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REGIONAL DIFFERENCES IN NORMALLY OCCURRING CELL DEATH IN THE DEVELOPING HAMSTER LATERAL GENICULATE NUCLEI

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Normal cellular degeneration occurs in the lateral geniculate nuclei (LGN) of the hamster thalamus early in postnatal development. Degenerative debris can be observed in the ventral and dorsal nuclei at postnatal days 2–10 and is present in greater and more variable amounts in the ventral nucleus. Cell degeneration in the dorsal LGN is maximal at postnatal day 5, identical to the degeneration pattern of the hamster retina and superior colliculus, but shows a second peak at postnatal day 8 which may relate to the establishment of cortical connectivity. The incidence of degenerative debris is significantly higher in the peripheral margins of the dorsal nucleus, a pattern also seen in the retina and the superior colliculus, suggesting that a differential cell death may be involved in the formation of regional specializations in the visual system.

Cell death during normal development has been shown to be characteristic of the retina and its central target structures in a variety of species [3, 4, 9, 15, 16, 18]. The role of this pervasive and substantial cell death is as yet unclear, but at least two functions, the matching of neuronal numbers in interconnecting populations and the correction of errors in connectivity, have extensive experimental support [10, 11, 14, 17].

In prior studies we have described the spatial and temporal distribution of degenerating cells in the retina and superior colliculus of the hamster during the period of normally occurring cell death [4, 18]. Normal cell death occurs during the first 10 postnatal days in the retinal ganglion cell layer and the superficial gray layer of the superior colliculus, a primary retinal target. In both of these structures there is a striking inhomogeneity in the distribution of degenerating cells; the degeneration rate in the peripheral retina and the retinotopically defined peripheral regions of the superior colliculus is greater relative to central regions. In the retinal ganglion cell layer, the greater cell degeneration in the periphery has been implicated in the

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creation of the differential cell density. At birth, the distribution of cells in the retinal ganglion cell layer is uniform, and a differential cell distribution emerges over the period of greater peripheral cell loss [19], suggesting that cell death is involved in the production of the retina's central specialization.

Counts of beginning and end neuron numbers in the dorsal lateral geniculate nucleus (LGN) of mice have demonstrated a neuron loss of approximately 30% during normal development [9]. In this study, we have investigated normal cell degeneration in both the dorsal and ventral LGN of the hamster with emphasis on determining if there are spatial patterns in cell degeneration similar to those found in the retina and the superior colliculus. Comparisons of spatial patterns in cell degeneration across structures can be useful in determining how these spatial patterns and the resultant differences in local cell density are produced, as well as providing clues to their potential functional significance.

The methods used for this study have been described extensively in two prior papers [4, 18]. Twenty-two hamster pups (*Mesocricetus auratus*) of both sexes from 11 litters were used. Assessment of rate and distribution of cell degeneration were made for postnatal days 2, 3, 4, 5, 6, 7, 8 and 10 (postnatal day 1 = day of birth) for 3 hamsters at each postnatal day 3–10 and one hamster at day 2. All brains were embedded in paraffin, cut coronally at 10 μm and stained with cresylecht violet.

In the hamster, LGN neurons are produced from embryonic days 10 to 12 [2] and most, if not all, have migrated into their final position by the day of birth [12]. At all ages examined the LGN can be clearly delimited from surrounding structures. From each brain, 5 equally spaced sections through the rostral-caudal extent of the nuclei were examined, and a drawing and complete count of all degenerating cells were made at $\times 500$. Degenerating cells were recognized by their darkly and homogeneously stained, shrunken and sometimes fragmented nucleus, and their pale or

