PLASTICITY IN THE VISUAL SYSTEM:
From Genes to Circuits

PLASTICITY IN THE VISUAL SYSTEM: From Genes to Circuits

Edited by

Raphael Pinaud, Ph.D.
OHSU, USA

Liisa A. Tremere, Ph.D.
OHSU, USA

and

Peter De Weerd, Ph.D.
University of Maastricht, The Netherlands

Springer

Library of Congress Cataloging-in-Publication Data

Plasticity in the visual system : from genes to circuits / edited by Raphael Pinaud, Liisa A. Tremere, Peter De Weerd.
p. cm.
Includes bibliographical references and index.
ISBN-13: 978-0-387-28189-6
ISBN-10: 0-387-28189-4
ISBN-13: 978-0-387-28190-2 (e-book)
ISBN-10: 0-387-28190-8
1. Vision. 2. Neuroplasticity. I. Pinaud, Raphael. II. Tremere, Liisa A. III. De Weerd, Peter.

QP475.P62 2005
612.8'4—dc22

2005051576

Printed in the United States of America.

9 8 7 6 5 4 3 2 1 SPIN 11054382

springeronline.com

This book is dedicated to
my family.

To the origin: Luiz Fernando, Sandra and Rodolpho,
Vó Vilma, Vô Néo e Eunice; *To the present*, Liisa;
To the future, my Daniel.
(R.P.)

For my mentors, who have opened the doors that allowed
my entry into science. For my family, who has helped
me get through them . . . And for my husband, who lays
his coat down over the puddles along the way so, that
I may go the distance with a little more grace.
(L.A.T.)

To good friends and family.
(P.D.W.)

In Memoriam

After my colleagues and I secured a contract with Springer to publish this book, a large effort was put forward by us to recruit leading authors in the various fields tackled herein. In the "Plasticity in the Visual Thalamus" section, we extended an invitation to Dr. Bertram Payne, from Boston University. Dr. Payne had spent several decades investigating plasticity phenomena in the visual thalamus, in particular dynamic plasticity of thalamocortical relationships. Bertram Payne promptly accepted our invitation with enthusiasm and sent me a rough outline of his chapter. Two months before the deadline for submissions of the first drafts, Bertram contacted me asking whether I would have a problem with him including some novel ideas in his chapter concerning the effects of cooling in the lateral geniculate nucleus, which was the focus of his most recent research efforts. I obviously encouraged him strongly after reading some of his material. A month after this last exchange Peter contacted me and stated that Bertram had passed away. We recognize here the major contributions of Dr. Payne to the understanding of basic principles involved in visual system plasticity.

Raphael Pinaud

Contents

Preface

Light information represents the fastest and possibly the most physically complex source of physical energy processed by most mammals. All three editors share the bias that the visual system likely houses the most advanced evolutionary design for the encoding and efficient handling of sensory input. To understand the mechanisms of plasticity within the visual system, one must initially explore the extent to which reorganization at higher levels could be explained by changes that occur at earlier stations such as the retina. The idea of plasticity in the retina is one of the controversial issues in the field of CNS reorganization and neural plasticity. In the present book, several experts in the field of visual system plasticity describe and discuss the extent of detectable change and the mechanisms proposed to underlie neural plasticity in the retina, sub-cortical structures, and cortex. To facilitate cross-talk between researchers with different technical backgrounds and perspectives, who conduct research in the visual system, we invited a wide range of investigators to discuss their own work, and to offer ideas and interpretations going beyond their own field of expertise. All authors were encouraged to suggest future applications of research findings from neural plasticity in the visual system with an emphasis on potential clinical uses and engineering within the biomedical sciences.

This book was born well after midnight on a kitchen table in Arizona, amid bottles of good wine and fine Belgian chocolates. After having solved the world's other problems, the three editors fell upon a discussion of neural plasticity and its involvement in the complex activities of perception, learning and memory. With Raphael's formation in molecular biology and neural plasticity, Peter's background in psychophysics and mechanisms of attention and learning in the visual system, and Liisa's training in neural plasticity and inhibitory processing in sensory systems, it was amazing we could establish sufficient common ground to hold an informed discussion at all. It was then that we identified a contribution that we could make: We decided to repeat our kitchen table discussion, this time by pooling the findings and perspectives of leading scientists interested in neural plasticity, working at the level of molecular and cellular biology, systems neuroscience and most areas in-between. So, wherever you may fall on this spectrum of

interests, we hope that you will enjoy reading "Plasticity in the Visual System: From Genes to Circuits".

An edited volume stands or falls with the chapters produced by its contributing authors. We feel lucky to have worked together with the present group of researchers, and we offer our sincerest thanks to all of the authors for their generous contributions and excellent chapters. We have greatly appreciated their preparedness to share their efforts and wisdom towards the completion of this project, and we thank them for their productive interactions and support throughout the editorial process.

Finally, we would also like to thank our partners at Springer: Joe Burns, Marcia Kidston, Sheri Campbell and Marc Palmer. Their enthusiastic support, advice and cooperation were indispensable in the creation of this work.

Raphael Pinaud, Portland, OR, USA
Liisa A. Tremere, Portland, OR, USA
Peter De Weerd, Maastricht, The Netherlands

Contributors

LUTGARDE ARCKENS
Laboratory of Neuroplasticity and Neuroproteomics
Katholieke Universiteit Leuven
Leuven, Belgium

GIUSEPPE BERTINI
Department of Morphological and Biomedical Sciences
University of Verona
Verona, Italy

CHRISTINE E. COLLINS
Department of Psychology
Vanderbilt University
Nashville, TN

YUZO M. CHINO
College of Optometry
University of Houston
Houston, TX

STEVEN K. FISHER
Neuroscience Research Institute
University of California Santa Barbara
Santa Barbara, CA

ANTONIO F. FORTES
Department of Neuroscience
University of Minnesota
Minnesota, MN

STEPHEN GROSSBERG
Department of Cognitive and Neural Systems and
Center for Adaptive Systems
Boston University
Boston, MA

BRYAN W. JONES
John A. Moran Eye Center
University of Utah School of Medicine
Salt Lake City, UT

JON H. KAAS
Department of Psychology
Vanderbilt University
Nashville, TN

GEOFFREY P. LEWIS
Neuroscience Research Institute
University of California Santa Barbara
Santa Barbara, CA

ROBERT E. MARC
John A. Moran Eye Center
University of Utah School of Medicine
Salt Lake City, UT

HUGO MERCHANT
Instituto de Neurobiología
UNAM, Campus Juriquilla
Queretaro Qro.
Mexico

VICENTE MONTERO
Department of Physiology and Waisman Center
University of Wisconsin
Madison, WI

BERTRAM R. PAYNE
Center for Advanced Biomedical Research
Department of Anatomy and Neurobiology
Boston University School of Medicine
Boston, MA

