Published in final edited form as:

Sci Am. 1988 December ; 259(6): 56–64.

Plasticity in Brain Development

Chiye Aoki and Philip Siekevitz

Abstract

The final wiring of the brain occurs after birth and is governed by early experience. A protein called MAP2 seems to take part in the molecular events that underlie the brain's ability to change

Anyone who has watched an infant reach for a toy will realize that adult capacities of perception and movement are not inborn but instead must develop over the course of time through the exercise of those faculties. The genetic program played out during gestation provides a newborn with intact sensory organs and a well-formed brain, whose 100 billion neurons, or nerve cells, are already linked in pathways that are specialized to perform specific functions. But before the developing brain can attain the full power to process and analyze sensory experience, experience itself must place its own imprint on the finer structure of the brain.

Even though the basic organization of the brain does not change after birth, details of its structure and function remain plastic for some time, particularly in the cerebral cortex, the tissue that forms the brain's convoluted surface. Experience—sights, smells, tastes, sounds, touch and posture—activates and, with time, reinforces specific neural pathways while others fall into disuse. A childhood imbalance in the use of the two eyes, for example, will cause permanent deficits in the visual perception through the underused eye. The developing brain can be likened to a highway system that evolves with use: less traveled roads may be abandoned, popular roads broadened and new ones added where they are needed.

How does experience mold the organization of the brain? We have postulated a sequence of molecular events, triggered by external stimuli, that may contribute to plasticity in one part of the cat brain. It is possible that similar scenarios are followed throughout the developing brain during early experience, not just in cats but in human beings as well. Such molecular events may shape many of the mental features underlying our common humanity. By translating variations in early experience into variations in brain organization, they may also underlie some of our individual differences.

Visual experience is easy to manipulate, and so our study of brain plasticity, like many earlier studies, focused on the visual system. The processing of visual stimuli begins in the retina of the eye, which contains a few hundred million neurons densely packed in a thin sheet. An array of about a million retinal ganglion cells sends the retinal output deeper into the brain. Their elongated processes, called axons, are bundled together to form the optic nerve. Some of the axons in the nerve project to two structures called lateral geniculate nuclei (LGN), one in each hemisphere of the brain. Each retina is connected to the lateral geniculate nucleus on both the opposite (contralateral) and same (ipsilateral) sides of the brain. The LGN neurons in turn send axons to the back of the brain, to a discrete zone called lamina IV, the fourth of six main layers in the primary visual cortex. The neurons in lamina IV form contacts with other layers of the visual cortex.

Patterns of light that fall on the retina are converted into electrochemical signals reaching the retinal ganglion cells, which turn the signals into impulses called action potentials. These impulses propagate along axons and reach the LGN neurons at junctions called synapses. At

every synapse, an impulse arriving at an axon terminal triggers the release of chemicals known as neurotransmitters, which cross the synaptic cleft and bind to specific receptors on the cell body or the dendrites—branching receptive processes—of the adjacent cell. Under appropriate conditions the neurotransmitter binding stimulates an LGN neuron to produce its own action potential, which in turn propagates along the axon and reaches neurons in the primary visual cortex. The stimulus is analyzed there and in other areas of the cortex receiving inputs from the primary visual cortex.

How many of these connections are governed by genetics and how many by early experience? A major breakthrough came in the early 1960's with the landmark experiments of David H. Hubel and Torsten N. Wiesel, both then at the Harvard Medical School, who later won a Nobel prize for their work [see "Brain Mechanisms of Vision," by David H. Hubel and Torsten N. Wiesel; *Scientific American*, September, 1979]. Hubel and Wiesel chose to use cats in studying the development of the visual system because, like human beings, cats have eyes at the front of the face, so that the visual fields of the two eyes overlap extensively. This overlap gives cats binocular vision in the central 90 degrees of their 180-degree field of view. Hubel and Wiesel studied binocular cells, which respond to stimulation of both eyes, in one part of the visual cortex called area 17. These binocular cells are important for depth perception and constitute about 40 percent of the neurons in area 17 in cats (60 percent in primates). The other neurons are monocular, responding to stimulation of one eye only.

