Development of Tonotopy in the Inferior Colliculus II: 2-DG Measurements in the Kitten

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Abstract

The development of size and tonotopy in the inferior colliculus of the kitten was studied using the [¹⁴C]2-deoxyglucose technique and tone stimulation with 2 and 15 kHz at a maximum 110 dB sound pressure level. At 2 days of age, frequency-specific labelling cannot be detected. Two kilohertz labelling is distinctly visible in the rostral and central inferior colliculus at day 6; 15 kHz labelling occurs first at day 11. In the rostral and central inferior colliculus, 2 kHz labelling starts at a ventral and central position and shifts dorsalwards and to a more lateral location between postnatal days 6 and 21. Such a shift is not seen in the caudal inferior colliculus. There, the focus of 2 kHz labelling remains rather constant; only the extension of the labelling increases in the older animals. In all parts of the inferior colliculus, 15 kHz labelling starts at a ventromedial position and shifts to a more lateral location while extending also more dorsalwards as the age increases. These changes in 15 kHz labelling continue up to 3 months. In addition to the ventromedial-to-dorsolateral shift and expansion of labelling, there is also a rostral-to-caudal gradient of maturation, in that in older animals frequency-specific labelling reaches farther caudalwards. The reported changes in frequency representation in the inferior colliculus can be explained on the basis of a shift in frequency input and input sensitivity to the laminae of the inferior colliculus, mainly due to maturational changes within the cochlea and/or as a consequence of the increasing size of the inferior colliculus.

Introduction

Tonotopy, the regular order of frequency representation in centres of the auditory pathway, is a general feature of most vertebrate auditory systems and may function as a system-inherent basic reference for sound analysis. The frequency map has its origin in the frequency-place transformation within the cochlea (v. Békésy, 1960) which leads to a gradient of high to low characteristic frequencies of auditory nerve fibres innervating inner hair cells from base to apex respectively (Liberman, 1982). This adult pattern of cochlear frequency representation is the result of cochlear functional maturation, in the course of which substantial changes in frequency output have been reported (Mikaelian and Ruben, 1965; Romand, 1971, 1983, 1984; Harris and Dallos, 1984; Dolan *et al.*, 1985; Puel and Uziel, 1987; Walsh and McGee, 1987). Cochlear morphology in young mammals is generally most developed in the middle or upper basal coil (Wada, 1923; Larsell *et al.*, 1944; Bast and Anson, 1949; Kikuchi and Hilding, 1965; Pujol and Marty, 1970; Sher, 1971) with a responsiveness of the cochlear nerve fibres to rather low frequencies compared to adults. With increasing age, nerve fibres derived from the basal part respond to increasingly higher frequencies, and fibres in the mid and apical cochlear regions start responding to mid and low frequencies (Romand, 1983, 1987; Harris and Dallos, 1984; Yancey and Dallos, 1985; Arjmand *et al.*, 1988; Echterler *et al.*, 1989; Sanes *et al.*, 1989). These maturational patterns of the mammalian cochlea can be expected to

influence the tonotopy in higher brain centres (Rubel, 1984; Lippe and Rubel, 1985).

There are considerable variations, however, in the results of studies concerning the maturation of tonotopy in the central auditory systems of various mammals. They range from no change (Friauf, 1992) to changes mainly in mid- and high-frequency representation areas (Rübsamen *et al.*, 1989; Webster and Martin, 1991) to changes that affect the whole range of frequency representation (Ryan and Woolf, 1988; Romand and Ehret, 1990; Rübsamen and Schäfer, 1990). It remains to be shown whether major differences in the results relate to methodological or species differences. In addition, it has to be clarified how far developmental changes in central tonotopic maps relate to ontogenetic changes in peripheral frequency responsiveness or to plasticity in higher auditory centres. Such data will be important for the understanding of how young animals and human infants might perceive the acoustic world during the time of the maturation of their auditory systems.

