Development of retinal projections to the cat's lateral geniculate nucleus

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In mammals, synaptic connections formed between axons of retinal ganglion cell and neurons of the lateral geniculate nucleus are complex and yet strikingly precise. This poses a formidable problem for the development of these connections. Research performed in a number of laboratories during recent years has provided glimpses into many of the interacting mechanisms that work to control this development. Because so much of the relevant research has been performed on cats, this brief review will concentrate on the normal and abnormal development of the retinogeniculate pathway in this species. The reader can find a more thorough discussion of the mammalian visual system and its development in several recent reviews[1–6]. The evidence discussed below is organized around the hypothesis that development of the cat's retinogeniculate pathway is largely (but not entirely) controlled by competitive interactions among developing axons. The competitive development can at least conceptually be divided into three partially overlapping and related processes. First is the overproduction of ganglion cells and their axons followed by the loss of those that fail to make appropriate connections in the lateral geniculate nucleus; second is the formation of clear lamination in the lateral geniculate nucleus during the same period that retinogeniculate axons develop extensive arbors within their appropriate laminae; and third is the shaping and pruning of arbors as they continue to develop. The first two processes occur mostly prenatally and the third extends several months into postnatal life, although different axonal classes seem to engage in these processes during somewhat different prenatal and postnatal periods. However, the actual evidence presently available makes only a circumstantial if at times compelling case that the overproduction and subsequent death of excess ganglion cells, the development of lamination, and the pruning of retinogeniculate axon arbors are consequences of competition.

Normal adult cats

X and Y pathways

The population of ganglion cells innervating the lateral geniculate nucleus is heterogeneous and contains several distinct physiological and morphological classes. The two chief ones are called X and Y cells. (W cells, which comprise the remainder, are poorly understood, are tentatively thought to play a minor role in retinogeniculo-cortical innervation and conscious visual perception[4,6], and will not be considered further; as our knowledge of W cells increases, such a cavalier dismissal of them may, with hindsight, seem ludicrous.) X and Y cells give rise to separate, independent, and parallel pathways through the lateral geniculate nucleus and to visual cortex. Geniculate cells receive retinal input from one or a small number of either X or Y axons, but not from both. X and Y cells are thus readily distinguished in the lateral geniculate nucleus as well as in the retina. Finally, the X and Y pathways are also thought to perform distinct functions in the analysis of visual stimuli[1,3,4,6].

Geniculate lamination

A prominent feature of the cat's lateral geniculate nucleus is its lamination. As many as nine laminae have been described with various experimental techniques[7,8]. However, only laminae A, A1, C, 1, and 2 are obviously innervated by retinal X and/or Y axons (Fig. 1). (Other laminae, such as C1 and C2, are innervated by W axons.)

Fig. 1 schematically summarizes the relationship between geniculate lamination and the different types of retinogeniculate afferents[5,6]. The contralateral retina innervates laminae A, C, and 1; the ipsilateral retina innervates laminae A1 and 2. Ocular input is thus a prominent concomitant of the lamination, and in the normal adult each of these laminae receive retinal input from one or the other eye, with no binocular overlap. Another correlate of the lamination is X or Y innervation from retina. X axons innervate essentially only laminae A and A1, whereas Y axons innervate laminae A, A1, 1, 2, and C.

Morphology of individual retinogeniculate X and Y axon arbors

The morphology of individual retinogeniculate axon arbors has been described by injecting horseradish peroxidase (HRP) into single axons after physiologically identifying them as X or Y (Refs 9–11). Fig. 2 illustrates the morphology of X and Y arbors