Using electrical probes capable of detecting signals generated by individual neurons, Hubel and Wiesel systematically recorded the number of neurons in area 17 that responded to stimulation of the ipsilateral eye only, to the contralateral eye only and to both eyes. They also recorded whether the binocular cells had a preference for one eye over the other. They found that in kittens that had one eye sutured shut during the first several months after birth, the proportion of neurons in area 17 responding to stimulation of the closed eye dropped markedly. As a result the visually responsive neurons in area 17 were nearly all monocular and remained so even after the animal was allowed to use both eyes again. This profound shift in favor of the open eye—a shift in ocular dominance—was permanent, and the animal remained blind in the deprived eye for the rest of its life.

What part of the brain had been affected by the deprivation? Hubel and Wiesel showed that after a period of monocular deprivation, neurons in the retina and the LGN continued to respond normally to light. In other words, the visual pathway from the retina to the LGN was not affected by experience and therefore must be genetically predetermined to a large degree. This result meant that the changes accompanying monocular deprivation must have taken place in the organization of the cortical neurons.

The effect depends crucially on the timing of the deprivation. Hubel and Wiesel later found that monocular deprivation during adulthood did not change the neuronal organization of area 17. Carl R. Olson and Ralph D. Freeman of the University of California at Berkeley systematically studied the effect of an animal's age on the shift in ocular dominance after 10-day periods of monocular deprivation. They found that whereas monocular deprivation begun one month after birth causes a dramatic shift, the effect diminishes as the age at which the animal is deprived increases until, at the age of about four or five months, monocular deprivation ceases to have an effect on area 17. Hubel and Wiesel called the interval spanning the second through the fourth month after birth the critical period, because it is only during this period that the visual cortex is plastic enough to change its organization in response to input from the retina.

In an effort to detect the changes in cortical structure that underlie such shifts in ocular dominance Hubel, Wiesel and Simon D. LeVay employed a technique for tagging neural pathways with radioactive amino acids. The investigators anesthetized monkeys and injected radioactive amino acids into one eye. Cell in the retina incorporated the amino acids into their proteins; the proteins were transported along the axon and passed on to neurons in the LGN, which in turn relayed them to neurons in lamina IV of the visual cortex. Cortical slices from the injected monkey were placed on photographic film, where the radioactivity carried along the visual pathway created ghostly silhouettes of the areas connected to the injected eye.

The radioactive zones of area 17 in lamina IV formed distinct bands that alternated with nonradioactive zones. Each zone turned out to be the target for axons from LGN neurons that receive input from a single eye; adjacent zones receive signals from the opposite eye. In a normal monkey these ocular-dominance columns were equal in width: roughly half a millimeter across. But in a monocularly deprived monkey the columns representing the active eye were markedly expanded, whereas those representing the deprived eye were reduced. LeVay, together with Michael P. Stryker and Carla J. Shatz, got similar results with cats.

Those anatomical findings, together with the electrophysiological evidence, suggest that in monocularly deprived cats synaptic contacts between axons from the LGN and neurons in lamina IV develop in favor of the functionally active visual pathway. The phenomenon resembles the development of muscles that are exercised and the atrophy of muscles that are idle. The peculiarity here, however, is that the activity-dependent development occurs within a narrow window of time—the critical period.

In the 20 years since Hubel and Wiesel carried out their initial experiments, plasticity of the visual cortex has been studied intensively, both electrophysiologically and neuroanatomically. In 1979 we became interested in a new question: What molecular mechanisms translate visual experience during the critical period into neural architectures?

We began by looking for biochemical changes that mark the beginning and end of the critical period. To do so we needed a strategy for picking the biochemical processes that play a specific role in cortical plasticity from among those that accompany general growth and maintenance. Here we found another advantage to studying the cat's visual system: it is possible to delay the onset of the critical period by rearing kittens in total darkness, thereby allowing all other developmentally related changes to occur. The critical period for ocular dominance can then be studied in isolation. This strategy, called dark-rearing, was first explored by Max S. Cynader, then at Dalhousie University in Nova Scotia. It enabled Cynader to initiate shifts in ocular dominance in cats that were as much as two years old, even though normally the critical period ends at the age of about four or five months.