In the present study, we investigate the development of frequency representation in the inferior colliculus (IC) of kittens by labelling frequency-response areas with [¹⁴C]2-deoxyglucose. This technique of labelling local functional activity (Kennedy *et al.*, 1975; Sokoloff, 1982) and active synaptic areas (Nudo and Masterton, 1986) has successfully been used to demonstrate frequency-specific responses

in the auditory pathway of adult (Nudo and Masterton, 1984; Servière *et al.*, 1984; Webster *et al.*, 1984; Huang and Fex, 1986; Martin *et al.*, 1988; Scheich *et al.*, 1993) and young (Ryan *et al.*, 1982; Horner *et al.*, 1987; Ryan and Woolf, 1988; Webster and Martin, 1991) mammals.

Materials and methods

Deoxyglucose autoradiography

Seventeen kittens, delivered after 66–67 days of gestation by normal healthy house cats (*Felis catus*), were supplied by the animal breeding facilities of the Universities of Konstanz and Ulm between 1987 and 1990. The animals were anaesthetized with 40 mg/kg sodium pentobarbital (Nembutal) and 3 mg/kg chlorprothixene (Taractan) intraperitoneally and then injected with a pulse of 170 μ Ci/kg 2-fluoro-2-deoxy-D-[U- 14 C]glucose (Amersham) intravenously. They were placed in an industrial sound-proof and anechoic room in which they were stimulated binaurally with tone bursts for 45 min. Immediately after the end of acoustic stimulation the animals were decapitated and the brains were quickly removed and frozen at -40°C . Frontal sections (20 μ m) through the IC and the brainstem were cut on a freezing microtome (Reichert-Jung, 2700 Frigocut). The slides with the brain sections were put into a Kodak X-Omatic cassette and exposed to an X-ray film (Kodak NMB) for 21 days.

Densitometric measurements of the autoradiographs were made with a computerized image-processing system (VIPER 2, Gesotec; Scheich, 1983; González-Lima and Scheich, 1984, 1986). A selectable area of an autoradiograph was scanned with a TV camera (Hamamatsu C2400) mounted on a Wild microscope. The picture was converted into a 256×256 matrix with eight-bit intensity resolution and stored on disk in a Toshiba T350 computer. In order to compare the digitized autoradiographs among animals, every picture was taken with the same magnification of the microscope, processed in absolutely the same way and calibrated to a reference of 207 on the 256-point intensity scale, which could be verified in the periaqueductal grey next to the IC of all the animals. By this normalization, densitometric profiles (Fig. 2) have the same baseline. Such profiles were generated in the following way: the 256 horizontal lines of the computer matrix were divided into 32 horizontal rows (eight lines per row) and the optical densities within each row were integrated and plotted as a three-dimensional profile of relative optical density. Density values can be expressed in arbitrary units above the common baseline. Autoradiographs were photographed with a Zeiss photomicroscope III (1.25 $\times$ objective) on Kodak TMX 100 film.

Sound system

Tones of 2 and 15 kHz frequency (Kontron counter-timer 6001) were produced in two generators (Wavetek 130 and 132) and fed into a two-channel electronic switch in which a series of 2 or 15 kHz or 2 and 15 kHz alternating tone bursts (40 ms flat top, 30 ms rise and fall times, 50 ms intervals) was formed. The output of each channel of the switch went through an attenuator (Hewlett-Packard 350D) and voltage amplifier (Hewlett-Packard 465A) to a stereo power amplifier (Filtronic FPA-200). The 2 kHz tone was delivered through a compression chamber speaker (Philips LBC 3404 + LBN 9001/00), the 15 kHz tone through two piezo horns (PCT-4000). The speakers were mounted 30 cm from the midline of the animal. Kittens of the following postnatal ages were exposed to an alternating series of 2 and 15 kHz tone bursts: 2 days (two animals), 6 days (two animals), 11 days (three animals), 21 days (two animals) and 3 months (one animal). Further, two 6-day-old and two 11-day-old

animals were exposed to a series of only one tone frequency, one animal to 2 kHz and one to 15 kHz in each age group. Finally, three kittens (each 2, 6 or 11 days old) served as control without any sound stimulation, but were otherwise treated the same as the stimulated animals. Sound pressure levels (SPLs) of each tone frequency were calibrated (re 20 μ Pa; Brüel and Kjaer condenser microphone 4133 plus measuring amplifier 2606) at the pinnae of the animals to 110 dB (2 and 6 days old), 95 dB (11 days old) or 70 dB (21 days and 3 months old). The SPL of 110 dB was the maximum undistorted output of the equipment. The other SPLs were selected to be $\sim$ 30 dB above the behavioural response threshold of kittens (Ehret and Romand, 1981).

