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Keywords
medial, projections, ascending, auditory, parallel, thalamus, multiple, pathways, evidence, cat, body, geniculate

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ASCENDING PROJECTIONS TO THE MEDIAL GENICULATE BODY OF THE CAT: EVIDENCE FOR MULTIPLE, PARALLEL AUDITORY PATHWAYS THROUGH THALAMUS[1]

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Abstract

The sources of ascending input to the medial geniculate body (MGB) of the cat were studied using the retrograde transport of horseradish peroxidase (HRP). HRP injections were made iontophoretically through micropipettes which were also used to record physiological properties at the injection sites. This technique produced small injections which appeared to be restricted to single subnuclei.

The tectothalamic projection of the auditory system was found to consist of at least four distinct and separate pathways. The ventral division of the MGB receives a topographical projection from the central nucleus of the inferior colliculus (ICC) which preserves tonotopicity and provides short latency, sharply frequency-tuned responses. The medial part of the ICC projects to the deep dorsal nucleus, which contains only units tuned to high frequencies. The major inputs to the caudodorsal nucleus (DC) stem from nucleus sagulum and the pericentral nucleus of the inferior colliculus (ICP). Units in DC and the ventrolateral nucleus, which also receive input from ICP, have very broad tuning properties and late, habituating responses. Injections of HRP into the medial division (MGM) produced labeled cells scattered throughout the external nucleus of the inferior colliculus and the ventral part of ICC. This widespread input is reflected in the wide range of auditory responses found in MGM. Auditory responses in the suprageniculate nucleus were poorly defined and many units did not respond to tonal stimuli; following HRP injections no filled cells were found in the inferior colliculus, but labeled cells were found in the deeper layers of the superior colliculus and in the interstitial nucleus of the brachium of the inferior colliculus.

Together with recent findings on the auditory thalamocortical projection, these results provide evidence for multiple parallel auditory pathways through the thalamus.

The subdivision of the medial geniculate body (MGB)[3] on the basis of cellular morphological differences (Morest, 1964, 1965a) has been found consistent with differentiation by single unit auditory response properties (Calford, 1983; Calford and Webster, 1981) and with the pattern of efferent and afferent connections with the auditory cortical fields (Andersen et al., 1980a, c; Merzenich, 1981). A limited body of information also suggests that the subnuclei have different patterns of input from midbrain sources (Aitkin et al., 1981; Andersen et al., 1980b; Oliver and Hall, 1978). However, currently available data do not allow a full description of the sources of ascending input to each of the MGB subnuclei. Most information has been provided by anterograde tracing techniques utilizing midbrain lesions or injections; hence,

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[3] Abbreviations are as follows: AI, primary auditory cortical field; AII, secondary auditory cortical field; A, anterior auditory cortical field; BIN, nucleus of the brachium of the inferior colliculus; DC, caudodorsal nucleus of MGB; Dd, deep dorsal nucleus of MGB; IC, inferior colliculus; ICC, central nucleus of the IC; ICP, pericentral nucleus of the IC; ICX, external nucleus of the IC; LV, pars lateralis of MGB; MGB, medial geniculate body; MGM, medial division of MGB; MGV, ventral division of MGB; NS, suprageniculate nucleus of MGB; OV, pars ovoidea of MGB; SAG, nucleus sagulum; SCD, deeper layers of the superior colliculus; VL, ventrolateral nucleus of MGB.

some sources of input to the MGB may, as yet, be unidentified, and the relative proportions of input from the various auditory midbrain structures to each thalamic subnucleus can be assessed only by indirect means.

This study has examined the sources of ascending input to each MGB subnucleus using the retrograde transport of horseradish peroxidase (HRP) from iontophoretic injection sites which were restricted to single subnuclei. The location of an injection site was determined by reference to the single unit auditory response properties identified with the same micropipette used for the injection, and by reference to the Nissl cytoarchitecture. The extent to which these properties differentiate subnuclei has been discussed in the previous paper (Calford, 1983). As in the previous paper, the MGB has been divided into seven subnuclei: pars lateralis (LV) and pars ovoidea (OV) which together form the ventral division (MGV), the medial division (MGM), the caudodorsal nucleus (DC), the deep dorsal nucleus (Dd), the suprageniculate nucleus (NS), and the ventrolateral nucleus (VL). It was found that each subnucleus has a distinctive pattern of input from the auditory midbrain and that the response properties of single units in a given subnucleus are mostly consistent with the known properties of units in the midbrain.

Materials and Methods

Single unit recordings were made in the MGB of adult cats using micropipettes filled with 10% HRP (Sigma Chemical Co., type VI) in 0.9% NaCl. On completion of recording a region was chosen in which a small quantity of HRP cation was extruded by passing a low positive current. After allowing retrograde transport for 16 to 20 hr, cats were perfused and brains were removed and sectioned. Free sections were histochemically treated to produce a dense HRP reaction product, which allowed the identification of those cells projecting to the region of the HRP injection site. Sections were examined under a light microscope, labeled cells were plotted onto outline drawings of the sections, and cytoarchitectonic boundaries were drawn from adjacent Nissl-stained sections or by reference to a neutral red counterstain of the reacted sections.

The regions examined for the presence of HRP-labeled cells were limited to the midbrain and posterior diencephalon. Frontal sections were collected from a level 3 to 4 mm posterior to the inferior colliculus (IC) to 1 to 2 mm anterior to the MGB; sagittal sections were collected from the lateral extreme of the MGB to within 1 mm of the midline sagittal plane.

Micropipettes and recording procedures. Micropipettes were drawn from 1.5-mm diameter glass tubing which incorporated a microfilament (Clark Electromedical, type GC150F-15). The tips of micropipettes were broken against a glass bead under a microscope, to a tip diameter of 3 to 5 μm. They were back-filled by injecting the HRP solution via a 27 gauge needle into the micropipette at the point at which the taper begins, and affixed in a vertical position with modelling clay and left to stand for a few minutes, until the solution filled to the tip.

These micropipettes typically had impedances of 6 to 12 megohms (at 1 kHz) and proved to be excellent both in terms of single unit recording and with regard to iontophoresis. In these micropipettes the cation concentration is lower than normal for a recording electrode in order to optimize the extrusion of positive charge carried by HRP during iontophoresis; as a consequence their impedances were relatively high.

Recording procedures are fully outlined in the previous paper (Calford, 1983) and will be only briefly described here. During recording cats were anesthetized with combinations of pentobarbital, ketamine, and xylazine. The dorsolaterocaudal surface of the MGB was exposed by ablation of overlying tissues and micropipettes advanced into the MGB in either a parasagittal or a near-frontal transverse plane. Auditory stimuli were presented dichotically and discharge characteristics (tuning, latency, discharge pattern, and binaural responses) were assessed mainly by viewing the amplified signal on an oscilloscope, and with some use of an on-line Nova computer.

Iontophoresis of HRP. Micropipettes were coupled to the positive output of a constant current source by a short strand of silver wire. This device was capable of producing a constant current output, variable from 250 nA to 25 μA, achieved by a variable voltage output of up to 200 VDC. The signal was pulsed at a rate of 5 Hz (semi-rectified, square wave) during iontophoretic injections, as suggested by Graybiel and Devor (1974).

The magnitude and duration of the iontophoretic current and the number of injection sites were varied to suit the physiological characteristics recorded. Typically, two to six injections were made over a range of 0.2 to 1.4 mm. Since both larger currents and longer durations would be expected to produce more extensive efflux of HRP, a trade-off was made between these two parameters. Pulsed current durations of 2 to 3 min were used; an interval of 1 to 2 min between successive injections seemed to produce more consistent efflux at each site, perhaps because of a replenishment of HRP at the micropipette tip via diffusion from the overlying electrolyte. Currents used varied from 750 nA to 5 μA. The size of the injection site, as determined by the extent of the dense HRP reaction product, was larger with increased current but seemed also to depend upon other variables, such as the micropipette impedance and tip diameter.

Following an HRP injection, animals were allowed to recover for 16 to 20 hr, when they were again anesthetized and perfused with 2 liters of 0.9% NaCl followed by 1 liter of cold (4°C) 2.5% glutaraldehyde in 0.1 mol/liter of phosphate buffer (pH 7.2). The brain was removed intact and placed in 1 liter of the fixative containing 30% sucrose for at least 24 hr, after which it was transferred to 30% sucrose in phosphate buffer.

After about 1 week (minimum of 4 days) the brain was removed and trimmed. Sections were cut at 50 μm on a freezing microtome either in a sagittal plane or parallel to a near-frontal plane defined by the orientation of the caudal surface of IC. This plane is tilted 5° to 8° toward a dorsocaudal to ventrorostral orientation from the standard frontal plane. Sectioning in this plane simplified the collection of sections containing the caudal part of IC. Alternate sections, collected in cold phosphate buffer, were destined for HRP histochemistry or Nissl staining with thionine, although in some early experiments in