Cynader found that as soon as dark-reared kittens are brought into the light, the experience-dependent changes in cortical connections begin. What is more, George D. Mower and his colleagues at the Boston Children's Hospital found that in dark-reared kittens exposed to just a few hours of light the cortical changes activated by the light continue even if the kittens are then returned to darkness. This result suggested that a biochemical event important in plasticity lies dormant until it is triggered by light.

We initiated the search for this light-triggered biochemical event by studying the effects of a small molecule called cyclic adenosine monophosphate (cyclic AMP). Cyclic AMP is a standard "second messenger" in cells: it relays messages received at the cell surface to specific sites within the cell. There were several reasons for our choice. Analogues of cyclic AMP have been found in vitro to stimulate the development of neuronal precursor cells into

neurons. More pertinent, Takuji Kasamatsu and his colleagues, then at the California Institute of Technology, had found evidence leading them to propose that norepinephrine, a common neurotransmitter, may play a role in cortical plasticity by activating the synthesis of cyclic AMP. Kasamatsu's proposal led us to examine the role of cyclic AMP in greater detail.

Cyclic AMP might conceivably have an effect through a series of well-documented biochemical events. Norepinephrine binding to a receptor on the cell surface acts as a "first messenger," which together with a protein called G-protein activates the enzyme adenylate cyclase, which in turn synthesizes cyclic AMP. Cyclic AMP then acts as an intracellular second messenger by activating another enzyme, cyclic AMP-dependent protein kinase, which phosphorylates (adds phosphate groups to) particular proteins in the cell. For many of these proteins the effect of phosphorylation is not known, but it is thought the addition of negatively charged phosphate groups to specific sites on a protein molecule may change the protein's three-dimensional folding pattern and thereby alter its biological activity.

We decided to search the visual system of cats for proteins that are phosphorylated by the cyclic AMP-dependent protein kinase. To identify phosphorylated proteins, we homogenized cells from the visual cortexes of developing cats and incubated the preparation with radioactive adenosine triphosphate (ATP), which served as a source of phosphate groups. Any proteins that were phosphorylated during the incubation would carry a radioactive phosphate group. When the proteins were separated by gel electrophoresis, the radioactive label made it possible to detect phosphorylated proteins on X-ray film.

We looked for proteins that became more phosphorylated when cyclic AMP was added to the homogenized cells than when it was not. Several proteins did appear to be phosphorylated by the protein kinases that are activated by cyclic AMP. One of them was synapsin, which is found in high concentrations at synapses. We ruled it out as an intermediary in cortical plasticity, however, because we found that the phosphorylation of synapsin was the same for dark- and light-reared cats. A second candidate was the cyclic AMP-dependent protein kinase itself. We found that this enzyme is present in equal amounts at birth and in adulthood and is not affected by dark-rearing. Its phosphorylation also does not change during development.

Our search focused on a third phosphorylated protein, an unusually large molecule weighing around 300,000 daltons. We identified it as microtubule-associated protein 2, or MAP2, by means of antibodies specific for the protein, which were given to us by Lester I. Binder of the University of Virginia and Andrew Matus of the Friedrich Miescher Laboratory in Basel. The concentration of this protein is the same in cortexes of both dark- and light-reared animals. But we found that the phosphorylation of MAP2 is different before and after the critical period. In tissue taken from the visual cortex of normally raised cats whose critical period was over, MAP2 was easy to phosphorylate in vitro, which indicated that many sites on the protein were not phosphorylated in the living animals. In contrast, in the visual cortex of dark-reared cats (in which the onset of the critical period had been delayed) MAP2 could barely be phosphorylated, indicating it had been fully phosphorylated in vivo.

Could the apparent difference in phosphorylation be related to the difference in plasticity before and after the critical period? To test that possibility we examined tissue taken from kittens whose critical period had been delayed by dark-rearing and then triggered by exposure to a few hours of light. We found MAP2 could be easily phosphorylated in vitro, like MAP2 from normally reared cats. Thus the protein seemed to remain fully phosphorylated throughout the dark-rearing but became dephosphorylated as soon as light began to stimulate the visual pathway.