Colliculus size

The autoradiographs of all animals were used to measure the size of the IC in the rostrocaudal, dorsoventral and mediolateral dimensions. The rostrocaudal extent was defined as the distance (measured by the number of 20 μ m sections) between the caudal pole and that rostral location at which the IC no longer reached the dorsal margin of the brain because of the spreading of the superior colliculus. The rostrocaudal extent defined thus does not include the most rostral part and rostral pole of the IC, which could not unambiguously be determined, however. The dorsoventral and mediolateral extents were measured 400, 800 and 1200 μ m from the caudal pole of the IC on the video screen that was calibrated with a calibrated micrometer scale. The dorsoventral extent was determined as the distance between the dorsal margin of the IC and the most ventral point of background labelling in the IC, which coincided with the ventral margin of the IC as defined from the original sections viewed under phase-contrast microscopy. The mediolateral extent was defined at rostral and central locations as the distance between the most medial point of background labelling at the border with the periaqueductal grey (verified by comparison with original brain sections) or the medial margin (caudal location) of the IC and the most lateral point of the IC.

Results

Development of frequency representation

Autoradiographic pictures (Fig. 1) and densitometric profiles (Fig. 2) characterize the course of the development of frequency representation in the IC of kittens.

At 2 days of age (Fig. 1) only in the ventralmost and lateral part of the IC is some weak label present, although the lateral lemniscus shows stronger labelling. There is no indication of frequency-specific labelling because the stimulated and control animal look very similar.

At 6 days of age (Fig. 1) the labelling of the ventralmost and lateral part of the IC is intensified in the control animal compared with day 2. A short stripe reaching dorsalwards in the rostral and central IC appears in the stimulated animals. This stripe can be regarded as specific for a 2 kHz response since it does not occur with only 15 kHz stimulation. A specific 15 kHz response is absent or may be included in the labelling at the ventral margin of the IC. There is no label in the most caudal $\sim$ 400 μ m of the IC.

At 11 days of age (Fig. 1) the labelling by 2 and 15 kHz can now be clearly discriminated in all parts of the IC. The 15 kHz stripe becomes distinct in the ventromedial area of the IC. In the rostral and central IC, the 2 kHz stripe still starts at the ventral margin of the IC but reaches farther dorsalwards compared with the 6-day animals. The most caudal $\sim$ 300 μ m of the IC is without specific label.

At 21 days of age (Fig. 1) the distance between the 15 kHz stripe and the ventromedial margin of the IC is increased compared with

FIG. 1. Examples of autoradiographs demonstrating the labelling pattern in the inferior colliculus at various postnatal ages (2 days, 2 d; 6 days, 6 d; 11 days, 11 d; 21 days, 21 d; 3 months, 3 m). For control animals without sound stimulation a 'c' is added to the age; for animals stimulated with 2 and 15 kHz simultaneously an 's' is added to the age. Unilateral frontal sections (all of the same magnification) are shown, taken from locations 250–600 μ m (caudal), 600–900 μ m (central) and 1000–1400 μ m (rostral) from the caudal pole of the inferior colliculus. Arrows point to labelling due to sound stimulation. d, dorsal; l, lateral. Bar: 5 mm.

11-day-old animals. The 2 kHz stripe extends farther dorsalwards. Labelling is absent in the most caudal ~200 μ m.

At 3 months of age (Fig. 1) the 2 and 15 kHz stripes have the maximum dorsal extent in the IC of all tested ages. The 15 kHz stripe has reached the maximum distance from the ventromedial border of the IC and the 2 kHz stripe is now clearly separated from non-specific labelling in the ventral IC. There is no label in the most caudal ~150 μ m of the IC.