RAPHAEL PINAUD
Neurological Sciences Institute and Vollum Institute
Oregon Health & Science University
Portland, OR

BARRY J. RICHMOND
Laboratory of Neuropsychology
National Institute of Mental Health
National Institutes of Health
Bethesda, MD

THOMAS A. TERLEPH
Department of Psychology
Rutgers University
Piscataway, NJ

ELLEN TOWNES-ANDERSON
Department of Neurology and Neurosciences
New Jersey Medical School
University of Medicine and Dentistry of New Jersey
New Jersey, NJ

LIISA A. TREMERE
Center for Research on Occupational and Environmental Toxicology
Oregon Health & Science University
Portland, OR

CARL B. WATT
John A. Moran Eye Center
University of Utah School of Medicine
Salt Lake City, UT

PETER DE WEERD
Department of Psychology
University of Maastricht
Maastricht, The Netherlands

NAN ZHANG
Department of Neurology and Neurosciences
New Jersey Medical School
University of Medicine and Dentistry of New Jersey
New Jersey, NJ

1

Introduction to Plasticity in the Visual System: From Genes to Circuits

PETER DE WEERD[1], RAPHAEL PINAUD[2] AND LIISA A. TREMERE[3]

[1]Department of Psychology, University of Maastricht, Maastricht, The Netherlands,
[2]Neurological Sciences Institute, OHSU, Portland, OR, USA and
[3]CROET, OHSU, Portland, OR, USA

In this edited volume, the visual system is used as a model to study contemporary issues in central nervous system plasticity in the developing and adult organism. We evaluate plasticity induced by injury, sensory experience, and learning at all three anatomical levels of the ascending visual pathway: the retina, visual thalamic relays such as the lateral geniculate nucleus (LGN), and various visual cortical areas, with a particular focus on the striate cortex (V1) (Tessier-Lavigne, 2000; Wurtz & Kandel, 2000a,b; Lennie, 2000). One definition proposed for the term plasticity is the changing of connectivity between neurons (Hebb, 1949), which forms the basis for altered perception, cognition, and behavior. Plastic changes in neuronal activity and morphology in the visual system have been studied for decades in a variety of preparations using anatomical, electrophysiological and brain imaging techniques in both humans and animals. In parallel with advances in the neurosciences, research in the field of molecular biology has uncovered some principles underlying the physical basis for neuronal plasticity. These recent developments permit the realization of a conceptual bridge between plasticity viewed as changes in neuronal activity and morphology, and the molecular basis of these changes. The principal aim in generating this book, therefore, was to foster new perspectives on the topic of visual plasticity by integrating data obtained from systems neuroscience with insights from molecular and cellular biology. In a sense, this book will provide a zoom lens that will permit the reader to consider visual plasticity from the level of genes, proteins, and altered synaptic weights, to altered electrical activity measured in single neurons as well as in large neuronal circuits or populations.

The advent of modern visual neuroscience has been associated with studies in retinal ganglion cells by Kuffler (1953), who described the center-surround characteristics of retinal receptive fields (RFs) and a series of studies from

R. Pinaud, L. A. Tremere, P. De Weerd (Eds.), Plasticity in the Visual System: From Genes to Circuits, 1-10, ©2006 Springer Science + Business Media, Inc.

Hubel and Wiesel (1959, 1962), who described the orientation tuning and other response properties of neurons in striate and extrastriate cortices. Their studies represent the start of a long tradition of single-unit recording studies that aimed to elucidate the response properties of (visual) neurons. While these studies were typically conducted in the anesthetized cat, the development of techniques to record single-neuron activity in awake, behaving primates (Wurtz, 1969; Evarts, 1968) soon allowed the study of perceptual, motor, and cognitive performance while neuronal activity was recorded simultaneously. Relating (changes in) perception, cognition and behavior with (changes in) neuronal activity has been one of the great accomplishments of modern neuroscience. A powerful example of this approach was the discovery by Fuster (1973) of neuronal activity in pre-frontal cortex that bridged a time interval between the presentation of a sample stimulus and a test stimulus that the animal had to judge as matching or non-matching. This type of 'delay activity' has been considered to be a behavioral correlate of working memory or attention. In the context of such studies, it was discovered that high-level cognitive factors such as attention (Moran & Desimone, 1985) and learning (Yang & Maunsell, 2004) could be read-out from neuronal activity within sensory areas, including primary visual cortex (Gilbert et al., 2000). In addition, it was discovered that injury to the retina could lead to profound reorganization of retinotopic maps in visual cortex (Kaas et al., 1990). The discovery that primary visual cortex remains plastic in adulthood went against long-held beliefs that cortical plasticity was limited to developmental plasticity occurring before closing of the critical period. In the present book, evidence will be presented that adult plasticity extends even to the retina itself.

The use of a single electrode to correlate neural activity with perception or cognition can lead to the fallacy of believing that the response properties of neurons observed at the tip of the electrode are generated locally. That the contrary is true has become evident from several lines of work. Anatomical studies have demonstrated the complexity and extent of the neural network that can influence the activity of any single neuron (Press et al., 2001). Neural network modeling studies have been instrumental in demonstrating how the properties of individual nodes are a product of interactions with many other nodes at a number of levels in the system (e.g., Rumelhardt, 1987; Tielscher & Neumann; Xing & Andersen, 2000). Finally, it has become clear that data from ensemble recordings are more readily correlated with behavior than with data from single neurons. The idea that stimulus values or movement parameters are encoded by invariant patterns of firing in large sets of neurons is also known as population coding, a concept championed by Georgopoulos (1986). Thus, when one is interested in learning behavior and associated neural plasticity, techniques that could evaluate plasticity in extended neural networks would be highly useful.

Functional magnetic resonance imaging (fMRI) and other imaging techniques such as positron emission imaging (PET) and optical imaging can reveal plastic changes in large neural networks at a macro scale. fMRI, pio-

neered by Ogawa et al. (1990), is an ideal technique to use in humans, because it can be used repeatedly and non-invasively. fMRI signals reflect increased blood flow in activated cortex, and research in monkeys has shown that the fMRI signal correlates only partly with spiking behavior (Logothetis & Wandell, 2004). Nevertheless, many findings on perception and learning originally done using extracellular recordings in animal studies have been replicated in humans with fMRI (Ungerleider, 1995). Among those findings are the time-dependent roles of a number of brain structures such as basal ganglia and cerebellum during skill learning (Doyon et al., 2003), and the function of hippocampus during episodic memory formation (Ryan et al., 2001). In addition, fMRI has permitted the study of the topography of human sensory and motor cortex (for review in visual cortex, see Orban et al., 2004), as well as plastic changes in topography induced by skill learning and peripheral injury, thereby corroborating many findings previously reported in animal studies.

