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ONTOGENY OF AUDITORY SYSTEM FUNCTION

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INTRODUCTION

Knowledge evolves much faster than nature. It is, however, by definition an inaccurate abstraction (31). Any attempt to describe the ontogeny of mature function is limited by the accuracy of our current abstraction. This review, with the exception of the final section, is therefore biased toward ontogenetic analyses of those physiological processes that we best understand. Space limitations kept many important areas and contributors from being treated.

Why study the ontogeny of auditory information processing? One reason is to understand the development of audition, per se, including such phenomena as the endocochlear potential (9) or the ontogeny of the frequency/place principle (74, 110). Another reason is to use unique qualities of the auditory system to approach more general issues of developmental neurobiology (106). Such issues include the demonstration that afferents influence cell death (73) or the ontogenetic elimination of supernumerary inputs in the central nervous system (60). Development can also be used as a tool to further understand the principles underlying adult function. Pujol and his colleagues, for example, have used the fact that inner hair cell differentiation precedes that of outer hair cells to investigate functional differences between these two cell types (18).

DEVELOPMENT OF CONDUCTIVE ELEMENTS: EXTERNAL EAR AND MIDDLE EAR

Maturation of the elements that collect, focus, and transmit mechanical motion to the cochlea sets physical limits on the capacities of the maturing inner ear and central processing network. Recent reviews cover functional development

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(120), the embryology (81, 144), and the maturational pattern observed in humans (2).

External Ear

The shape of the pinna and size of the ear canal influence sound reaching the tympanic membrane differentially as a function of frequency (123). Therefore, as the pinna and ear canal grow, a process which is largely postnatal, we might expect to see major changes in the pattern of spectral sensitivity. Saunders et al (120) point out that the relatively small ear canal and pinna of the newborn will tend to resonate at higher frequencies, where the newborn is relatively less sensitive, than that of adults. In addition, the immature ear canal is more compliant than that of the adult, so the maximum gain due to resonance will be less in the neonate. These factors probably result in an overall loss of sensitivity in the upper half of the frequency range due to external ear immaturity.

Decreased high frequency sensitivity, along with the reduced head size of neonates, also has implications for binaural sound localization. Smaller head size will mean that the maximum interaural intensity differences (123) will occur at higher frequencies in neonates than in adults; as the head approaches adult size, progressively lower frequencies produce an interaural intensity difference (78). Therefore, sound localization using binaural cues should be more difficult for the newborn, especially in the middle frequencies where interaural intensity cues can play less of a role. Furthermore, maturation of the temporal microstructure of receptor and neural responses, usually thought to be important for the processing of interaural time differences, is prolonged. In summary, we might expect young animals and humans to show difficulties with sound localization. While it has been shown that young animals and humans can localize sounds (19, 20, 80), neither the extent to which binaural cues are used nor the accuracy of localization ability have been thoroughly studied as a function of development.

Middle Ear

Middle ear structures, tympanic membrane and ossicular chain, provide a 35–40 dB pressure gain; their development, therefore, can impose strict boundary conditions on the ontogeny of auditory sensitivity. Saunders and colleagues (121) provide a detailed and lucid review of this material; only the most important points will be mentioned here.

Most early studies, using tympanometry to measure developmental changes in tympanic membrane immittance, found a precipitous drop in the magnitude of compliance 40–80 days after birth in human neonates (11, 63, 66, 67, 133). It now appears that when the component quantities of admittance (conductance and susceptance) are considered, there is instead a net increase in admittance during the first three months after birth (55). The latter results are in accord with recent developmental studies using hamsters and chicks (98, 121). Using a capacitive probe, Relkin & Saunders (97) were able to measure developmental changes in displacement of the tympanic membrane at frequencies up to 35 kHz. Displacement increased up to 75 days of age in the hamster. Below 10 kHz the developmental change was flat across frequency. Above 10 kHz, however, displacement appeared to have a sharper roll-off, with increasing frequency in young animals than in the adults.

