Molecular Neurobiology

ISSN0893-7648/96/12(2): 133–144/$8.00

Retinal Ganglion Cell Dendritic Development and Its Control

Filling the Gaps

Richard J. T. Wingate

Department of Developmental Neurobiology, Division of Anatomy and Cell Biology, UMDS, Guy's Hospital, London Bridge, London, SE1 9RT, UK

Abstract

The way in which central neurons acquire their complex and precise dendrite arbors is of considerable developmental interest. Using retinal ganglion cells (RGCs) as a model, the mechanisms that pattern dendritic development are beginning to emerge. As in other systems, final dendrite phenotype is achieved by a mixture of intrinsic and extrinsic determinants. The extrinsic determinants of RGC dendrite shape reflect the anatomical constraints of producing a paracrystalline mosaic of arbors that laminates the inner plexiform layer of the retina. In this article, the key features of RGC dendrite development are reviewed. The emerging molecular mechanisms behind dendritic laminar segregation and "dendritic competition" are described. The role of afferent extrinsic influences are contrasted with those of retrograde, activity-dependent target influences that may regulate the final maturational phase of dendrite remodeling.

Index Entries: Dendritic competition; inner plexiform layer; neurogenesis; TTX; NMDA; APV; APB; lucifer yellow.

Introduction

The diversity of dendritic form is one of the most impressive hallmarks of the complexity of the brain. The startling differences between the basic dendrite branching geometries of different neuronal types hint at far more than just different solutions to the problem of efficiently occupying space. The tendency to think of dendrite arbors as passive collators of incoming information no longer holds true given recent advances in imaging techniques *(1)*. Dendritic arbors actively process incoming signals *(2,3)*, their branch points potentially acting as switches for the flow of information *(4)*. This revitalization of a complex functional role for dendrite architecture inevitably leads to the question of how its morphological precision arises.

Dendritic phenotype is established by a combination of intrinsic determinants acted on by extrinsic factors. The final form of an arbor is often the product of both a period of exuberant growth and a phase of remodeling in which its shape can be radically altered *(5–7)*. Afferent inputs are an obvious potential influence on dendritic development *(8,9)*, although syn-

aptic activity *per se* may only regulate specific elements of maturation *(10)*. A clear role for retrograde influences of axonal targets on global dendritic properties has been described in the peripheral nervous system (PNS) *(11)*. By contrast, the involvement of target-derived factors in the dendrite development of central neurons is still relatively unexplored. In order to understand the basis of these various interactions, many studies have focused on the retina, a relatively accessible sheet of central neuronal circuitry, which has a single class of output neuron, the retinal ganglion cell (RGC).

RGCs as a Model System

RGCs are an excellent model for the study of dendrite development. Their dendrites are planar and within each retina there are several parallel classes of RGC, each with distinct dendritic morphologies and functional characteristics (Fig. 1; *12–14*). Since the development of RGC axons has been intensively investigated, it is also possible to consider their dendritic development in the context of not only retinal interactions, but also events at their axonal terminals.

Intrinsic Determinants: Formation of Dendritic Classes

Ganglion cells are the first retinal neurons to be born *(15)*. Within the period of their neurogenesis, tritiated thymidine studies have revealed that different classes of RGCs (distinguished by their soma size) have distinct ranges of overlapping birthdates (carnivore, *16,17*; rodent, *18*). Lineage analysis *(19–22)* and in vitro assays *(23–26)* suggest that this generalized relationship between cell class and birthdate within the retina reflects a changing microenvironment of locally acting molecular cues. Of these, FGF-1 in particular potentiates ganglion cell differentiation *(26)*. Dissociated ganglion cells can develop dendritic arbors that resemble their in vivo stereotyped forms *(27,28)*.

The development of ganglion cell dendritic trees follows a characteristic pattern in a variety of different mammals *(29)*. Each arbor undergoes phases of growth and refinement (Fig. 2; *30*) such that, by adulthood, the dendritic arbors of a single morphological class, viewed *en face*, have a mosaic coverage of the retina, whereas viewed in cross-section they are restricted to a distinct plane within the inner plexiform layer (Fig. 3; *31*). The details of the anatomical and molecular events surrounding dendritic elaboration are best understood in the cat. After ganglion cells are born (E21 onward; *16,32*), they extend a proximal axon, perhaps while the vitreal endfoot is still attached (as in marsupial *33*; chick, *34*). Dendrites emerge subsequently from the opposite pole to the axon *(35)*. Dendritic elaboration is concomitant with a variety of anatomical and physiological events, summarized in Fig. 4 *(16,36–40)*. Perhaps most significantly for development, "horizontal" synaptic connectivity develops before the "vertical" connections that transmit visual information in the adult. Synapses between ganglion cells and amacrine cells are apparent by E56, but it is likely that these two cell types have already been electrically coupled by gap junctions *(41)*. In the ferret, gap junctions facilitate waves of correlated activity within the developing retina *(42,43)*, which are mediated by fluxes in intracellular calcium *(44)*. This spontaneous activity requires voltage-gated sodium channels but is not dependent on exogenous glutamate from afferent circuitry. In the cat, "vertical connections" (ribbon synapses from afferent bipolar cells) are not made until at least the day of birth *(32,45)*.

