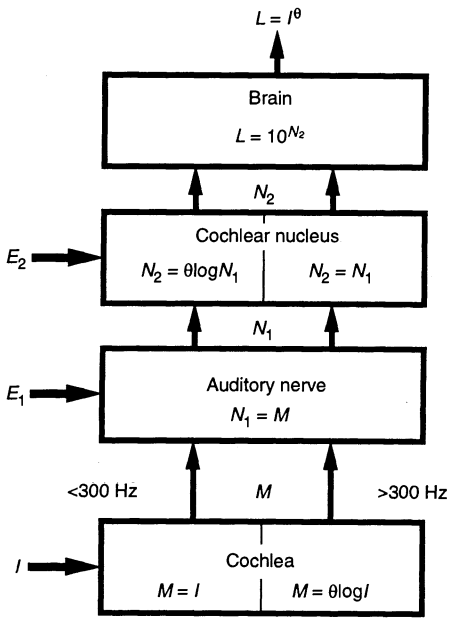

Fig. 3. The frequency-dependent, two-stage loudness-coding model. Auditory processing is represented as ascending paths from peripheral to central stages. The left ascending path is for low-frequency processing and the right path is for high-frequency processing. The stimulus amplitude in normal acoustic hearing is denoted by I, whereas E_1 and E_2 denote the amplitudes of electric stimulation in the auditory nerve and the cochlear nucleus, respectively. M, N_1, and N_2 denote the nominal outputs of the cochlea, the auditory nerve, and the cochlear nucleus, respectively. Loudness (L) is assumed to be the output of the brain.

jects suggests that a neural mechanism in the cochlear nucleus produces a logarithmic transformation to a low-frequency neural event from the auditory nerve, and that the nonspecific stimulation of the cochlear nucleus precludes this transformation in brainstem implant subjects (*12*). Because the mechanical vibration of the cochlea in response to low-frequency stimuli is essentially linear (*13*), a logarithmic transformation must be supplied by a neural compensation mechanism for low-frequency stimuli for the normal auditory system to maintain a uniform power loudness function for all frequencies. Our data suggest that such a mechanism resides in the cochlear nucleus.

We suggest a frequency-dependent, two-stage model (*14*) to account for both the present pattern of results and Stevens's power law (Fig. 3). First consider the case in acoustic hearing. For high-frequency stimuli, the brain performs an exponential transformation to an incoming neural response that is proportional to a logarithmic transformation of stimulus intensity I in the cochlea, which results in a power function for loudness

$$L = 10^{N_2} = 10^{N_1} = 10^{M} = 10^{\theta \log I} = I^{\theta} \quad (4)$$

where N_2 is the neural output of the cochlear nucleus, N_1 is the neural output of the auditory nerve, and M is the mechanical output of the cochlea. For low-frequency stimuli, the logarithmic transformation of stimulus intensity does not occur until the cochlear nucleus level is reached, but the resulting loudness still follows the same power law.

In electric stimulation of the auditory nerve (E_1), the power function still holds for low-frequency stimuli; similar to acoustic stimulation, there is a linear relation between stimulus amplitude and neural response magnitude in the auditory nerve. For high-frequency stimuli, the electric stimulus E_1 bypasses the logarithmic compression in the cochlea. The loudness abides by an exponential function

$$L = 10^{N_2} = 10^{N_1} = 10^{E_1} \quad (5)$$

Finally, direct electric stimulation of the cochlear nucleus (E_2) bypasses the logarithmic compression mechanisms in both the cochlea and the cochlear nucleus so that an exponential loudness function occurs for both low and high frequencies in the brainstem implant subjects. The present data suggest that even an apparently unitary perceptual dimension such as loudness requires two distinct processing mechanisms at multiple neural stages.

REFERENCES AND NOTES

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2. J. C. Eccles and V. B. Mountcastle, Eds., *Touch, Heat and Pain* (Churchill, London, 1966); S. S. Stevens, *Science* **170**, 1043 (1970); M. B. Sachs and P. J. Abbas, *J. Acoust. Soc. Am.* **56**, 1835 (1974); G. K. Yates *et al.*, *Trends Neurosci.* **15**, 57 (1992).
3. One version of the two-stage model is a double-log hypothesis [D. M. MacKay, *Science* **139**, 1213 (1963)]. Stevens's power law states that the sensation ψ grows in proportion to the stimulus ϕ raised to a power with an exponent of β

$$\psi = k\phi^{\beta}$$

where k is a constant. Applying a logarithmic transformation to both sides yields

