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Noise-Induced Reduction of Inner-Ear Microphonic Response: Dependence on Body Temperature

Abstract. *The rate of reduction of chinchilla cochlear microphonic response with exposure to steady noise is less at lower body temperatures and greater at higher body temperatures. Before exposure to noise, this auditory response is invariant within the range of temperatures employed. The mechanism of reduction of cochlear response appears to involve processes sensitive to body temperature.*

Carder and Miller (*1*) first showed by behavioral methods that continuous noise of sufficient intensity produces a progressive loss of auditory sensitivity in chinchillas until a steady state is reached in which auditory sensitivity is stable with continued exposure to noise. Recovery to normal auditory thresholds occurs within 3 to 6 days after cessation of the noise, but not without some risk of sensory-cell loss (*2, 3*). Similar behavioral results have been obtained for man (*4*). Such changes in auditory sensitivity are known as asymptotic threshold shifts and may include permanent as well as temporary components (*5*). Thus, these phenomena appear related to progressive, noise-induced hearing losses in man (*6*).

In the work reported here, the cochlear microphonic response (CM), which arises in the inner ear (*7*) and is correlated with auditory sensitivity (*2*), is progressively decreased at a rate dependent on body temperature during exposure of the ear to noise. Procedures used for surgical exposure of the cochlea and electrophysiological recording were those described by Tasaki *et al.* (*8*). Electrodes were inserted into the second turn of the chinchilla cochlea. Sound was delivered through a PDR-10 earphone and speculum (*2*) and consisted of either octave-band noise with center frequency at 1 khz at an overall level of 90 db referenced to 0.0002 μbar or short tone bursts at 200 hertz. A LINC computer controlled the signals and recorded the wave forms of CM on magnetic tape. Complete input-output functions for CM to tone bursts were obtained during 45-second interruptions in the noise. Body temperature of each anesthetized animal was rapidly adjusted to 29°, 37°, or 39°C by appropriate cooling or heating and held constant under control of a thermostat with thermistor probe. When the first measurements were taken the cochlear temperature was within about 1°C of body temperature.

In the absence of noise, CM showed no significant change with temperature or time for as long as the animal lived. When noise was presented, CM progressively decreased and approached an asymptote (Fig. 1). The rate of decrease of maximum voltage was significantly different for the three temperatures. The times for half-maximal loss of voltage were 5, 70, and 170 minutes at 39°, 37°, and 29°C, respectively (Fig. 1A). The CM values did not differ significantly at asymptote. In addition, maximum voltage at 29°C remained near initial values for almost an hour before decreasing. A different measure of CM, the sensitivity (in microvolts per microbar) obtained from sound pressure necessary to produce a criterion voltage in the region of linear output, showed a pat-

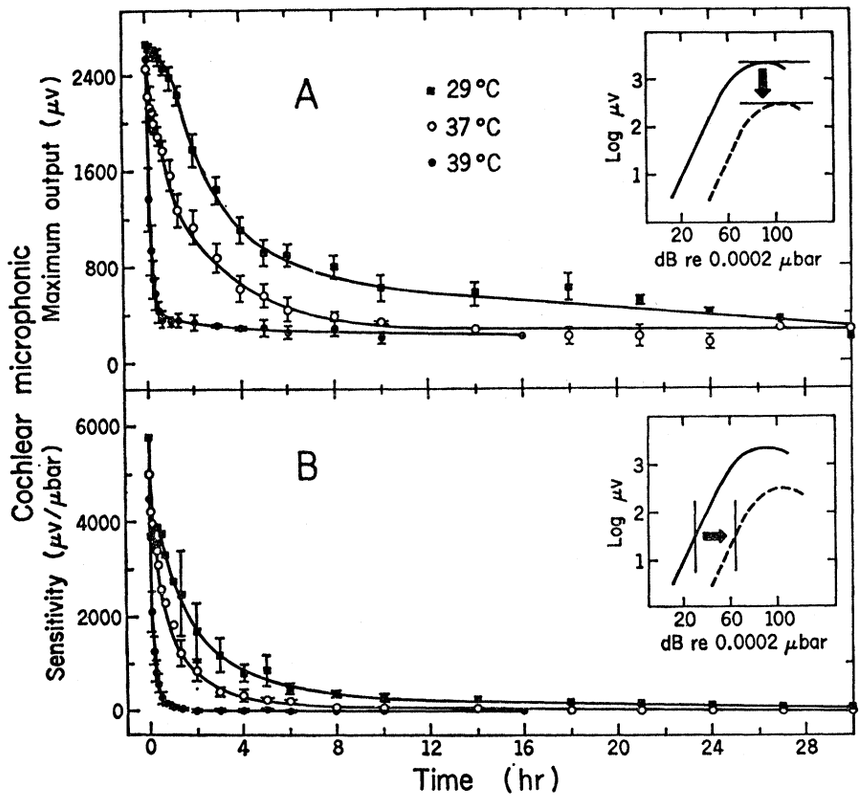

Fig. 1. Temperature dependence of the loss of (A) maximum voltage (peak to peak) and (B) sensitivity of cochlear microphonic response. The CM was recorded from the second turn of the cochlea of chinchilla during exposure to octave-band noise with center frequency at 1 khz at 90 db referenced to 0.0002 μbar. Body temperatures are listed. Significant differences are indicated with vertical bars denoting ± 1 standard error of the mean ($N = 3$, 4, and 4 for 29°, 37°, and 39°C, respectively). The insets are diagrams of the normal test input-output functions for CM (solid curves) and the corresponding functions after exposure to noise for an arbitrary period of time (dashed curves); reduction of (A) maximum and (B) sensitivity are illustrated.

tern of temperature dependence largely similar to that for maximum output (Fig. 1B).

