The Lateral Geniculate Nucleus in Human Strabismic Amblyopia

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Cell shrinkage in monkey lateral geniculate nucleus (LGN) layers supplied by the amblyopic eye have been described in experimental amblyopia caused by visual deprivation, anisometropia, and strabismus. A human brain from a strabismic amblyope became available for study and the authors compared cell sizes in LGN layers receiving input from the normal and the amblyopic eye. Significant cell shrinkage was present in layers connected with the amblyopic eye, and was most evident in the ipsilateral LGN. These findings support the validity of the monkey model for the study of strabismic amblyopia by showing, for the first time, changes in the brain from a human strabismic amblyope that are similar to those previously described in monkeys. Invest Ophthalmol Vis Sci 33:2729–2732, 1992

Experiments in macaque monkeys with artificial esotropia, created by surgery on the extraocular muscles during infancy, have shown that strabismic amblyopia similar in its clinical aspects to human amblyopia may occur.† Histologic examination of the lateral geniculate nucleus (LGN) of these monkeys has shown cell shrinkage in all layers of the LGN that receive input from the amblyopic eye.‡ Not known is whether the afferent visual system of human strabismic amblyopes with naturally occurring esotropia undergoes similar histologic changes. If this were true, considerable support could be added to the validity of the monkey model in the study of amblyopia. We report here the histologic study of the LGNs from a man who had ophthalmologically confirmed strabismic amblyopia.

Materials and Methods

A 66-year-old man whose two brothers and father were ophthalmologists died after a brief illness of unknown etiology. Except for granting permission to remove the brain, the family refused an autopsy to determine the cause of death. The ophthalmologic history was obtained from the records of the patient’s father and brothers, who treated him throughout his life. An esotropia was noted between the first and second year of life and was diagnosed by the patient’s father to be of accommodative origin. A strabismic amblyopia of the left eye was noted soon afterward. Glasses were prescribed and accepted by the patient, but attempts to treat the amblyopia were unsuccessful because the patient refused to wear a patch over the sound eye. Atropinization of the sound eye was equally futile because the patient still preferred the sound eye for fixation. Corrected visual acuity was recorded to be 20/20 in the right and 20/200 in the left eye during childhood and remained the same throughout the patient’s life.

The refractive error was +1.00 dipter spherical in each eye at the age of 14 yr. Fundus examinations performed on several occasions were reported to be normal. Glasses were discontinued by the time the patient entered his freshman year in high school. At that time, his refractive error was minus 0.50 spherical in each eye and the presence of a small esophoria was recorded. When the patient was 40 yr old, his brother diagnosed an esotropia of the left eye with the Hirschberg corneal reflection test. At age 46, the patient received a presbyopic correction.

The patient’s brain was removed 22 hr after his death and was placed in a 20% formalin solution. Within 6 hr, we dissected selected portions of the visual system and placed the tissue into a cold solution of 2% paraformaldehyde and 0.5% glutaraldehyde.

The LGNs with short portions of the optic tract attached were infiltrated with nitrocellulose over the following several weeks. The tissue blocks were hardened, trimmed, oriented, and mounted on stages for sectioning in the coronal plane on a sliding microtome. Serial sections of 40 μm thickness were collected for subsequent staining with Nissl’s stain.

Sections from two locations in the middle position
of the right and left LGNs were examined under a Zeiss (Oberkochen, Germany) microscope. Cell sizes were determined in each LGN layer using a tracing tube and oil immersion optics. Only cells having a clear nucleus and nucleolus were accepted for measurement with the further stipulation that all such cells in the field of study were measured. The profiles of 50 cell bodies were traced for each layer of the right and left LGN at two locations within the nuclei. A sample of 50 cells was taken from the middle and another from a more posterior portion of the LGNs. A stage micrometer was used to project a calibration scale. The cell soma profiles were entered into a computer with a digital tablet, where the area of each profile was computed using the software program SigmaScan (Jandel Scientific, Corte Madera, CA). Means and standard deviations of cell area sizes were determined for each of the six layers in the middle and posterior portion of the LGNs. Student's t-test was used to test for differences in the mean cell sizes connected with the right and left eye. All persons involved in the tissue collection, preparation, and cell measurements were kept uninformed of the clinical history.