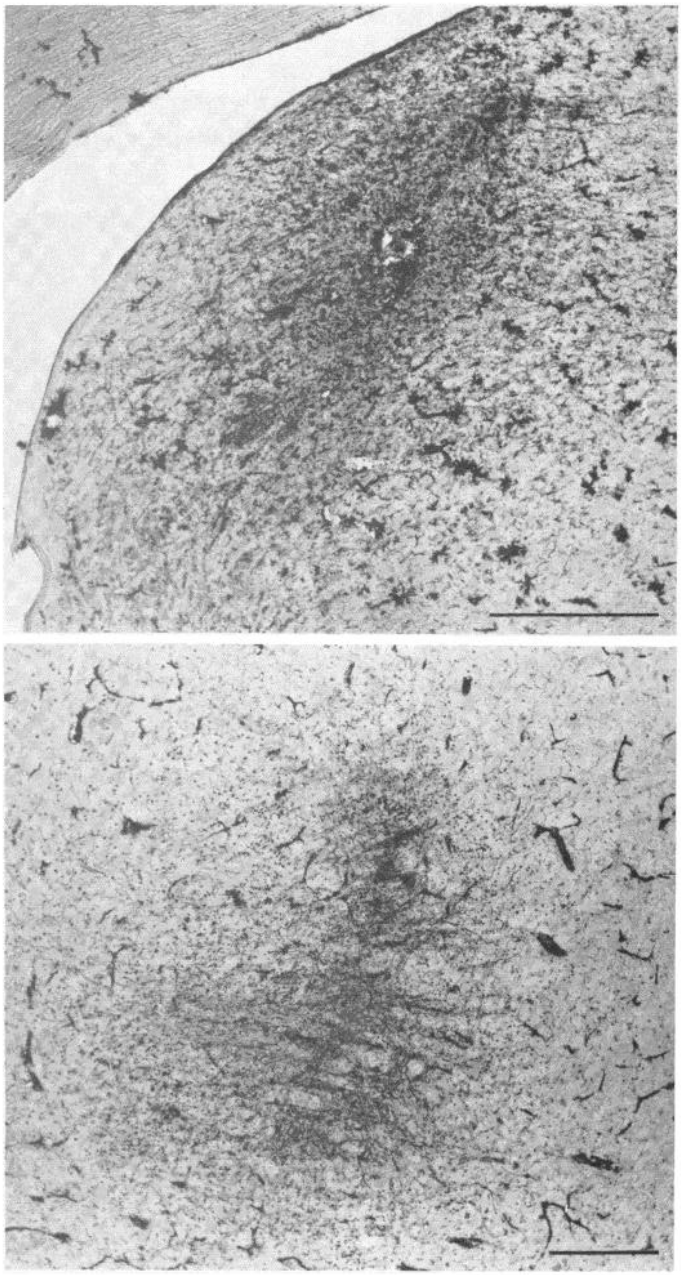


Figure 1.[4] Two photomicrographs show the injection sites in the MGB resulting from iontophoretic injections of HRP. The injection in the *upper photomicrograph* (experiment 81-37; see also Fig. 7) is contained within Dd; the *lower photomicrograph* (experiment 81-74) shows an injection into MGM. *Scale bars* indicate 500 μm (*upper*) and 440 μm (*lower*).

which parasagittal sections were cut, only every fourth section was histochemically reacted to demonstrate HRP labeling.

Sections were reacted according to a method described by Lane (1978), which uses tetramethylbenzidine (Sigma), and reacted sections were counterstained with neutral red as described by Mesulam (1978).

Identification of injection sites. The histochemical reaction used in this study is one of the more sensitive reactions available for determining the presence of HRP (Jones and Hartman, 1978; Lane, 1978; Mesulam, 1978), but, as a consequence, the size of the dense reaction area around the injection is large relative to some other methods. In this study, the injection site indicated in outline drawings represents the limits of the dense reaction product which gives way to a lighter region further from the center of the injection. This lighter region is quite large and extends for up to 2 mm from the injection site, whereas the dense region rarely exceeds 500 μm (smaller with low current iontophoresis).

Examples of two injection sites are shown in Figure 1. The dense reaction areas formed by four to five discrete iontophoretic injections with a low current, of 800 nA, were cigar-shaped cylinders of diameter 200 to 300 μm and a length determined by the separation of the injection sites. Injections resulting from the use of larger currents were larger and less symmetrical. The injection site shown in the *upper photomicrograph* of Figure 1 resulted from a 2-min iontophoresis of 2 μA with the electrode positive and the current pulsed at 5 Hz at five sites over 600 μm of the electrode track. The injection site in the *lower photomicrograph* of Figure 1 was produced by two iontophoretic injections, 800 μm apart, with a current of 5 μA pulsed at 5 Hz for 2 min. In each case the dense reaction product was contained within the nucleus in which the injection was made, Dd and MGM, respectively.

Injection sites were ascribed to subnuclei of the MGB, by reference to both the adjacent thionine-stained sections and by consideration of the single unit response properties of the recording track. This procedure was identical to that used for the assignment of single units to subnuclei described previously (Calford, 1983). Some experiments were not considered in the analysis because the injection site was close to a border and HRP may have spread into an adjacent nucleus. Two large pressure injections were made with a solution of 30% HRP in a 5-μl microsyringe to determine the total projections to a region of the MGB that may involve more than one subnucleus. The histochemical procedures were identical to those described above.

Microscopic procedures. For each experiment, outline drawings were made, using a Leitz Micropromar, of rel-

[4] Abbreviations used in the figures are: *B*, too broad to specify BF; *N*, responds to white noise but not total stimuli; *Physiological:* BF, best frequency; latency, minimum response latency; $\sqrt{F_2} - \sqrt{F_1}$, a measure of sharpness of tuning (the tuning curve bandwidth 20 dB above minimum threshold on a square root scale), lower values indicate sharper tuning (see Calford, 1983). *Anatomical:* A, P, SP, and M are used to describe the approximate plane of sections, anterior, posterior, sagittal plane, and medial, of the lateral extreme of the MGB, respectively. *BC*, brachium conjunctivum; *BIC*, brachium of the inferior colliculus; *CNF*, *CUN*, cuneiform nucleus; definition; *FTC*, central tegmental field; *ICA*, intracellular area; *ICO*, commissure of the inferior colliculus; *LGD*, dorsal nucleus of the lateral geniculate body; *LLD*, dorsal nucleus of the lateral lemniscus; *5ME*, terminal nucleus of the fifth nerve; *OT*, optic tract; *PAG*, periaqueductal gray; *PB*, parabrachial; *PBG*, parabigeminal nucleus; *PP*, pes pedunculi; *PTP*, posterior pretectal nucleus; *SC*, superior colliculus; *SCS*, superficial layers of the SC; *SN*, substantia nigra; *VR*, ventrorostral process of the inferior colliculus.

evant sections at magnifications of × 10 or × 17.5. All distinguishing features were marked (nuclear boundaries, large blood vessels, etc.). These aided in the accurate plotting of the position of labeled cells, identified under high power microscopy, on to the outline drawings. Sections were examined for the presence of labeled cells with a Leitz Dialux 20 compound microscope at a magnification of × 250.

Labeled cells were identified by the presence of numerous small granules in the cytoplasm of the soma, and sometimes in the proximal dendrites. These granules represent the aggregates of polymerized chromogen which result from local peroxidase activity (due to HRP presence) during the histochemical reaction. Granules are not found within the cell nucleus, and this sometimes aids in the differentiation of label from artifact. A nongranular crystalline artifact is sometimes present but is clearly distinguishable from filled cells, as are erythrocytes and capillary fragments. An analysis of the morphology of filled cells will be the subject of a future report.

The identification of midbrain divisions was restricted to those regions clearly distinguished by Nissl-stained sections. The differentiation of IC into the central (ICC), pericentral (ICP), and external nuclei (ICX), nucleus sagulum (SAG), interstitial nucleus of the brachium of the IC (BIN), and other regions follows that described by Berman (1968) except that a ventrorostral (VR) process of ICC was recognized (after van Noort, 1969). The term "deeper layers of the superior colliculus" (SCD) refers to all layers deeper than the retino-recipient superficial layers.

Results

The number of HRP-labeled cells identified in midbrain regions varied considerably between experiments, even if the iontophoresis parameters and the apparent size of the HRP injection site were similar. Although this may depend upon technical factors such as transport time and histochemistry, it may also reflect a difference between regions. Consequently, in Table I, which gives a summary of the origins of ipsilateral ascending afferents in all experiments, the density of a given projection (the number of labeled cells in a given nucleus) is assessed only within each experiment and is expressed by assigning three X's to the densest projection and judging the other projections relative to this by a decreasing number of X's for lighter projections.

Clear differences exist in the patterns of ascending projections to the various MGB subnuclei, but similar projection patterns are seen when HRP deposits are made in the same thalamic nucleus (Table I). Overall, it is clear that LV receives its input almost entirely from ICC; Dd receives a major input from ICC and a lesser input from ICX; DC receives projections mainly from SAG and ICP; projections to MGM arise from ICC and ICX; VL receives input from ICP, while NS does not receive projections from the IC but from BIN and SCD.

Projections to the ventral division. Five small iontophoretic injections of HRP were made into the ventral division of the MGB. In all cases labeled cells were found in ICC and, in two cases, also in ICP. Since both MGV and ICC are tonotopically organized (Aitkin and Webster, 1972; Calford and Webster, 1981; Merzenich and

TABLE I

Summary of experiments indicating the site of HRP injections and the nuclei in which HRP-filled cells were found

Experiment No.	MGB Subnuclei	ICC	ICX	ICP	SAG	VR	BIN	SCD
C219	LV	XXX[a]						
81-7	LV	XXX		X				
80-93	LV	XXX						
80-100	LV/OV	XXX						
80-98	LV	XXX		X				
81-3	Dd	XXX						
81-37	Dd	XXX	X					
81-49	Dd	XXX	X	X				
81-62	Dd	XXX	XX					
81-61	Dd/LV	XXX	XX	XX				
MC1	DC/(Dd)	X	XX	XXX	XXX			
MC2	DC			?[b]	XXX			
80-106	DC		X	X	XXX		X	
80-57	DC	X	X	XXX	XXX			
80-45	DC			X	XXX			
80-13	DC			XX	XXX			
81-63	NS						XX	XXX
80-63	NS						XXX	XXX
81-2	NS						XXX	X
80-102	MGM/(NS)	XX	XXX	X			X	
81-74	MGM	XXX	XXX					
82-16	MGM	XXX	XXX					
81-96	VL	X		XXX				
80-40	VL			XXX				

[a] The "X's" represent the density of a projection relative to the most dense in a given experiment.

[b] The question mark indicates that relevant sections could not be properly examined.