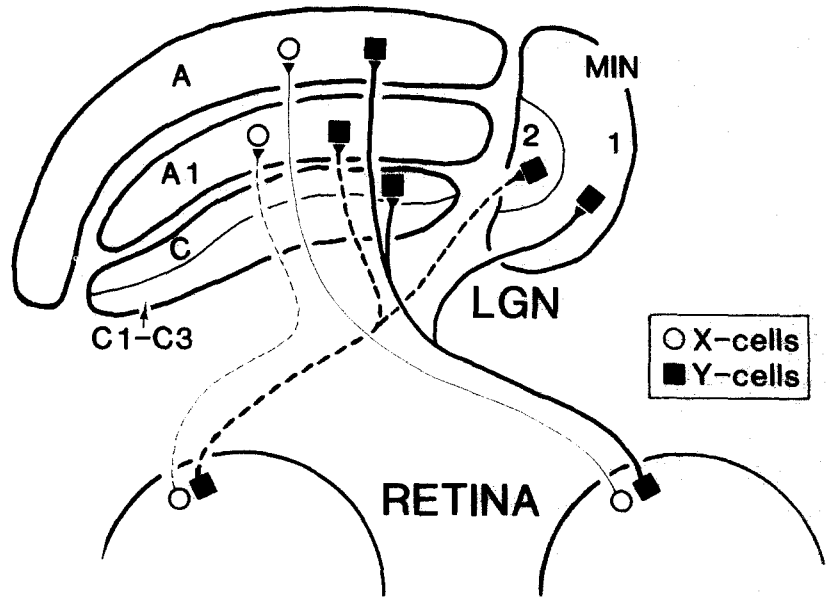

Fig. 1. *Schematic diagram of the retinogeniculate X and Y pathways, with coronal view of left lateral geniculate nucleus (LGN). A, A1, C, C1–C3, 1, and 2 refer to the various geniculate laminae. Laminae 1 and 2 lie in the medial interlaminar nucleus (MIN), which is a division of the lateral geniculate nucleus common to carnivores.*

from the retina. Single X axons innervate relatively small zones of lamina A or A1 with arbors typically containing 500–1000 boutons. These boutons are prominent swellings that have been confirmed with electron microscopy as the retinal synaptic terminals[12,13]. Single Y axons branch to innervate relatively large zones in several regions, including laminae A, C and 1 if from the contralateral retina, and laminae A1 and 2 if from the ipsilateral retina. It is typical for 1000–2000 boutons from a single Y axon to be found in lamina A or A1 alone. Normally, then, every X and Y axon innervates lamina A or A1, and Y axons innervate much larger geniculate zones with more boutons than do X axons.

Prenatal development

Retinal ganglion cell and axon numbers

Many neuronal pathways seem to develop by first overproducing cells and axons and then eliminating the excess, perhaps in a competitive manner by removing all that fail to establish or maintain appropriate connections[14]. Stone *et al.*[15] concluded that retinal ganglion cell numbers fall sharply from an overabundance at embryonic day 48 (E48; the kitten's gestation period is approximately 63 days) to normal adult values at birth. This correlates well with the observation that the number of optic nerve axons increases sharply from E30 to about E50, after which time the number gradually declines until adult values are finally reached at or just after birth[16] (Fig. 3A). In an interesting confirmation and extension of these observations, Williams *et al.*[17] report that slightly fewer axons are eliminated in the optic nerve after E48 if the other eye is removed *in utero* at E45 or E46.

Although these data seem to indicate that development of retinogeniculate connections follows the general rules of early overproduction followed by selective pruning, there is no direct evidence for this process. The studies cited above were not designed to identify that subpopulation of retinal ganglion cells or axons fated to innervate the lateral geniculate nucleus, and since other brainstem structures are also innervated from retina[5], it is not clear how accurately these patterns of overproduction and elimination reflect those of *retinogeniculate* axons. Also, no attempt was made to study these phenomena separately for X and Y cells. Since Y cells form only about 5% of the retinal ganglion cells and axons[18], counts of the entire ganglion cell and axon population might not accurately reflect the developmental sequelae for the subpopulation of Y cells. Nonetheless, Y axons form roughly 50% of the geniculocortical projection[4,19], presumably because the relatively large arbors of retinogeniculate Y axons (Fig. 2) seem to innervate roughly an order of magnitude more geniculate relay cells than do the smaller X arbors[4,19]. Knowledge of the developmental sequelae for the relatively small numbers of retinal Y cells can thus be quite important functionally.