Definitive dendrite cell classes are established some time prior to this, at the end of the period of naturally occurring cell death in the ganglion cell layer (E60; *46,47*). These two events are correlated in a number of species *(29)* and may even be functionally related. Cell death might eliminate indeterminate morphologies leaving only the more stereotyped dendritic forms. Alternatively, a reduction in ganglion cell density could potentiate innate

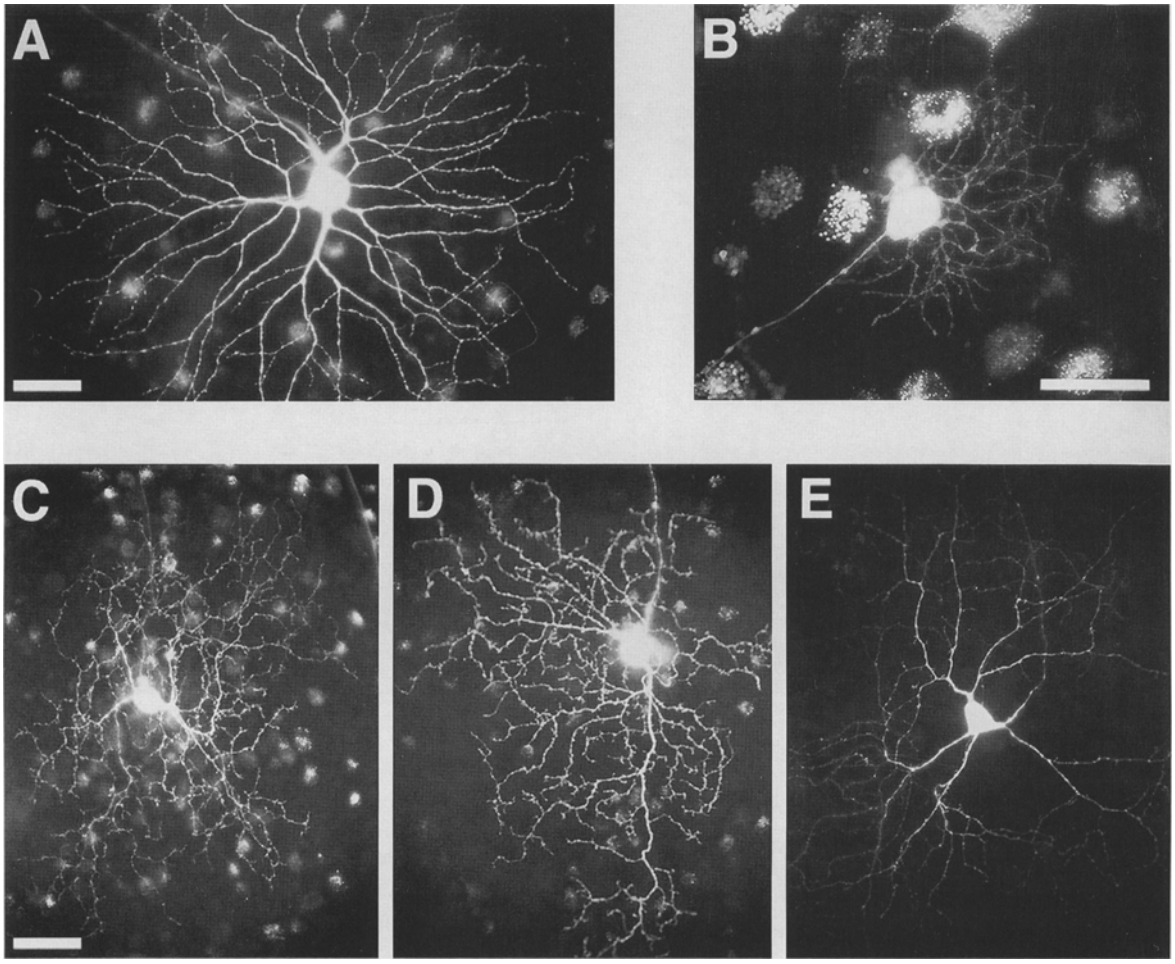

Fig. 1. Morphological types of RGC in the ferret retina *(12)*. Cells were intracellularly filled in vitro in fixed retina, with the fluorescent dye lucifer yellow under direct visual control. Cell bodies of ganglion cells were preidentified by retrograde label (fluorescent microspheres) previously injected in vivo into subcortical visual nuclei. There are three main classes of carnivore dendritic morphology, α **(A),** β **(B),** and γ. The γ class can be further subdivided into three main variants; "tight" **(C),** "loose" **(D),** and "sparse" **(E),** each shown to the same scale. Neighboring α and β cells can also be distinguished by their characteristically different soma sizes. Mosaics of congruous dendritic fields have been demonstrated for α and β cells in the cat *(13)*. These two classes of cell correspond to the physiologically defined "Y-" and "X-" cell classes, which have transient and sustained responses to changes in light intensity, respectively *(14)*. Each class is composed of both ON- and OFF-cells, responding to increases and decreases in illumination, respectively, which would be expected to have separate, structurally distinct mosaics (*see* Fig. 2). Scale bars = 50 μm.

dendritic growth patterns by reducing "competitive" interactions for synaptic "space" within the retina.

Subsequent phases of dendritic segregation and dendritic remodeling involve modifications to the dendritic arbors that become apparent at this stage. The extent to which intrinsic mechanisms are involved in these later modifications is unclear. Although various observations suggest this latter phase of dendritic development is directed by extrinsic mechanisms, the possibility that extrinsic factors act only to initiate intrinsic programs of dendritic remodeling can not be excluded *(9)*.

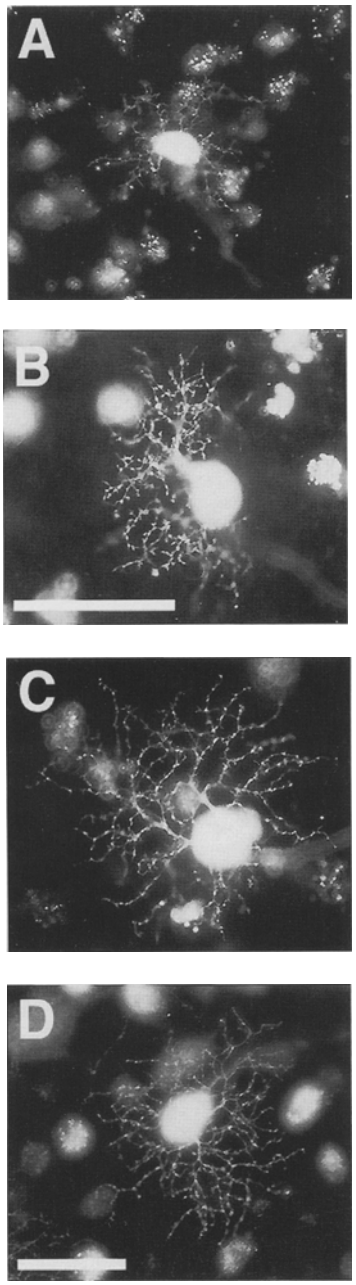

Fig. 2. The development of dendritic morphology. Photomicrographs of lucifer-yellow-filled ganglion cells show the maturation of β dendritic trees in the ferret *(30)*. The distinct branching geometry of this cell class emerges between P5 **(A)** and P9 (**B,** both to the same scale). From this stage onward there is progressive dendritic elaboration and exuberant growth. At the peak of complexity when the eyes open at P32 **(C),** dendrites are elaborated with numerous small spines. Adult dendritic arbors (**D,** to the same scale as C) have considerably fewer branches and spines. Scale bars = 50 μm.