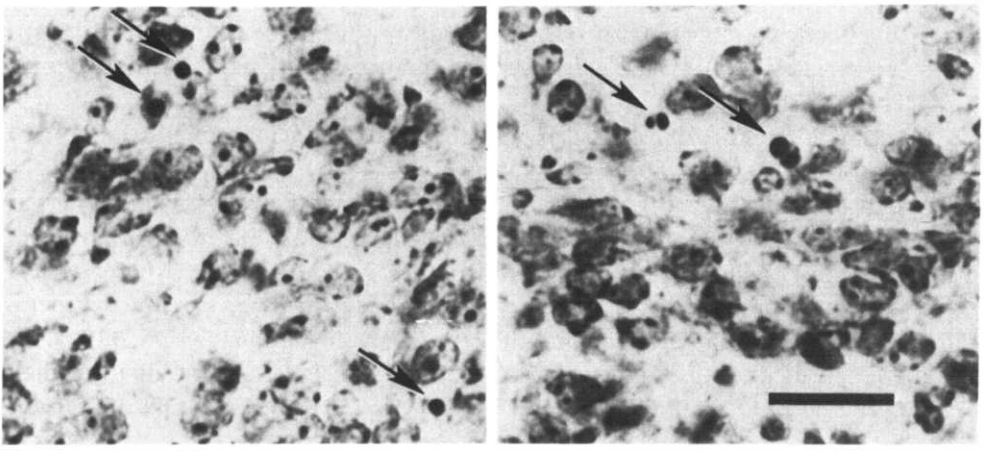

Fig. 1. Photomicrographs of coronal sections through the dorsal (left) and ventral (right) LGN at postnatal day 5. Arrows indicate degenerating cells. Scale bar = 20 μm.

absent cytoplasm [18] (Fig. 1). The relative density of degenerating cells was computed using normal cell counts of the same sections. A normal cell was counted if it contained a bounded nucleus and at least one nucleolus; normal cell counts included both neurons and glia because of the problems in distinguishing cell type with light microscopy at these ages. Counts of both normal and degenerating cells were corrected for frequency of encounter by size and section thickness using the method of Abercrombie [1], and the relative amounts of cell degeneration were expressed as the ratio of degenerating cells to normal cells. This method has been shown to be a sensitive indicator of differences in cell degeneration within structures and over time, and normal differences as well as experimentally induced changes in this ratio accurately predict end cell number [5, 6, 17–19, 21].

Normally occurring cell death in the dorsal and ventral LGN followed the general temporal pattern already observed in the retina and superior colliculus (Fig. 2). Cell degeneration is visible from postnatal days 2 through 10 and is maximal on postnatal day 5. The ventral LGN showed markedly higher and more variable rates of cell degeneration than the dorsal LGN. Unlike the retina and superior colliculus (and ventral LGN), there is a secondary peak in cell degeneration in the dorsal LGN on postnatal day 8.

To compare the relative amounts of cell degeneration in central versus peripheral regions, geniculate sections were divided into sectors representing the central 90° of gaze compared to a peripheral annulus of the same angular extent, according to the retinotopic map of the hamster LGN [8], and degeneration rates were determined for each region. As can be seen in Fig. 3, cell degeneration in the dorsal LGN was

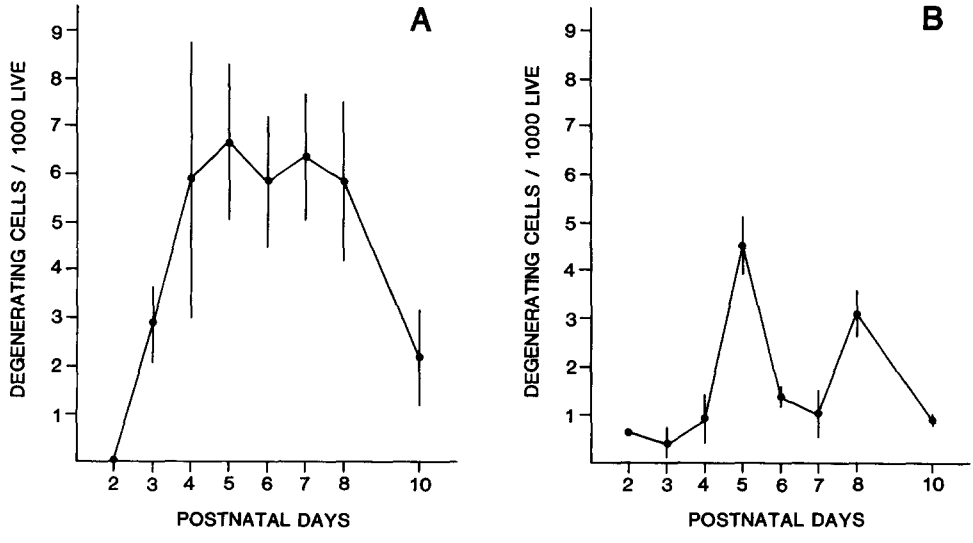

Fig. 2. Ratio of degenerating cells to normal cells in the ventral (A) and dorsal (B) LGN over the first 10 postnatal days. Points represent averaged values ± S.E.M.