From these results there can be little doubt that at the youngest ages middle ear function is an important factor limiting hearing sensitivity. In both the chick and the hamster, however, it appears that adult thresholds mature *prior* to final maturation of middle ear function, at least for low frequencies (7, 46, 68, 96, 119). In addition, middle ear function in the young animals cannot account for ontogenetic changes in sensitivity across frequency (98). Therefore, developmental changes in middle ear contribute to, but do not appear to account for, maturation of adult hearing sensitivity.

In order to understand the development of hearing we must document changes in the efficiency and spectral purity of information transfer from the acoustic environment to the inner ear. Future studies simultaneously measuring input-output functions of the middle ear and the cochlea across age will be important. This gap in our knowledge is particularly apparent when we consider differences that must exist between animals which develop hearing prenatally (humans, most ungulates, and precocial birds) and those which begin hearing after birth (such as most rodents and carnivores). In animals that hear prenatally, the external and middle ear spaces are fluid-filled. Therefore, the role of the tympanic membrane and ossicular chain must be very different. Presumably the conduction of sound to the inner ear in an aquatic embryo will follow principles similar to bone conduction (136). Empirical studies of the transfer function under these conditions, however, are not available.

DIFFERENTIATION OF THE INNER EAR

Normal inner ear development has been reviewed from several perspectives (106, 143, 145, 158). The tissue interactions important for the determination and early differentiation of inner ear tissues are being intensely investigated in vivo (40, 56) and in vitro (84, 142). Of the most interest here are the final stages of differentiation which immediately precede or overlap with the maturation of auditory function.

Some of the best descriptions of the final stages of inner ear differentiation are those of Retzius (99). Over the past century his observations have been confirmed and elaborated using modern methods and on a variety of animals (18, 38, 72, 89, 91, 92, 106, 125, 130). While some generalizations are possible, such as the differentiation of inner hair cells prior to outer hair cells and the establishment of afferent synapses before efferent connections, the major point to emphasize is that no single event triggers the onset of cochlear function. As suggested by Wada (147), the events leading up to the onset of function include the simultaneous and synchronous maturation of many mechanical and neural properties, including thinning of the basilar membrane, formation of the inner spiral sulcus, maturation of the pilar cells, freeing of the inferior margin of the tectorial membrane, development of tissue spaces in the organ of Corti, differentiation of the hair cells, establishment of mature cilia structure, and the maturation of synapses.

The final stages of maturation do not occur simultaneously throughout the length of the cochlea. Retzius (99) showed a clear gradient of differentiation extending from the basal turn. This gradient may not be present in the early stages of differentiation (27, 112), but substantial evidence supports its existence during the final stages of maturation (e.g. 1, 3, 10, 26, 37, 57, 93, 95, 99, 147). In species ranging from chicken to man, differentiation occurs first in the mid-basal region and spreads in both directions, with the apex maturing last. A corresponding pattern of differentiation has been described at more central locations, including myelination of kitten spiral ganglion cells (104), axon growth into the hamster dorsal cochlear nucleus (134), and a variety of morphological and physiological events in the chick brain stem auditory nuclei (59, 108, 128). Functional implications of this developmental gradient are discussed in the next section. It is important to note that essentially nothing is known about how this gradient arises, what factors regulate it, or why it occurs. Studies aimed at these questions are needed.

The pattern of synaptic development at the base of inner and outer hair cells has been studied in detail by Pujol and his colleagues (72, 90, 91, 95, 124). Synapse formation on inner hair cells occurs early and undergoes only minor modifications. Outer hair cells are initially surrounded by afferent terminals, which are gradually replaced by numerous efferents. Then the large calyciform efferent terminal, typical of the mature cochlea, forms. Pujol speculates that the development of efferent terminals and the concurrent reduction of afferent terminals on the outer hair cells is responsible for changes in frequency selectivity.

The relationships of stereocilia structure to the tuning properties of the mature cochlea are only beginning to be appreciated (137, 138, 139). At present there is little information on the development of these structures. In the chick, stereocilia first arise near the apex and their orientation specificity emerges gradually at about the time function begins (27). The stereocilia, kinocilium, and an associated bulbous structure have been described in five- and seven-month-old human fetuses (39). In view of recent findings, indicating that the tuning properties of the cochlea may shift during ontogeny (see below), it is of obvious importance to rigorously examine the developmental relationship between cilia structure and frequency selectivity.