Some examples of densitometric profiles from the central IC are shown in Figure 2. These plots demonstrate clearly the increasing distinctness and intensity of the frequency-specific labelling with increasing age of the animals. They also show that this labelling reaches more dorsalwards in the IC the older the animals are.

Densitometric profiles as shown in Figure 2 and an arbitrary but constant criterion of grey level (height) in these profiles were used to determine the dorsal extent of the 2 and 15 kHz stripes in the IC.

FIG. 2. Examples of densitometric profiles of frontal sections through the right inferior colliculus stimulated with 2 and 15 kHz at various ages. All profiles shown are calculated from autoradiographs from the centre of the inferior colliculus (~750 μ m from the caudal pole) with the same calibration for optical density (see text). Arrows indicate frequency-specific labelling. d, dorsal; l, lateral; m, medial; LL, lateral lemniscus.

FIG. 3. Maximum extent of frequency-specific labelling towards the dorsal surface of the inferior colliculus at various postnatal ages. Values are estimated from densitometric profiles (Fig. 2) in the centre of the inferior colliculus. Values at 4–5 months are estimates taken from Servière *et al.* (1984). Closed circles, 2 kHz; open circles, 15 kHz; crosses, non-specific.

In Figure 3, the distances between the dorsal surface of the IC and the dorsal margin of the frequency-specific labelling are plotted for all animals. For a given stimulus frequency, each animal contributed one value from the central IC to the plot, taken between 600 and 900 μ m from the posterior pole. It is evident that the distance between the most dorsal extent of the stripes and the dorsal margin of the IC decreases continuously during the first 3 months.

FIG. 4. Maximum extent of frequency-specific labelling towards the caudal pole of the inferior colliculus at various postnatal ages. Each animal contributed only one point (from either 2 or 15 kHz activity) to the plot.

Figure 1 shows that a 2 kHz response is present in the rostral and central but not the caudal IC at 6 days of age. This shows that the caudal IC develops metabolic responsiveness later than more rostral parts.

In Figure 4, the distance from the caudal pole of the IC to the first appearance of the frequency-specific labelling to 2 or 15 kHz more rostralwards is plotted as a function of the age of the animals. It can be seen that in young kittens frequency-responsive areas in the IC do not reach as far caudalwards as in older kittens. Thus we demonstrate a rostral-to-caudal gradient of development in addition to the ventral-to-dorsal gradient.

Development of colliculus size

The size of the IC increases, in the dimensions measured, between 2 days and 3 months of age, as shown in Figure 5. All increases are statistically significant ($P < 0.01$) by regression analysis. Rostrocaudally, the size of the IC increases by a factor of 1.39 (39% of the day 2 value). In the dorsoventral dimension, the IC size increases between 1.72 times (72.0%) caudally and 1.83 times (82.3%) rostrally. The size increase in the mediolateral dimension varies between 1.31 times (30.9%) caudally and 2.03 times (103.3%) rostrally. These values indicate that the growth of the IC is highest rostrally and least caudally.

Discussion

The present results on the dynamics of tonotopy in the inferior colliculus during functional maturation show three major gradients of development. (i) Responsiveness to a low frequency (2 kHz) starts earlier than to a high frequency (15 kHz). Responsiveness starts in the rostral and central IC. (ii) Labelling of activity to low and high frequencies starts in the ventromedial portion of the IC and, with increasing age, both extends and shifts further dorsally and laterally. The exception to this maturational pattern is the 2 kHz response in the caudal IC, which does not show a dorsolateral shift but only a dorsalward expansion. (iii) There is a rostral-to-caudal gradient of frequency-specific labelling with increasing age. The older the animals are, the farther caudalwards proceed the 2 and 15 kHz activities.

