Neural Activity and the Development of Brain Circuits

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Introductory article

Article Contents

The development of highly interconnected circuits in the brain relies on patterns of neural activity. These patterns produce a cascade of events that refine initially imprecise connectivity into precise circuits. The presence of neural activity is particularly important during well-defined critical periods in early life.

Overview

The behaviour of an animal depends fundamentally on how the neurons in its nervous system are connected with one another and the motor output. During early human development over 100 billion neurons each establish from dozens to thousands of connections with one another and with muscle fibres. At all levels of the nervous system, precise connections emerge from initially imprecise patterns of contact. How is this enormously complex brain circuitry organized with any degree of fidelity during development?

Among brain systems, the question has been addressed most extensively in the developing visual pathway. Data show that the final precision of brain circuitry in the visual system relies heavily on neural activity, while the initial targeting of axons to the appropriate regions of the nervous system occurs independently of it. This activity is generated by the transduction of stimuli in the environment, but it can also occur spontaneously in early development before the sensory mechanisms are fully functional. Appropriate patterns of neural activity can lead to the modification of synaptic 'strengths'. Changes in synaptic strength, then, may provide a signal for identifying functionally useful circuits. Particular molecules that act downstream of electrical activity to shape brain circuitry and modify synaptic strength have been identified. These include the *N*-methyl-D-aspartate (NMDA) receptor, nitric oxide and a class of molecules called neurotrophins. The sensitivity of brain circuitry to the absence of patterned neural activity is limited to 'critical periods' during early development. Interestingly, the degree of plasticity of synaptic strength is highest during these times. The critical periods themselves exhibit some plasticity; they can be shifted by altering the rearing environment or by increased neurotrophin production.

Visual system

The importance of neural activity in the development of functional brain circuits has been established as a general principle of the developing nervous system. For example, the transduction of appropriate stimuli in the environment into neural activity is crucial for the normal development of the somatosensory and olfactory systems in rats, the auditory system in chicks and cats, and motor systems in songbirds.

Most of the research on the role of neural activity in the development of brain circuitry, however, has taken place in the mammalian visual system. The visual system occupies the largest portion of sensory processing tissue in most carnivores and primates, and its input can be manipulated easily. Incoming light to one or both eyes can be controlled precisely, contact lenses or goggles can provide calculated distortions, images can be presented on computer screens, and so on.

Most importantly, however, both subcortically and in the cortex, dramatic anatomical patterns of circuitry in the visual system provide convenient assays of the effect of manipulations of visual experience on the development of normal circuitry (**Figure 1**). In the ferret (a common animal for studying brain development due to its immature state at birth and prolonged postnatal development), retinal axons that project to the lateral geniculate nucleus (LGN) from the two eyes are initially overlapped extensively but soon segregate to form eye-specific layers. Subsequently, within each of the eye-specific layers, inputs from the two major cell classes, ON-centre and OFF-centre retinal ganglion cells, segregate to form distinct sublaminae. From the LGN, visual input is propagated to layer 4 of the primary visual cortex. There, axons from the LGN carrying inputs from the two eyes are again initially overlapped but subsequently segregate to form columns that are dominated by inputs from one or the other eye.