Despite the explosion of knowledge in the visual neurosciences, there are two major limitations that characterize the majority of the studies conducted in this field. One limitation is the correlative nature of the data, which does not permit the establishment of causal relationships. The other limitation is the difficulty in studying cell functioning and plasticity of neural networks on a cell-by-cell basis.

It would do injustice to the field of the neurosciences to claim that it would not have provided its own answers to these two fundamental questions. Anatomical lesions (Sprague et al., 1985; Heywood & Cowey, 1987; De Weerd et al.,1999), pharmacological lesions by local injection of toxins, such as ibotenic acid (Murray & Mishkin, 1998), or NMDA (Hampton et al., 2004), and reversible lesions by cooling (Lomber et al., 1999) or pharmacological means (Logothetis, 2004) have directly and successfully tested whether correlative relationships between neuronal activity and behavior could be interpreted in a more causative manner. Furthermore, important microstimulation studies in behaving rhesus monkeys by Newsome and colleagues (Seideman et al., 1998) have shown that the electrical stimulation of clusters of neurons encoding a particular direction of motion biased movement perception towards the movement encoded by these neurons, and microstimulation has also been reported to influence other types of perception and cognition (Cohen & Newsome, 2004); such findings will remain essential in order to transcend what can be achieved based on correlative study alone.

The development of ensemble recording techniques (Nicolelis et al., 2003; Hoffman & McNaughton, 2002), in which multiple neurons can be recorded over a number of sessions, have permitted the correlation between neural activity in large populations of neurons with cognitive behavior and learning/plasticity. For example, ensemble recordings in the rat and monkey hippocampus have successfully demonstrated the encoding, consolidation or memory formation during sleep, and retrieval of different spatial environments (Hoffman & McNaughton, 2002; Wilson & McNaughton, 1993,

1994). Ensemble codes in the hippocampus have been used to predict the position of rats in their environment (Wilson & McNaughton, 1993), and ensemble codes in primary motor cortex have been used successfully to steer and control robotic arms (Carmena et al., 2003). Such findings indicate that initially correlative findings can acquire such a strong causative footing that they can become useful in the design of therapeutic intervention.

Many of the initial insights into the molecular basis of neuronal plasticity have come from the use of simple invertebrate systems, such as *Aplysia* and *Drosophila*, which were introduced in the late 1950's to analyze elementary aspects of behavior and learning at the cellular and molecular level. A series of studies from Eric Kandel's group (e.g., Castellucci et al., 1970, 1989) has shown that the long-term sensitization of the gill-withdrawal reflex in *Aplysia* requires *de novo* protein synthesis and, consequently, gene expression. A perceptive, early insight by Thorpe (1956) that learning and memory might be universal features of the nervous system is confirmed by current research. For example, synaptic enhancement described in *Aplysia* shares a number of features with synaptic enhancement observed in mammalian hippocampus (Bailey et al., 1996; Bailey et al., 2000; Kandel, 2001). Furthermore, the hours-long consolidation periods reported for both skill learning and episodic memory formation seems to reflect the time period during which genes are expressed that regulate plastic structural changes of synapses and neurons (Bailey & Chen, 1983; Bailey and Kandel, 1993), and, in line with the above-referred data in *Aplysia,* these types of memory formation can be blocked by protein synthesis inhibitors (Luft et al., 2004; Agnihotri et al., 2004; Fisher et al., 2004). A number of findings also show that several late-response genes, which putatively regulate structural changes associated with plastic changes are controlled by a class of fast-responding genes known as immediate early genes (IEGs). IEGs are activated within minutes of cell stimulation or learning experience. The expression of these IEGs in certain cells can thus be used both as a marker of activity, and many IEGs are currently under review as candidate-plasticity genes (see Pinaud, 2004, and Chapter 8).

In contrast to electrophysiological recording methods, which offer high temporal resolution in a limited part of the brain, the use of IEGs offers the possibility to mark activity on a cell-by-cell basis throughout the brain, at the cost of temporal resolution. IEG expression profiles can be used as a tool to localize the effects of recent sensory-driven activity throughout the brain. For example, Ribeiro and colleagues. (1998) have used stimulus-dependent activation of the IEG *zenk* to visualize tonotopic organization in the songbird auditory system. Guzowski and collaborators have monitored the distribution of the IEG *arc* to reveal different hippocampal ensemble activity while rats were exposed to different spatial environments (Vazdarjanova & Guzowski, 2004). These examples show that molecular tools can be used to image activity in large numbers of cells recruited during perception, with single-cell resolution, and during various forms of memory formation and learning paradigms (Kaczmarek and Robertson, 2002). By applying these techniques at different

moments in a learning process, plastic changes in a neuronal network could be revealed directly. The main price to be paid for the high spatial resolution afforded by these techniques is the loss of certain time windows for studying plasticity related events, as changes occurring milliseconds or seconds after a manipulation cannot be captured histologically (Kaczmarek and Robertson, 2002). Furthermore, the above techniques have the disadvantage that animals must be sacrificed, and that particular IEGs can be expressed in more than a single anatomically defined cell type. New developments may soon enable the *in vivo* measurement of activity in neural networks of known cell type using sensors for membrane voltage, intracellular messengers and pH, which can be targeted to specific cell types by use of vectors such as viruses (Miesenbock et al., 1998; Bozza et al., 2004). These techniques applied at different learning stages, or during experience-dependent reorganization, could become invaluable tools to study neural network plasticity.

Knowledge of the molecular basis of neuronal plasticity also offers ways to directly test the causative status of links between manifestations of neuronal plasticity, and their perceptual, cognitive and behavioral correlates. Such tests avoid some of the limitations characteristic of the lesion and reversible deactivation approaches used in the field of the neurosciences, and they offer their own specific opportunities. In particular, a drawback of anatomical lesion methods and (reversible) deactivation methods is that they indiscriminately deactivate or destroy all neurons in a given region, even though different cell types in that region might contribute differently to the sensory or cognitive function being studied. An attractive alternative approach offered by molecular biology is to generate functional lesions by interfering with normal genetic contributions to a particular perceptual or cognitive function, though the delivery of antisense molecules (Hebb & Robertson, 1997; Lee et al., 2004). Antisense molecules bind to the mRNA encoded by a specific gene of interest and, its delivery to a particular cortical or brain region (iontophoretically or through other means, such as pressure injection) can thus block the contribution of a single gene to a particular cortical function, or to a particular perceptual or cognitive ability. Other approaches, such as viral-mediated gene targeting and conditional gene expression, have been used extensively more recently and enhance the potential of gene expression control in-vitro and in-vivo (Mansuy et al., 1998; Mower et al., 2002). Although it is an ambitious goal to start parsing the contribution of individual genes to neuronal plasticity (Goldberg & Weinberger, 2004), and associated cognitive behavior, these approaches are being successfully used in a number of animal models (Lee et al., 2004; Izquierdo & Cammarota, 2004; Ogawa & Pfaff, 1996; Liu et al., 2004). Studies of this type have contributed significantly to the generation of deep insights into the nature of learning and memory formation, and continue to hold tremendous promise for applied use. As a case in point, human gene therapy, in which viral vectors are used to insert genetic material into particular chromosomes of targeted cells to remediate specific illnesses (e.g., Amado et al.,

1999) plausibly could be expanded in the future to also treat sensory, motor, and cognitive deficits (Fink et al., 2003; Tinsley & Eriksson, 2004).