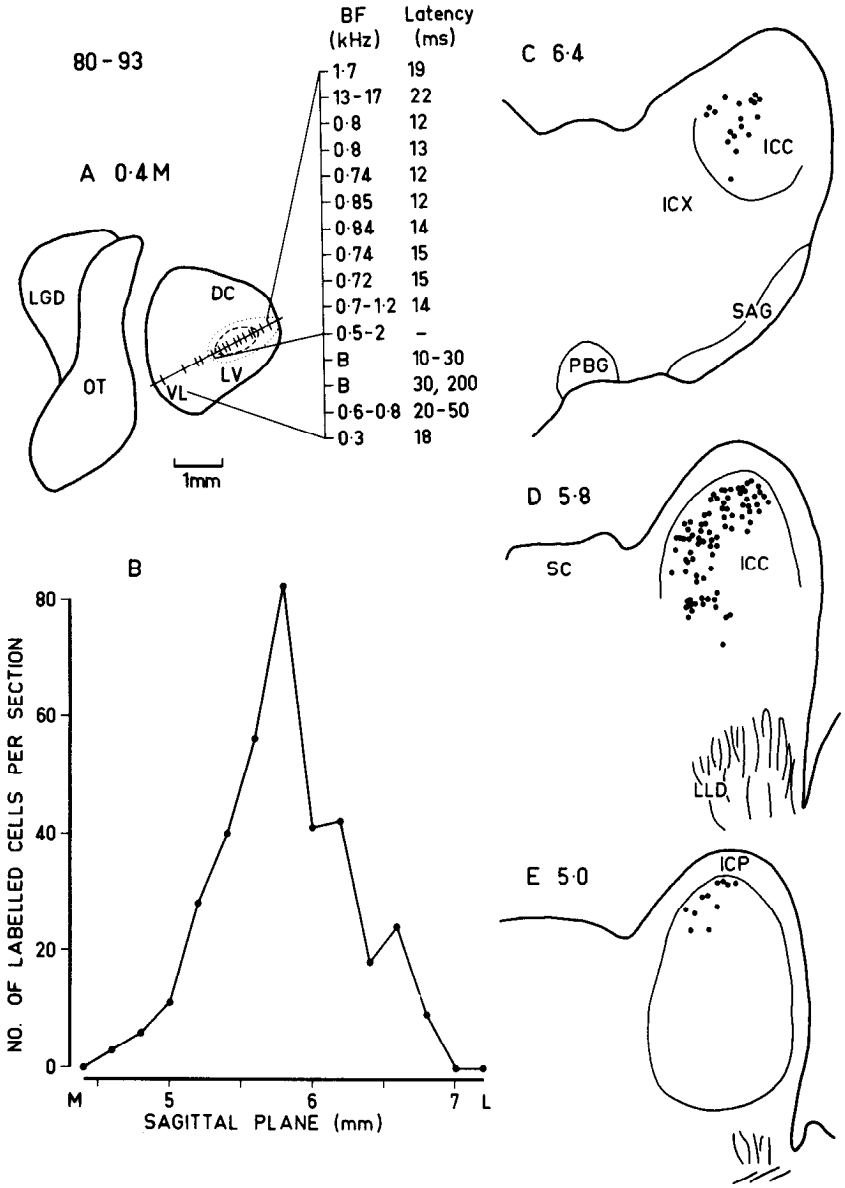


Figure 2. A, Outline drawing of a sagittal section through MGB showing the electrode track, position of units, and HRP injection site (*dashed line,* intense reaction; *dotted line,* diffuse reaction) of experiment 80-93. The electrode track was very lateral (0.4 mm medial of lateral extreme; *0.4 M*) and passed from DC into low BF LV and into VL. *B,* Distribution of labeled cells in ICC plotted against the sagittal plane. *M,* medial; *L,* lateral. *C* to *E,* Representative sections at the indicated sagittal plane showing the position of labeled cells in these sections.

Reid, 1974; Semple and Aitkin, 1979), an attempt was made to restrict the range of best frequencies (BFs) covered by the injection site. Figures 2 and 3 show examples where the HRP deposit covers a similar range of BFs (0.6 to 0.9 kHz), in which the planes of section were parasagittal and near frontal, respectively. Together these two examples allow an appreciation of the extent of the projection to this region of MGV.

The electrode in experiment 80-93 (Fig. 2), placed very laterally in the MGB, isolated nine low-BF units in LV after passing through DC (in which units were broadly tuned and not organized tonotopically) and finally entered VL (Fig. 2*A*). The properties of units recorded corresponded with those expected for these nuclei (Calford, 1983). An intense reaction product was observed following an iontophoretic injection of HRP (five sites, 800 nA for 4 min/site) in the 0.72 to 0.85 kHz region (Fig. 2*A*). The large number of HRP-labeled cells which resulted (Fig. 2*B*) were all located in the lateral extreme of ICC, restricted to the dorsorostral sector (Fig. 2, *B* to *E*). This same region of ICC contained the vast majority of HRP-labeled cells found in experiments 81-83 (Fig. 3), in which the HRP injection (six sites over 900 μm; 5 μA for 1 min at each site) was made in a region with 0.62

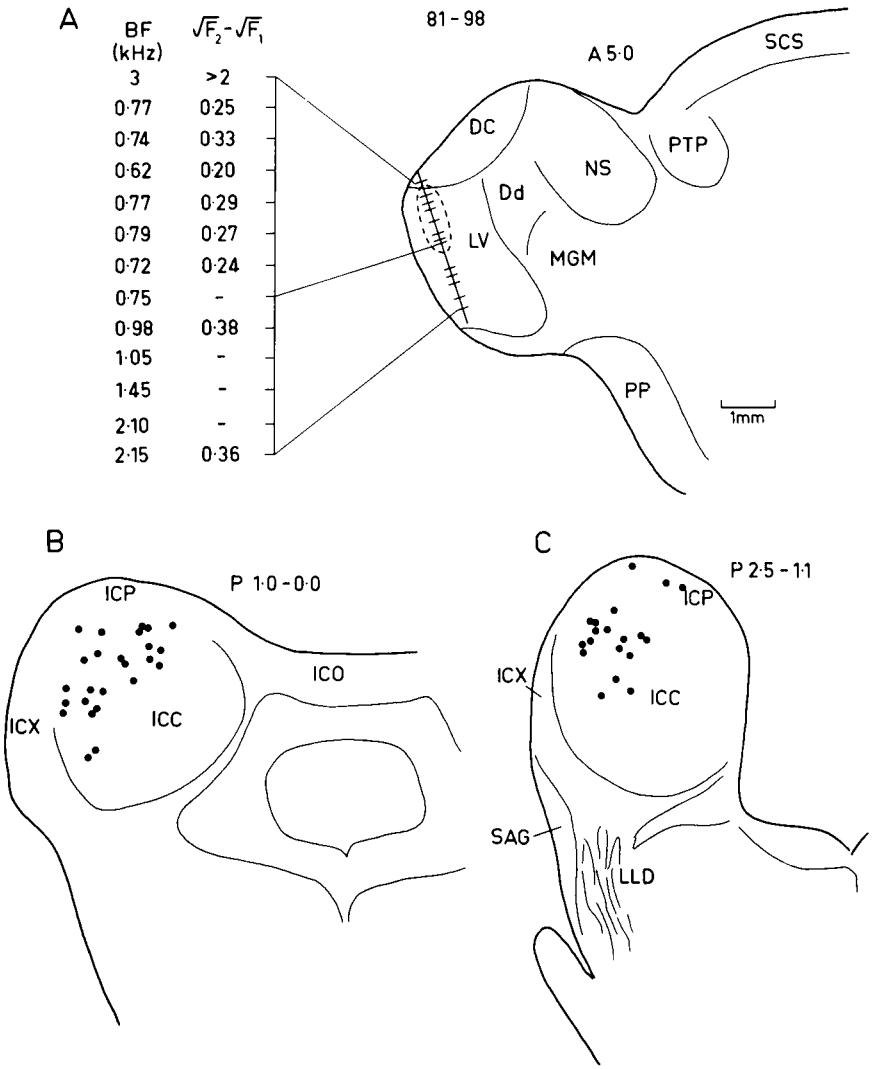


Figure 3. A, Outline drawing of a near-frontal section showing the electrode track and injection site in LV of experiment 81-98. The sharply tuned units in LV show a slowly increasing tonotopic sequence with increasing electrode depth. *B* and *C,* Sections through the midbrain showing the positions of resultant HRP-labeled cells in ICC and ICP at rostral (*B*) and caudal (*C*) levels.

to 0.79 kHz unit BFs. Throughout the rostrocaudal extent of ICC each transverse section contained a few labeled cells in the dorsolateral quadrant. A few labeled cells were found in ICP.

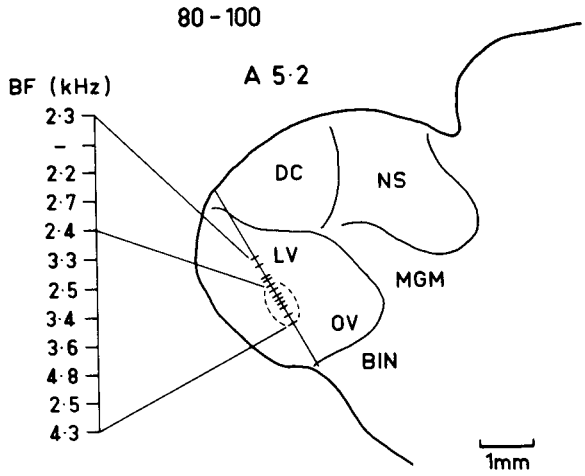
The distribution of labeled cells following the 2.4 to 4.8 kHz injection of Figure 4 (80 to 100) was shifted ventrally and medially in ICC compared with that for Figure 3. In this experiment, labeled neurons formed an irregular patch (Fig. 4, *lower*) located in a region in which BFs in this range would be expected (Semple and Aitkin, 1979). In this, as in most experiments in this study, the number of unlabeled neurons within the patch was well in excess of the number labeled. With all five injections into the ventral division, a discrete array of projecting neurons was identified in ICC. The topographical relationships between injection location and source of afferents will be examined later in this paper.