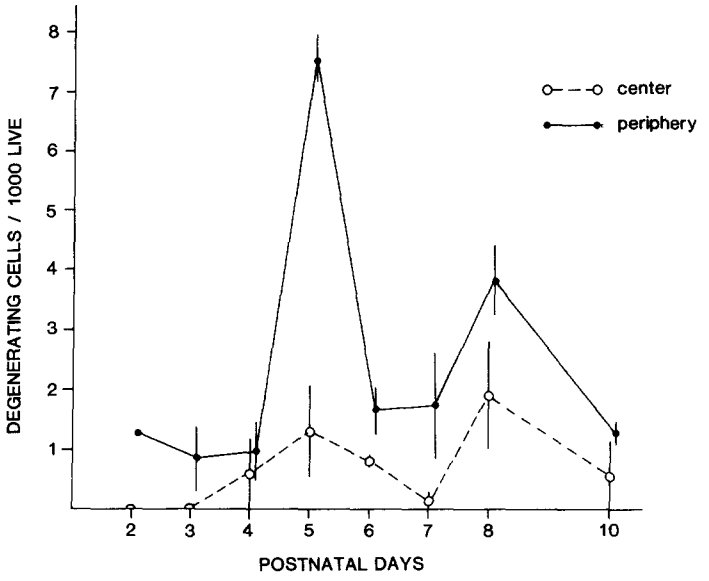

Fig. 3. Ratio of degenerating cells to normal cells for the retinotopically defined center (broken line) versus the peripheral margins (solid line) of the dorsal LGN. Points represent averaged values ± S.E.M.

significantly higher in the peripheral regions of the nucleus ($F = 38.23$, df = 1,28, $P < 0.0005$). Nearly all of the cell degeneration in the dorsal LGN was contributed by its peripheral margins with the largest concentration of degenerating cells seen at the ventral margins of the nucleus. There were no significant center/periphery differences in cell degeneration in the ventral LGN.

Like the other visual system structures we have examined to date, this study shows the presence of degenerating cells in the LGN during development, contrary to prior assertions [9]. Although the number of degenerating cells seen at any one time is small, when the rapid clearance of cellular debris in the developing nervous system is considered [7, 13], low rates can correspond to substantial cell losses. This cellular degeneration appears to be coincident with the establishment of efferent and afferent connectivity. The day of maximal cell degeneration (postnatal day 5) in the dorsal LGN and the superior colliculus, two major retinal targets, is the same as that in the retinal ganglion cell layer, the primary source of their innervation. Interestingly, the second peak (postnatal day 8) in cell degeneration seen only in the dorsal LGN is roughly coincident with the peak in cell degeneration of its primary target, cortical area 17 [6].

The observation of greater cell loss in the peripheral regions of the dorsal, but not the ventral LGN, presents an interesting problem. Both the retinal ganglion cell layer and the superficial layers of the superior colliculus show the same enhancement in cell degeneration in their peripheral margins, and it is tempting to speculate that the pattern seen in the dorsal LGN and superior colliculus is imposed by the

retina, the major source of their innervation. However, the greater rate of cell degeneration in the periphery of the geniculate and colliculus is still present after removal of the contralateral eye at birth [5, 20] and thus cannot be imposed by the retina. Alternatively, cells in the peripheral margins of structures could be more vulnerable to loss as a result of a less-favored position with regard to intrinsic connectivity. However, the intermediate and deep layers of the superior colliculus have a greater early cell loss centrally [4] and the ventral LGN does not show any spatial differences in cell degeneration, thus this argument cannot be advanced as a general statement about all bounded nuclei in the CNS.

Interestingly, these differences in the spatial distribution of cell degeneration do map onto the known differences in representation of central and peripheral visual fields in these structures and their projections. For example, neurons representing the central visual field in the dorsal LGN may be capable of establishing more terminal area in their target, area 17, than those neurons representing the peripheral visual field, resulting in the differential death of neurons representing the periphery. This differential survival of subpopulations of neurons could underlie the preferential representation of the central visual field seen in both the dorsal LGN and area 17. Thus, the substantial and pervasive cell death seen across vertebrates during normal development may be a mechanism which produces or enhances local specializations in larger neuronal arrays.

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