DEVELOPMENT OF THE PLACE PRINCIPLE

The most fundamental principle of auditory science is the place principle (4). Simply stated, there is a progression of positions along the basilar membrane that are most sensitive to (i.e. "tuned to") successively higher frequencies. Apical positions (distal in birds) are most sensitive to low frequencies; progressively more basal regions (proximal in birds) are selectively responsive to successively higher frequencies. This relationship is thought to be due to the mechanical properties of basilar membrane motion and the characteristics of the stereocilia (see reviews by Rhode and T. Weiss, this volume). Most animals do not simultaneously begin hearing all frequencies that are included in their adult dynamic range. Behavioral and physiological responses are first elicited by low or mid-low frequencies, and responsiveness to the highest frequencies develops last (44, 105, 106). Other measures of auditory system function show a corresponding developmental pattern, e.g. attainment of adult thresholds (79), phase locking by neurons in the cochlear nucleus (13), and most sensitive frequency (35, 96). While there may be exceptions (155), the pattern is remarkably universal across both avian and mammalian species.

Since responsiveness to relatively low frequencies develops early, and high frequency responsiveness matures last, the place principle predicts that apical or mid-apical regions of the cochlea are the first to mature and that basal regions mature last. As noted above, just the opposite result is consistently found: cochlear differentiation occurs first in the basal or mid-basal region, and the *last* part of the cochlea to undergo differentiation is the apex.

Developmental changes in the external and middle ear cannot account for this paradox (97). An alternative explanation, that the values of the place code along the cochlea are changing during development (106, 108), has recently been tested (74, 110). Its implications are shown in Figure 1. The upper diagram in each part schematically shows the cochlea, from base to apex, and the relative positions of the traveling waves produced by several different pure tones. In the bottom section of this diagram the orderly, "tonotopic" representation of input to the central nervous system is shown. The CNS neurons are selectively tuned to the frequencies indicated (in kHz). Our hypothesis, shown in the left and middle diagrams, was that during the early stages of hearing the base or mid-basal region of the cochlea and the basal representation areas of the central nervous system are the first to respond to sound. But these areas are initially most sensitive to relatively low frequencies. With maturation of both mechanical and neural properties, the values of the place code gradually shift toward the apex until the mature organization is achieved.

Two testable predictions emerged from this hypothesis. The first (upper part of Figure 1) was that there would be a systematic ontogenetic shift in the position of hair cell damage produced by pure tone high intensity sound exposure. Low or midrange frequencies should produce maximum damage at

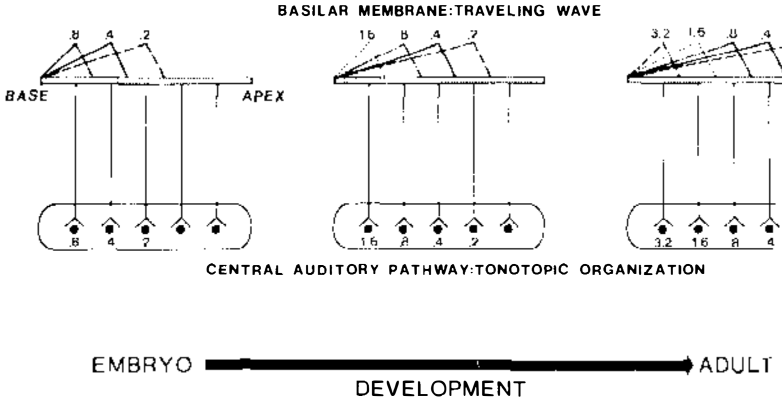

Figure 1 Model of inner ear functional development. The sequence of development is shown from left to right. The basilar membrane, from base to apex, is depicted at the top of each section; the positions of the traveling waves produced by pure tones of several frequencies (in kHz) are indicated. A region of the central auditory pathways that is tonotopically organized is shown connected to each basilar membrane. The numbers indicate the "best frequency" (in kHz) of neurons at each location. At the beginning of auditory function (left diagrams) the basal half of the cochlea is responsive to relatively low frequencies and the central nervous system areas receiving projections from the base respond to low frequencies. With maturation, middle and right sections, the apex of the cochlea begins responding to low frequencies and the base becomes more and more sensitive to high frequencies. The resulting shift in neuronal best frequencies is indicated at the bottom of each diagram.