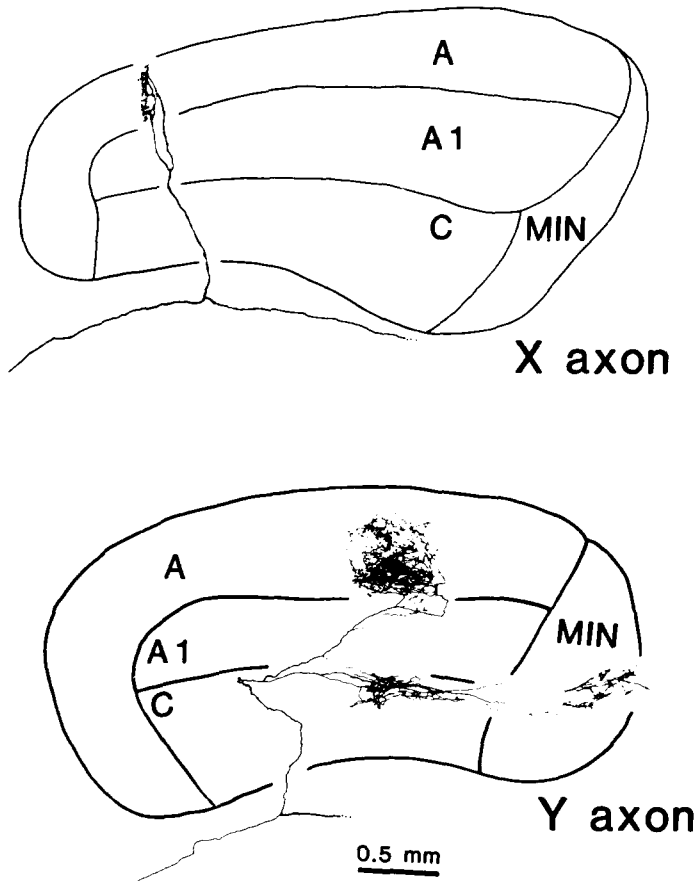

Fig. 2. *Tracing of physiologically identified and HRP-filled retinogeniculate arbors; labelling as in Fig. 1. These axons innervate the left lateral geniculate nuclei, which are shown in coronal view, and derive from the contralateral retina. The axons arrive from the lateral (left) side, and both have branches that were not traced further but seem to pass medially beyond the lateral geniculate nucleus. The X arbor innervates lamina A only, while the Y arbor innervates laminae A and C plus lamina 1. Similar differences between X and Y arbors are seen from the ipsilateral retina (not illustrated), except that the X arbors innervate lamina A1 only, while the Y arbors innervate laminae A1 and lamina 2 of the medial interlaminar nucleus. These examples are from a normal 12 week old kitten, since at that age the arbors have developed their final adult morphology.*
(Redrawn from Fig. 1 of Sur, Weller and Sherman[28].)

Development of lamination

Shatz and her colleagues[20–22] have shown that retinogeniculate connections are first formed prenatally. The first retinal axons reach the lateral geniculate nucleus around E32, and during the next two weeks or so there is considerable overlap in the areas innervated by the two eyes. Starting at roughly E47, segregation of each retina's input into appropriate laminae begins, and an adult-like pattern is achieved by birth[20] (Fig. 3B). The prenatal timing of segregation of these axons into appropriate laminae coincides closely with the loss of extra ganglion cells and axons (Fig. 3A,B), as if many of the axons innervating the

inappropriate laminae are lost through a competitive process. This coincidence of events, however, does not constitute proof of a cause-and-effect relationship.

Physiological studies are consistent with this anatomical pattern[21]. Geniculate cells are first responsive to stimulation of the optic nerves at E39, albeit quite poorly and immaturely. These early responses exhibit excitation from each optic nerve, thereby indicating binocular activation. This binocular pattern gradually changes so that the adult-like pattern of monocular inputs is evident by birth. This developmental pattern seen physiologically corresponds with the anatomical pattern of the gradual segregation of ocular inputs into distinct laminae[21].