Results

In a preliminary study, we determined whether differences in cell area sizes existed between the two samples obtained from the medial and posterior portions of the LGNs. Because no significant differences were found, we selected at random the medial sections from the LGNs for further study and comparisons. Table 1 shows the means and standard deviations of cell area measurements from each layer of the right and left LGN. Cell area sizes in layers 2, 3, and 5 of the left LGN, which received input via uncrossed fibers from the ambiolyptic eye, were significantly smaller (18–25%) than those in the respective layers of the right LGN, connected with the normal eye. Intrageniculate comparisons between layers receiving input from the right and left eye were less consistent. No significant difference existed in the left LGN, and small but significant differences (9–16%) were found between layers of the right LGN. However, in all significant cases, cells having input from OS were smaller.

Figure 1 shows a comparison of the means of cell area sizes from the LGN under study to those from a previously described esotropic macaque monkey (VDM 4).2,3 with strabismic amblyopia. In this monkey, contra- and ipsilateral LGN layers fed by the amblyopic eye had smaller cell area sizes but, as in the human, the greatest difference existed in the ipsilateral layers. Similar conclusions can be drawn from a comparison to the LGNs from a human anisometric amblyope (Fig. 2), on which we reported elsewhere.4 In both specimens, the most pronounced cell shrinkage occurred in ipsilateral layers 2, 3 and 5, but contralateral layer 4 also was involved in the LGN from an anisometric patient.

Discussion

The human LGN is separated into six layers, of which the ventral layers contain the larger cells (magnocellular layer) and the dorsal layers the smaller cells (parvocellular layer). Laminae 1, 4, and 6 are innervated via crossed fibers from the nasal retina of the contralateral eye, and laminae 2, 3, and 5 via uncrossed fibers from the temporal retina of the ipsilateral eye. No appreciable differences exist between the average cell sizes in ipsi- and contralateral laminae of magnocellular and parvocellular layers of normal human LGN.5 Thus, a difference in cell area sizes between LGN layers innervated by the normal and amblyopic eye in the LGN from a human strabismic amblyope, as shown in this study, is important. The magnitude of this cell shrinkage is similar to that reported in monkeys with strabismic amblyopia.3

Strabismic amblyopia seems to be initiated and maintained by an active inhibition within the retinocortical pathway and controlled by the nondeviating eye. This inhibition is provoked by the overlap of two different retinal images that are localized in a common visual direction, causing visual confusion. Removal of the normal eye by accident6 or by surgery7 may result in an appreciable recovery of visual acuity in the deviated eye. Electrophysiologic studies in monkeys with behaviorally confirmed strabismic amblyopia have shown an altered cortical dominance pattern. Striate neurons, which normally respond in equal numbers to stimulation from either eye, lose their functional connection with the strabismic amblyopic eye.8 In vivo studies in human amblyopes have shown decreased metabolic activity in the primary visual cortex while viewing through the amblyopic eye.9

In light of these findings that suggest the visual cortex is the primary site of amblyopia, the decrease in cell size area described in the LGNs from human and sub-

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Table 1. Comparisons of the means of lateral geniculate nucleus (LGN) cell area sizes (in square microns) from a human patient with strabismic amblyopia of the left eye