In order to establish a role for MAP2 phosphorylation in cortical plasticity, however, we still had to rule out the possibility that we were observing only some aspect of an unrelated adaptation to darkness. To do so, we studied adult cats that had been reared normally and then put in the dark. We knew that this procedure had no effect on cortical plasticity, because the critical period of these animals had long since ended. The phosphorylation of MAP2 in these cats was not significantly different from that in adult cats living in normal lighting. Nor did it change when the cats were brought out to the light again.

We also had to rule out the possibility that the phosphorylation of MAP2 was caused by a general effect of dark-rearing on development, such as retarded growth of the entire brain. We therefore examined the phosphorylation of the protein in dark-reared cats' auditory cortex, the part of the brain that processes sound. We reasoned that because dark-reared cats were not deprived of sound stimuli, the timing of the critical period for the auditory cortex would remain unaffected, so that any general effect of dark-rearing on MAP2 phosphorylation would show up. We found that phosphorylation of MAP2 in the auditory cortex was in no way influenced by dark-rearing or subsequent exposure to light.

Might the phosphorylation be associated with changes in visual stimulation per se and not with plasticity? To rule out that last suspicion, we studied MAP2 in the LGN. Hubel and Wiesel had shown that cells in the LGN do not exhibit plasticity after birth and continue to respond normally to light after a period of monocular deprivation. We found no change in MAP2 phosphorylation in the LGN before and after the critical period. This final result supported our conjecture that the phosphorylation of MAP2 in the visual cortex is not caused simply by stimulation of the visual pathway but is directly involved in the plasticity of the visual cortex.

The MAP2 molecule is one of the cytoskeletal proteins, so called because they are thought to serve as structural elements in a cell, giving it form just as the skeleton gives form to the body. Many of these proteins are also involved in the transport of molecules and organelles within cells. The microtubule-associated proteins, or maps, are found together with a major component of the cytoskeleton, the microtubules, which are formed by a protein called tubulin.

MAP2 itself is found only in neurons, where it is associated not only with microtubules but also with actin (which forms another cytoskeletal component, the microfilaments) and neurofilament protein (which forms the neurofilaments, cytoskeletal structures that are unique to neurons). In fact, MAP2 has been detected in every kind of neuron that has been examined, which suggests it may play a role in plasticity not just in the visual cortex during the critical period but in regions throughout the brain and throughout life. (Interestingly, an abnormal tangling of cytoskeletal proteins, including MAP2, is seen in the brain of patients with Alzheimer's disease, and its degree seems to be correlated with the degree of dementia.)

How might MAP2 influence cortical plasticity? First of all, as a cytoskeletal protein it must help to dictate the shape of neurons, which is under particularly strict control. Most neurons have a characteristic branching pattern of axons and dendrites. There is good evidence to suspect that MAP2 is involved in determining the morphology of the dendrites in particular. Electron microscopy, for example, shows that microtubules (which are associated with MAP2) are oriented along the lengths of dendrites and dendritic branches, and Matus has used an antibody staining technique to show that MAP2 is concentrated in dendrites.

What is more, Richard Bernhardt, working with Matus, observed that MAP2 accumulates in newly formed dendrites before tubulin, the major component of microtubules, appears at the site. Matus and Bernhardt have suggested that MAP2 initiates and controls the assembly

within dendrites of structures consisting of MAPS, tubulin, neurofilament protein and actin. In this way MAP2 may dictate the details of dendritic shape, as well as the intracellular traffic of molecules between dendrites and the cell body.

Dendritic shape can influence neuronal function in several ways. For example, the more branched and extended the dendrites of a neuron are, the more signals it can receive and integrate from other neurons. In addition dendritic branching can affect the efficacy with which a neuron relays a signal. When the dendrites of a neuron receive excitatory or inhibitory inputs from other neurons, the dendrites initiate their own signal, which is conducted toward the cell body. If a strong enough signal reaches the cell body, the cell generates an action potential of its own. The shape and size of a dendrite determine how fast and how far the signal can spread and thereby influence the cell's ability to respond to incoming signals. For instance, a signal generated in a large dendrite close to the cell body has a better chance of triggering an action potential than a signal generated at a small dendrite far from the cell body.