This gradual segregation of inputs is reminiscent of the development of segregated ocular dominance columns in the visual cortex[23]. That is, afferents from the different geniculate laminae are substantially overlapped in layer IV of cortical area 17 at birth, but they segregate over the next few weeks to form separate 0.5 mm wide patches or columns that alternately represent inputs from one or the other eye via the appropriate geniculate laminae. In cortex, this segregation has been thought to represent a competitive process whereby afferents innervating the 'wrong' column are pruned as the 'correct' afferents continue to grow.

However, morphological visualization of single prenatal axons requires a modification of this general view of competition, at least for retinogeniculate axons[22]. The earliest retinal axons to arrive at the lateral geniculate nucleus are simple in shape and quite restricted in lateral extent, with short side-branches emitted throughout their course within the lateral geniculate nucleus. Thus the binocular overlap evident in pathway tracing studies does not reflect extensive invasion of the 'wrong' laminae as much as it reflects short side-branches that are later retracted as the arbor grows extensively into the 'correct' lamina. By birth, these axons exhibit dense arbors limited to lamina A or A1. It may be worth noting that orthograde pathway tracing techniques (e.g. autoradiographic labelling) provide similar evidence for initial overlap and subsequent segregation in retinogeniculate and geniculocortical projections[20,23]. However, published evidence is still lacking for the development of single geniculocortical arbors, so the possibility exists that prior interpretations of the autoradiographic data (i.e. that initially exuberant axons are later pruned[23]) may have to be reconsidered.

Interestingly, fetuses monocularly enucleated at E23 (i.e. *before* retinal axons even arrive at the optic chiasm, which thus precludes any prior binocular interactions) and studied for remaining retinogeniculate axons at E59 still display restricted arbors; these arbors appear to be grossly normal and distribute in tiers similar to laminae, although no clear laminae can be seen in such preparations[24]. Restricted arbors can thus form in the absence of binocular interactions and competition, at least prenatally. Of course, many other features of normal arbor development, other than their grossly restricted shape, might depend critically on binocular interactions among the growing axons.

As noted above, there is no direct means of distinguishing X from Y axons in prenatal material, and it is not clear if this initial development reflects the growth of X axons, Y axons, or both. However, Walsh *et al.*[25] provide indirect evidence that retinal X cells and their axons develop before Y cells and their axons. Medium-sized (i.e. X) ganglion cells are generated before large (i.e. Y) ganglion cells. Furthermore, the first axons to enter the optic tract seem to occupy a position furthest from the pia, while later arriving axons are added to the outside, nearest the pia. Since, in the adult optic tract, the diameter spectrum of fibers furthest from the pia matches that of X axons and the spectrum of fibers closest to the pia includes that of Y axons[25], it follows that X axons probably pass through the optic tract earlier in development that do Y axons.

Postnatal development

Normal development

The adult-like pattern of geniculate lamination and number of retinogeniculate axons are already present at birth (Fig. 3A,B). However, retinogeniculate synapses require several weeks of postnatal development to achieve mature structural features[26]. Myelination of retinal axons also occurs postnatally[16,27].

Particularly striking is the differential postnatal development of retinal X and Y axons[28,29]. This is summarized in Fig. 3C. At 3–4 weeks postnatal (the earliest age at which X and Y cells can be electrophysiologically distinguished), X axons have robust arbors that are larger and with more boutons than exist in adults, while Y axons have smaller arbors with many fewer boutons than in adults. During the next two months, these arbors gradually develop their adult form due to shrinkage of the X arbors and concomitant expansion of the Y arbors. Y arbors thus have a much later phase of growth than do X arbors. Furthermore, since some of the immature Y axons from the contralateral retina exhibit little innervation of lamina A despite a relatively mature arbor already present in lamina C, it may be that the lamina A or A1 arbors of Y axons mature last[29].