Much of the work on neural plasticity and associated forms of cognition that precedes any human applications remains to be done. In order to increase our understanding of plasticity in the human brain, it is necessary to develop model systems in higher mammals and primates. In this book, the visual system of higher mammals, including primates, is used to study plasticity from the molecular to the systems neuroscience level. We hope that the combination of different viewpoints and approaches of plasticity will contribute, ultimately, to a deeper understanding of higher order cognitive processes such as learning and memory formation. Briefly, the book is divided into three parts, with Part I (Chapters 2–6) devoted to retinal and thalamic plasticity, Part II (Chapters 7–14) to cortical plasticity, and Part III (Chapters 15–16) to some theoretical and integrative considerations. Chapters 2–5 will treat structural neurochemical and functional aspects of retinal plasticity induced by various types of damage and degeneration, as well as the experience-dependent expression of IEGs. In Chapter 6, Fos imaging is used to reveal cortico-thalamic networks recruited by attention. Chapters 7 and 11 discuss effects of neuromodulatory transmitters and inhibition on normal sensory processing and during experience-induced plasticity in primary visual cortex, while Chapters 8 and 9 focus on the molecular, biochemical and cellular mechanisms that participate in the control of plasticity in the visual cortex. The outcomes of plastic re-arrangement of circuitry in V1 and related lower-order visual cortex are discussed at the systems level in Chapters 10, 12 and 13. Chapter 14 is an example of the type of knowledge that emerges when high-level cognition is studied by a combination of systems neuroscience and molecular approaches. The final chapters aim to provide a theoretical framework for a number of topics covered in this volume, with Chapter 15 emphasizing a computational modeling approach at the systems level, and Chapter 16 providing an integrative view of molecular and systems approaches of neuronal plasticity.

References

Agnihotri NT, Hawkins RD, Kandel ER, Kentros C (2004) The long-term stability of new hippocampal place fields requires new protein synthesis. *Proc Natl Acad Sci USA* 101, 3656–3661.

Amado RG, Mitsuyasu RT, Zack JA (1999) Gene therapy for the treatment of AIDS: animal models and human clinical experience. *Front Biosci* 4, D468–475.

Bailey CH, Kandel ER (1993) Structural changes accompanying memory storage. *Annu Rev Physiol* 55:397–426.

Bailey CH, Bartsch D, Kandel ER (1996) Toward a molecular definition of long-term memory storage. *Proc Natl Acad Sci* U S A 93:13445–13452.

Bailey CH, Giustetto M, Huang YY, Hawkins RD, Kandel ER (2000) Is heterosynaptic modulation essential for stabilizing Hebbian plasticity and memory? *Nat Rev Neurosci* 1:11–20.

Bailey CH, Chen M (1983) Morphological basis of long-term habituation and sensitization in Aplysia. *Science* 220, 91–93.

Bozza T, McGann JP, Mombaerts P, Wachowiak M (2004) In vivo imaging of neuronal activity by targeted expression of a genetically encoded probe in the mouse. *Neuron* 42(1), 9–21.

Carmena JM, Lebedev MA, Crist RE, O'Doherty JE, Santucci DM, Dimitrov DF, Patil PG, Henriquez CS, Nicolelis MA (2003) Learning to control a brain-machine interface for reaching and grasping by primates. *PLoS Biol* 1(2):E42.

Castellucci VF, Pinsker H, Kupperman I, Kandel ER (1970) Neuronal mechanisms of habituation and dishabituation of the gill-wthdrawl reflex in Aplysia. *Science* 167, 1745–1748.

Castellucci VF, Blumenfeld H, Goelet P, Kandel ER (1989) Inhibitor of protein synthesis blocks long-term behavioral sensitization in the isolated gill wthdrawall reflex of Aplysia. *J Neurobiol* 20, 1–9.

Chawla MK, Lin G, Olson K, Vazdarjanova A, Burke SN, McNaughton BL, Worley PF, Guzowski JF, Roysam B, Barnes CA (2004) 3D-catFISH: a system for automated quantitative three-dimensional compartmental analysis of temporal gene transcription activity imaged by fluorescence in situ hybridization. *J Neurosci Methods* 139(1), 13–24.

Chew SJ, Mello C, Nottebohm F, Jarvis E, Vicario DS (1995) Decrements in auditory responses to a repeated conspecific song are long-lasting and require two periods of protein synthesis in the songbird forebrain. *Proc Natl Acad Sci USA* 92, 3406–3410.

Cohen MR, Newsome WT (2004) What electrical microstimulation has revealed about the neural basis of cognition. *Curr Opin Neurobiol* 14(2), 169–77.

Cole AJ, Saffen DW, Baraban JM, Worley PF (1989) Rapid increase of an immediate early gene messenger RNA in hippocampal neurons by synaptic NMDA receptor activation. *Nature* 340(6233), 474–476.

De Weerd P, Peralta MR 3rd, Desimone R, Ungerleider LG (1999) Loss of attentional stimulus selection after extrastriate cortical lesions in macaques. *Nat Neurosci* 2(8), 753–758.

Doyon J, Penhune V, Ungerleider LG. (2003). Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. *Neuropsychologia* 41, 252–262.

Evarts EV (1968) A technique for recording activity of subcortical neurons in moving animals. *Electroencephalogr Clin Neurophysiol* 24(1), 83–86.

Fink DJ, Glorioso J, Mata M (2003) Therapeutic gene transfer with herpes-based vectors: studies in Parkinson's disease and motor nerve regeneration. *Exp Neurol* 184(S1), S19–24.

Fischer A, Sananbenesi F, Schrick C, Spiess J, Radulovic J (2004) Distinct roles of hippocampal de novo protein synthesis and actin rearrangement in extinction of contextual fear. *J Neurosci* 24, 1962–1966.

Fuster JM (1973) Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *J Neurophysiol* 36(1), 61–78.

Georgopoulos AP, Schwartz AB, Kettner RE. Neuronal population coding of movement direction. *Science* 233(4771):1416–1419.

Gilbert CD, Minami Ito M, Kapadia M, Westheimer G (2000) Interactions between attention, context and learning in primary visual cortex. *Vision Res* 40, 1217–1226.

Goldberg TE, Weinberger DR (2004) Genes and the parsing of cognitive processes. *TINS* 8, 325–334.