progressively more apical locations as the animals mature. When tested by Rubel & Ryals (110) using three different frequencies on three age groups of young chickens, the position of maximum damage shifted systematically as predicted. This experiment was carried out during the very late stages of hearing development, after nearly all thresholds had already reached adult values, probably corresponding to the perinatal or immediate postnatal period in humans.

The second prediction was that in each tonotopically organized auditory region of the brain stem, the position at which neurons are responsive to a particular frequency will shift during development. Stated differently, the neurons at any given location within an auditory area of the central nervous system should respond to successively higher frequencies during development. In collaboration with William Lippe, electrophysiological "mapping" was used to determine the relationship between the location of neurons and the frequency to which they were most sensitive (75). In each area of the brain stem investigated, embryonic neurons were most sensitive to tones 1–1.5 octaves below the frequencies that activate the same neurons a few weeks after hatching.

Taken together, these two experiments strongly support the model of a shifting place code during development. In all likelihood, the underlying mechanisms in this process include both mechanical and neural changes. An exciting possibility is that the changing tuning properties are also reflected by changes in the structure of stereocilia (139).

The generality of this process across species is also supported by data available on mammals: (*a*) As noted above, the paradoxical relationship between cochlea development and functional ontogeny is nearly universal across species; (*b*) Ryan & Woolf (113) have shown an ontogenetic shift in the position of neurons in the gerbil dorsal cochlear nucleus that increases glucose uptake in response to a 3 kHz tone; (*c*) Pujol & Marty (94) noted that only relatively low frequency tones produced recognizable evoked potentials in the cerebral cortex of very young kittens, but the potentials were found in the "high frequency" region (157); and (*d*) Harris & Dallos (53) have recently reported a systematic developmental increase in the cut-off frequency of cochlear microphonic potentials recorded from the basal turn of the gerbil cochlea.

The functional implications of this model are that at some point during development each part of the cochlea, and thereby each tonotopic region of the central nervous system, will be maximally responsive to relatively low frequency tones. With maturation, each area will be responsive to successively higher frequencies until adult values are reached. It is perhaps not coincidental that low frequencies are present in the environment of young organisms, whether in a burrow, in an egg, or in utero (5, 48, 146). If the development of normal function is dependent on external stimulation, then the developmental pattern we have proposed will provide a mechanism to insure that each neuronal region receives adequate stimulation from the environment.

DEVELOPMENT OF NEURAL RESPONSE PROPERTIES

Over the past ten years many investigators have examined the ontogeny of responses to sound by neurons at several levels of the auditory pathways. There are two purposes of such studies.

First, we would like to understand the ontogeny of auditory "coding." Certain acoustic parameters are represented in the pattern of neuronal activity. This information allows the organism to "perceive" sound and to differentially act as a function of its temporal and spectral properties. By studying the development of neuronal responses, investigators hope to understand the neural events underlying the ontogeny of sensation and perception. The implicit assumption is that the neural response parameters that we have chosen to study in adult organisms, and therefore developmentally, are the ones that code relevant acoustic dimensions. To the extent that this assumption is correct, current studies will be useful for understanding the development of perception. It is important to note that as our understanding of the coding of acoustic information by the mature auditory system evolves (see Sachs, this volume), the methods and approaches for studying developmental information processing must also change.

The second reason for studying the coding properties of developing neurons is to assess structure-function relationships. Thus, development can be used to assess the structural properties necessary for a particular pattern of responsiveness to sound or to assess the relative maturity of more peripheral parts of the auditory system. The implicit assumptions are: (*a*) that the same structural features underlie a particular pattern of activity in young and adult organism; and (*b*) that causal relationships can eventually be experimentally detected among the myriad of temporal correlations.