Abnormal development

From the above, it is clear that, although adult-like lamination and numbers of retinogeniculate axons are attained by birth, X and Y axons continue to mature postnatally with different time courses (Fig. 3C). The postnatal development of these retinogeniculate arbors can be dramatically affected by abnormalities in the visual environment, such as monocular deprivation by eyelid suture or monocular enucleation. Most of the observed postnatal plasticity is consistent with a competitive mechanism whereby abnormal projection patterns of the later-developing Y arbors compromise the ability of these Y arbors to prune the earlier-developed X arbors.

Monocular deprivation. Since the pioneering studies of Wiesel and Hubel, there have been many demonstrations of the deleterious effects of monocular deprivation on development of the visual system (reviewed in Ref. 5). Although the deprived retina develops normally under these conditions, geniculate cells in deprived laminae (i.e. those laminae innervated by the deprived eye) do not. Geniculate effects include abnormal neuronal morphology and a failure of Y cells to develop[5,30].

The first evidence that monocular deprivation affects development of retinogeniculate connections was provided by Friedlander *et al.*[19,30]. In normal cats, geniculate Y cells, which are innervated by retinal Y axons, are morphologically distinct from X cells, which are innervated by X axons. Normally, the Y cells have class 1 morphology according to Guillery's[31]

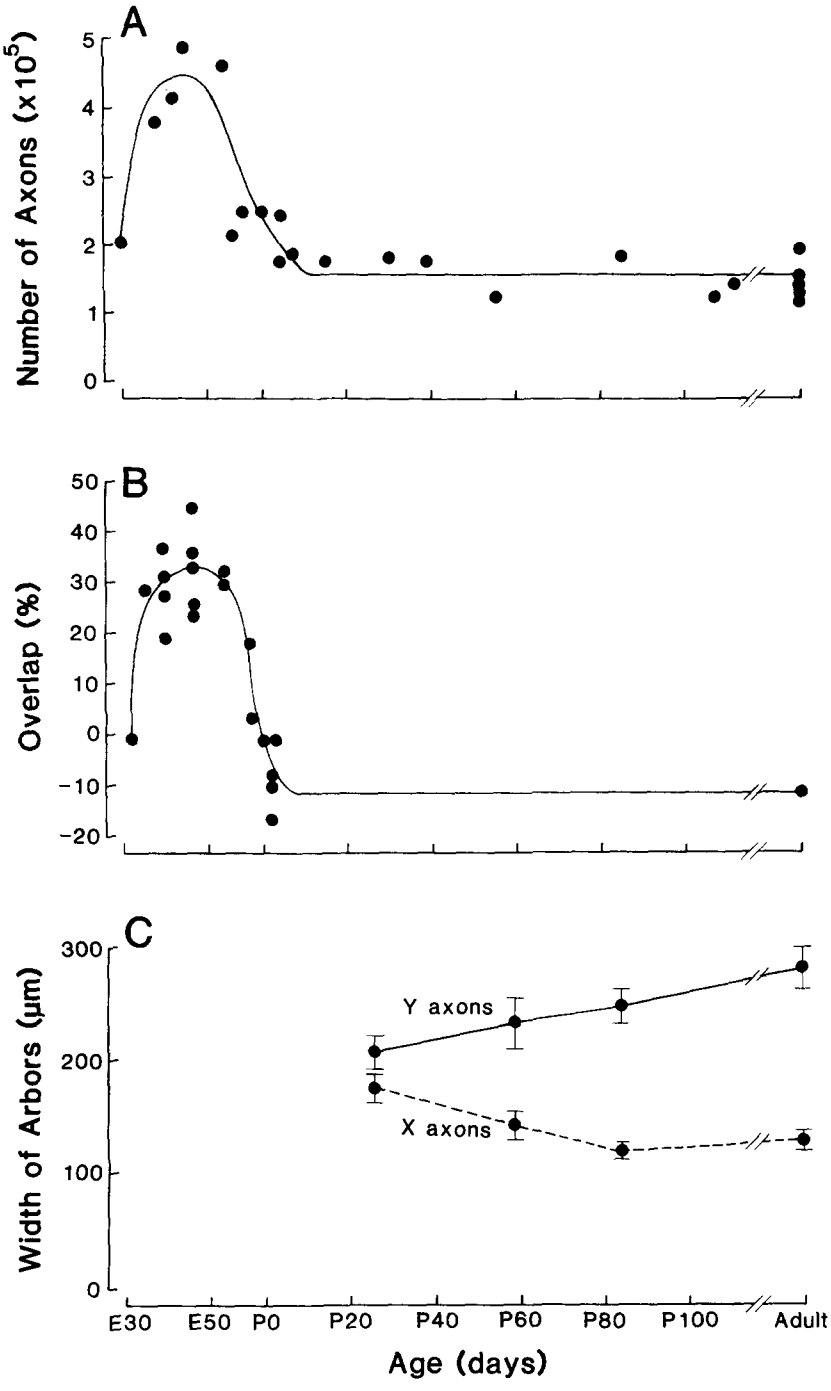

Fig. 3. *Sequelae of various developmental phenomena drawn to the same time scale. E and P followed by numbers on the abscissa refer to embryonic and postnatal days, respectively.* **A.** *Number of optic nerve axons as a function of age; curve drawn by eye. Each point represents a single kitten.* **B.** *Percentage overlap of afferents from the two eyes in the kitten's lateral geniculate nucleus as a function of age; curve drawn by eye. Overlap was estimated by plotting the percentage of geniculate area taken up bilaterally by a label (e.g. tritiated amino acids or HRP) orthogradely transported from one retina; it was assumed that a mirror-symmetric pattern of label results from the other retina. This permits an estimate of the total geniculate percentage covered by label, and when 100% is subtracted from this value, an estimate of overlap is obtained. Overlap is negative postnatally because zones between many laminae (e.g. A and A1, A1 and C) contain no label by that time. Each point represents an average from a single kitten.* **C.** *Maximum mediolateral extent of terminal arbors in lamina A or A1 as a function of age. This shows the mean and standard error of values for individual axons.*