Guzowski JF, McNaughton BL, Barnes CA, Worley PF (1999) Environment-specific expression of the immediate-early gene Arc in hippocampal neuronal ensembles. *Nat Neurosci* 2(12), 1120–1124.

Guzowski JF, McNaughton BL, Barnes CA, Worley PF. (2001) Imaging neural activity with temporal and cellular resolution using FISH. *Curr Opin Neurobiol* 11(5), 579–584.

Hebb (1949) *The organization of behavior: A neuropsychological theory*. New York, John Wiley & Sons.

Hebb MO, Robertson HA (1997) End-capped antisense oligodeoxynucleotides effectively inhibit gene expression in vivo and offer a low-toxicity alternative to fully modified phosphorothioate oligodeoxynucleotides. *Brain Res Mol Brain Res* 47, 223–228.

Heywood CA, Cowey A (1987). On the role of cortical area V4 in the discrimination of hue and pattern in macaque monkeys. *J Neurosci* 7(9), 2601–2617.

Hoffman KL, McNaughton BL (2002) Coordinated reactivation of distributed memory traces in primate neocortex. *Science* 297(5589), 2070–2073.

Hubel DH, Wiesel TN (1959) Receptive fields of single neurons in the cat's striate cortex. *J Physiol (Lond)* 148: 574–591.

Hubel DH, Wiesel TN (1962) Receptive fields, binocular interaction and functional architecture in the cats's visual cortex. *J Physiol (Lond)* 160, 106–154.

Izquierdo I, Cammarota M (2004) Zif and the survival of memory. *Science* 304, 829–830.

Kaas JH, Krubitzer LA, Chino YM, Langston AL, Polley EH, Nlair N (1990) Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina. *Science* 248, 229–231.

Kaczmarek L, Robertson HA (2002) *Immediate early genes and inducible transcription factors in mapping of the central nervous system function and dysfunction.* Amsterdam: Elsevier Science B.V.

Kandel ER (2001) The molecular biology of memory storage: a dialogue between genes and synapses. *Science* 294:1030–1038.

Kuffler SW (1953) Discharge patterns and functional organization of mammalian retina. *J Neurophysiol* 16(1), 37–68.

Lee JL, Everitt BJ, Thomas KL (2004) Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science* 7, 839–843.

Lennie P (2000) Color vision. In Kandell ER Schwartz JH, Jessell TM (Eds). *Principles of neural science*. NY, McGraw-Hill, pp 572–589.

Liu Z, Richmond BJ, Murray EA, Saunders RC, Steenrod S, Stubblefield BK, Montague DM, Ginns EI (2004) DNA targeting of rhinal cortex D2 receptor protein reversibly blocks learning of cues that predict reward. *Proc Natl Acad Sci USA* 101, 12336–12341.

Logothetis NK, Wandell BA (2004) Interpreting the BOLD signal. *Annu Rev Physiol* 66, 735–769.

Logothetis NK (2003) MR imaging in the non-human primate: studies of function and of dynamic connectivity. *Curr Opin Neurobiol* 13, 1–13.

Lomber SG, Payne BR, Horel JA (1999) The cryoloop: an adaptable reversible cooling deactivation method for behavioral or electrophysiological assessment of neural function. *J Neurosci Methods* 86(2), 179–194.

Luft AR, Buitrago MM, Ringer T, Dichgans J, Schulz JB (2004) Motor skill learning depends on protein synthesis in motor cortex after training. *J. Neurosci* 24, 6515–6520.

Mansuy IM, Winder DG, Moallem TM, Osman M, Mayford M, Hawkins RD, Kandel ER (1998) Inducible and reversible gene expression with the rtTA system for the study of memory. *Neuron* 21:257–265.

Miesenbock G (2004) Genetic methods for illuminating the function of neural circuits. *Curr Opin Neurobiol* 14(3), 395–402.

Moran J, Desimone R (1985). Selective attention gates visual processing in the extrastriate cortex. *Science* 229, 782–784.

Mower AF, Liao DS, Nestler EJ, Neve RL, Ramoa AS (2002) cAMP/Ca^{2+} response element-binding protein function is essential for ocular dominance plasticity. *J Neurosci* 22:2237–2245.

Murray EA, Mishkin M (1998) Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *J Neurosci* 18: 6568–6582.

Nakazawa K, Quirk MC, Chitwood RA, Watanabe M, Yeckel MF, Sun LD, Kato A, Carr CA, Johnston D, Wilson MA, Tonegawa S. (2002) Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science* 297, 211–218.

Nicolelis MA, Dimitrov D, Carmena JM, Crist R, Lehew G, Kralik JD, Wise SP (2003) Chronic, multisite, multielectrode recordings in macaque monkeys. *Proc Natl Acad Sci U S A* 100(19), 11041–11046.

Ogawa S, Lee TM, Nayak AS, Glynn P (1990) Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med* 14(1):68–78.

Ogawa S, Pfaff DW (1996) Application of antisense DNA method for the study of molecular bases of brain function and behavior. *Behav. Genet* 26, 279–292.

Orban GA, Van Essen D, Vanduffel W (2004) Comparative mapping of higher visual areas in monkeys and humans *Trends Cogn Sci* 8(7), 315–324.

Pinaud R (2004) Experience-Dependent Immediate Early Gene Expression in the Adult Central Nervous System: Evidence from Enriched-Environment Studies. *Int J Neurosci* 114, 321–333.

Press WA, Olshausen BA, Van Essen DC (2001) A graphical anatomical database of neural connectivity. *Philos Trans R Soc Lond B Biol Sci* 356(1412), 1147–1157.

Qian Z, Gilbert ME, Colicos MA, Kandel ER, Kuhl D (1993) Tissue-plasminogen activator is induced as an immediate-early gene during seizure, kindling and long-term potentiation. *Nature* 361(6411), 453–457.

Ramirez-Amaya V, Vazdarjanova A, Mikhael D, Rosi S, Worley PF, Barnes CA (2005) Spatial exploration-induced arc mRNA and protein expression: evidence for selective, network-specific reactivation. *J Neurosci* 25(7), 1761–1768.

Ribeiro S, Cecchi GA, Magnasco MO, Mello CV (1998) Toward a song code: evidence for a syllabic representation in the canary brain. *Neuron* 21(2), 359–371.

Rumelhart DE (1987) *Parallel Distributed processing*. MIT Press.

Ryan L, Nadel L, Keil K, Putnam K, Schnyer D, Trouard T, Moscovitch M (2001). Hippocampal complex and retrieval of recent and very remote autobiographical memories: evidence from functional magnetic resonance imaging in neurologically intact people. *Hippocampus* 11(6):707–714.

Seidemann E, Zohary E, Newsome WT (1998) Temporal gating of neural signals during performance of a visual discrimination task. *Nature* 394(6688), 72–75.

Sprague JM, Berlucchi G, Antonini A (1985) Immediate postoperative retention of visual discriminations following selective cortical lesions in the cat. *Behav Brain Res* 17(2):145–162.