Projections to the caudodorsal nucleus. Four iontophoretic injections and one small pressure injection of HRP were restricted to DC. The pattern of labeling in experiment 80-57 clearly reveals the origin of ascending input to this region (Fig. 5). The micropipette in this experiment was orientated from dorsocaudal to ventrorostral and 16 units, recorded over the first 2.5 mm, showed a variety of auditory properties but were mostly broadly tuned and habituated rapidly (Fig. 5*A*). Such properties have been shown to be typical of units in DC (Calford, 1983). Toward the end of the penetration five units with properties consistent with those described for the ventral division were isolated (Fig. 5*A*). An HRP injection was made in the center of the dorsal part of the track (four sites, 800 nA for 4 min/site; *dashed ellipse* in Fig. 5*A*). The large number (576) of resultant labeled cells was found spread throughout the full lateromedial extent of the ipsilateral IC, particularly in ICP. Labeled neurons were found in all sectors of ICP (445 labeled cells), including dorsal and caudal tiers (Fig. 5*D*) and rostromedially (Fig. 5*E*).

Most of the remaining labeled neurons were located in SAG, where a high proportion of cells contained HRP reaction product (Fig. 5C). A small number of labeled cells was found scattered throughout ICX and dorsally in medial ICC.

Each experiment in which an HRP injection was made into DC confirmed the projection from SAG to DC, but not all showed such a large proportion of labeled cells in ICP (Table I). In experiment 80-106 (Fig. 6) the micropipette passed through the caudal tip of the MGB, and all units sampled had properties typical of DC (Fig. 6A). Injections of HRP were made at 100-μm intervals over 700 μm in the middle of the track (1 μA for 3 min at each site; *dashed elliptical region* in Fig. 6A). Resultant labeled cells were found in ipsilateral SAG, ICX, ICP, and BIN (Fig. 6, B to H). Most of the filled cells were located in SAG, whereas only two were found in ICP and none in ICC.

Projections to the deep dorsal nucleus. In four experiments iontophoretic injections of HRP were restricted to Dd, and in one additional case there was some spread from the injection in Dd to the dorsal sector of LV.



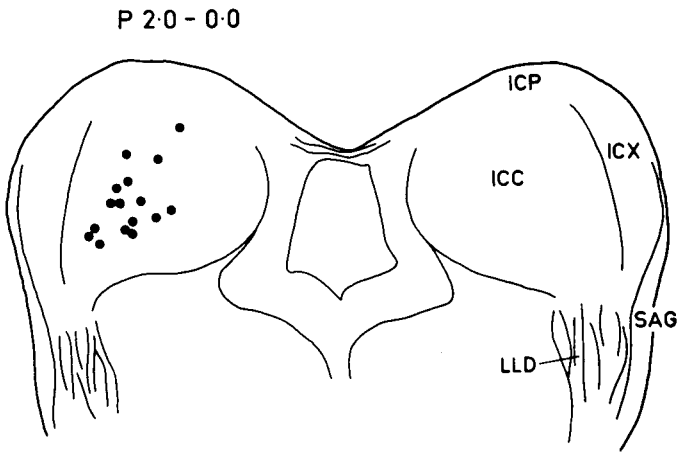


Figure 4. Upper, Outline drawing of a near-frontal section (A 5.2) showing an electrode track in experiment 80-100. The position of units sampled, their BF, and the position of the injection site are indicated. The *lower outline drawing* displays the position of HRP-labeled cells in ICC summed over 2 mm, which in this experiment covered 10 sections.

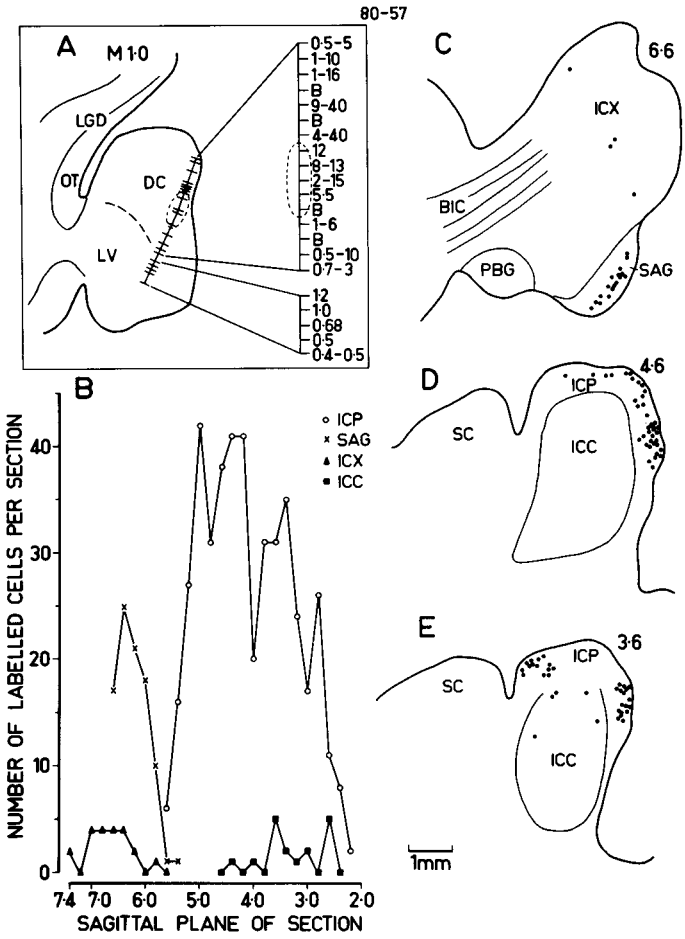


Figure 5. A, Outline drawing of a sagittal section through the MGB showing an electrode track, passing from DC into LV, and the HRP injection site, of experiment 80-57. The BF or most sensitive frequency range for sampled units is indicated. *B,* Distribution of resultant HRP-labeled cells in the indicated nuclei plotted against the sagittal plane of section. *C* to *E,* Three representative sections (lateral to medial) illustrating the position of labeled cells in ICP, SAG, ICX, and ICC.

Penetrations in these five experiments covered most of Dd, and labeled cells were found in ICC, ICX, and ICP but not elsewhere in the midbrain.

As an example, the micropipette in experiment 81-37 isolated five units in rostral Dd; each of these units and the background activity were tuned to high frequencies and responded at approximately 20 msec latency (Fig. 7A). The HRP injection (see also Fig. 1) was made at five sites over 600 μm in the dorsal part of the track (2 μA for 2 min/site), and the spread of tracer seemed confined to Dd. The majority of approximately 200 HRP-labeled cells identified was located medially in ICC (Fig. 7, B to E). In most sections these formed a dorsomedial to ventrolaterally oriented band, located in a region of ICC where high BFs would be expected (Merzenich and Reid, 1974; Semple and Aitkin, 1979). A smaller number of cells was found in ICX and a few in ICP.

Projections to the suprageniculate nucleus. In the three cases of iontophoretic injections restricted to NS, resultant retrogradely labeled cells were not found in any subnucleus of IC, or in SAG, but were located in the BIN

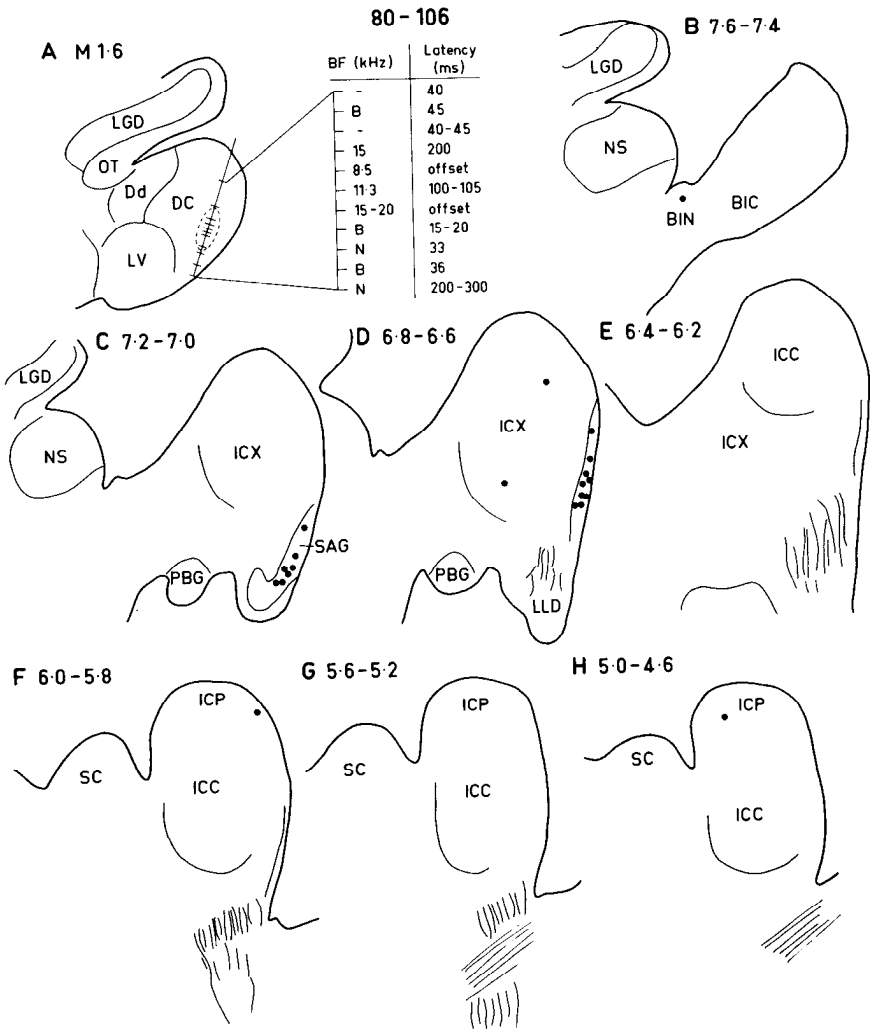


Figure 6. A, Outline drawing of a sagittal section through the MGB showing the HRP injection site and the position, BF, and latency of 11 units recorded in DC of experiment 80-106. *Offset* indicates that unit discharges were time-locked to the offset of the stimulus. *B* to *H,* Distribution of HRP-filled cells in the midbrain at the indicated sagittal planes.