(A is redrawn from Fig. 2 of Ng and Stone[16]; B is redrawn from Fig. 15 of Shatz[20]; C is redrawn from Fig. 2 of Sur, Weller and Sherman[28].

classification, and X cells have class 2 or 3 morphology. However, in deprived laminae of lid-sutured cats, few responsive Y cells could be found, and two general reasons for this have been noted. First, several cells were found with poor visual responsiveness and abnormal dendritic morphology; these were judged to be Y cells that failed to develop normal retinal innervation. Second, roughly one-third of the X cells possessed Y-like (i.e. class 1) morphology. No X cell in normal cats was found with such structure. Many of the geniculate cells normally destined to receive input from retinal Y axons thus appear to retain or develop input from X axons instead as a result of the deprivation. Interestingly, development of this abnormal retinal input does not seem to affect the cell's morphology as seen through the light microscope: these deprived geniculate X cells are anatomically identical to normal Y cells.

These results suggest the presence of comparable changes in the arbors of deprived retinal axons. X arbors should be abnormally large and contain an overabundance of boutons to account for their exuberant innervation of cells with Y-like morphology, while Y arbors should be correspondingly small with fewer boutons than normal. Sur *et al.*[32] reported just such a result. Most deprived X arbors are larger than normal in lamina A or A1, and many innervate the medial interlaminar nucleus, which is normally a target only for Y axons. In contrast, many Y axons completely fail to innervate lamina A or A1 and the medial interlaminar nucleus, although, curiously, the arbors in lamina C from the deprived contralateral retina appear normal. In some ways, the appearance of deprived X and Y arbors is similar to their appearance in young kittens, since at 3–4 weeks postnatal the X arbors are abnormally large while the Y arbors are quite immature, and some Y axons fail to innervate lamina A despite input to lamina C (see above).