These major developmental changes in the frequency responsiveness of the IC are summarized in Figure 6. Taking the tonotopy of the adult cats (Servière *et al.*, 1984) as reference, the 2 kHz representation in the central IC shifts by ~1.5 octaves between the

FIG. 5. Development of colliculus size in the rostrocaudal (A), dorsoventral (B) and mediolateral (C) dimensions. Average values with standard deviations calculated from the right and left inferior colliculus of all animals are shown for the indicated distances (400, 800 and 1200 μ m) from the caudal pole of the inferior colliculus.

age of 6 days and 3 months, and the 15 kHz responsiveness by <1 octave between 11 days and 3 months. Comparable data have been obtained from the developing cochlear nucleus of the Mongolian gerbil (Ryan and Woolf, 1988). There, the responsiveness to low frequencies started earlier than that to high ones, and a shift of ~2 octaves in the position of labelling in the dorsal cochlear nucleus occurred for a low frequency between postnatal day 14 and adult age.

The data presented here are at variance in some respects with the results of Webster and Martin (1991) on the development of frequency responsiveness in the IC of the kitten, also obtained with deoxyglucose autoradiography. While these authors found a shift in 15 kHz

FIG. 6. Diagrams of normalized unilateral sections through the inferior colliculus of the cat summarizing the development of representation of 2 and 15 kHz frequencies. Normalization was done by drawing the labelling pattern after superposition of the ventromedial borders (dashed lines) of the inferior colliculus of all animals. The outlines of the margins of the inferior colliculus (heavy lines) are drawn only as orientation aids. Isofrequency contours at the estimated positions for 2 and 15 kHz of adult cats from Servire *et al.* (1984) are also indicated by dotted lines in the central part of the inferior colliculus. d, dorsal; v, ventral; m, medial; l, lateral.

representation between postnatal days 10 and 35 similar to that described here, they do not report a shift in 2 kHz representation. One reason for this discrepancy is that Webster and Martin (1991) seemed not to have looked at the rostral IC locations for which we found the most obvious 2 kHz shifts. Second, they used SPLs of only 75–80 dB for stimulation, so that they might have been unable to find a 2 kHz response at 7 days of age in the central IC. Third, a number of sections presented in their paper might have been considered by us as belonging to the caudal third of the IC, in which we do not find a shift of 2 kHz responsiveness, in agreement with these authors. Finally, we have generally less conspicuous non-specific labelling in the control animals, perhaps by the use of Nembutal anaesthesia. Reduced non-specific background, especially in the ventral IC, could have enhanced the chance of visibility of sound-related labelling.

The shift in the tonotopic gradient accompanied by an expansion of the represented frequency response range towards higher frequencies and of frequency responsiveness towards dorsal IC locations has its probable origin in changes in cochlear frequency input. As discussed by Romand (1987) and Walsh and Romand (1992), two major gradients have been postulated for cochlear structures after the onset of hearing, one proceeding from the mid-basal cochlea to the apex (the original idea of Rubel, 1978; Lippe and Rubel, 1983; Rubel and Ryals, 1983), the other from the modiolus centrifugally to the lateral margin of the cochlea (for a review see Rbsamen, 1992).

According to the first gradient (mid-basal to apex), which is reflected by a number of features of structural maturation that may affect cochlear mechanics and hair cell function (Pujol and Hilding, 1973; Romand *et al.*, 1976; Romand and Romand, 1982; Roth and Bruns, 1992), cochlear nerve fibres innervating the apical region start to become active later than those making connections to more basal areas. Since apical cochlear nerve fibres project to low-frequency representation sites of the adult auditory brainstem nuclei, these sites have to remain unresponsive to sound until the respective nerve fibres can be activated. With regard to the development of tonotopy in the inferior colliculus, this means that the dorsal and lateral parts, where low frequencies are represented in the adult animal (Merzenich and

Reid, 1974; Servière *et al.*, 1984), should be late to show a frequency response. This is what we find (Figs 1–3), and has been described before by electrophysiological mapping in the IC of the mouse (Romand and Ehret, 1990) and the horseshoe bat (Rübsamen and Schäfer, 1990).

