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Sensitive Periods of Susceptibility to Auditory Trauma in Mammals

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Evidence is presented to support the hypothesis that the cochleae of young animals are more susceptible to auditory trauma than the cochleae of the adult. A sensitive period of heightened susceptibility to acoustic trauma from noise exposure has been demonstrated in three mammalian species. The cochlear pathology associated with this trauma is severe damage to the outer hair cell system. Abnormal growth of auditory evoked responses recorded in central auditory nuclei accompanies the receptor damage during the sensitive period. There is evidence of a similar sensitive period of susceptibility to cochlear insult from ototoxic drugs. The time frame of the sensitive period may be different for drug or noise insult to the cochlea, but the principal pathology of outer hair cell loss remains the same in both cases. The implication of these sensitive periods to auditory trauma, for human development is considered.

Introduction

The question of whether the developing ear is more vulnerable to auditory trauma than the adult ear has a short history. However, animal models of early auditory trauma during the past 5 to 7 years offered some interesting observations, and it is the purpose of this paper to summarize some of these findings.

Is the Developing Ear More Susceptible to Acoustic Trauma?

Data from five mammalian species support the hypothesis that exposure to intense sound in the developing ear is more traumatic than in the adult ear. We will examine these data with respect to exposures that produce either a permanent hearing loss or a temporary hearing loss. We will also consider data which indicate that the cochlea passes through a sensitive period of enhanced susceptibility to acoustic trauma. The central consequences of this trauma will also be noted.

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Permanent Damage

The cochlear microphonic (CM) response has been measured in 8-week-old kittens and adult cats (*1*) 30 days after exposure to intense pure tones (50 min of a 5.0 kHz tone at a sound pressure level (SPL) that varied somewhat between test groups, but which was typically 105 dB). The results, for certain stimulus levels, indicated a loss in CM sensitivity in the kittens which was greater than in the adult. The CM response reflects the integrity of the cochlear receptor cells (particularly the outer hair cells) and it is likely that the kitten hair cells were more traumatized by the exposure than those in the adult. Noise exposure in the neonatal guinea pig (30 hr of white noise at 120 dB SPL) beginning at either 2 or 8 days postpartum has also been shown to produce significantly greater cochlear pathology (loss of outer hair cells) than the same exposure in the 8-month-old adult (*2*). This observation has been extended to less traumatic noise exposures in neonatal and adult guinea pigs (*3*). It has also been shown that the auditory system of the guinea pig fetus in utero is susceptible to noise exposure (*4*). In the guinea pig studies, the pathology observed along the neonatal organ of Corti was generally the same. Hair cells were permanently damaged, and in particular the outer cochlear hair cells suffered the greatest loss. The inner hair cells were rela-

tively unaffected. This evidence indicates that the cochlea of younger animals is more severely traumatized by intense sound than that of the adult.

Temporary Fatigue

The permanent loss of cochlear structures and function cited above may represent one aspect of a more general process within the receptor organ. If younger ears are more generally susceptible to overstimulation, then exposure to sound at levels that do not cause permanent hearing loss, ought to produce heightened levels of temporary auditory impairment. The process of auditory fatigue was examined in five groups of neonatal hamsters at selected ages between 15 and 85 days. The animals were anesthetized, a recording electrode was placed in the inferior colliculus, and the ear was exposed to intense pure tones (10 min of a 3.0 kHz tone at 110 dB SPL) (*5*). Inferior colliculus evoked responses were used to test auditory threshold sensitivity. Threshold shift (TS) 1 min post exposure was lowest in the 15- and 85-day-old groups, and showed complete recovery to the pre-exposure threshold within 100 min. At 40 days, however, the threshold shift was greatest, and recovery took much longer than 100 min. These data are important, for they indicate that the young cochlea is sensitive to overstimulation at both high and moderate levels. Moreover, the results also show a period of enhanced susceptibility to auditory fatigue which reached a peak around 40 days of age.