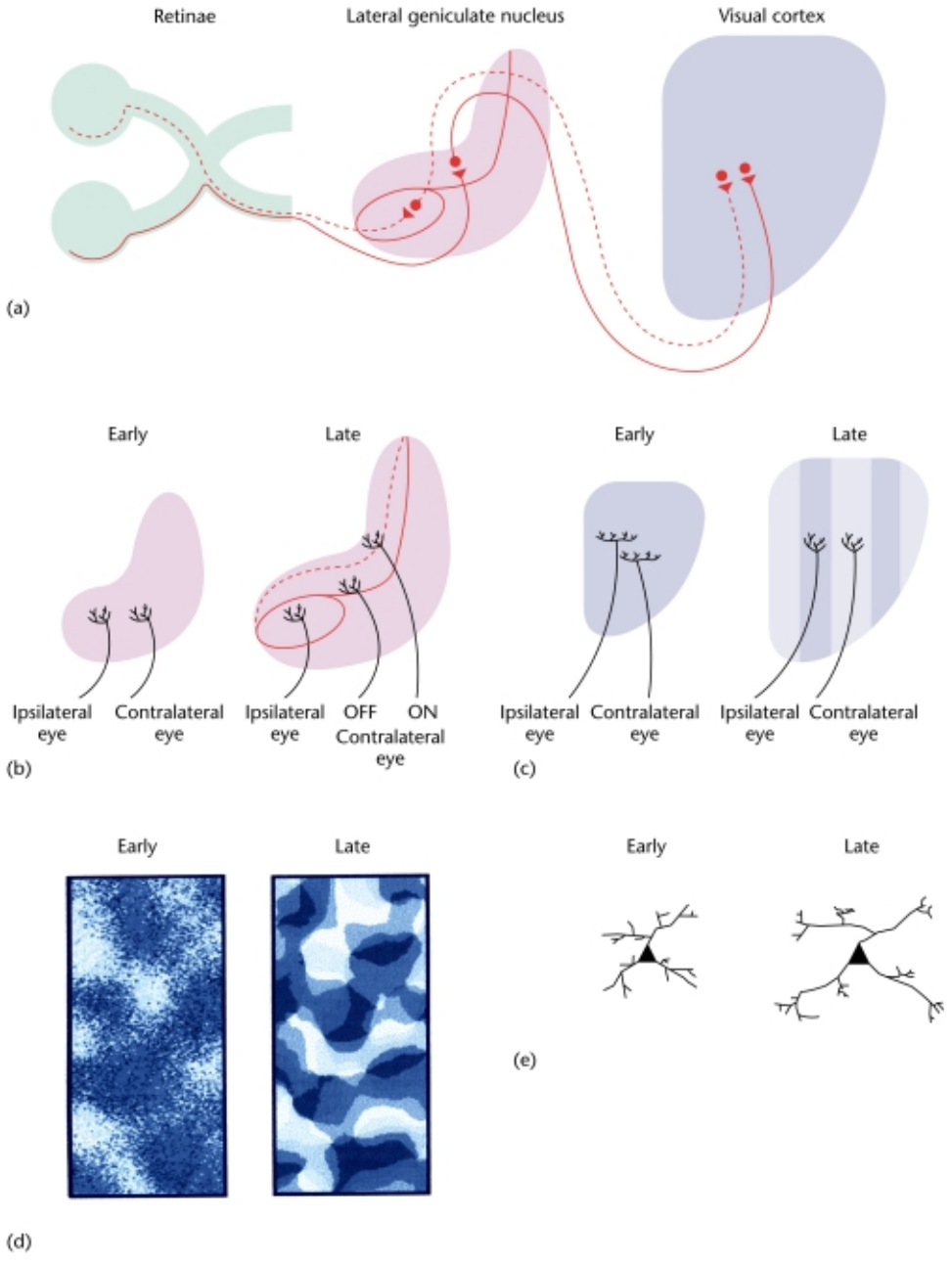

Figure 1 The primary visual pathway and examples of the activity-dependent development of brain circuits. (a) Retinal ganglion cells mediating perception of a visual hemifield project their axons to the contralateral lateral geniculate nucleus (LGN). Relay cells of the LGN innervate layer 4 of the visual cortex. (b) Early in development axons from the ipsilateral and contralateral eyes are intermingled in the LGN. Later, axons from the two eyes segregate to form eye-specific laminae and, shortly thereafter, sublaminae that receive inputs from either ON- or OFF-centre retinal ganglion cells. (c) Similarly, axons from both LGN laminae initially overlap at their target, layer 4 of the visual cortex, and are subsequently refined such that they occupy distinct ocular dominance columns. (d) Maps of the orientation preference of neurons (depicted as shades of blue) in visual cortex show relatively little clustering of neurons with like orientation preferences in early development. As the circuitry matures, maps reveal extensive clustering of similar orientation preferences in a pinwheel-like organization. (e) Developing pyramidal neurons in the superficial layers of visual cortex extend their axons horizontally in a relatively crude manner, showing little preference for any particular area within their reach. As development proceeds, the axonal arborization is elaborated in areas of similar orientation preferences, and branches are removed from dissimilar areas.

The normal physiology of the visual system also provides a number of useful measures of appropriate circuitry. As would be expected from the segregation of geniculocortical axons into ocular dominance columns, cells in layer 4 of the immature visual cortex respond equally to inputs from either eye, whereas after the formation of ocular dominance columns, cells respond to inputs from only one or the other eye. Additionally, cells are precisely 'tuned' to particular features in the environment. So, for example, particular cells respond most vigorously to bars of light that are oriented at a particular slant and often moving in a particular direction. Moreover, experiments using imaging techniques have shown that cells with similar orientation preferences are grouped together. Finally, clusters of neurons with the similar orientation preference are linked by horizontal connections that often traverse long distances within the superficial cortical layers. The degree to which a visual cortical cell is dominated by one or the other eye, the precision with which it is tuned to a particular orientation, and the grouping of orientation preferences can be used to determine the functional consequence of manipulations of visual experience in early development.

Neural Activity

As early as the 1930s, it became clear that appropriate sensory experience is necessary for the normal development of perception. Children with cataracts, for example, who are not treated in early life, have permanent deficits in form perception. In the past three decades experiments have demonstrated that visual experience, and more specifically neural activity, is crucial for the development of appropriate brain circuitry in the visual centres of the brain.