Tessier-Lavigne M (2000) Signal processing by the retina. In Kandell, ER, Schwartz JH, Jessell TM (Eds). *Principles of neural science*. NY, McGraw-Hill, pp 507–522.

Thielscher A, Neumann H (2005) Neural mechanisms of human texture processing: texture boundary detection and visual search. *Spat Vis* 18(2):227–257.

Thorpe WH (1956) *Learning and instincts in animals*. Cambridge, Massachussetts, Harvard University.

Tinsley R, Eriksson P (2004) Use of gene therapy in central nervous system repair. *Acta Neurol Scand* 109, 1–8.

Ungerleider LG (1995) Functional brain imaging studies of cortical mechanisms for memory. *Science* 270(5237):769–775.

Vazdarjanova A, Guzowski JF (2004) Differences in hippocampal neuronal population responses to modifications of an environmental context: evidence for distinct, yet complementary, functions of CA3 and CA1 ensembles. *J Neurosci* 24:6489–6496.

Wilson MA, McNaughton BL (1993) Dynamics of the hippocampal ensemble code for space. *Science* 261(5124), 1055–1058.

Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* 265(5172), 676–769.

Wisden W, Errington ML, Williams S, Dunnett SB, Waters C, Hitchcock D, Evan G, Bliss TV, and Hunt SP (1990) Differential expression of immediate early genes in the hippocampus and spinal cord. *Neuron* 4, 603–614.

Wurtz RH (1969) Visual receptive fields of striate cortex neurons in awake monkeys. *J Neurophysiol* 32(5), 727–742.

Wurtz RH, Kandel ER (2000) Central visual pathways. In Kandell ER Schwartz JH, Jessell TM (Eds). *Principles of neural science*. NY, McGraw-Hill, pp 523–547.

Wurtz RH, Kandel ER (2000) Perception of motion, depth, and form. Kandell ER Schwartz JH, Jessell TM (Eds). *Principles of neural science*. NY, McGraw-Hill, pp548–571.

Xing J, Andersen RA (2000) Memory activity of LIP neurons for sequential eye movements simulated with neural networks. *J Neurophysiol* 84(2), 651–665.

Yang T, Maunsell JH (2004) The effect of perceptual learning on neuronal responses in monkey visual area V4. *J Neurosci* 24, 1617–1626.

Part I

Retinal and Thalamic Plasticity

2

Synaptic Plasticity and Structural Remodeling of Rod and Cone Cells

ELLEN TOWNES-ANDERSON AND NAN ZHANG

Department of Neurology and Neurosciences, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, NJ, USA

Introduction

It is well documented that neural activity affects synaptic plasticity, a phenomenon known as activity-dependent plasticity. Synaptic plasticity in response to injury, known as injury-induced plasticity, is also well recognized. The vertebrate photoreceptor cell displays plasticity, in the form of structural synaptic change, in both these situations. Structural synaptic change in the photoreceptor refers to 1) change in the size and shape of the rod or cone terminal, 2) increase or decrease in the number of presynaptic active zones, or 3) new growth of neurites and/or development of new presynaptic varicosities. As the first synapse in the visual pathway, structural changes in the synapse between photoreceptors and second order neurons may influence all subsequent visual processing. Thus, an understanding of the mechanisms that initiate and promote plasticity in the outer synaptic layer of the retina where rod and cone cells interact with horizontal and bipolar neurons is critical to understanding the plasticity of the visual system as a whole.

Activity-dependent change of the photoreceptor synapse will be briefly discussed first. Photoreceptor synaptic plasticity in response to disease, is a more recently recognized phenomenon and will be reviewed in more detail. Our own current work has focused on the mechanisms that might be involved in injury-induced plasticity and an overview of this work will be presented. Finally, some future directions and outstanding questions will be discussed.

Types of structural plasticity in photoreceptors

Activity-dependent plasticity

Neurotransmission by rod and cone cells occurs by calcium-dependent vesticle exocytosis. However, the photoreceptor synapse differs from most chemical

R. Pinaud, L. A. Tremere, P. De Weerd (Eds.), Plasticity in the Visual System: From Genes to Circuits, 13-31, ©2006 Springer Science + Business Media, Inc.

synapses because it is controlled by graded membrane potential changes, not action potentials. Its presynaptic active zone is distinguished by the presence of a flat sheet, known as the ribbon, surrounded by a halo of vesicles and attached to the plasma membrane by an arciform density. In addition, there are several molecular differences between photoreceptor synapses and conventional synapses. For instance, retinal ribbon synapses contain no synapsin (Mandell et al., 1990) and L-type calcium channels in rod cells and L-type and cGMP-gated channels in cone cells control exocytosis and neurotransmitter release (Rieke and Schwartz, 1994; Schmitz and Witkovsky, 1997; Taylor and Morgans, 1998; Nachman-Clewner et al., 1999; Morgans, 2001) whereas other calcium channel types are present in conventional synapses. Other molecular differences include the presence of syntaxin 3 in ribbon synapses, instead of syntaxin 1 for vesicle fusion (Morgans et al., 1996), and the protein RIBEYE, a unique component of the ribbon which may form the backbone of the ribbon structure (Schmitz et al., 2000).

In response to activity, both the size of the presynaptic terminal and the configuration of the ribbon change. In the dark, when the photoreceptor is depolarized, the size of the terminal increases whereas in the light, the terminal size decreases. This is presumably due to the balance of membrane exo- and endocytosis. Endocytosis dominates in the light but synaptic vesicle exocytosis proceeds continuously in the dark in the presence of endocytosis (Schaeffer and Raviola, 1978). Thus, in the light, plasma membrane is removed from the terminal whereas in the dark, more membrane is added than removed. For the ribbons, there are changes in shape, length, and location. Such changes occur in a diurnal pattern in many species (reviewed by Vollrath and Spiwoks-Becker, 1996). In rat rod cells, for instance, ribbons are flat and attached to the plasmalemma in the dark; in the light, spherical ribbons that are disconnected from the plasmalemma are more abundant (Adly et al., 1999). The change in ribbon shape to a spherical form and/or disassociation from the active zone is presumably due to inactivity and has also been observed in squirrel cone cells during hibernation (Remé and Young, 1977) and in cultured photoreceptors where the terminal is separated from its postsynaptic partners (Townes-Anderson, personal observations, Fig. 2.1). The molecular mechanism for the dissociation of the active zone in photoreceptors is unknown. However, mutant mice, lacking the protein bassoon in functional form, have aggregations of ribbons detached from the active zone (Dick et al., 2003) suggestive of what is seen with a reduction of activity (Abe and Yamamoto, 1984). It is possible therefore that bassoon plays some role in ribbon configuration and/or attachment to the membrane.