Extrinsic Afferent Determinants of Dendrite Growth

Each RGC class is believed to form a complete and independent mosaic of congruous dendrite fields (Fig. 3). In such a view, the individual cells that compose each separate, overlapping mosaic have similar response properties and tile the retina in such a way that there are no holes in visual space *(13)*. Cells of the same class, sharing the same mosaic, vary only in the spatial extent of their dendritic fields, and then in a way that is systematic and corresponds to regional variations in visual acuity across the retina.

Such a model suggests various anatomical constraints on the growth of individual ganglion cell arbors and has raised some important developmental questions. First, how do the dendrites grow to occupy a single sublamina of the inner plexiform layer (dendritic sorting)? Second, how do neighboring dendritic arbors become spatially organized into continuous sheets that can be both congruous and yet accommodate changes in ganglion cell density at various retinal locations? In both cases, interactions between developing dendrites and afferent retinal circuitry have been invoked to at least partly explain dendritic developmental refinement.

Dendritic Sorting: How Do Functional Laminae Arise?

The stratification of a ganglion cell's dendritic arbor within the inner plexiform layer determines whether it will respond to the onset (ON) or offset (OFF) of a visual stimulus (Fig. 3C). This functional layering arises because of the different levels at which afferent ON and OFF bipolar cells terminate *(48)*. The functional coherence of a ganglion cell's response hence depends on developing a precise dendritic stratification pattern within one sublamina. This organization appears only relatively late, over the period in which bipolar-ganglion cell synapses are formed (P2–5 in the cat; *37*). Bodnarenko and Chalupa *(8,9)* have recently investigated factors that might regulate its

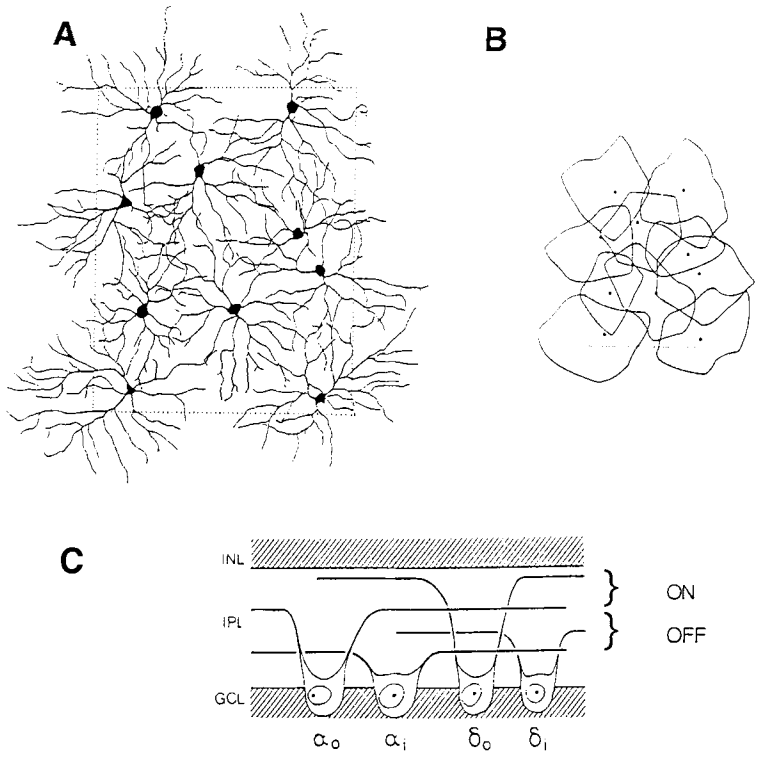

Fig. 3. The principle of dendritic mosaics and lamination as demonstrated in rat α RGCs (taken from ref. *31*). **(A)** Reconstructions of all the outer (OFF) α ganglion cells within a particular retinal field. **(B)** The dendritic territories of these cells are shown in outline and cover the retina such that there are no holes in "visual space." **(C)** The relative displacement of cell bodies and dendritic fields shown to scale in cross-section through the retina. The lamination of inner and outer α cell dendrites (α_i and α_o) is contrasted with that of the "delta" cell class, which also has ON- and OFF-responsive cells (δ_i and δ_o). The dendrites of each morphological and functional class lie in different layers within the ON and OFF sublaminae of the inner plexiform layer (IPL). The IPL is sandwiched between the ganglion cell layer (GCL) and the inner nuclear layer (INL).

development in the carnivore. Inhibiting glutamate release from the afferent bipolar cells by chronic intraocular injection of APB (2-amino-4-phosphonobutyric acid) reversibly blocks the segregation of the dendrites of the dominant β RGC class. It is not clear whether bipolar terminals themselves also segregate during this period. At this age, the eyes are still closed and the photoreceptor-bipolar synapse is immature *(32,45)*. Segregation is hence driven by a constitutive release of glutamate from bipolar cells: A postsynaptic blockade of spontaneous activity within the ganglion cell layer does not prevent segregation *(49)*, suggesting that all the cues for dendrite segregation are generated within the inner plexiform layer. In some species, the axons of ON and OFF ganglion cells form layers at the target through a glutamate-mediated sorting process. This happens as dendritic segregation is almost complete *(50)* and is downstream of events in the retina. Axonal sorting is probably driven by the onset of subtle differences in patterns of correlated spontaneous activity between ON and OFF mosaics that emerge as dendrites become functionally segregated *(51)*.