According to the second gradient of cochlear maturation (medial–lateral), inner hair cells may become active earlier than outer hair cells (Pujol *et al.*, 1978; Dolan *et al.*, 1985). Responses of cochlear nerve fibres presumably based only on functioning inner hair cells have rather high thresholds and broad tuning in the low frequency range (tail of tuning curve) without the tip region of the tuning curve at higher frequencies (Robertson *et al.*, 1980; Liberman and Dodds, 1984). Hence, if cochlear function starts at a rather basal location without major contributions of outer hair cells to the output, then the cochlear nerve fibres can be expected to have high-threshold, shallow tuning to frequencies lower than their appropriate characteristic frequency normal for the basal region in the adult cochlea.

This might explain the recently observed frequency increase during maturation at a constant basal location in the gerbil cochlea (Echteler *et al.*, 1989). This high-threshold low-frequency response from the cochlear base is sent to high-frequency auditory regions of the brain. Thus, the medial–lateral gradient of cochlear maturation leads to responsiveness to comparably low frequencies at places in brain centres which, in adult animals, would respond best to higher frequencies with lower thresholds. This may be the reason for our observed shift of 2 and 15 kHz labelling in the inferior colliculus from a ventromedial towards a more dorsal and lateral position.

Still further factors may contribute to the developmental changes we see in the IC of kittens. It has been shown for the cat that the dorsal nucleus of the lateral lemniscus (DNLL) has its main projections to the dorsal and medial portion of the central nucleus of the IC while the ventral nucleus of the lateral lemniscus (VNLL) projects predominantly to the ventral and lateral parts (Kudo, 1981). 2-Deoxyglucose studies on the maturation of function in the auditory system of the Mongolian gerbil (Ryan *et al.*, 1982) demonstrate frequency responsiveness in the VNLL prior to the DNLL. If this lemniscal maturational pattern is also valid in the cat, it could contribute to the presently observed expansion of activation along a lamina from a ventral location dorsally during ontogeny. Further, it has been shown that tone–response thresholds on an isofrequency plane in the IC of the mouse are distributed regularly, in that neurons with the lowest thresholds are located in the centre and those with higher thresholds towards the margins within a plane (Stiebler, 1986). The highest threshold increase (~50 dB) from the centre of the IC was found in the dorsomedial and caudal directions. Since behavioural and neuronal response thresholds of young kittens are considerably higher than in adults (Aitkin and Moore, 1975; Brugge *et al.*, 1978; Ehret and Romand, 1981; Ehret, 1985; Walsh and McGee, 1987), the presently available sound pressure levels may have been too low to be superthreshold for all units of an isofrequency plane for the younger ages studied. If response thresholds of neurons in the cat IC have a distribution similar to the one described for the mouse, then we could predict the presently found age-related gradients of frequency-specific labelling proceeding dorsally and caudally along the major gradients of threshold increase on an isofrequency plane.

Finally, the growth of the IC can contribute to shifts in frequency-related activity during the observed postnatal period. The laminated orientation of dendritic trees is present in the central nucleus at birth of the kitten (González-Hernández *et al.*, 1989) and reaches adult orientation after the first postnatal week (Meininger and Baudrimont,

1981). The orientation of dendritic laminae is congruent with that of isofrequency planes in the central nucleus of the adult cat (Servière *et al.*, 1984), and the orientation of isofrequency planes of the kitten IC (Figs 1 and 6) is similar compared with the adult cat. The observed growth of the IC (Fig. 5) in the dorsoventral and mediolateral directions may then lead to increased spacing between dendritic (isofrequency) laminae and dorsalward expansions. If the increase in spacing between laminae happens disproportionately in the IC because of disproportionate growth favouring ventromedial and rostral IC areas, then the largest shifts in the positions of isofrequency laminae would be expected just in these areas and could explain our observed changes in the frequency representation pattern (Fig. 6). Since anatomical data about the possible changes in spacings between and shifts of dendritic laminae in the developing IC are not available, the relation between growth of the IC and changes in tonotopy must remain speculative. Data from the development of frequency representation in the IC of the mouse have shown (Romand and Ehret, 1990) that changes in the tonotopy similar to those reported here for the kitten can occur on a background of constant colliculus size.

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Abbreviations

IC	inferior colliculus
SPL	sound pressure level

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