Monocular enucleation. Neonatal removal of one eye during the first 10 postnatal days alters the pattern of laminar inputs from the remaining eye[33,34]. The appearance of the lateral geniculate nucleus after such rearing is grossly normal, but the denervated lamina A or A1 is clearly much thinner than is the normally innervated lamina. When pathway tracing techni-

ques are used to visualize the patterns of axon terminations derived from the remaining eye, it is clear that some axons can innervate the 'wrong' laminae. That is, ipsilateral to the remaining eye, some terminations can be traced into the shrunken lamina A, and vice-versa for the contralateral side and lamina A1. Since Shatz[20] has reported complete segregation of the afferents from each eye by birth (Fig. 3B), which is before the time of enucleation in the studies under discussion, the results suggest 'sprouting' or later growth of afferents into the previously denervated laminae.

Results from single axon filling help to clarify the picture in these neonatally enucleated cats. Robson[35] used bulk-filling (i.e. extracellular filling of a small number of damaged or cut axons), and was able to demonstrate the existence of retinal synapses formed by the translaminar sprouts. Garraghty *et al.*[36] filled identified X and Y axons and found that *all* of the translaminar sprouts were derived from Y axons that also innervated their appropriate target laminae. Although the X axons faithfully limited their arbors to the proper lamina (A or A1), these arbors were nonetheless hypertrophied, much like X arbors in neonatal kittens or in monocularly deprived cats.

Conclusions

The general rule for development of retinogeniculate connections may be one of competition among the growing axons as they struggle for synaptic space. This is hardly a novel suggestion and, indeed, has been promoted as a general rule of visual and neural development[5,14,23]. For the retinogeniculate pathway, this competitive development may involve overproduction of retinal ganglion cells and their axons followed by elimination of excess neurons, growth of retinogeniculate axons into segregated geniculate laminae, and the final development and shaping of the axonal arbors. However, most of the available evidence does not rule out alternative explanations to those requiring competitive mechanisms (see below), and many gaps still exist in the data.

Plausible competitive processes in retinogeniculate development

Direct evidence for competitive processes during development is rather difficult to obtain. The best strategy to date, in the author's opinion, requires the comparison of development between two cell groups that differ because one is placed in a competitive situation and the other is not. This strategy and examples of it have been extensively discussed elsewhere[5]. One example is the comparison of development of a portion of the visual system representing a monocular crescent of visual field (i.e. a monocular segment) with a portion representing the binocularly viewed region (i.e. the binocular segment); binocular competition is possible only in the latter. Since, in a monocularly deprived cat, deprived geniculate cells in the binocular segment develop quite abnormally while those in the monocular segment develop relatively normally (reviewed in Ref. 5), it follows that binocular interactions and competition strongly affect the development of these geniculate cells. Unfortunately, designing an experimental protocol analogous to the monocular/binocular segment comparison is impractical for most studies. One is thus forced to accept less direct evidence for competitive interactions. For instance, other explanations can be offered to counter the conclusion that postnatal development of retinogeniculate X and Y arbors in normal and monocularly deprived cats reflects competitive interactions[28,32]. The growth of X (or Y) arbors may depend only on the nature of the visual environment without regard to development of Y (or X) arbors. The analog to the monocular/binocular segment comparison requires comparison of X and Y arbor development in regions in which they interact (such as lamina A or A1) and regions in which they do not interact but that are otherwise totally equivalent to laminae A and A1; such a protocol is not feasible, and thus less direct evidence has been used to support the concept of competitive interactions between developing X and Y arbors. With this proviso in mind, it seems reasonable to consider plausible candidates for competitive interactions during development.

Prenatally, competition may exist among retinogeniculate axons as they strive to form connections in the appropriate laminae[20]. This is accomplished more by expansion of arbors within the correct laminae than by retraction of extensive arbors from incorrect laminae[23]. Since this development coincides with the elimination of excessive retinal ganglion cells and axons[15,16], it is likely that not all axons successfully develop such extensive arbors, and many of those that fail die. However, the relationship between cell death and development of retinogeniculate arbors has yet to be taken beyond this preliminary level. It is also not at all clear whether these prenatal events reflect development of the X pathway, the Y pathway, or both, and this is unfortunate, particularly in view of postnatal development.