Within ON and OFF sublaminae in the inner plexiform layer, different dendritic classes may further stratify to occupy different levels (Fig. 3C). This independent stratification of cell classes was described by Cajal *(52)*, yet little attention has been paid to this aspect of gan-

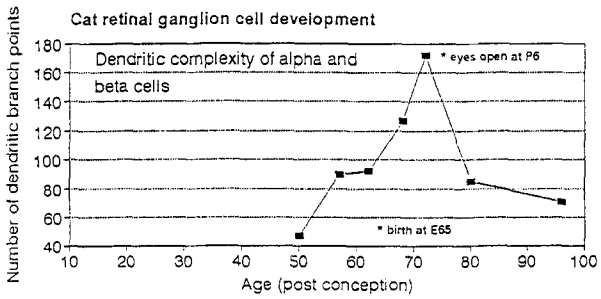

Fig. 4. The graph summarizes key events in the development of cat RGCs. Since the maturation of the cat retina is not uniform *(16,36)* some of these dates are approximate. Age is given in days post-conception. Cats are born on E65 (P0). The information shown was taken from a variety of sources *(32,37–40)*. E21, first RGCs are born; E30, one-third of RGCs are electrically active; E55, all RGCs electrically active; E56, first RGC-amacrine synapses; E60, end of period of cell death; P1, first ribbon synapses (bipolar); P2–5, dendritic segregation; P7, dendritic remodeling.

glion cell development. In addition to their broad subdivision into ON and OFF subtypes, different dendritic classes of ganglion cell receive inputs from different afferent pathways. For example, in the cat, β cells synapse mainly with bipolar cells directly, whereas α cells receive the majority of bipolar signals via amacrine cells *(53)*. For animals with trichromatic color vision, color-sensitive ganglion cells receive their dominant (center) input from the axons of only one of the three different types of bipolar cell *(54,55)*. It is unclear whether class-specific dendritic segregation is a functional correlate of this level of synaptic organization (as for ON and OFF pathways). If so, dendrite stratification might be a strategy for the development of specific connectivity given the way that neighboring ganglion cells are transiently electrically coupled. Morphologically distinct α and γ cells of the carnivore retina are dye-coupled to like neighbors and to amacrine circuitry (ferret; *41,44*) during the period of dendritic segregation (*51*; Wingate and Thompson, unpublished observations). β cells, which have direct bipolar synaptic input, are not. Gap junctions might allow other cell classes to organize their respective dendritic sublaminae and relatively more complex circuitry with respect to this simpler β cell dendrite "template." This would be analogous to the way that RGC axon classes become segregated at their target through an activity-dependent mechanism *(56–58)*.

Dendritic Competition: Making Congruous Mosaics

The uniform spatial array of polyhedral dendritic arbors that compose each mosaic ensures that the visual field is sampled at every point. The development of a continuous sheet of dendritic processes places special requirements on dendritic growth. If a ganglion cell class has a relatively more tightly packed mosaic, its cells have smaller dendritic trees. In addition, dendritic field sizes respond to differences in ganglion cell density within the retina that are high centrally and low at the periphery. This optimal tiling virtually predicts developmental interaction between neighboring dendritic trees *(13)*. Investigations into the degree to which cells interact within or between classes and how such an interaction might be regulated have demonstrated that "dendritic competition" *(59)* has an important role to play in making congruous mosaics.

Dendritic competition was first demonstrated by making focal retinal lesions. Dendritic growth in surrounding RGCs is oriented toward this cell-depleted region *(59,60)*. An effect can be induced over several dendritic field diameters, suggesting that dendritic interactions are regulated trophically rather than by contact inhibition *(61)*. The response of cells of one class can be moderated by the presence of other ganglion cell classes, indicating that competition is not class-specific *(62)*. Global changes in ganglion cell density, induced by extraretinal lesions, have the expected results within this competitive framework. Increasing ganglion cell density by prenatal monocular enucleation *(63)* results in smaller dendritic arbors at a given retinal eccentricity. Similarly, decreasing ganglion cell density and hence

competitive constraints by pathway lesions (optic tract in cat; *64;* superior colliculus in rat; *65*), result in larger dendritic arbors. Again, there is some evidence that different classes can compete with each other for retinal territory *(66)*.

As a phenomenon, dendrite competition is an attractive explanation for the even dendritic tiling of the retinal surface, the orientation of dendritic fields where maturational gradients across the retina are particularly steep *(67,68)*, and the evolutionary flexibility that allows closely related species to accommodate sharp, adaptive changes in ganglion cell distribution that may accompany visual specialization *(69,70)*. However, the molecular basis of dendritic competition is still unknown. As yet, there is no direct evidence for a proposed afferent-derived growth factor, such as BDNF *(61,71)*, in mediating this phenomenon. Growth factors are, however, not the only candidate molecules for directing dendritic competition. Recent insights from other systems suggest that neurotransmitter receptor activation may influence dendritic growth in vitro *(72)* and in vivo through both inhibitory *(73)* and *N*-methyl-D-aspartate (NMDA)-gated channels *(74)*. Neurotransmitters can act as trophic factors, orienting the growth of neurites in culture *(75)*. Glutamate, which is present in the retina during the emergence of distinct dendritic morphologies *(76,77)*, is known to have a powerful, calcium-mediated affect on neurite outgrowth *(78,79)*. However, since glutamate blockade does not result in unusual dendritic arbor size or orientation *(9)*, a direct role in dendritic competition would appear to be excluded. Another candidate is acetylcholine, which is released by amacrine cells and which can directly influence calcium concentrations within developing RGCs *(80)*, potentially influencing dendritic form. The response of relatively distant dendrites to a focal lesion *(61)*, which have suggested a diffusible afferent-derived growth factor, might partly reflect focal changes in intracellular calcium flux, spreading to more distant cells via gap junctions *(44)*.