We know remarkably little about the ontogeny of auditory perception. Threshold changes during development have been examined in a few species (e.g. 33, 35, 46, 106, 122), but psychophysical studies attempting to evaluate the spectral, temporal, or spatial resolving power of the developing auditory system are rare (34, 44a, 46, 68, 83). In order to relate the development of neurophysiological response properties to the ontogeny of perception, a great deal more emphasis must be placed on evaluating the ontogeny of behavioral abilities.

The common strategy of applying the same techniques to neurophysiological studies of young animals as to adults can lead to invalid conclusions. Young animals respond differently to anesthetics, blood loss, changes in body temperature, and the host of other physiological conditions that influence auditory responsivity. In addition, differences in responsivity along "standardized" dimensions (e.g. repetition rate) (58, 76, 107) may be influencing responses to the dimensions under investigation (e.g. thresholds or tuning).

There have now been a large number of neurophysiological studies examining developmental changes in thresholds and tuning properties of neurons in the mammalian auditory system. Reviews of this work are available (12, 103, 106, 152). At the level of the eighth nerve, cochlear nucleus, and inferior colliculus, thresholds improve and tuning curves of individual neurons become sharper (e.g. 14, 79, 101, 153). The recent methodological advance of using tone-on-tone masking paradigms for physiological studies of frequency selectivity (29, 30, 51, 52) in developing animals (16, 120, 125) has also demonstrated ontogenetic "sharpening" of frequency selectivity. Although use of the evoked potential tuning curve method makes some assumptions that have yet to be verified in developing animals, its application to developmental questions can be of great value. For example, using these techniques it will be relatively easy to simultaneously record from several regions of the auditory system, to quantitatively assess their relative developmental rates. In addition, chronic preparations are feasible.

Physiological response latencies decrease as a function of both peripheral and central changes (12, 106). The dynamic range of neurons increases, probably primarily due to changes in threshold and in the ability of synapses to follow high rates of activation (13, 59, 77). In general, the response changes that have been examined in the human fetus or neonate follow parallel developmental trends (c.f. 115, 116, 132).

Recent emphasis on the temporal microstructure of neuronal responses (see Sachs, this volume) makes developmental analysis particularly interesting. The lone published study (13) indicates that the development of phase-locking, particularly to high frequencies, is quite prolonged. This is especially interesting because maximum firing rates mature early.

Other properties of the spike train responses, peculiar to certain subsets of CNS neurons, are also receiving increasing attention by developmental neurophysiologists (e.g. 15, 77, 102, 126, 154). At present, most investigators are content with cataloging the developmental history of these properties and correlating their time-course to the myriad of morphological events that are occurring over the same time period (64, 75, 100, 114, 128, 134).

EXTRINSIC INFLUENCES ON AUDITORY SYSTEM ONTOGENY

Hypersensitive Period

Saunders & Bock (118) summarized the literature on age-dependent differential susceptibility to aminoglycosides and noise exposure. Exposure of young rodents to drugs or noise at levels that do not produce damage in adults can cause severe hearing loss and histological damage to the cochlea (6, 17, 70, 71, 88). Pujol and coworkers have proposed that the period of hypersensitivity corresponds to the final stages of anatomical and functional development of the cochlea. They hypothesized that the development of efferent endings is involved. However, the biological mechanisms underlying differential susceptability of young animals is not known. When and if hypersensitivity occurs in human infants, and if it occurs during other periods of life (e.g. aging) (54), are also still undetermined. A fruitful approach toward understanding hypersensitivity may be provided by examining age-related differences in temporary threshold shift (7).