Competition in postnatal development may be manifested in the growth of retinal X and Y arbors; this competition can occur among axons from the same retina as well as between axons from each retina. Normally, the X arbors mature earlier, and, like many early-developing connections, form large arbors to occupy the maximum available synaptic space, at least within the predetermined lamina (A or A1) appropriate for them (cf. Ref. 24). As the Y axons grow into this geniculate territory, the X arbors are reduced in size, perhaps by a competitive process[28]. If one eye is deprived during the critical period[5] (i.e. 4–12 weeks postnatal, which is after establishment of the X arbors and before that of the Y arbors), its Y axons lose their competitive advantage and fail to prune the X arbors[32]. If one eye is removed at birth, which is after formation of adult-like laminar inputs from the eyes, translaminar sprouting results[33–36]. This sprouting forms only from Y arbors. However, X arbors retain much of their neonatal exuberance within their appropriate laminae, as if they had not been significantly trimmed by the developing Y arbors[36].

Speculations for X and Y axon development

The above description of prenatal and postnatal development of retinogeniculate arbors may seem hopelessly complicated. However, with three assumptions that can be experimentally tested, it is possible to form a hypothesis and provide a theoretical framework for these observations.

Assumptions. First, competitive interactions are a general feature of retinogeniculate development, despite the mostly indirect evidence for such interactions.

Second, as retinogeniculate axons grow into the lateral geniculate nucleus and compete with one another for synaptic space, certain advantages might exist that favor particular connections over others. For example,

extensive development of arbors from one retina might be favored only in the laminae appropriate to that retina, which may be the reason that binocular competition normally leads to segregation of ocular inputs into laminae. Also, Y arbors might be favored over X arbors to innervate a certain class of geniculate cells (i.e. those with Y-like or class 1 morphology[19,31]).

Third, as the postnatal data suggest, X arbors might have an earlier time-course and critical period for their development than do Y arbors, such that X arbors grow mainly during the prenatal period and first two or three weeks postnatally, while Y arbors continue to develop extensively until about 3 months after birth. Both the earlier generation of X than of Y retinal ganglion as well as the relative location of X and Y axons in the optic tract, which suggests that X axons arrive earlier[25], are consistent with this assumption. Indeed, it is tempting to suggest that the single arbors stained prenatally by Sretavan and Shatz[22] are mostly or exclusively X arbors, but it must be emphasized that there is absolutely no direct evidence for this, and the distinct possibility that many are immature Y arbors cannot be excluded. Nonetheless, the immature X arbors might compete with one another to form retinogeniculate connections that, by birth, obey laminar boundaries but occupy more space within laminae due to the absence of extensive Y arbors. the main wave of Y arbor expansion may mimic that of X arbors, but occur later and well into the postnatal period, after X arbors have passed through their critical period for continued growth.

Hypothesis. It is possible with these assumptions to explain many of the postnatal observations. Normally, if later developing Y arbors successfully compete with X arbors for synaptic space onto many (class 1) geniculate cells, this would explain the reduction in size of X arbors as Y arbors grow. If lid suture interferes with this developmental process during the critical period of Y arbor development, this displacement of X arbors by Y arbors fails to transpire. Finally, if the neonatal enucleation occurs after the critical period for continued growth of X arbors but not of Y arbors, only the latter maintain the plasticity to expand into the denervated laminae. It is also possible that X arbors never have the potential to form translaminar sprouts, although this remains to be determined (i.e. might X arbors demonstrate sprouting if the enucleation were performed sufficiently early?). Because the Y arbors have more open territory to conquer in the denervated laminae, the X arbors are not under such competitive pressure for postsynaptic space and do not become as severely pruned within their appropriate laminae as occurs normally.

This hypothesis is speculative and tentative. However, it provides a theoretical framework for many of the experimental observations and helps to shape specific questions that might be productively pursued.

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