Extrinsic Retrograde Determinants: Dendritic Remodeling

Dendritic segregation and competition both appear to take place within a framework of afferent-derived extrinsic regulation. By comparison, less is known of either the functional significance or the regulation of the phase of dendritic remodeling, which appears to be common to the development of all mammalian RGCs (cat; *39,40,81,82;* rat; *83;* hamster; *84;* ferret; *30*). The acquisition of spines and the excessive branching of dendritic arbors prior to eye opening (*see also* refs. *35,85–87*) leads naturally to speculation that spines might be "reaching out" for potential afferent synapses *(88)*. Spines are retracted and dendritic branches pruned after synapses are formed. However, spines are not the site of synapse formation *(89)* and several studies have indicated that dendritic remodeling is autonomous of retinal conditions: Manipulating ganglion cell density has no affect on spine loss *(90)*. Although NMDA receptor blockade may delay spine retraction (by chronic application of 2-amino-5-phosphonovaleric acid [APV]; *91*), altering ganglion cell activity, by either dark-rearing *(92)* or tetrodotoxin (TTX) application *(49)*, has no appreciable affect on overall dendritic remodeling (*see also* ref. *10*). This is despite the observation that in a number of species the onset of remodeling correlates with eye opening and the onset of patterned visual input (Fig. 3; *29*).

What, then, is the role of remodeling and what is the significance of eye opening in its regulation? Remodeling may be related to processes of dendritic segregation and competition: In cat, ganglion cell dendrites remain "reactive" to changes in cell density during the prolonged phase of dendritic resculpting *(60)*. However, an additional insight into this question is that remodeling is selectively enhanced in RGCs that display axonal targeting errors *(84)*. The selective enhancement of the severity of pruning in aberrantly projecting cells can be blocked by either creating more space at the target nucleus or by dark-rearing. Although activity itself is not required for dendritic

remodeling *(49)*, the degree of resculpting may involve an "awareness" of targeting accuracy, which relates to both axonal crowding and patterns of activity at the target. Axonal remodeling precedes that of dendrites, suggesting that any retrograde response is a reflection of established axonal arborization patterns.

Although such a mechanism in aberrant cells is useful in downregulating visually anomalous ganglion cell activity, why are there regressive events in all ganglion cell dendritic arbors? One explanation is that remodeling is an intrinsic program that allows RGCs to average synaptic input between neighboring cells. Activity is used to compare their output at the target and promote differential retrograde responses. Where the discrepancy between a cell's output and that of its neighbors is large, such as for those cells that make targeting errors, the severity of dendritic remodeling in that cell increases. All ganglion cell dendrites undergo remodeling; retrograde signals modulate only its degree. Hence, blocking activity has no significant effect on overall levels of dendritic pruning *(49)*, but rather rescues the dendritic arbors of a very small minority of aberrant cells *(84)*. In primate, for example, where the percentage of aberrant axons is very small, whereas remodeling is a prominent feature of dendritic development, only a very few cells would undergo extreme dendritic resculpting.

There are few precedents for the retrograde modulation of dendritic morphology in central neurons. Clarke and colleagues have shown that the orientation of dendritic fields in the isthmo-optic nucleus of the chick can be influenced by a retrograde, activity-dependent signal during development *(93,94)*. However, whether alignment arises by pruning of more exuberant arbors is unknown. Recently, Rand and Breedlove *(95)* have shown that the dendritic morphology of adult spinal motor neurons is sensitive to steroid levels at their axonal target.

The best example of retrograde modulation comes from the PNS, where target size directly correlates to the degree of dendritic elaboration of superior cervical ganglion neurons *(11,96)*. This observation has led to a concept of "trophic linkage," whereby quantitative dendritic extent of a population of input cells is regulated by a limited supply of a target factor *(96)*. For RGCs, and perhaps other central neurons, dendritic remodeling might depend on the supply of a target-derived factor, but this supply is moderated by activity-dependent interactions between an axon and its neighbors at the target.

Conclusions

As a model of neuronal development, RGCs have generated a wealth of studies of both their axonal and dendritic form. For dendrites, the laminar, mosaic organization of their arbors has allowed various developmental predictions to be made and tested. In particular, there has been some exploration of the phenomenon of dendritic exuberance followed by refinement, which is common to the development of many neurons. A rough hierarchy of developmental influences is emerging. Intrinsic determinants related to birth date and the retinal microenvironment establish basic dendritic geometry and a growth program that is influenced by various afferent and retrograde extrinsic factors. Dendritic growth and the formation of mosaics are regulated by intraretinal neighbor interactions in "competition" for an afferent-derived factor (perhaps glutamate or acetylcholine). Dendritic segregation into functional laminae is driven by an NMDA-mediated mechanism during a period when synaptic connections to afferent bipolar cells are established. Ganglion cells undergo an intrinsic program of dendritic remodeling after eye opening, the degree of which is influenced by activity-dependent target interactions. These may ensure a consistent synaptic input to individual dendritic arbors across the retinal mosaic of each cell class.

Acknowledgments

I would like to thank Ian Thompson and Gilles Fortin for their comments on this manuscript. R. J. T. W. is a Training Fellow of the UK Medical Research Council.