$$\log\psi = \log k + \beta\log\phi$$

suggesting that a logarithmic transformation of the stimulus coupled with a logarithmic transformation of the sensation can result in a power function. MacKay further suggested a physiological "comparator" model that uses a "self-inhibition" feedback loop, in which the brain actively generates a neural output ($\log\psi$) to match a peripheral neural response ($\log\phi$) evoked by the stimulus. In terms of mathematical transformation, MacKay's model effectively exponentiates the output of the peripheral transducer.
4. D. K. Eddington *et al.*, *Ann. Otol. Rhinol. Laryngol.* **87** (suppl. 53), 5 (1978).
5. G. M. Clark *et al.*, *Adv. Oto-Rhino-Laryngol.* **38**, 1 (1987).
6. This experimental auditory prosthesis has been used for neurofibromatosis type 2 patients who are totally deaf and have no residual auditory nerve after removal of bilateral vestibular schwannoma [D. E. Brackmann *et al.*, *Otolaryngol. Head Neck Surg.* **108**, 624 (1993); R. V. Shannon *et al.*, *ibid.*, p. 634].
7. All subjects participated with fully informed consent. The Institutional Review Board of the House Ear Institute and St. Vincent Medical Center approved this study and the informed consent form. All implant subjects in this study had a percutaneous plug interface, which allows direct access to the electrodes and precision of electric stimulation.

8. The exponential loudness model for the 1000-Hz standard stimulus has been established in a previous study that used binaural loudness balance data between electric and acoustic stimulation in three brainstem implant subjects who had substantial hearing in their nonimplanted ears [F.-G. Zeng and R. V. Shannon, *Hear. Res.* **60**, 231 (1992)]. A similar finding was reported in two additional cochlear implant subjects [(*4*); M. F. Dorman *et al.*, *Ear Hear.* **14**, 290 (1993)].
9. An implant listener first listened to a pulsed stimulus train consisting of the 1000-Hz sinusoid standard. By pointing on a touch-sensitive tablet, the subject would hear a comparison sound alternating with the standard. The amplitude of the comparison sound was changed as the subject moved the pointing position up and down. The amplitude range on the touch-sensitive tablet was changed so that the absolute pointing did not indicate an absolute level. The consistency of the balance technique was indicated by the reproducibility of the measurement across sessions for some individual subjects and by the demonstration of transitivity among stimuli (for example, if A was balanced to B, and B was balanced to C, then A should be balanced to C). The comparison stimuli were sinusoids of 100 Hz, 300 Hz, and 3000 Hz, and biphasic pulse trains (100 μs per phase) of 100 Hz and 1000 Hz. All stimuli had a duration of 200 ms and a linear ramp of 5 ms. Stimuli were digitally generated through a 12-bit D/A converter at a sampling rate of 20 kHz (Data Translation DT2801-A) and controlled by a portable PC computer. Electric stimulation was delivered through an optically isolated constant-current source [L. S. Vurek *et al.*, *Ann. Otol. Rhinol. Laryngol.* **90** (suppl. 82), 21 (1981)]. Subjects were connected to the current source through a safety cutoff switch that allows a rapid disconnection from the stimulation setup in the event of experimenter error or hardware failure that might cause loud or unpleasant stimulation. In cochlear implants, the most apical electrode and monopolar stimulation were used. In brainstem implants, electrodes without nonauditory side effects were used.
10. The dynamic range was defined as the level difference between the absolute threshold and the uncomfortable loudness level (ULL), which were measured with a combination of Bekesy tracking and the method of limits (*15*). The threshold and the ULL (in microamperes) for each stimulus are represented by the two numbers in the parentheses following the subject's initials. For 100-Hz sinusoid: BO (0.8, 38), DC (1, 60), JB (0.7, 15), JP (1, 13), MK (3, 89), MM (1, 44), MP (1, 89), and RM (3, 38). For 300-Hz sinusoid: BO (5, 67), DC (10, 135), and MK (15, 112). For 1000-Hz sinusoid: BO (13, 106), DC (20, 200), JB (9, 141), JP (14, 75), MK (21, 167), MM (30, 180), MP (15, 224), and RM (24, 119). For 3000-Hz sinusoid: BO (20, 177), DC (35, 360), and MK (31, 112). For 100-Hz pulse: BO (80, 348), DC (120, 540), JB (97, 317), JP (85, 199), and KM (117, 488). For 1000-Hz pulse: BO (32, 224), DC (60, 440), JB (34, 313), JP (41, 189), KM (73, 357), and MP (33, 263). For three brainstem implant listeners, the threshold and the ULL were as follows. For 1000-Hz sinusoid: CB (150, 550), JP (60, 320), and KM (250, 600). For 100-Hz pulse: CB (310, 660), JP (220, 680), and KM (600, 950).
11. Only the 100-Hz pulse was tested because the high threshold for the 100-Hz sinusoid would have exceeded the safety level in brainstem implant subjects [R. V. Shannon, *IEEE Trans. Biomed. Eng.* **39**, 424 (1992)].
12. Neural synchrony or timing may be involved in determining the difference in loudness functions observed between the cochlear and brainstem implant subjects. Though the neural synchrony has been shown to occur for stimuli as high as 10 kHz in the auditory nerve, the usable range by the central auditory system may be limited to only 300 Hz. This is evidenced by both neural recording in the central auditory system, in which the synchronized response to modulation or signal frequencies rarely exceeds 300 Hz [for example, A. R. Moller, *Brain Res.* **57**, 443 (1973); R. D. Frisina *et al.*, *Hear. Res.* **44**, 99 (1990); J. J. Eggermont, *ibid.* **56**, 153 (1991)] and by the measurement of temporal pitch with sinusoid-modulated noise in normal-hearing subjects [E. M. Burns and N. F. Viemeister, *J. Acoust. Soc. Am.* **60**, 963 (1976)] or in cochlear implant subjects (*15*). One possible temporal mechanism for the coding of loudness is that loudness is related to a measure of the synchronized rate for low-frequency stimuli and of the overall rate for high-frequency stimuli. This suggestion is based on the observation of the auditory nerve recording that the ratio of the synchronized rate to the overall rate appears to be a logarithmic function of the sound intensity [D. O. Kim and C. E. Molnar, *J. Neurophysiol.* **42**, 16 (1979)], analogous to the present logarithmic loudness balance function between low- and high-frequency electric stimuli.
13. In animals with acoustic hearing, the cochlear mechanics approaches linearity at the apex of the cochlea, a phenomenon that has been suggested to reflect a smaller degree of involvement of the active process at low frequencies [P. Wilson, in *Auditory Physiology and Perception*, Y. Cazals, K. Horner, L. Demany, Eds. (Pergamon, Oxford, 1992)]. In humans, the cochlear linearity has been measured indirectly with the level dependence of the auditory filter bandwidths, which showed that the cochlea is essentially linear at 125 Hz, with no level effect on the bandwidths of the auditory filter centered at this frequency. The cochlea becomes more nonlinear as frequency is increased from 250 Hz to 1000 Hz [S. Rosen and D. Stock, *J. Acoust. Soc. Am.* **92**, 773 (1992)]. This boundary of low versus high frequency is similar to that suggested by the present study.
14. For brevity, noncritical constants are intentionally neglected, and the brain is assumed to perform an exponential transformation in the model. The specific exponential mechanism could be a double-log transformation as suggested by MacKay (*3*).
15. R. V. Shannon, *Hear. Res.* **11**, 157 (1983).
16. Supported by National Institutes of Health (RO1-DC01526 to R.V.S. and RO3-DC01464 to F.-G.Z.). We thank M. Baser, M. Don, D. Nielsen, and C. Ponton for suggestions on the manuscript.