Afferent Influences on Central Auditory Pathways

Another class of "extrinisic influences" are afferents from the inner ear to the central nervous system. In a series of studies since 1975, we have been examining how the integrity of the basilar papilla influences the development of neurons in the chick brain stem auditory system. After 11 days of incubation, when function normally begins and the second-order neurons are innervated, the presence of an intact receptor exerts a profound influence on the postsynaptic neurons (8, 32, 62, 73, 85, 111). In embryos, newly hatched chicks, or 6-week-old chickens receptor removal resulted in the loss of 25–40% of the cells in n. magnocellularis and a marked reduction in the size of the remaining cells. In the postnatal animals, cell loss and cell atrophy were evident by two days and metabolic changes in the neurons were evident within six hours. Strikingly different results were found in 66-week-old chickens: cell loss was less than 10%, and the reduction in cell size was negligible. Yet, the auditory system of the chick is quite mature at hatching and adultlike in every way we've observed even before one month posthatch (45, 46, 61, 109, 110, 119, 128). The period of susceptibility, therefore, may be determined by general maturational factors (e.g. pituitary or adrenal function) not specific to the auditory system.

The results of peripheral destruction appear to be similar in mammals. Trune (140, 141) recently reported marked changes in cell number, cell size, and dendritic size in the mouse cochlear nucleus following neonatal cochlear destruction. In newborn gerbils, cochlear removal results in similar changes accompanied by alterations of the projections of the intact cochlear nucelus to the inferior colliculus (82). Cell loss following adult cochlear removal has not been reported in mammals (65, 87, 150). Studies on other sensory systems have also reported that deafferentation in young animals results in profound cell loss or atrophy, whereas similar manipulations in adults have much less effect (28, 41, 49, 86, 156).

Monaural or binaural occlusion also influences neuronal structure or function in the brain stem auditory nuclei of birds and mammals, a number of studies have shown. Webster & Webster first reported that ear occlusion and quiet rearing result in significant reductions of perikaryon area in many areas of the cochlear nucleus and superior olivary complex (149, 151); conductive hearing deficits in adult mice did not produce reliable differences. Anatomical changes produced by presumed conductive hearing losses during development have also been shown in the rat and chick (23, 24, 25, 36, 47, 129). One serious shortcoming of all these studies is that the normalcy of inner ear function has not been verified. Clinically, the existance of normal bone conduction thresholds is required to rule out combined conductive and sensorineural deficits. These same criteria should be applied to experimental investigations.

What do these studies tell us about the relationship between the acoustic environment, neuronal activity, and development of neurons in the auditory system? Laying aside the caveat mentioned above, they imply that cellular morphology can be altered by chronically abnormal activity. Little more can be concluded at this time. Only a few studies have sought to determine whether the abnormal condition was disrupting a normal developmental trend or producing an abnormal condition following normal ontogeny (43, 131). In some cases abnormal development has been found (47) or implicated (36); in others it appears that the effects of altered hearing are superimposed on normal development (24, 148). Moreover, it is by no means certain that a conductive hearing loss will cause a simple proportional reduction in ongoing activity in the eighth nerve, much less in the cochlear nuclei or other auditory nuclei in the brain. For example, a flat 40-decibel hearing loss can produce different effects in different frequency regions that may be due to alterations in bone conduction and/or internally generated activity superimposed on the conductive loss (129). Finally, we don't even know at which stage of development activity from the ear can begin to influence the central nervous system. Webster & Webster (148) and Brugge & O'Connor (15) indicate that the ontogeny of major anatomical and physiological processes are independent of "environmental events." However, it is important to consider activity along eighth nerve fibers, whether or not influenced by sound in the external environment, as part of the "environment" of the cells in the cochlear nuclei. Thus, in order to understand how activity from the ear influences development of central auditory system structures we need to know when a functional synaptic network is established, the ontogenetic activity pattern in the eighth nerve, and how sound influences that activity pattern throughout ontogeny.

Behavioral studies on animals subjected to altered acoustic environments (42, 68, 135), examinations of language development in children suffering chronic conductive hearing loss (50), and observations of clinicians all concur that normal function can be disrupted by an abnormal acoustic environment. Yet, to date there are only scattered results indicating altered physiological function following deprivation or altered stimulation (21, 22, 117, 127). Over the next few years it is certain that considerable effort will be expended in this area and a "battery" of changes will be demonstrated. Of paramount importance is a theoretical structure by which to interpret such changes in relation to the environment of the developing organism, activity in the neuronal network, and behavioral abilities.

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