Just how might MAP2 affect cytoskeletal structure, as Matus and Bernhardt suggest it does? One clue may lie in the observation that tubulin requires the presence of dephosphorylated MAP2 in order to polymerize and become assembled into microtubules. Indeed, as a general rule dephosphorylated MAP2 promotes stable interactions of the cytoskeletal proteins tubulin, actin and neurofilament protein, whereas phosphorylated MAP2 weakens them. Thus when MAP2 inside a neuron is dephosphorylated, dendrites may be static, whereas when the MAP2 is phosphorylated, dendrites may become dynamic, readied for changes in shape and length.

In our earlier studies we postulated that MAP2 from dark-reared kittens is phosphorylated in vivo, and that when light triggers the onset of experience-dependent synaptic changes, MAP2 becomes dephosphorylated. We suspect that as long as MAP2 remains fully phosphorylated—the state it is in when the kittens are kept in darkness—the cytoskeletal architecture of cortical neurons remains indeterminate. The cortex is therefore fully primed to change its organization in response to neuronal activity evoked by exposure to light. The subsequent decline in plasticity during the critical period may be caused in part by the progressive dephosphorylation of MAP2, which makes the neuronal cytoskeleton increasingly rigid. The process stabilizes the shape of neurons, thereby limiting the degree to which neuronal interconnections in the visual cortex can be reorganized.

The notion that details of neuronal architecture remain undetermined until the critical period ends is supported by studies of the visual cortex in dark-reared monkeys and rodents. Neurons there show a conspicuous paucity of dendritic spines, the short, protruding processes normally found on the surface of dendrites. These spines are the major sites for synaptic contact between neurons. Hence the lack of spines could profoundly affect neuronal connectivity. It may be that MAP2 acts on microtubules to control the formation and alteration of spines as well as dendrites.

Through its influence on the cytoskeleton, MAP2 might also influence cortical plasticity by controlling the transport and anchoring of molecules necessary for synaptic transmission and growth. Such molecules may include receptors for hormones, neurotransmitters and growth-promoting factors, as well as membrane proteins that modulate neuron excitability.

We have identified one molecule, MAP2, whose biochemical characteristics in the visual cortex change with the onset of the critical period. It is the first such protein to be identified, but it will undoubtedly not be the last. There may be other proteins that our methods simply were not able to detect. For example, the biological activity of many proteins may be altered at the start of the critical period by means other than phosphorylation. And although the

evidence for MAP2's role is strong, we cannot be certain yet whether. MAP2 dephosphorylation actually causes the change in plasticity or instead is merely an effect of the change. We think, however, that molecular changes must precede the structural changes in the dendrites.

Even though the precise function of MAP2 phosphorylation remains uncertain, the observation has generated new questions. In particular, how might the stimulation of the visual pathway by light change the state of MAP2's phosphorylation in the visual cortex? Does the change result from a change in the intracellular concentration of cyclic AMP (which activates the protein kinase that phosphorylates MAP2)? We thought perhaps exposure to light can affect the level of cyclic AMP by changing the density of receptors for norepinephrine, the neurotransmitter for which Kasamatsu proposed a role in cortical plasticity. (Bear in mind that the binding of norepinephrine to a receptor activates adenylate cyclase, which catalyzes the production of cyclic AMP.)

To test this hypothesis, we identified the receptor sites by incubating sections of the visual cortex with a radioactive probe that binds specifically to the receptors. We found that the distinctive layered distribution of norepinephrine receptors did not differ in any obvious way in the brain of normal cats, dark-reared cats and dark-reared cats that had been exposed to light. This result indicated that changes in MAP2 phosphorylation were not correlated with any crude changes in the location and density of these receptors. Our technique, however, would not have detected any redistribution of receptors among different cell types within a given layer. Detailed microscopic analyses need to be done to answer this question.

Another possibility is that a different transmitter- or hormone-receptor system is altered by exposing the visual system to light. An interesting recent finding by Mark F. Bear of Brown University and Wolfe Singer of the Max Planck Institute for Brain Research in Frankfurt indicates that cortical plasticity is maintained not by norepinephrine alone, as Kasamatsu had thought, but by the synergistic action of norepinephrine and a second neurotransmitter, acetylcholine, which is abundant in the visual pathway. Still another transmitter, glutamate, has also been hypothesized to play a role.