Injury-induced plasticity

Although there are changes in the shape of the photoreceptor presynaptic ending and its synaptic ribbon in the adult retina, the terminal normally stays within the outer synaptic layer of the retina where it is in contact with post-

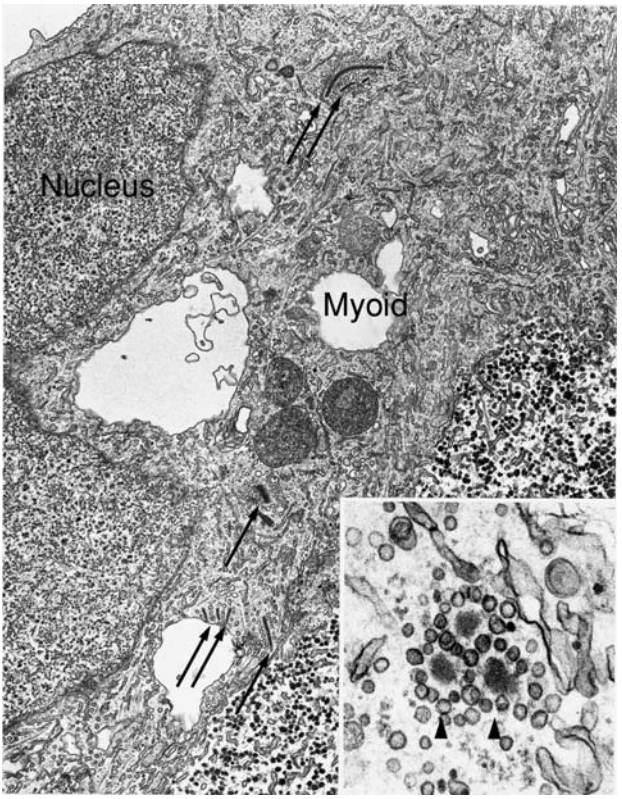

FIGURE 2.1. Movement and shape change are characteristics of ribbon plasticity. Electron micrographs from cultured cone cells isolated from the adult tiger salamander retina and maintained for 7 days in a defined medium. In vivo, cone terminals have multiple active zones and therefore ribbons. In cultured cone cells, ribbons are frequently observed in the myoid region (arrows), which normally contains only the cell organelles. The ribbons appear in linear form. Inset: Some ribbons, however, take on a spherical shape (arrowheads). Here three such ribbons share synaptic vesicles. It is highly likely that the spherical ribbons are detached from membrane. For linear ribbons, serial sectioning is necessary to determine whether or not they have remained associated with the plasma membrane.

synaptic bipolar and horizontal cell processes. In 1995, examination of several human retinas affected with retinitis pigmentosa (RP) revealed the presence of neurites coming from rod cells and extending into the inner retina (Li et al., 1995). These neurites could be observed because of the abnormally high levels of rod opsin in the plasma membrane of the cell. Some mutations of the opsin gene cause mislocalization of opsin because the C-terminus, which targets opsin to vesicles destined for the outer segment, is mutated.

In other cases, mislocalization of opsin occurs as the outer segment becomes disorganized and/or shortened. Opsin containing vesicles may then fuse with plasma membrane in the cell body by default. Finally, some conditions may lead to a fusion of the inner and outer segment membranes which allows a back flow of opsin from the outer to the inner segment and the rest of the cell (Spencer et al., 1988; Townes-Anderson, 1995). Regardless of the mechanism of mislocalization, the high density of the opsin protein in the plasmalemma of patients with RP demonstrated the extent of neurite growth and that the growth came from rod cell terminals. When stained for the presence of synaptic vesicles, the neurites were seen to have swellings along their length filled with synaptic vesicles. However, electron microscopy did not reveal differentiated synaptic contacts between these presynaptic varicosities and inner retinal neurons.

Retinitis pigmentosa is an inherited form of retinal degeneration that affects rod cells which degenerate and die leading to night blindness; cone cells die after rod cells have gone and the loss of cone cells results in total blindness. The mutations, which lead to blindness, occur in many different genes; most of them are for rod cell proteins (reviewed by Molday, 1998). The ectopic rod cell neurites were observed initially in retinas with autosomal dominant, X-linked, simplex and multiplex forms of the disease (Li et al., 1995; Milam et al., 1996). Since then, sprouting by rod cells has been observed in human retinas after laser photocoagulation, in age-related retinal degeneration, in retinal detachment, and in several animal models of retinal injury and disease (Table 2.1). In all cases, neurites were observed by immunolabeling for opsin; when synaptic immunolabels were applied, all presynaptic swellings were positive for synaptic vesicle proteins. Rodent models of retinal degeneration, however, do not show neuritic sprouting (Li et al., 1995). It has been suggested, for these models, that neurites are not formed due to the rapidity of the disease which does not provide time for neurite formation before cell death.

Rod axons have been reported to retract towards the cell body in response to injury as well. Initially observed as the early stages of rod cell degeneration several days after retinal detachment (Erickson et al., 1983), it is now apparent that axonal retraction occurs very soon after the detachment injury (Lewis et al., 1998) and that it does not necessarily lead to cell death: virtually all rod axons retract but not all rod cells die if reattachment is done in a timely fashion (Mervin et al., 1999). After reattachment of retina, rod cells have been shown, using anti-opsin immunolabeling, to extend neurites into the inner retina in a manner and with a morphology similar to what is seen in retinal disease (Table 2.1). Whether the same cell both retracts and extends neurites is likely and has been observed directly in cultured rod cells using video time-lapse microscopy (Nachmen-Clewner and Townes-Anderson, 1996).

Cone cells are affected by retinal detachment but appear not to dramatically retract their terminals. Instead the terminal shape changes by flattening so that the synaptic invagination is lost. This has been observed both in vivo and in vitro (Fisher et al., 2001; Khodair et al., 2003).

TABLE 2.1. Rod cell axonal plasticity in vivo.

Species	Response	Insult or disease	Reference
human	neurite sprouting/varicosity formation	retinitis pigmentosa (RP)	Li et al. 1995 Milam et al. 1996
human	neurite sprouting	laser irradiation in diabetic retina	Xiao et al. 1998
human	neurite sprouting/varicosity formation	reattachment after detachment	Lewis et al. 2002a
human	neurite sprouting	late-onset retinal degeneration	Gupta et al. 2003
human	neurite sprouting	age-related macular degeneration	Gupta et al. 2003
human	neurite sprouting/varicosity formation	detachment with proliferative retinopathy	Sethi et al. 2005
pig	filopodial growth	transgenic for RP	Li et al. 1998
cat	neurite sprouting	rod/cone dysplasia	Chong et al. 1999
cat	neurite sprouting/varicosity formation	reattachment after detachment	Lewis et al. 2002a
human	retraction of spherule	detachment after reattachment	Fisher and Lewis 2003
cat	retraction of spherule	3d after detachment	Erickson et al. 1983
cat	retraction of spherule	24hr after detachment	Lewis et al. 1998
mouse	increased synaptic contacts	rds mutation, homozygous	Jansen and Sanyal 1984 Jansen et al. 1997
mouse	increased synaptic contacts	rds mutation, heterozygous	Jansen and Sanyal 1992 Jansen at el. 1997
mouse	increased synaptic contacts	rd/wild type chimeras	Sanyal et al. 1992
mouse	increased synaptic contacts	constant light	Jansen and Sanyal 1987 Jansen at al. 1997
mouse	increased synaptic contacts	KO, cone cGMP channel & rod opsin	Claes et al. 2004