and SCD. Figure 8 gives an example in which the electrode was oriented parallel to the sagittal plane medial in the MGB (3.8 mm from the lateral extreme). In counterstained sections the region through which the electrode first passed was clearly distinguishable as NS because its large cells formed a clearly circumscribed aggregate. In this region seven single units were studied (Fig. 8*A*); all were broadly tuned, had long latencies, and habituated to repeated stimuli. Deeper in the track two units which responded to tactile stimulation of the head and back were isolated, followed by three auditory units of which one was sharply tuned. The larger cells in this region identified it as the medial extreme of MGM. An iontophoretic HRP injection was made in the dorsal part of the track (five sites; 1 μA/site for 3 min) and was restricted to NS (Fig. 8*A*). Labeled cells were found mainly in ipsilateral BIN with a smaller number in SCD (Fig. 8, *B* and *C*). In two other experiments with injections restricted to NS, similar numbers of labeled cells were found in BIN and SCD.

Projections to the medial division. Three iontophoretic injections of HRP were made into MGM. One of these injection sites (experiment 80-102) was very large, resulting from the use of a 25-μA current to produce iontophoresis. This experiment provided a large number of labeled cells in ipsilateral ICX, a small number in ICC, and scattered labeling in ICP, BIN, and contralateral ICX. In this experiment the injection area almost covered MGM, but there was considerable spread into adjacent regions of LV and NS.

The results of two smaller iontophoretic injections were similar, and one of these experiments (82-16) in which the micropipette sampled 14 units in MGM is summarized in Figure 9. These units showed a wide variety of frequency-tuning properties and, although BFs were identifiable for most of them, no tonotopic organization was suggested. An iontophoretic HRP injection was made over 1.2 mm in MGM (five sites, 2.5 μA for 2 min/site). A large number of labeled cells was subsequently found in ipsilateral ICX and ICC. Filled cells

were scattered throughout ICC and ICX but were more common mediorostrally; none were found in ICP or in the posteriormost millimeter of the IC (Fig. 9, *B* to *H*).

Although the two small HRP injections produced similar numbers of labeled cells in ICC and ICX, the larger injection resulted in a far greater number and proportion of labeled cells in ICX compared to ICC. The reasons for these differences are not clear, but collectively these data suggest that ICX is a major source of input to MGM.

Projections to the ventrolateral nucleus. Two iontophoretic injections of HRP were made into the ventrolateral nucleus, as verified physiologically and cytoarchitecturally. In experiment 81-96 (Fig. 10) the micropipette, oriented nearly parallel to the frontal plane, entered ventroposterior MGB and isolated seven single units (Fig. 10*A*). The first three, located near the DC/VL border areas, were not assigned to either nucleus because no "physiological boundary" could be detected to assist in this determination. Four units were isolated in the deeper part of the track which, by virtue of its position, was clearly in VL; a small iontophoretic injection (four sites over 1.2 mm, 5 μA for 1 min/site) was made in this region (Fig. 10*A*). A moderate number of HRP-filled cells was found in the ipsilateral IC, and all are shown in Figure 10, *B* to *G*. Most of these cells were distributed throughout ICP; a small number were located in ICC and ICX but none were found in SAG.

Contralateral projections. Very few labeled cells were found in the contralateral midbrain. Compared to the ipsilateral projection the contralateral projection is weak, and in those experiments in which small iontophoretic HRP injections were made no labeled cells were found contralaterally. Labeled cells were only found contralaterally in ICX and ICC in two experiments (81-61, Dd/LV; 80-102, MGM/NS) in which very large numbers of labeled cells were found in these areas ipsilaterally. Labeled cells were not found in contralateral ICP, SAG, SCD, or BIN in any experiment. This study does not provide detailed information on the pattern of innervation, in the MGB, by contralateral projections.

Correlation of topographic labeling with tonotopical organization of the central nucleus of the inferior colliculus. Experiments in which HRP injections were made into regions with a restricted range of unit BFs provide a means for describing the topography of the connections from ICC.

The distribution of HRP-labeled cells was found to be restricted to small regions of ICC following nine HRP injections into limited unit BF regions (five in LV; four in Dd). To illustrate the organization of projecting arrays in ICC, the labeled cells found in six experiments at anteroposterior plane P1.0 (*upper*) or sagittal plane SP5.0 (*lower*) are shown in Figure 11. Only those cells in the section judged closest to these planes have been plotted.

Figure 11 (*upper*) shows the pattern of labeled cells

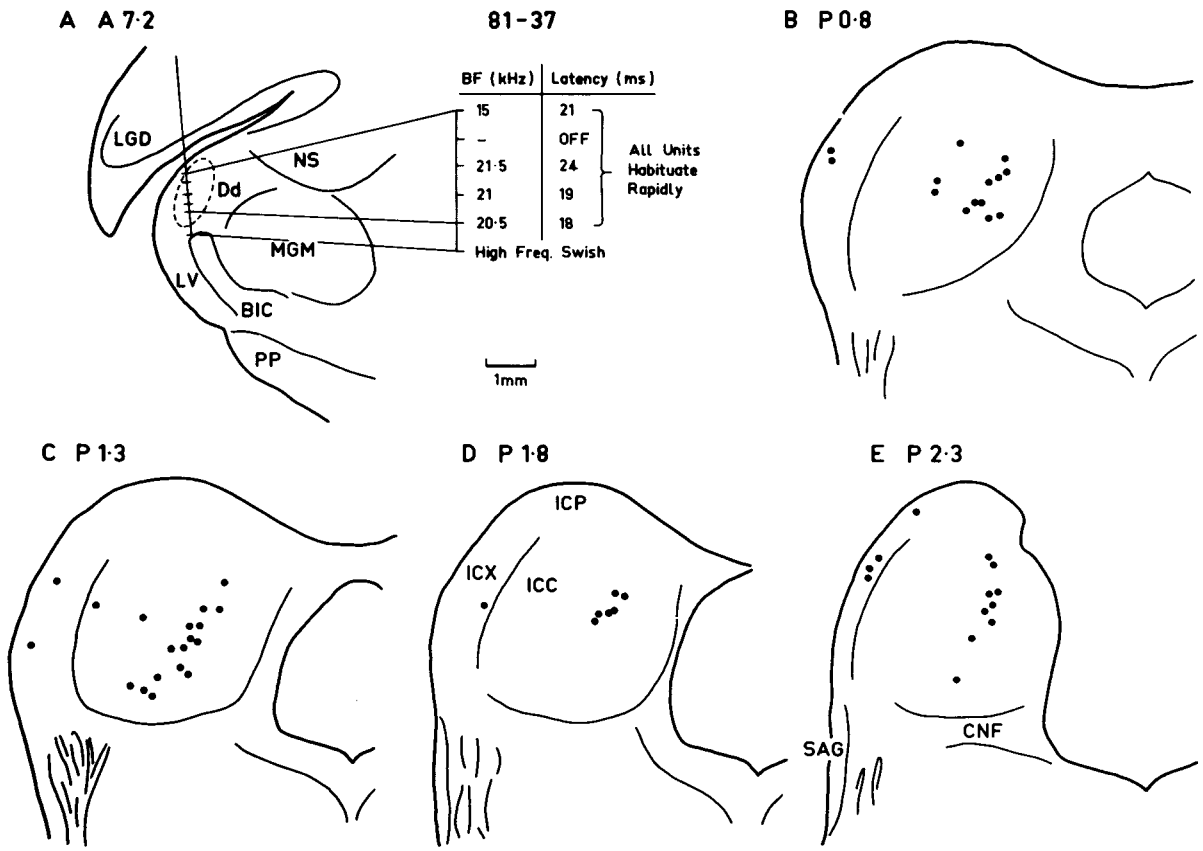


Figure 7. A, Passage of the electrode track in experiment 81-37 shown in near-frontal section at A7.2. The electrode sampled five units in Dd with the indicated BFs and latencies and then entered the BIC where background activity was present to high frequency tonal stimulation. The injection is indicated by the *dashed boundary. B* to *E,* Representative near-frontal sections through the midbrain showing the position of HRP-labeled cells in ICC and ICX.