<table>
<thead>
<tr>
<th>Layer</th>
<th>Left LGN</th>
<th>% LE/RE</th>
<th>Right LGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>258, SD 58</td>
<td>ns</td>
<td>278, SD 58</td>
</tr>
<tr>
<td>2</td>
<td>235, SD 54</td>
<td>-18</td>
<td>286, SD 49</td>
</tr>
<tr>
<td>3</td>
<td>142, SD 33</td>
<td>-18</td>
<td>171, SD 34</td>
</tr>
<tr>
<td>4</td>
<td>143, SD 32</td>
<td>ns</td>
<td>144, SD 33</td>
</tr>
<tr>
<td>5</td>
<td>126, SD 32</td>
<td>-25</td>
<td>168, SD 35</td>
</tr>
<tr>
<td>6</td>
<td>121, SD 32</td>
<td>ns</td>
<td>142, SD 42</td>
</tr>
</tbody>
</table>

SD, standard deviation. ns, non significant.
Fig. 1. Lateral geniculate nucleus (LGN) cell sizes from the human strabismic amblyope (N/H = normal eye; A/H = amblyopic eye) and from a monkey with strabismic amblyopia (N/M = normal; A/M = amblyopic). The average size of 50 cells measured from each LGN layer is shown, with the overall mean values shown to the right (MM and MP). The magnocellular layers (M1, M2) and the parvocellular layers (P3-6) are identified. Note that in both species the largest cell shrinkage occurred in the ipsilateral layers (M2, P3).

Fig. 2. LGN cell sizes from a human anisometropic amblyope (N/A = normal eye; A/A = amblyopic eye) and comparable measurements from the strabismic amblyope (N/S = normal; A/S = amblyopic eye). Note that in both conditions the greatest effects were found in the ipsilateral layers.

Human primates may be caused by retrograde influences originating in the visual cortex. The mechanism of amblyopic inhibition on a cellular level is still unknown.

An explanation for the greater shrinkage of cells in ipsilateral LGN layers connected with the amblyopic eye, as shown in this report, was suggested by Ikeda and coworkers, who noted that the loss of functional LGN cells and shrinkage of perikaryal cell size in kittens raised with convergent squint was restricted to the ipsilateral LGN. This was interpreted as a visual deprivation effect from constriction of the nasal field.
of vision by the bridge of the nose. If there were such an effect from nasal field constriction, a correlation might be expected between the angle of esotropia and the degree of amblyopia. However, clinical studies have failed to find such a correlation. We propose that the predisposition for ipsilateral LGN involvement may be associated with the severity of the amblyopia, with the lesser degrees affecting the uncrossed geniculate terminals and the most severe amblyopia affecting crossed and uncrossed LGN layers. For example, the monkey whose cells in layers connected with the amblyopic eye were smaller in ipsi- and contralateral LGN (although this effect was greatest in the ipsilateral layers; Figure 1) had the most severe amblyopia of only light perception in his amblyopic eye. In comparison, the human anisometropic amblyope in whom we found the ipsilateral but also one contralateral layer involved (Figure 2) had a visual acuity of only 4/200 in his amblyopic eye. On the other hand, the strabismic patient reported in this paper had a relatively milder amblyopia of 20/200, and significant cell shrinkage was greatest in the ipsilateral LGN.

Another indicator for the proposed greater vulnerability of the ipsilateral LGN in strabismic amblyopia is our previous observation in esotropic monkeys of the recovery of LGN cells after enforced usage of the sound eye. Such recovery was restricted to LGN cells that received (crossed) input from the nasal retina. Cell sizes in the ipsilateral LGN layers, fed by the temporal retina, remained reduced despite a reversal of the cortical dominance patterns resulting from suturing of the formerly sound eye.

The similarity between the LGN anomalies in human strabismic and anisometropic amblyopia is striking when the psychophysical differences between these conditions are considered. Despite these differences, certain basic anomalies in the visual pathways, such as shrinkage of LGN cells, appear to be shared by both forms of amblyopia. Determination of whether the same holds for amblyopia caused by form vision deprivation must await the availability of a brain from a patient with that condition for histologic study. Based on experiments in kittens and monkeys, which show LGN cell shrinkage after the lid of one eye is sutured in infancy, the human brain can be expected to be similarly affected in visual deprivation amblyopia.

Key words: amblyopia, strabismus, anisometropia, monkey, lateral geniculate nucleus

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References