Changes in temperature between 30° and 40°C have little effect on normal CM (*9, 10*), in agreement with results presented here. However, Bornschein and Krejci (*11*) found that the rate of loss of CM in anoxia is decreased at lower temperatures. Fernández *et al.* (*9*) suggested that during oxygen deprivation, hypothermia reduces the metabolic rate of the generators of CM, the hair cells and vascular stria (*7*), and thereby prolongs survival of the response, presumably by sparing energy reserves (*12*). The noise-induced loss of CM (Fig. 1) exhibits temperature dependence in the same direction as does CM loss in anoxia, but over a much more extended time period (*11*). While anoxia affects both hair-cell and strial generators (*13*), noise affects mainly the hair cells and influences the stria to a lesser extent (*2*).

The CM is thought to arise as ion current by modulation of a voltage gradient across the hair cells in the reticular lamina (*7*). It is therefore likely that continuous acoustic stimulation results in redistribution of ions across hair-cell membranes. Undoubtedly, energy is required for ion transport to maintain an electrical gradient between the interior of the hair cells and the external fluid space of scala media (*7*). The decreased rate of noise-induced reduction of CM at lower temperatures and the increased rate at higher temperatures may result from differential use of energy stores by active transport and temperature-dependent metabolic processes in the cochlea. Structural changes that do not affect normal response may also be involved. In these experiments, interpretations employing temperature coefficients or Arrhenius energies of activation are made difficult by the invariance of CM with temperature before exposure to noise, the initial retardation of noise-induced loss of CM at 29°C, and the greater change with temperature in rate of loss above 37°C than below 37°C. However, the mechanism of noise-induced reduction of cochlear response apparently involves processes markedly dependent on body temperature.

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Gelation of Sickle Cell Hemoglobin: Effects of Hybrid Tetramer Formation in Hemoglobin Mixtures

Abstract. *The altered gelation behavior found in mixtures of sickle cell hemoglobin with other hemoglobins is due to the formation of hybrid hemoglobin tetramers from unlike dimers. The hemoglobins need not possess the deoxy quaternary structure for gelation to occur; liganded forms are also capable of participation in gelation.*

If erythrocytes from patients with sickle cell anemia are deoxygenated, aggregation of their sickle cell hemoglobin, HbS (*1*) occurs, which produces the distortion of the erythrocyte into the characteristic sickle or holly-leaf shape. If the hemoglobin from these patients is purified and deoxygenated, similar aggregation may occur, which leads to the formation of a solid phase, a nematic gel. Gelation is highly dependent on hemoglobin concentration; the critical concentration, below which no gelation will occur, is known as the minimum gelling concentration (MGC) and is a function of other variables such as temperature, *p*H, ionic strength, and presence of organic phosphates. In addition, determination of the structural features which the hemoglobin must possess if this gelation is to occur is central to an understanding of the molecular mechanism of sickling.

A productive approach to this problem has been adopted by Bookchin, Nagel, and Ranney (*2*), after the initial studies of Singer and Allison (*3*). They have studied the dependence of the MGC on the composition of a series of deoxygenated mixtures of HbS with other, non-S hemoglobins (HbA, HbF, HbC Harlem, and Hb Korle-Bu) and with CNmet-HbS. In this way, the extent of interaction between these other hemoglobins, with different structures, and normal deoxy-HbS can be readily determined. In short, they find that in mixtures of these hemoglobins with HbS, the MGC increases, but the partial concentration of HbS at gelation decreases. These other hemoglobins are therefore able to replace HbS in gelation, in a manner that is still unknown.

A recent quantitative analysis of such data (*2*) by Minton (*4*) assumes that aggregation proceeds via two steps: the first involves linear polymerization of hemoglobin tetramers into filaments, and the second, side-by-side aggregation of these filaments to form the gel. These two steps are assumed to be affected differently by the nature of the amino acid side chains at positions 6β (Glu in HbA and Hb Korle-Bu; Val in HbS and HbC Harlem), and at 73β (Asp in HbA and HbS; Asn in HbC Harlem and Hb Korle-Bu), and by the quaternary structure of the hemoglobins. I demonstrate here that these data (*2*) may be fitted quantitatively by a somewhat simpler model, based on the presence of hybrid hemoglobin tetramers formed by association of unlike dimers in such binary mixtures (*5*). Further, I show experimentally that if the formation of such hybrid tetramers is prevented, then the MGC is increased. The role of hybrid tetramer formation in the gelation of binary hemoglobin mixtures has been discussed (*2, 6, 7*), but no quantitative analysis or experimental test has hitherto been applied.