Sensitive Periods

The observation of a heightened period of susceptibility to acoustic trauma as demonstrated in the hamster, has also been shown in other experiments. These studies, conducted with mice, hamsters and rats, systematically varied the neonatal age at which the animals were exposed. The recovery interval (between 5 and 14 days), as well as all other test conditions were held constant for each group. It has long been known that certain strains of mice can be rendered susceptible to audiogenic seizures by exposure to sound during a specifically defined time after birth (*6*). The noise exposure that renders these mice susceptible to seizures is remarkably mild (90-120 sec of wide or narrow band noise at 100-110 dB SPL) given the profound effect it has on the animal (*6*). Recent work investigating the physiological basis of the sensitive period has revealed that the cochlea is severely damaged by noise exposure at this time (*7*). Furthermore, the senstivity of CM-isopotential thresholds or cochlear nucleus evoked-response thresholds may show a loss of

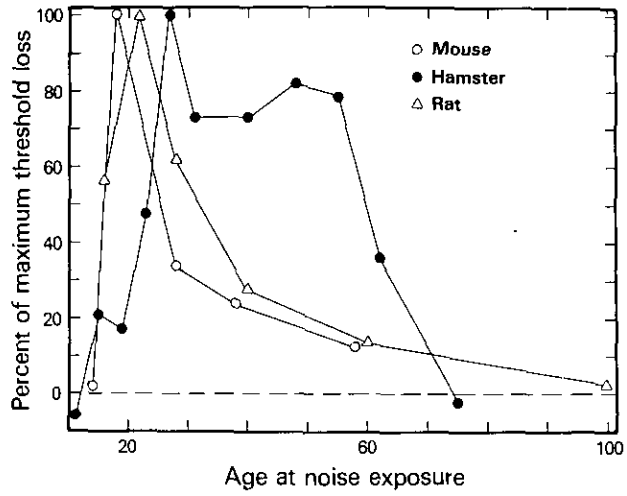

FIGURE 1. Time course of the sensitive period is plotted in three species: (○) mouse; (●) hamster; (Δ) rat. The curves represent the percent of maximum threshold loss at the most affected frequency across time. Redrawn from Saunders and Tilney (*13*).

between 25 and 40 dB after noise exposure during the sensitive period (*8*, *9*). Exposure to the same noise in older animals (40-50 days) has relatively little effect on threshold sensitivity (*9*). The most sensitive period in the C57BL/6J mouse appears to be between 17 and 19 days while in the BALB/c mouse it occurs between 21 and 23 days. Similar studies have revealed a sensitive period for acoustic trauma in the hamster between 30 and 40 days (*10*, *11*) and in the rat between 20 and 25 days (*12*). Again, the same exposure conditions presented to hamsters older than 65 days or rats older than 40 days has no traumatic effect. The characteristic time course of the sensitive period for acoustic trauma in these three species is summarized in Figure 1. In this figure, the percent of maximum threshold loss at the most affected frequency is plotted as a function of age.

In mouse, rat and hamster, the onset of the sensitive period corresponds well with the final stages of functional and structural maturation of the cochlea. The cochlear histopathology observed in both rat and mouse after noise exposure during the sensitive period is geneally the same. There is massive outer hair cell damage widely distributed throughout the cochlea (*7*, *14*, *15*). Remarkably, the inner hair cell system appears undamaged. These observations are similar to those reported in the kitten and guinea pig; however, the degree of outer hair cell loss in these species was less pronounced than that reported for the mouse and rat. In the kitten and guinea pig, the age at exposure was not

manipulated specifically, and the results in these neonates may lie outside the most effective time of the sensitive period.

Central Consequences

In two of the species studied (hamster and mouse) an interesting phenomenon in the central auditory pathway accompanies the loss in peripheral auditory function after noise exposure during the sensitive period. There is evidence from a number of sources that outer hair cell pathology is associated with the abnormal growth of intensity in central auditory nuclei, or in the animal's behavioral judgement of loudness, with increasing stimulus intensity. Abnormal growth in evoked response amplitude with increasing stimulus intensity has been observed in the inferior colliculus and the cochlear nucleus of the mouse and hamster (*16-18*). The interesting feature of this abnormal growth in response amplitude in the noise exposed animals is that at high stimulus levels, the response far exceeds that seen in control animals. For example, in the BALB/c mouse exposed to noise at 21 days of age and then tested at 27 days of age, the cochlear nucleus evoked response to a click stimulus at 95 dB SPL averages about 220 μV. Control animals at the same age show a similar evoked response amplitude to a 95 dB click. At 110 dB SPL, however, the noise-treated subjects exhibit a 510 μV response, whereas the control animals show only a 305 μV response! The abnormally large response to intense sound in the noise exposed neonate has been called over-recruitment (*16*) and an example of the growth in evoked-response amplitude with increasing stimulus intensity, in control and noise-exposed mice, is presented in Figure 2.