After retinal reattachment and in most diseases, cone cells do not form long neurites although smaller sprouts and filopodial extensions into the outer plexiform layer and sometimes into the inner retina have been described in retinitis pigmentosa (Table 2.2). These processes were observed with antibodies to cone transducin-α and synaptic proteins. It is possible that these markers are not as effective as rod opsin in highlighting cone synaptic change. In retinal detachment, for instance, the expression of many cone-specific proteins declines within a few days (Rex et al., 2002). Nonetheless, available evidence indicates that there is a significant difference in the response of rod and cone cell terminals to injury and disease.

TABLE 2.2. Cone cell axonal plasticity in vivo.

Species	Response	Insult or disease	Reference
human	axon elongation	retinitis pigmentosa (RP)	Li et al. 1995 Milam et al. 1996
cat	axon elongation	reattachment after detachment	Lewis et al. 2003
mouse	neurite sprouting/varicosity formation	rd1 mutation	Fei 2002
human	enlarged terminals	cone-rod dystrophy	Gregory-Evans et al. 1998
pig	increased synaptic contacts	transgenic for RP	Peng et al. 2000
mouse	increased synaptic contacts	rd1 mutation	Peng et al. 2000
rat	increased synaptic contacts	RCS strain	Peng et al. 2003
rat	increased synaptic contacts	transgenic for RP	Cuenca et al. 2004

At present, there is one instance where long neurites have been reported to come from cone cells (Fei, 2002). This is the mouse model rd1, which is an autosomal recessive type of retinal degeneration with a mutation in the beta subunit of rod phosphodiesterase. The cone processes were visualized using transgenic mice with GFP linked to a cone promoter. The presence of GFP delineated long neurites with varicosities going both into the inner retina and horizontally in the outer plexiform layer. These neurites arose from multiple locations, cone terminals, axons and cell bodies. Canine models of this type of RP (Aquirre et al., 1978) have not yet been examined for cone, or rod, cell synaptic plasticity.

Finally, photoreceptors have been reported to make new synapses in response to retinal degeneration (Tables 2.1 and 2.2). Within the outer plexiform layer, rod cells will increase the number of synapses they make with existing postsynaptic bipolar dendrites in the rd and rds mouse models of RP, after light damage, and in a rod opsin knockout mouse. It is possible that as adjacent rod cells die, remaining cells try to compensate by increasing their synaptic input to second order neurons. Cone cells also have been reported to form new synapses. In transgenic pigs with a mutation in the opsin gene, in the rd1 mouse, and in the RCS and P23H transgenic rat (Table 2.2), all models of RP, cone cells make synapses with rod bipolar cells that would not be present in the normal, healthy mammalian retina.

In summary, several forms of structural plasticity are present in the photoreceptors of injured (detachment, reattachment and excess light) and diseased (retinitis pigmentosa and age-related macular degeneration) retina: retraction of axons, sprouting of axons, neurite formation, development of presynaptic varicosities, and synaptogenesis (Fig. 2.2). These structural changes require special morphological techniques to be discerned and would not be easily visible in routine histopathology. They can occur in the absence of an outer segment and in the presence of mislocalized opsin but it is not known if these are requirements. They can be a prelude to cell death but not necessarily. Finally, it is not known if these changes are permanent or

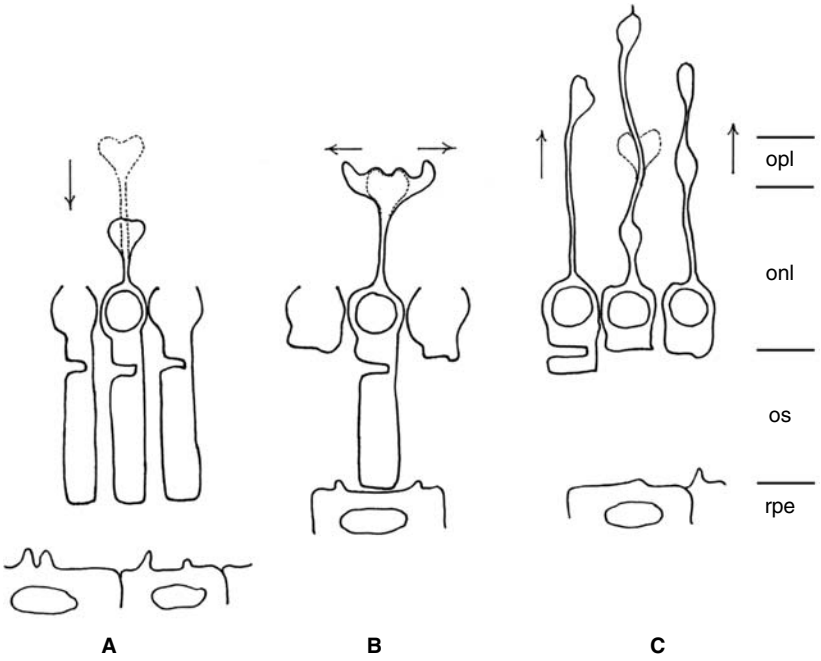

FIGURE 2.2. Summary of structural plasticity in adult photoreceptors. Rod cells show three general types of plasticity: A. retraction of the axon and terminal; B. enlargement of the terminal concomitant with new synaptic development; and C. neurite sprouting and varicosity development. Retraction occurs after retinal detachment, terminal enlargement occurs in retinal degeneration, and sprouting and varicosity formation have been seen in all types of degeneration and injury. Dotted lines indicate original synaptic outline before structural change. Arrows indicate overall direction of change. Cone cells (not shown) produce less plasticity. They do not exhibit retraction but do increase synaptic interaction in retinal disease. In one type of retinal degeneration (rd1) they produce varicosity-containing neurites similar to what is produced by rod cells. Opl, outer plexiform layer; onl, outer nuclear layer; os, outer segment layer; rpe, retinal pigmented epithelium.

transient or whether they can completely resolve or revert back to pre-injury morphology after therapeutic intervention (Lewis et al., 2002a, b, 2003).

Mechanisms producing structural plasticity in photoreceptors

Calcium

Because the plasticity described for rod and cone terminals is different, a key assumption that can be made about the mechanisms of structural plasticity is that they differ between the two sensory receptor types. A known difference