We are now examining the possibility that visual input triggers the release of other molecules known to activate adenylate cyclase and thereby stimulate the synthesis of cyclic AMP. We are also trying to determine whether visual input affects the level of cyclic AMP by modifying the activity of cyclic AMP phosphodiesterase, an enzyme that degrades cyclic AMP. A third possibility is that visual input affects MAP2 directly. For example, it may be that during dark-rearing MAP2 is situated near cyclic AMP-dependent protein kinases, so that it is maintained in a phosphorylated state. When light first stimulates the visual system, MAP2 may somehow become translocated to a site distant from the kinases. A fourth possibility is that an enzyme called protein phosphatase, which dephosphorylates proteins, may become activated by visual stimulation.

A full understanding of MAP2's role in the critical period requires a more detailed understanding of the protein itself. Richard B. Vallee and William E. Theurkauf of the Worcester Foundation for Experimental Biology in Shrewsbury, Mass., report that the MAP2 molecule has 22 sites at which phosphorylation can take place, of which 13 depend on the amount of cyclic AMP. Perhaps the biological function of MAP2 is subtly altered depending on how many sites are phosphorylated, or in what combination. Indeed, intracellular cyclic AMP-dependent protein kinases continue to phosphorylate MAP2 throughout adulthood, suggesting that the phosphorylation and dephosphorylation of MAP2 plays other critically important roles besides endowing the cortex with developmental plasticity.

We are only beginning to understand how molecular events influence the structure of neurons and how these structural changes are translated into changes in brain function. As we try to answer such questions, we hope to get closer to understanding how the external world comes to be mirrored in the microscopic structure of the brain. Ultimately the answer will lead to a profound appreciation of how each individual person, in spite of being formed by inexorable genetic processes, is also the unique product of experience.

FURTHER READING

Visual Neural Development. J. Anthony Movshon and Richard C. Van Sluyters in *Annual Review of Psychology*, Vol. 32, pages 477–522; 1981.

Modification of Microtubule Steady-State Dynamics by Phosphorylation of the Microtubule-associated Proteins. Larry Jameson and Michael Caplow in *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 78, No. 6, pages 3413–3417; June, 1981.

Ontogenetic Changes in the Cyclic Adenosine 3', 5'-Monophosphate-stimulatable Phosphorylation of Cat Visual Cortex Proteins, Particularly of Microtubule-associated Protein 2 (MAP2): Effects of Normal and Dark Rearing and of the Exposure to Light. Chiye Aoki and Philip Siekevitz in *Journal of Neuroscience*, Vol. 5, No. 9, pages 2465–2483; September, 1985.

The Role of Norepinephrine in Plasticity in the Visual Cortex. B. Gordon, E. E. Allen and P. Q. Trombley in *Progress in Neurobiology*, Vol. 30, No. 2–3, pages 171–191; 1988.

Biography

CHIYE AOKI and PHILIP SIEKEVITZ are respectively instructor in the department of neurology at the Cornell University Medical College and professor of cell biology at Rockefeller University. Aoki received a B.A. at Barnard College in 1978 and a Ph.D. in neuroscience from Rockefeller University in 1985. Siekevitz got a B.S. at the Philadelphia College of Pharmacy and Science in 1942 and a Ph.D. in biochemistry from the University of California, Berkeley, in 1949. Aoki was a graduate student in Siekevitz' laboratory at the time the work described in this article was done.

Figure 1.

MAP2 MOLECULES form bridges between neurofilaments and microtubules in this electron micrograph of a dendrite, the receptive portion of a nerve cell. Neurofilaments and microtubules are part of an internal skeleton that affects a neuron's growth and structure; by controlling interactions among their component proteins, MAP2 may mediate the formation of new neural pathways. This image of a dendrite in rat spinal cord was made by Nobutaka Hirokawa and his colleagues at the University of Tokyo

Figure 2.