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[URE3] as an Altered *URE2* Protein: Evidence for a Prion Analog in *Saccharomyces cerevisiae*

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A cytoplasmically inherited element, [URE3], allows yeast to use ureidosuccinate in the presence of ammonium ion. Chromosomal mutations in the *URE2* gene produce the same phenotype. [URE3] depends for its propagation on the *URE2* product (Ure2p), a negative regulator of enzymes of nitrogen metabolism. *Saccharomyces cerevisiae* strains cured of [URE3] with guanidium chloride were shown to return to the [URE3]-carrying state without its introduction from other cells. Overproduction of Ure2p increased the frequency with which a strain became [URE3] by 100-fold. In analogy to mammalian prions, [URE3] may be an altered form of Ure2p that is inactive for its normal function but can convert normal Ure2p to the altered form. The genetic evidence presented here suggests that protein-based inheritance, involving a protein unrelated to the mammalian prion protein, can occur in a microorganism.

Prions are infectious proteins, a concept that arose from studies of the spongiform encephalopathies, including scrapie of sheep, human kuru, and Creutzfeldt-Jakob disease (*1*). A prion protein is an altered form of a normal cellular protein that causes a detectable phenotype or disease in the affected individual. The altered (prion) protein transmits the disease to a new individual, without transmitting any genetic material, by inducing the normal cellular form of the new host to change to the prion form. As one would predict, a transgenic mouse lacking the cellular prion gene (*PrP*), and hence its protein product, is unable to propagate the prion and is resistant to its disease-inducing effects (*2*).

Yeast viruses are generally passed from cell to cell by cytoplasmic mixing such as occurs when cells mate. Such events are sufficiently frequent in nature that known yeast viruses are found in most strains examined (*3*). A yeast prion would be expected to have the same kind of infectivity and similarly appear as a non-Mendelian genetic element, but with certain special characteristics (Fig. 1).

Aspartate transcarbamylase is an enzyme in the pyrimidine biosynthetic pathway that produces ureidosuccinate from carbamyl phosphate and aspartate (*4*). Mutants in aspartate transcarbamylase can grow if supplemented with ureidosuccinate, but its uptake is repressed by ammonium (*5*). In 1971, Lacroute, starting with a strain lacking this enzyme, isolated mutants called URE (for ureidosuccinate) that could grow on ureidosuccinate despite the presence of ammonium (*6*).

One group of recessive mutants when crossed with wild type showed the 2+:2− meiotic segregation typical of mutation in a single chromosomal gene. These mutants defined the chromosomal *URE2* gene (*6*) whose normal role is repression of nitrogen

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