References

1. Barinaga M. (1995) Dendrites shed their dull image. *Science* **268,** 200,201.
2. Jaffe D., Johnston D., Lasser-Ross N., Lisman J., Miyakawa H., and Ross W. (1992) The spread of Na^+ spikes determines the pattern of dendritic Ca^{2+} entry into hippocampal neurons. *Nature* **357,** 244–246.
3. Magee J. C. and Johnston D. (1995) Synaptic activation of voltage-gated channels in the dendrites of hippocampal pyramidal neurons. *Science* **268,** 301–304.
4. Spruston N., Schiller Y., Stuart G., and Sakmann B. (1995) Activity-dependent action potential invasion and calcium influx into hippocampal CA1 dendrites. *Science* **268,** 297–300.
5. Koester S. E. and O'Leary D. D. M. (1992) Functional classes of cortical projection neurons develop dendritic distinctions by class-specific sculpting of an early common pattern. *J. Neurosci.* **12,** 1382–1393.
6. Vercelli A., Assal F., and Innocenti G. M. (1992) Emergence of calossally projecting neurons with stellate morphology in the visual cortex of the kitten. *Exp. Brain Res.* **90,** 346–358.
7. Kaspar E. M., Lubke J., Larkman A. U., and Blakemore C. (1994) Pyramidal neurons in layer 5 of the rat visual cortex. III. Differential maturation of axon targeting dendritic morphology and electrophysiological properties. *J. Comp. Neurol.* **339,** 495–518.
8. Bodnarenko S. R. and Chalupa L. M. (1993) Stratification of ON and OFF ganglion cell dendrites depends on glutamate-mediated afferent activity in the developing retina. *Nature* **364,** 144–146.
9. Bodnarenko S. R., Jeyarasasingam G., and Chalupa L. M. (1995) Development and regulation of dendritic stratification in retinal ganglion cells by glutamate-mediated afferent activity. *J. Neurosci.* **15,** 7037–7045.
10. Dalva M. B., Ghosh A., and Shatz C. J. (1994) Independent control of dendritic and axonal form in the developing lateral geniculate nucleus. *J. Neurosci.* **14,** 3588–3602.
11. Voyvodic J. T. (1989) Peripheral target regulation of dendritic geometry in the rat superior cervical ganglion. *J. Neurosci.* **9,** 1997–2010.
12. Wingate R. J. T., FitzGibbon T., and Thompson I. D. (1992) Lucifer yellow retrograde tracers and fractal analysis characterise adult ferret retinal ganglion cells. *J. Comp. Neurol.* **323,** 449–474.
13. Wässle H., Peichl L., and Boycott B. B. (1981) Dendritic territories of cat retinal ganglion cells. *Nature* **292,** 344,345.
14. Enroth-Cugell C. and Robson J. G. (1966) The contrast sensitivity of retinal ganglion cells of the cat. *J. Physiol. (Lond.)* **187,** 517–552.
15. Altshuler D., Turner D., and Cepko C. (1991) Specification of cell type in the vertebrate retina, in *Development of the Visual System* (Lam D. and Shatz C. J., eds.), MIT Press, Boston, MA, pp. 37–58.
16. Walsh C., Polley E. H., Hickey T. L., and Guillery R. W. (1983) Generation of cat retinal ganglion cells in relation to central pathways. *Nature* **302,** 611–614.
17. Reese B., Thompson W., and Peduzzi J. (1994) Birth dates of neurons in the ganglion cell layer of the ferret. *J. Comp. Neurol.* **341,** 464–475.
18. Dräger U. C. (1985) Birth dates of retinal ganglion cells giving rise to the crossed and uncrossed optic projections in the mouse. *Proc. R. Soc. Lond. (Biol.)* **224,** 57–77.
19. Turner D. L. and Cepko C. L. (1987) A common progenitor for neurons and glia persists in rat retina late in development. *Nature* **328,** 131–136.
20. Holt C., Bertsch T., Ellis H., and Harris W. (1988) Cellular determination in the *Xenopus* retina is independent of lineage and birth date. *Neuron* **1,** 15–26.
21. Wetts R. and Fraser S. (1988) Multipotent precursors can give rise to all major cell types of the frog retina. *Science* **239,** 1142–1145.
22. Williams R. W. and Goldowitz D. (1992) Structure of clonal and polyclonal cell arrays in chimeric mouse retina. *Development* **89,** 1184–1188.
23. Altshuler D. and Cepko C. (1992) A temporally regulated, diffusible activity is required for rod photoreceptor development in vitro. *Development* **114,** 947–957.
24. Watanabe T. and Raff M. C. (1990) Rod photoreceptor development in vitro: intrinsic properties of proliferating neuroepithelial cells change as development proceeds in the rat retina. *Neuron* **4,** 461–467.
25. Lillien L. and Cepko C. (1992) Control of proliferation in the retina: temporal changes in responsiveness to FGF and TGFa. *Development* **115,** 253–266.