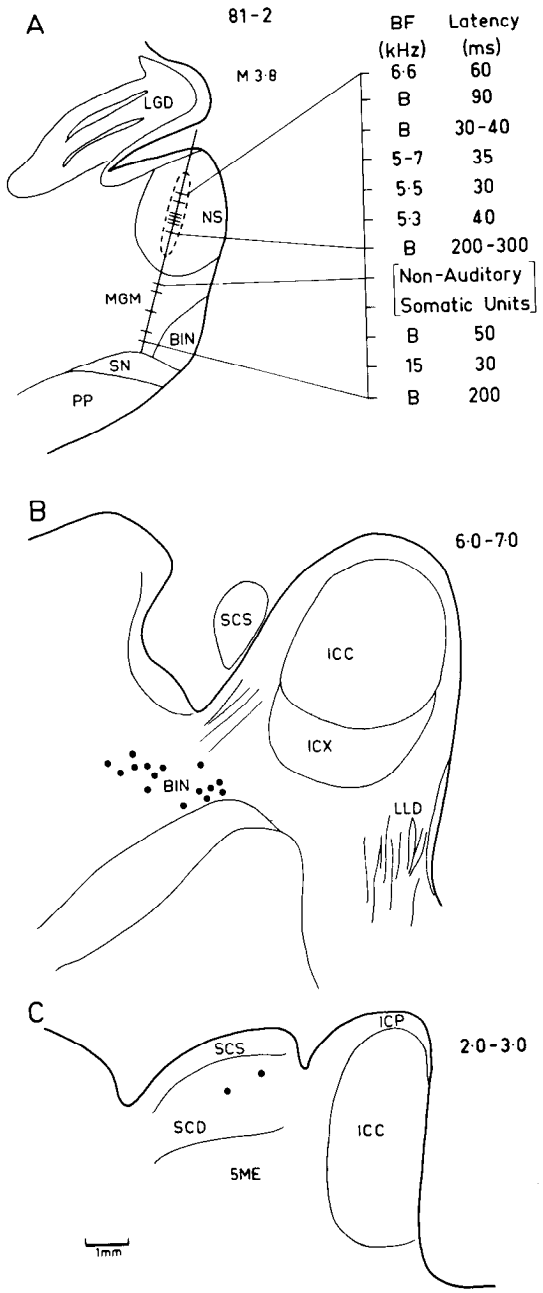


Figure 8. A, Outline of a sagittal section through medial MGB, showing the passage of the electrode track through NS and MGM and the location of HRP injection in experiment 81-2. *B,* Outline of a sagittal section through the midbrain showing the positions of HRP-labeled cells in ipsilateral BIN. *C,* Outline of a medial section showing the position of two labeled cells in SCD. The total number of labeled cells found in this experiment is shown.

formed in three experiments with the indicated injection site center frequencies (in LV, LV/OV, and Dd, respectively), at P1.0. There is a clear dorsolateral to ventromedial shift in the position of ventrolaterally to dorsomedially oriented bands of labeled cells, with increasing injection site frequency. Figure 11 (*lower*) shows the distribution of labeled cells resulting from three limited BF injections into LV (80-93, 81-7, and C219) at SP5.0. With increasing frequency there is a ventral shift in the position of labeled cells in ICC, which seem to form bands with a rostroventral to caudodorsal orientation (e.g., Fig. 2).

The organization suggested by these results agrees with that found in physiological studies which have investigated the tonotopical organization of cat ICC (Merzenich and Reid, 1974; Roth et al., 1978; Semple and Aitkin, 1979). An electrode oriented dorsal to medial would encounter a slowly increasing tonotopic sequence of unit BFs; one oriented from lateral to medial would produce a rapidly increasing tonotopic sequence, and one oriented caudal to rostral would sample a very slowly decreasing tonotopic sequence. Although these predictions are fulfilled in the results of the physiological studies, the orientations of isofrequency planes predicted in these studies and of single laminae in Golgi stains (Rockel and Jones, 1973) are closer to horizontal than those described by labeled cells. The orientations of bands of labeled cells, shown in Figure 11, are very similar to those described by high activity of labeled deoxyglucose following stimulation with pure tones (Serviere and Webster, 1981; Webster et al., 1978).

Interpretations of results. The differences which have been demonstrated in the patterns of midbrain labeling from injections restricted to different physiologically and anatomically delineated MGB subnuclei suggest that spread of tracer to other subnuclei is unlikely to have been significant in these experiments and that the incorporation of HRP by "axons of passage" at the injection site has not influenced the results. The five small injections, made into regions of MGV shown to represent a limited frequency range (Figs. 2, 3, 4, and 11), gave different and orderly distributions of labeled cells in ICC. Each distribution was restricted to a region which would be predicted, on the basis of BF maps, to represent a similar frequency range to the injection site. If axons passing through the injection site, in addition to terminal axons, had incorporated and transported HRP, then a larger number and more diffuse pattern of labeled cells would be predicted in ICC. Additionally, the finding that data for any one subdivision were similar argues for a minimal contamination by uncontrolled variables. The use of iontophoretic injections from micropipettes (to minimize damage) and of relatively short transport periods (to minimize uptake by axons of passage and terminals at the edge of the injection site) appears to have been successful in reducing the inherent problems of the use of HRP as a retrograde tracer.

Discussion

This study required the precise identification of the site of deposits of HRP within the MGB; this necessitated the adoption of an appropriate parcellation scheme and the development of a means for differentiation. In the previous paper (Calford, 1983) it was argued that the Golgi stain-based parcellation of Morest (1964, 1965a) was consistent with the parcellation stemming from the results of most studies of MGB afferent and efferent connections, and it was found that "physiological boundaries" corresponded with anatomical boundaries between subnuclei, confirming the functional validity of the adopted parcellation. These transitions in single unit

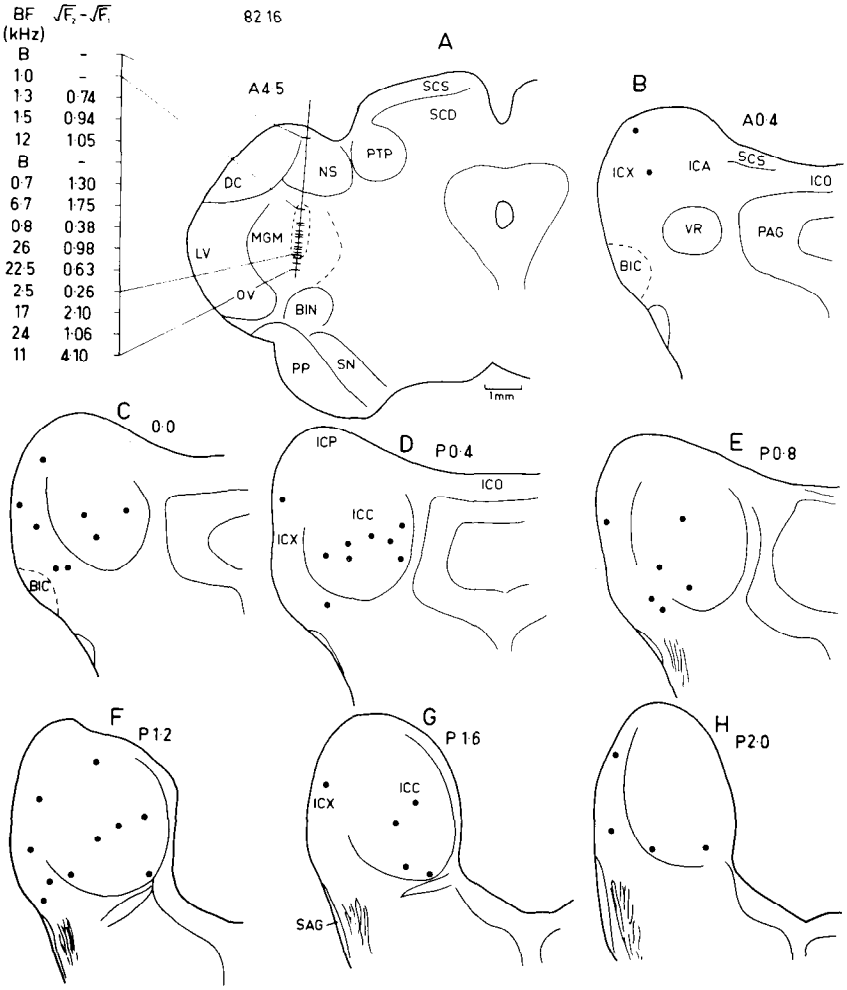


Figure 9. *A*, Outline of a near-frontal section through the MGB at A4.5 of cat 82-16. The positions of recorded units and the injection site are indicated with the BFs and tuning properties of units. *Dashed lines* are used to approximate the positions of borders that were difficult to specify. *B* to *H*, Positions of HRP-filled cells in single sections at the indicated planes.

auditory response properties form a useful basis on which to differentiate the sites for HRP injections during an experiment, providing that the effective spread of the tracer is small. In the majority of experiments the small size of the dense reaction product region suggested that this requirement was fulfilled, and the finding of different patterns of HRP-labeled cells in midbrain nuclei for each MGB subnucleus gave support for the conclusion.

The results of this study are summarized in Figure 12, which relates the auditory response properties that differentiate subnuclei to their sources of ascending afferent input in the midbrain. In summarizing, only some of the more distinguishing physiological features are given and some of the minor projections have been omitted.

The ventral division (MGV) shares borders with VL, DC, Dd, and MGM but can be distinguished physiologically from each of these. Units in both VL and DC are differentiated from the sharply tuned, short latency units of MGV by their long latency responses and broad tuning. The Dd/MGV boundary is distinguished by a transition from the longer response latencies, less frequency specificity, and less consistent discharges of Dd to the short latency, sharply tuned MGV responses. Auditory properties in MGM are far more variable than in MGV.

Within MGV, LV and OV are distinguished by differences in the organization of unit BFs; LV is clearly tonotopically organized whereas OV is marked by abrupt changes in unit BFs, and units appear less sharply tuned than in LV. In confirmation of a previous study from this laboratory (Aitkin et al., 1981), small deposits of HRP into limited-BF regions of LV produced small loci of labeled cells in ICC in positions which corresponded to the frequencies represented at the injection sites. Hence there is an orderly topographical projection from ICC to LV which preserves tonotopicity. No HRP injection was restricted to OV, but one which covered the LV/OV border area produced labeled cells only in ICC.