VISUAL PATHWAY is traced schematically in the human brain, seen from below. The path is shown only for signals originating from one side of the visual field. Light falls on the retina and is converted into nerve impulses that travel to the lateral geniculate nucleus (LGN), where signals from each eye are segregated into six layers. The signals are relayed to lamina IV in the primary visual cortex, where they remain segregated into bands corresponding to one eye or the other. Impulses then travel to other layers of visual cortex, where signals arising in both eyes are integrated. The parts of a neuron are labeled in the inset (*bottom*) showing three of the six layers in a small part of the visual cortex. The axon fiber carries a signal away from the cell body to the presynaptic terminal, releasing neurotransmitter chemicals that bind to receptors on the dendrite of the postsynaptic neuron, LGN and cortical cells are actually more densely packed than is shown here.

Figure 3.

OCULAR-DOMINANCE COLUMNS appear as bright and dark stripes in these autoradiographs of lamina IV in a monkey's visual cortex. Each column is defined by axon terminals from LGN neurons that receive signals from one eye only. The bright columns resulted when a radioactive label was injected into one eye and was carried along the visual pathway; columns corresponding to the other eye are dark. In a normally raised animal (*top*) columns that received signals from one eye are as wide as those that received signals from the other eye. In an animal that was deprived of the use of one eye (*bottom*) the bands representing the active (injected) eye are expanded, nearly obliterating the narrow bands representing the deprived eye.

Figure 4.

REORGANIZATION of neuronal connections during development leads to ocular-dominance shifts. The drawings depict lamina IV cells being contacted by axons from LGN neurons. The colors distinguish the paths of signals originating in different eyes. Many neurons in a one-week-old kitten (*top*) receive signals from both eyes. In normal development (*middle*) the LGN axons segregate into columns that serve only one eye or the other. If one eye is deprived (*bottom*), however, most of the cells form contacts with LGN axons carrying signals from the active eye and come to respond only to that eye.

Figure 5. BIOCHEMICAL DIFFERENCE is evident in MAP2 from the visual cortex of a cat that had been dark-reared for 52 days and a littermate that had been dark-reared and then was exposed to light. The dark bands in these autoradiographs indicate proteins that took up radioactive phosphate groups during phosphorylation and then were separated according to molecular weight by gel electrophoresis. Proteins from cortical cells were incubated with cyclic AMP and cyclic AMP-dependent protein kinase, together with the radioactive label. Two proteins—synapsin and the kinase—were phosphorylated to the same degree in both cats, but MAP2 clearly was not. In the visual cortex of the dark-reared cat, MAP2 was probably already fully phosphorylated, and so it did not take up the radioactive label, whereas in the cat that was exposed to light, MAP2 was dephosphorylated and so became strongly labeled. Exposure to light had no effect on MAP2 phosphorylation in the auditory cortex of the animals.

Figure 6.

DISTRIBUTION OF MAP2 in pyramidal cells (a common type of neuron) from the rat visual cortex is shown by the dark areas in this section, which was stained by a color indicator that was coupled to an antibody binding specifically to MAP2. Strong staining indicates MAP2 is concentrated in the dendrites radiating from the cell bodies, which also contain MAP2 except in their unstained nuclei. The presence of MAP2 in dendrites suggests that the protein may regulate the shape of dendrites.

Figure 7.

MAP2'S ROLE in rearranging dendrites is shown schematically here. (The drawings are not to scale.) A cortical cell (1) in a dark-reared kitten is contacted by an inactive axon. A neurotransmitter or hormone that exists during dark-rearing binds to receptors on the dendritic spine and destabilizes cytoskeletal proteins (2) by way of a cascade of molecular events (3). The binding of the neurotransmitter or hormone to a receptor activates adenylate cyclase, an enzyme that converts adenosine triphosphate (ATP) into cyclic AMP. Cyclic AMP activates another enzyme, a kinase that phosphorylates MAP2. Phosphorylated MAP2 prevents the formation of microtubules and also inhibits the interaction of microtubules with microfilaments and neurofilaments. When the kitten is exposed to light, the plastic nature of the dendrite enables it to move to an active axon (4). The dendrite proteins may stabilize (5) when unknown events that occur with visual stimulation cause MAP2 to become dephosphorylated and form cross bridges between the cytoskeletal proteins (6). The process may be reversible.