26. Guillemot F. and Cepko C. L. (1992) Retinal fate and ganglion cell differentiation are potentiated by acidic FGF in an in vitro assay of early retinal development. *Development* **114,** 743–754.
27. Montague P. R. and Friedlander M. J. (1989) Expression of an intrinsic growth strategy by mammalian retinal neurons. *Proc. Natl. Acad. Sci. USA* **86,** 7223–7227.
28. Montague P. R. and Friedlander M. J. (1991) Morphologies and territorial coverage by isolated mammalian retinal ganglion cells. *J. Neurosci.* **11,** 1440–1457.
29. Wingate R. J. T. and Thompson I. D. (1995) The morphological development of mammalian retinal ganglion cells. *Prog. Ret. Eye Res.* **14,** 413–435.
30. Wingate R. J. T. and Thompson I. D. (1995) Axonal target choice and dendritic development of ferret beta retinal ganglion cells. *Eur. J. Neurosci.* **7,** 723–731.
31. Peichl L. (1989) Alpha and delta ganglion cells in the rat retina. *J. Comp. Neurol.* **286,** 120–139.
32. Maslim J. and Stone J. (1986) Synaptogenesis in the retina of the cat. *Brain Res.* **373,** 35–48.
33. Dunlop S. A. (1990) Early development of retinal ganglion cell dendrites in the marsupial Setonix brachyurus, quokka. *J. Comp. Neurol.* **293,** 425–447.
34. Watanabe M., Rutishauser U., and Silver J. (1991) Formation of the retinal ganglion cell and optic fiber layers. *J. Neurobiol.* **22,** 85–96.
35. Maslim J., Webster M., and Stone J. (1986) Stages in the structural differentiation of retinal ganglion cells. *J. Comp. Neurol.* **254,** 382–402.
36. Maslim J. and Stone J. (1988) Time course of stratification of the dendritic fields of ganglion cells in the retina of the cat. *Dev. Brain Res.* **44,** 87–93.
37. Rapaport D. H. and Stone J. (1982) The site of commencement of maturation in mammalian retina: observations in the cat. *Dev. Brain Res.* **5,** 273–279.
38. Skaliora I., Scobey R., and Chalupa L. (1993) Prenatal development of excitability in cat retinal ganglion cells: action potentials and sodium currents. *J. Neurosci.* **13,** 313–323.
39. Ramoa A. S., Campbell G., and Shatz C. J. (1987) Transient morphological features of identified ganglion cells in living fetal and neonatal retina. *Science* **237,** 522–525.
40. Ramoa A. S., Campbell G., and Shatz C. J. (1988) Dendritic growth and remodelling of cat retinal ganglion cells during fetal and postnatal development. *J. Neurosci.* **8,** 4239–4261.
41. Penn A., Wong R. O. L., and Shatz C. J. (1994) Neuronal coupling in the developing mammalian retina. *J. Neurosci.* **14,** 3805–3815.
42. Meister M., Wong R. O. L., Baylor D. A., and Shatz C. J. (1991) Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. *Science* **252,** 939–943.
43. Wong R. O. L., Meister M., and Shatz C. J. (1993) Transient period of correlated bursting activity during development of the mammalian retina. *Neuron* **11,** 923–938.
44. Wong R. O. L., Chernjavsky A., Smith S., and Shak C. J. (1995) Early functional neural networks in the developing retina. *Nature* **374,** 716–718.
45. Cragg B. G. (1975) The development of synapses in the visual system of the cat. *J. Comp. Neurol.* **160,** 147–166.
46. Ng A. Y. K. and Stone J. (1982) The optic nerve of the cat: appearance and loss of axons during normal development. *Dev. Brain Res.* **5,** 263–271.
47. Williams R. W., Bastiani M. J., and Chalupa L. M. (1983) Loss of axons in the cat optic nerve following fetal unilateral enucleation: an electron microscopic analysis. *J. Neurosci.* **3,** 133–144.
48. Famiglietti E. V. Jr. and Kolb H. (1976) Structural basis for ON- and OFF-center responses in retinal ganglion cells. *Science* **194,** 193–195.
49. Wong R. O. L., Herrmann K., and Shatz C. J. (1991) Remodelling of retinal ganglion cell dendrites in the absence of action potential activity. *J. Neurobiol.* **22,** 685–497.
50. Hahm J. O., Langdon R. B., and Sur M. (1991) Disruption of retinogeniculate afferent segregation by antagonists to NMDA receptors (see comments). *Nature* **351,** 568–570.
51. Fischer K. R., Oakley D. M., and Wong R. O. L. (1995) Developmental changes in the pattern of correlated spontaneous bursting activity in the ferret retina. *Soc. Neurosci. Abstr.* **21,** 1559.
52. Cajal S. R. Y. (1893[1973]) La rétine des vertébrés, in *The Vertebrate Retina* (Rodieck R. W., ed.), W. H. Freeman, San Francisco, CA, pp. 781–904.
53. Kolb H. (1979) The inner plexiform layer in the retina of the cat: electron microscopic observations. *J. Neurocytol.* **8,** 295–329.
54. Wässle H., Grünert U., Martin P. R., and Boycott B. B. (1994) Immunocytochemical characterization and spatial distribution of midget bipolar cells in the macaque monkey retina. *Vis. Res.* **34,** 561–579.