The three nuclei of the dorsal division (DC, Dd, and NS) are easily distinguished electrophysiologically. The deep dorsal nucleus is differentiated from DC and NS by its shorter latency and relatively sharply tuned responses. NS is distinguished by the weak auditory responses of its constituent units, most of which responded inconsistently and habituated rapidly. Although this be-

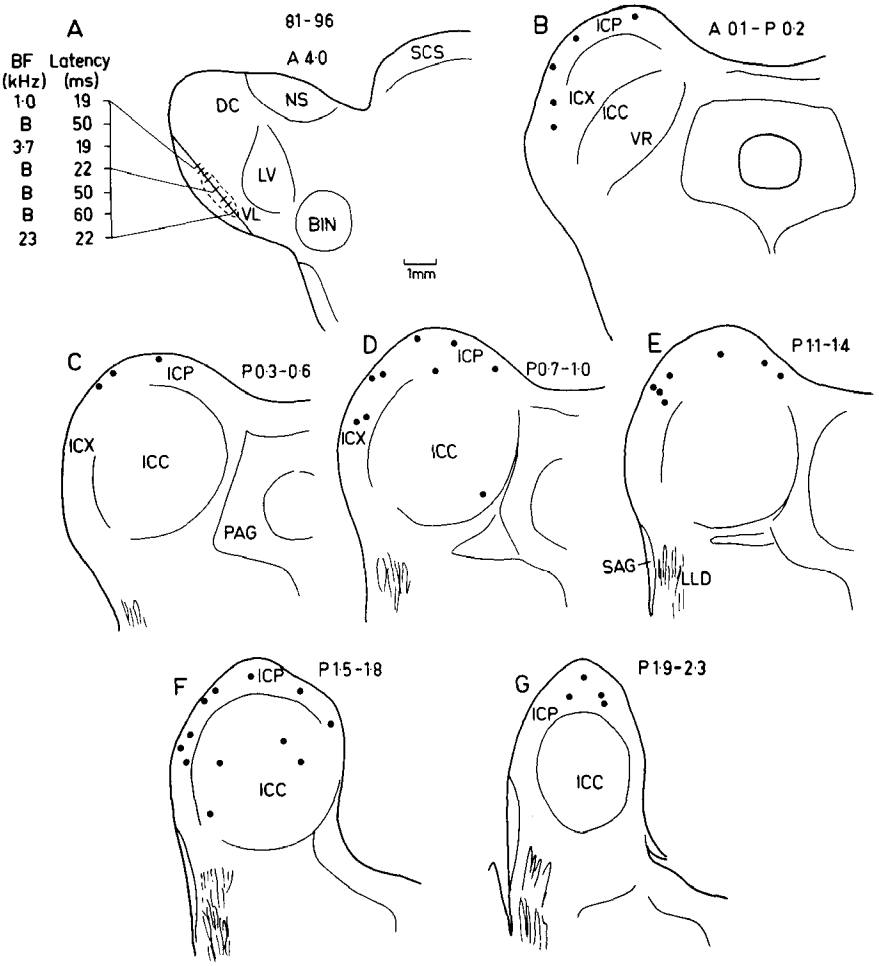


Figure 10. *A*, Outline drawing representing the electrode track, units and their properties, and the injection site of experiment 81-96. The units which were mainly broadly tuned with long latencies were recorded in DC and VL, and the injection site is mostly in VL. *B* to *G*, Outlines of near-frontal sections through the midbrain showing the distribution of labeled cells, which were mainly located in ICP.

havior is also present in DC, it is less common and there is an overall stronger auditory response. These three nuclei are also distinguishable on the basis of their patterns of ascending input. Injections of HRP into DC produced labeled cells mainly in SAG and ICP (see also Aitkin et al., 1981), whereas those following injections into NS were located in the deeper layers of the superior colliculus (SC) and in the BIN. Most units in Dd had BFs above 8.5 kHz and all injections of HRP into Dd produced labeled cells in the high frequency region of ICC, with a smaller number in ICX.

The borders of Dd and NS with MGM were recognized physiologically by an increase in response variability or a dramatic improvement in response strength, respectively, upon entering MGM. Considerable variability was found in unit auditory responses between, and within, penetrations through MGM. However, one large and two small injections of HRP into MGM produced labeled cells scattered throughout the ventral half of ICC and in ICX.

The auditory responses of units in VL were very similar to those of DC. Units in VL displayed extremely late responses and broad tuning characteristics. Injections of HRP into this area produced labeled cells almost totally restricted to ICP.

Comparison with previous studies

Early studies using anterograde degeneration techniques to trace connections from midbrain lesions reported degeneration in the rostral two-thirds of the principal division of the MGB following large lesions in the IC, corresponding to the ICC to MGV projection of this study (Moore and Goldberg, 1963; Powell and Hatton, 1969; Rasmussen, 1961; Woollard and Harpman, 1940). Five previous studies of tectothalamic connections of the cat auditory system have examined these pathways, taking into account the subdivisions of the MGB based on Morest's (1964, 1965a) Golgi studies (Aitkin et al., 1981; Andersen et al., 1980b; Kudo and Niimi, 1978, 1980; Morest, 1965b).

Morest's (1965b) study examined anterograde degeneration following midbrain lesions and was mainly concerned with the sources of pathways to the dorsal division which run through the parabrachial region. Although the

relatively large lesions limit the usefulness of the technique, there are some parallels with the present results. Morest described input to the dorsal nucleus (DC in the present study) from axons in the medial third of the brachium of the inferior colliculus and from cells of the lateral tegmentum, which would seem to correspond to the ICP to DC and SAG to DC projections of the present results, respectively. The projection from SCD to NS finds a parallel in Morest's superior parabrachial tract which consists of fine axons projecting from a "a midbrain region that includes the deep layers of the superior colliculus" (Morest, 1965b, p. 628) and terminating in NS, especially dorsally. Morest also describes an inferior parabrachial tract arising from juxtabrachial or interstitial neurons of the brachium of the inferior colliculus and projecting to a region of the dorsal division probably homologous to NS of the present study. Morest did not describe an input to Dd from ICC, although he describes similar cup-like synaptic endings in Dd and MGV (Morest, 1965b).

Andersen et al. (1980b), in their study of the projections from ICC and ICP, used a parcellation of the MGB similar to that used in the present study. They described the results of anterograde tracer injections into higher BF regions of ICC as producing label in LV, OV, and Dd, while ICP injections produced label in DC. Again these results are confirmed by aspects of the present study.

It is difficult to compare the present results with those of Kudo and Niimi (1978, 1980) due to their use of a very

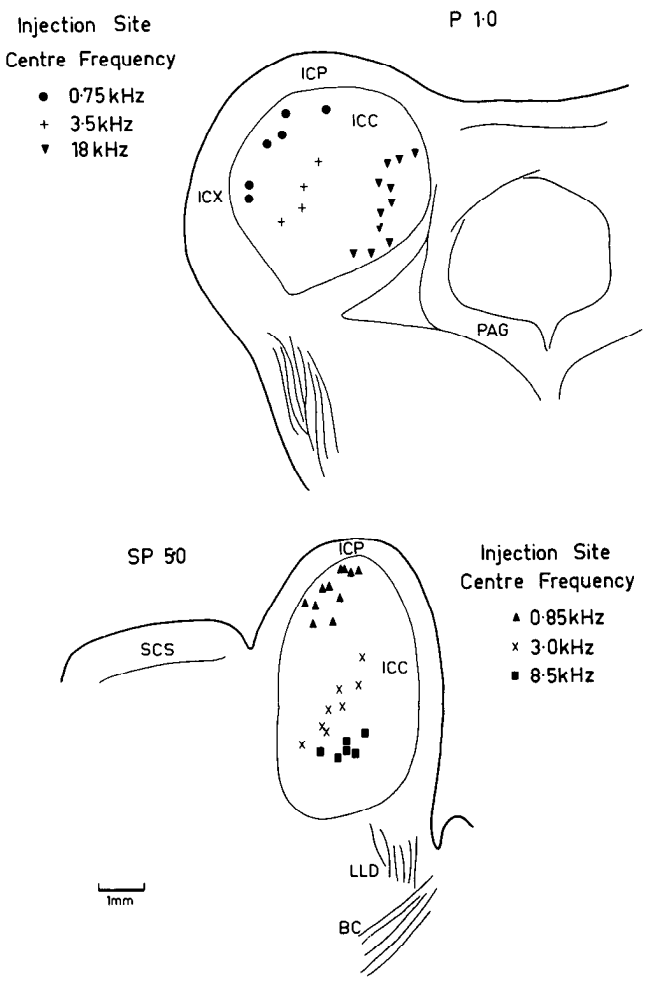


Figure 11. Standardized sections at P1.0 and SP5.0 through the IC showing the actual position of labeled cells resulting from limited frequency range HRP injections into LV or Dd (the latter made at an 18-kHz BF site) taken from the section, in each case, closest to these planes.