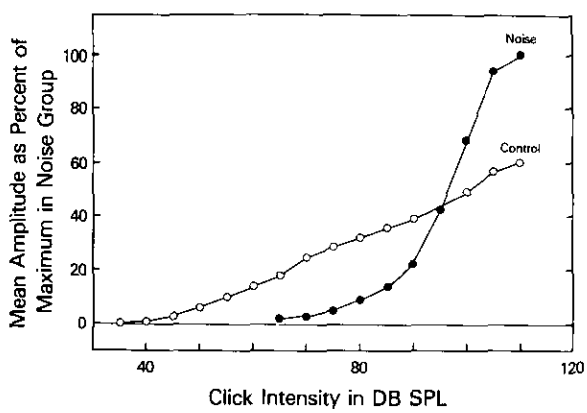

FIGURE 2. Growth in evoked response amplitude for a group of noise-exposed and control BALB/c mice. The noise exposure occurred at the peak of the sensitive period in this species. Amplitude is plotted as a percent of the maximum response in the noise group. Redrawn from Saunders and Bock (*18*).

Recent evidence also shows sustained after-discharges in the post-stimulus time histograms of inferior colliculus cells recorded in noise exposed neonatal mice (*19*). Similar after-discharges are not seen in the inferior colliculus cells of control mice. Whether or not this is the cellular counterpart of the "over-recruitment phenomenon" has yet to be determined. Furthermore, the peripheral (cochlear) or central origins of over-recruitment are not yet understood.

Is the Developing Ear More Susceptible to Ototoxic Trauma?

There is recent evidence suggesting a sensitive period for ototoxic insult to the cochlea. Mice of the BALB/c strain have been exposed to the ototoxic amino glycoside, kanamycin, and the data suggest that a 16-day treatment period (one injection of 400 mg/g per day) between 5 and 21 days produces a 40% to 60% loss of outer hair cells in the apical turn and a 70% to 90% loss in the basal cochlear turn. A 10-day treatment from 17 to 27 days produces a 40% loss of outer hair cells throughout the cochlea (*7*). In both instances the inner hair cells appeared normal. Unfortunately age and number of injections were confounded in this study, making it difficult to conclude if the pathology was due to age or number of injections. However, results from a recent experiment using the acoustic priming model to evaluate the ototoxic effect of kanamycin suggest that BALB/c neonates (10 to 14 days old) are at the peak of the sensitive period to ototoxicity, (Chen, personal communication). The dose levels used in this study were also 400 mg/g per day, but the number of injections was held constant for all age groups. The utility of the acoustic priming model for assessing the effects of ototoxic drugs has been discussed elsewhere (*20*). It is interesting to note that a 16-day injection period in the adult mouse (C3H strain) had a far less traumatic effect on hair cells or hearing (*21*). Data for the rat pup also indicate a profound cochlear pathology of outer hair cells, and a loss in auditory function, accompanying kanamycin treatment during days 11 to 20 postpartum. Identical treatments from the days 1 to 10 or from day 15 to day 23 had relatively little effect on auditory function or on cochlear structures (*22*). The profound loss of outer hair cells in these ototoxic poisioning experiments was the same as that observed from noise exposure during the sensitive period. The sensitive period to oto-

toxic trauma is difficult to precisely determine, but the initial evidence suggests that it precedes the sensitive period to acoustic trauma in the mouse and rat. The observation of a difference in sensitive periods is important and needs further elaboration, since it suggests different underlying developmental mechanisms for these two traumatic agents. As a final point there may be a sensitive period for ototoxic exposure in the fetal guinea pig. Drug delivery to the mother is very effective in altering the fetal auditory system during the last three weeks of pregnancy (*23*).

Conclusions

The data in rat, mouse and hamster indicate that the sensitive period of greatest susceptibility to acoustic trauma occurs around that time that the cochlea is achieving its final stages of maturation. If this observation can be generalized to all mammalian ears, then the cochlea of man may be susceptible to acoustic trauma as it reaches its final stages of development between the eighth and fifth week before birth. It must be strongly emphasized, however, that there is not a single piece of direct evidence, that the authors are aware of, in support of this conclusion for man. Furthermore, the situation in placental mammals is complicated because the attenuating properties of the acoustic pathway to the fetal ear are poorly understood. The attenuation of the abdominal wall and placental fluids, and the fact that the middle ear is fluid filled, preclude the possibility of accurately specifying the effective stimulus reaching the fetal ear. These arguments, of course, do not apply to the premature infant born 5-8 weeks early. Similarly, antibiotic drug treatment of the mother during the last trimester of pregnancy may have a profound influence on the cochlea of the developing fetus.

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