55. Wässle H., Grünert U., Martin P. R., and Boycott B. B. (1995) Color coding in the primate retina: predictions and constraints from anatomy, in *Structural and Functional Organization of the Neocortex, Exp. Brain Res.*, series 24 (Albowik B., Albus K., Kuhnt U., Nothdurft H.-C., and Wahle P., eds.), Springer-Verlag, Berlin, pp. 94–104.
56. Sur M., Humphrey A. L., and Sherman S. M. (1982) Monocular deprivation affects X- and Y-retinogeniculate terminations in cats. *Nature* **300,** 183–185.
57. Sur M., Weller R. E., and Sherman S. M. (1984) development of X- and Y-cell retinogeniculate terminations in kittens. *Nature* **310,** 246–249.
58. Garraghty P. E., Sur M., Weller R. E., and Sherman S. M. (1986) Morphology of retinogeniculate X and Y axon arbors in monocularly enucleated cats. *J. Comp. Neurol.* **251,** 198–215.
59. Perry V. H. and Linden R. (1982) Evidence for dendritic competition in the developing retina. *Nature* **297,** 683–685.
60. Eysel U. T., Peichl L., and Wässle H. (1985) Dendritic plasticity in the early postnatal feline retina: quantitative characteristics and sensitive period. *J. Comp. Neurol.* **242,** 134–145.
61. Perry V. H. and Maffei L. (1988) Dendritic competition: competition for what? *Dev. Brain Res.* **41,** 195–208.
62. Deplano S., Ratto G. M., and Bisti S. (1994) Interplay between the dendritic trees of alpha and beta ganglion cells during the development of the cat retina. *J. Comp. Neurol.* **342,** 152–160.
63. Kirby M. A. and Chalupa L. M. (1986) Retinal crowding alters the morphology of alpha retinal ganglion cells. *J. Comp. Neurol.* **251,** 532–541.
64. Leventhal A. G., Schall J. D., and Ault S. J. (1988) Extrinsic determinants of retinal ganglion cell structure in the cat. *J. Neurosci.* **8,** 2028–2038.
65. Bähr M., Wizenmann A., and Thanos S. (1992) Effect of bilateral tectum lesions on retinal ganglion cell morphology in rats. *J. Comp. Neurol.* **320,** 370–380.
66. Ault S. J., Thompson K. G., Zhou Y., and Leventhal A. G. (1993) Selective depletion of beta cells affects the development of alpha cells in car retina. *Vis. Neurosci.* **10,** 237–245.
67. Schall J. D. and Leventhal A. G. (1987) Relationships between ganglion cell dendritic structure and retinal topography in the cat. *J. Comp. Neurol.* **257,** 149–159.
68. Linden R. (1993) Dendritic competition in the developing retina: ganglion cell density gradients and laterally displaced dendrites. *Vis. Neurosci.* **10,** 313–324.
69. Wikler K. C. and Finlay B. L. (1989) developmental heterochrony and the evolution of species differences in retinal specialisations, in *The Development of the Vertebrate Retina* (Finlay B. L. and Sengelaub D. R., eds.), Plenum, New York, pp. 227–246.
70. Williams R. W., and Cavada and C., Reinoso S. F. (1993) Rapid evolution of the visual system: a cellular assay of the retina and dorsal lateral geniculate nucleus of the Spanish wildcat and the domestic cat. *J. Neurosci.* **13,** 208–228.
71. Perry V. H. (1989) Dendritic interactions between cell populations in the developing retina, in *The Development of the Vertebrate Retina* (Finlay B. L. and Sengelaub D. R., eds.), Plenum, New York, pp. 149–171.
72. Schilling K., and Dickinson M. H., Connor J. A., and Morgan J. I. (1991) Electrical activity in cerebellar cultures determines Purkinje cell dendrite growth patterns. *Neuron* **1,** 891–902.
73. Sanes D. H. and Chokshi P. (1992) Glycinergic transmission influences the development of dendrite shape. *Neuroreport* **3,** 323–326.
74. Kalb R. G. (1994) Regulation of motor neuron dendrite growth by NMDA receptor activation. *Development* **120,** 3063–3071.
75. Zheng J., Felder M., Connor J., and Poo M.-M. (1994) Turning of nerve growth cones induced by neurotransmitters. *Nature* **368,** 140–143.
76. Redburn D. A., Agarwal S. H., Messersmith E. K., and Mitchell C. K. (1992) Development of the glutamate system in rabbit retina. *Neurochem. Res.* **17,** 61–66.
77. Pow D. V., Crook D. K., and Wong R. O. L. (1994) Early appearance and transient expression of putative amino acid neurotransmitters and related molecules in the developing rabbit retina: an immunocytochemical study. *Vis. Neurosci.* **11,** 1115–1134.
78. Mattson M. P. (1994) Secreted forms of beta-amyloid precursor protein modulate dendrite outgrowth and calcium responses to glutamate in cultured embryonic hippocampal neurons. *J. Neurobiol.* **25,** 439–450.
79. Spitzer N. C. (1994) Spontaneous Ca^{2+} spikes and waves in embryonic neurons: signaling systems for differentiation. *TINS* **17,** 115–118.

80. Wong R. O. L. (1995) Cholinergic regulation of $(Ca^{2+})_i$ during cell division and differentiation in the mammalian retina. *J. Neurosci.* **15,** 2696–2706.
81. Dann J. F., Buhl E. H., and Peichl L. (1987) Dendritic maturation in cat retinal ganglion cells: a lucifer yellow study. *J. Neurosci. Lett.* **80,** 21–26.
82. Dann J. F., Buhl E. H., and Peichl L. (1988) Postnatal dendritic maturation of alpha and beta ganglion cells in cat retina. *J. Neurosci.* **8,** 1485–1499.
83. Yamasaki E. N. and Ramoa A. S. (1993) Dendritic development of abnormally projecting rat retinal ganglion cells. *J. Comp. Neurol.* **329,** 277–289.
84. Wingate R. J. T. and Thompson I. D. (1994) Targeting and activity-related dendritic modification in mammalian retinal ganglion cells. *J. Neurosci.* **14,** 6621–6637.
85. Perry V. H. and Walker M. (1980) Morphology of cells in the ganglion cell layer during development of the rat retina. *Proc. R. Soc. Lond. [Biol.]* **208,** 433–445.
86. Wong R. O. L. (1990) Differential growth and remodelling of ganglion cell dendrites in the postnatal rabbit retina. *J. Comp. Neurol.* **294,** 109–132.
87. Kirby M. A. and Steineke T. C. (1991) Early dendritic outgrowth of primate retinal ganglion cells. *Vis. Neurosci.* **7,** 513–530.
88. Wässle H. (1988) Dendritic maturation of retinal ganglion cells. *TINS* **11,** 87–89.
89. Wong R. O. L., Yamawaki R. M., and Shatz C. J. (1992) Synaptic contacts and the transient dendritic spines of developing retinal ganglion cells. *Eur. J. Neurosci.* **4,** 1387–1397.
90. Lau K. C., So K.-F., Tay D., and Jen L. S. (1991) Elimination of transient dendritic spines in ipsilaterally projecting retinal ganglion cells in rats with neonatal unilateral thalamotomy. *Neurosci. Lett.* **121,** 255–258.
91. Lau K. C., So K.-F., and Tay D. (1992) APV prevents the elimination of transient dendritic spines on a population of retinal ganglion cells. *Brain Res.* **595,** 171–174.
92. Lau K. C., So K.-F., and Tay D. (1990) Effects of visual or light deprivation on the morphology, and the elimination of the transient features during development, of type I retinal ganglion cells in hamsters. *J. Comp. Neurol.* **300,** 583–592.
93. Blaser P. F., Catsicas S., and Clarke P. G. H. (1990) Retrograde modulation of dendritic geometry in the vertebrate brain during development. *Dev. Brain Res.* **57,** 139–142.
94. Péquignot Y. and Clarke P. G. H. (1992) Changes in lamination and neuronal survival in the isthmo-optic nucleus following the intraocular injection of tetrodotoxin in chick embryos. *J. Comp. Neurol.* **321,** 336–350.
95. Rand M. and Breedlove S. (1995) Androgen alters the dendritic arbors of SNB motorneurons by actin upon their target muscles. *J. Neurosci.* **15,** 4408–4426.
96. Purves D., Snider W. D., and Voyvodic J. T. (1988) Trophic regulation of nerve cell morphology and innervation in the autonomic nervous system. *Nature* **336,** 123–128.