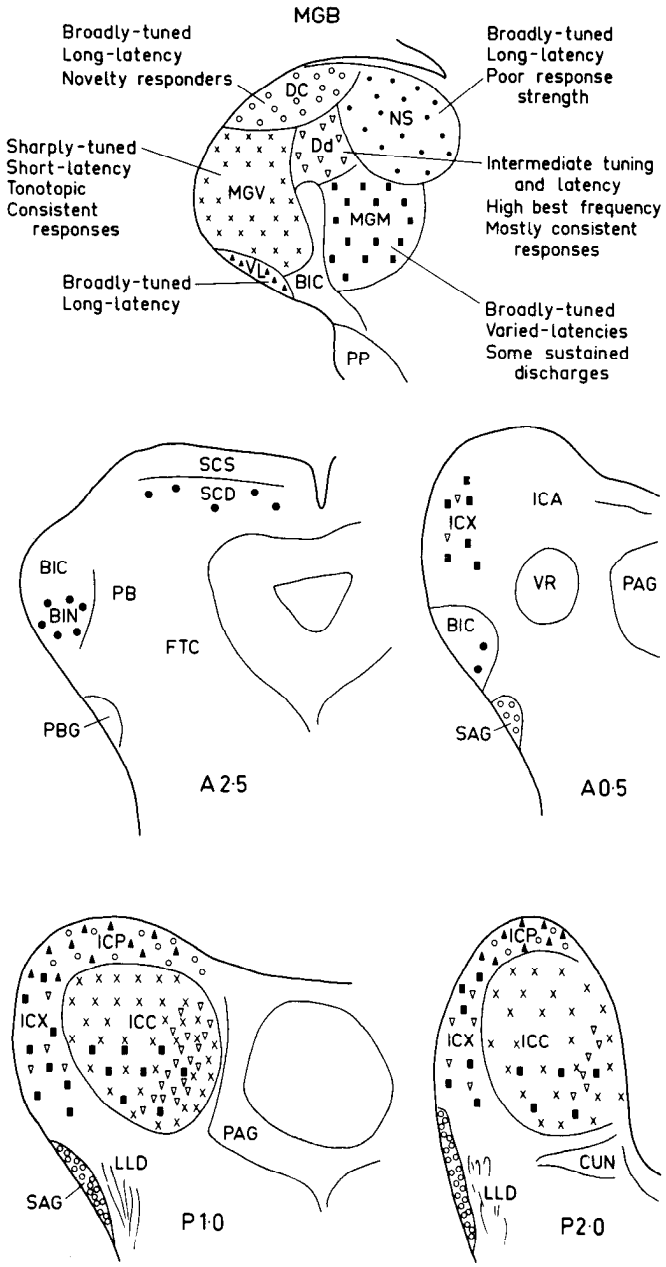


Figure 12. Summary of auditory midbrain to thalamus connections observed in this study. *Upper*, Outline drawing of a frontal section through the MGB (approximately A5.0) in which each of the subnuclei is outlined and marked with a *symbol.* A summary of the major auditory response properties of units in each subnucleus is presented. The *lower* four *outline drawings* are of frontal sections through the midbrain at near-frontal planes A2.5 to P2.0, where *symbols* indicate the regions where HRP-filled cells were found following injections into the areas with the same symbol in the MGB.

different parcellation scheme for the MGB. However, their experiments using anterograde tracers confirm the projections of ICX to MGM, ICC to MGV, and medial ICC to a region which is probably Dd (in addition to MGV).

Overall, the present results agree with the projections described using anterograde tracing techniques from the midbrain to the MGB in the cat. There is also considerable agreement with the findings of Oliver and Hall (1978) who used both anterograde and retrograde tracing techniques to study tectothalamic connections in the tree shrew. These authors have shown that ICC projects to MGV and that the magnocellular area (equivalent to MGM) receives input from the lateral zone (ICX), the roof nucleus (ICP), and ICC. In the tree shrew the dorsal division is divided into four nuclei (plus the caudomarginal nucleus which seems equivalent to VL) which are not easily equated with those of the cat dorsal division. However, Oliver and Hall (1978) show projections from SAG, the roof nucleus (ICP), and SCD to nuclei of the dorsal division, in agreement with the present results.

Parallel auditory pathways through the thalamus

The present data describe some largely separate and distinctive pathways between midbrain and thalamic auditory nuclei. This material, together with recent evidence on the cortical connections of the MGB subnuclei, suggests that there are multiple and, to some extent, parallel pathways along which auditory information may reach the cortex.

The ventral division and "core" pathway. Recent studies including the present one show clearly that ICC projects topographically upon LV. The latter in turn projects topographically upon auditory fields A, AI, P, and probably VP (Andersen et al., 1980a; Imig and Reale, 1981; Merzenich, 1981). However, since ICC is not a homogeneous nucleus, being composed of subregions with different response properties (Roth et al., 1978; Semple and Aitkin, 1979, 1980, 1981), it is interesting to speculate about the fine details of its projection upon LV. Is it totally topographic, so that an entire isofrequency contour of ICC maps onto an isofrequency contour of LV? Or is there some degree of convergence and divergence, in which tonotopicity is retained but further integration is possible?

There is some evidence for convergence of terminating ICC axons in the present data. In most cases where a small HRP injection in LV (see also Aitkin et al., 1981) was restricted to an area covering a discrete range of BFs, a band of filled cells was found in ICC, but not all cells in this band were labeled. Instead, filled cells seemed scattered throughout the area within ICC representing the same frequencies as at the injection site (Figs. 2, 3, 4, and 11). Similarly, Andersen and his colleagues showed that when anterograde tracer injections were made into single loci in ICC, labeled terminals occupied a much larger, although discontinuous, area in MGV than was occupied by the injection site (Andersen et al., 1980b).

These two findings suggest that there is both divergence and convergence in the projections from a locus in ICC to MGV. It would seem that this convergent/divergent projection must be confined to cells with the same BF, since neurons in MGV have a sharpness of tuning similar to that of neurons in ICC. Andersen and colleagues (Andersen, 1979; Andersen et al., 1980a; Merzenich, 1981) have further suggested that this convergence/divergence is restricted to cells with the same binaural characteristics, thus explaining the discontinuities seen in terminal labeling in MGV after a small injection of anterograde tracer in ICC. Alternatively, convergent projections to MGV from ICC could also account (through binaurally mixed connections) for the lower proportion of binaural excitatory-inhibitory (EI) units reported in LV (14 to 17%; Aitkin and Webster, 1972; Calford, 1983; Calford and Webster, 1981) compared to ICC (25 to 39%; Aitkin et al., 1975; Semple and Aitkin, 1979).

Deep dorsal nucleus. An unexpected finding of recent studies of the MGB (Andersen et al., 1980a; Calford, 1983) is the strength of the auditory representation in Dd. The few earlier reports of the properties of units in the dorsal division of the MGB described only labile and poorly defined responses (Aitkin, 1973; Aitkin and Webster, 1972; de Ribaupierre et al., 1975). However, the subsequent description of a projection from ICC to Dd by Andersen et al. (1980b) and in the present results, together with the finding of a majority of short latency, moderately sharply tuned units in Dd, are indicative of a well defined auditory representation in this nucleus.

Only units with high BFs were found in Dd in this study. This is reflected in the major source of input to Dd: the high BF medial region of ICC. LV also receives projections from this region of ICC, and it is appealing to speculate that different populations of cells project to LV and Dd, thus preserving some aspect of the segregated organization of ICC. The concept of a distinct pathway through Dd is supported by the finding that, although Dd projects to each of the tonotopically arranged cortical fields, it is most strongly connected with field A, whereas field AI is most strongly interconnected with MGV (Andersen et al., 1980a).

A problem with this interpretation of the present results is that we do not have a clear HRP injection into a high frequency region of LV with which to compare the Dd injections. One interpretation is that Dd, as identified here, may be the high BF region of LV. Although this is possible, it is unlikely because the sample of units in Dd is distinct from that in LV in terms of latency, tuning, and habituation properties (see Figs. 4, 7, 8, 9, and 10 of Calford, 1983), and high BF cells have been recorded in LV in other experiments in areas which are not adjacent to Dd (e.g., Fig. 8 of Calford and Webster, 1981).

The "diffuse" pathway. Andersen et al. (1980a, b, c) showed that ICP projects to DC and the latter projects to field AII, which in turn projects back to ICP. They argued that this formed a "diffuse" auditory pathway, in contrast to the "cochleotopic" pathways to fields A and AI. The present data support the finding that ICP projects to DC but suggest that SAG may also be involved in this information loop. In addition, it is clear that VL must be considered part of the diffuse pathway since it also receives its major input from ICP (Fig. 10) and is interconnected with field AII (Andersen et al., 1980a).

Suprageniculate nucleus. NS has a very different pattern of input compared with other MGB subnuclei: it

receives projections from SCD and BIN. Each of these projections has been suggested in earlier studies (Graham, 1977; Morest, 1965b). The cortical connections of NS are also distinctive, being mainly with insular-temporal cortex and, to a lesser extent, with AII (Diamond et al., 1969; Heath and Jones, 1971; Raczkowski et al., 1976; Winer et al., 1977).

Medial division. Both the auditory response properties and the connections of MGM are heterogeneous. Following injections of HRP into MGM, filled cells were scattered throughout ICX and the ventral half of ICC. Investigations of the cortical connections of MGM have, similarly, revealed reciprocal connections with most of the identified auditory cortical fields (Diamond et al., 1969; Merzenich, 1981; monkey: Burton and Jones, 1976).

The auditory response properties of units in MGM are consistent with its sources of input: short latency, relatively sharply tuned responses that often display a sustained discharge pattern (suggestive of an input from ICC), medium latency, broadly tuned responses (which could originate from ICX), and long latency responses with varied properties that may relate to corticofugal afferents. The variety of unit properties and sources of input to MGM also seems to be reflected in a greater variability of cell types than in other MGB nuclei (Morest, 1964), again suggesting that the area is not functionally homogeneous.

Summary

With some simplification four major tectothalamic pathways of the auditory system can be recognized. First, the output from ICC carrying short latency, sharply tuned information projects mainly to LV and OV, which form MGV, and to Dd. This pathway expands in its cortical projection to form at least three, and probably more, tonotopically arranged fields. Some aspects of the segregation, within ICC, of units with similar responses are preserved in this pathway.

Secondly, the so-called "diffuse" pathway involves a corticofugal loop by a return projection to ICP from field AII, which receives input from the thalamic areas DC and VL. ICP projects to DC and VL to complete the circuit. In addition, a major input to DC stems from cells in SAG, which may receive auditory information from brainstem and/or tectal auditory nuclei.

A third distinct pathway passes through NS which receives its input from SCD and from the BIN. NS is interconnected with insular-temporal cortex and to a lesser extent with field AII. A fourth pathway is formed by the pattern of efferent and afferent projections of MGM, which appears to be interconnected with each of the auditory cortical fields and which receives a minor input from ICC and a major input from ICX. The large number of sources of afferent input to MGM is reflected physiologically in a high level of variability in the auditory response properties of its units.

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