Visual cortex and thalamus

In the 1960s and 1970s, Torsten Wiesel, David Hubel and their colleagues provided evidence for the neuroanatomical and neurophysiological correlates of the impaired perception that results from visual deprivation. Geniculocortical axons normally terminate in alternating columns that are dominated by axons carrying inputs from one or the other eye. If one eye is sutured shut, resulting in monocular deprivation in early life, columns formed by axons carrying inputs from the open eye are much wider, and those formed by axons carrying inputs from the closed eye much narrower, than normal. Correspondingly, physiological investigations show that, after monocular deprivation, neurons in the visual cortex, which normally respond to inputs from either eye, no longer respond to inputs from the eye that was deprived. Prolonged monocular deprivation also leads to a reduction in the orientation selectivity of many cells, although some do show typical preferences. Interestingly, binocular deprivation or dark-rearing does not dramatically perturb the normal development of ocular dominance columns or orientation maps, suggesting that the role of visual experience is one of maintenance and not specification of brain circuitry.

While monocular deprivation, binocular deprivation and dark-rearing significantly reduce neural activity in the visual system, they do not eliminate diffuse light penetrating the eyelids or spontaneous neural activity. Pharmacological blockade of neural activity provides a more controlled, but more difficult, means of examining the role of neural activity in circuit construction. The use of tetrodotoxin, a potent toxin found in certain species of puffer fish that prevents action potentials by blocking voltage-gated sodium channels, has been used for this purpose.

The segregation of left and right eye inputs into ocular dominance columns is disrupted after chronic intraocular injections of tetrodotoxin. While geniculocortical axons continue to grow in length and complexity without retinal input, they are not appropriately organized into the clusters that make up the ocular dominance columns. Local tetrodotoxin infusions in the cortex that blocks both presynaptic and postsynaptic neural activity prevent the normal shift in physiological responsiveness of cells to the open eye after monocular deprivation.

Neural activity is also crucial to the normal development of brain circuitry in structures involved in earlier stages of visual processing. In the ferret, segregation of retinal inputs into eye-specific laminae is modulated by disrupting synchronous retinal activity, and the segregation into ON–OFF sublaminae is prevented by intraocular tetrodotoxin application. Following intracranial infusion of tetrodotoxin, retinogeniculate axons are abnormally large and/or terminate in inappropriate regions of the LGN; similarly, LGN cells show a dramatic increase in the number of dendritic spines. Other manipulations of activity cause the normal elimination of transient dendritic spines on LGN cells to be delayed or altered. These results suggest that brain circuits can grow in the absence of neural activity, but they are not appropriately refined.

Permissive versus instructive roles of activity

While it seems clear that neural activity is necessary for the development of appropriate brain circuits, it is less clear whether it simply allows predetermined growth to move forward or whether it plays a role in determining the brain circuitry. That is, is neural activity merely permissive, or is it also instructive?

One way to answer that question is to keep the quantity of neural activity the same, but to manipulate its quality to determine whether particular patterns of neural activity

lead to different brain circuits. This appears to be the case. When neural activity in the retina is blocked with tetrodotoxin, simultaneous stimulation of both optic nerves with electrodes is not sufficient to restore the pattern of ocular dominance columns. Only when the optic nerves are stimulated asynchronously does the development of the ocular dominance columns proceed normally; orientation selectivity in the visual cortex is also dampened if neural activity along the optic nerves is reduced or generated synchronously. Similarly, when all retinal ganglion cells of the retinae are induced to fire together by stroboscopic illumination, the retinotopic maps formed by retinal axons in the optic tectum do not fine-tune their connections. In these cases retinal axons experience a normal amount of activity, but it is not patterned appropriately. These types of experiments show that patterned activity is, in a limited sense, instructive. That is, normal patterns of neural activity guide the development of normal brain circuitry. Can unusual patterns of neural activity guide the development of unusual, but functional, brain circuitry?

In animals in which retinal projections are induced to provide input to the auditory cortex, neurons in that area develop properties such as orientation tuning that are characteristic of neurons in visual cortex. Presumably, patterns of neural activity that are normally associated with the visual system can guide the development of brain circuitry that is foreign, but functional. Similarly, many areas of the developing neocortex have the ability to take on the characteristics of other, functionally different, areas when transplanted at an early age, probably because of the type of neural input that they receive. Not only do these experiments demonstrate a more robust instructive role for neural activity, but they also suggest that whatever developmental mechanisms are at play in the visual system are likely to be involved in other systems.

At the same time, several lines of experiment demonstrate that activity does not write on a blank slate but serves to modify a basic scaffold of connections in the cortex. Orientation columns in visual cortex of cats develop normally for the first 3 weeks despite binocular deprivation, and degrade only afterwards, indicating that visually driven activity is needed to maintain the basic structure of columns rather than create them. A scaffold of horizontal connections that exists independently of activity and serves to position as well as constrain orientation columns is suggested by experiments that involve reverse or alternating lid suture. While monocular deprivation causes cortical territory related to the deprived eye to be drastically reduced, orientation-selective responses to be substantially weakened and orientation columns virtually to disappear, restoring vision in the deprived eye causes a rapid restoration of responses, including orientation columns that closely resemble the original columns in their detail. Even more surprisingly, alternately depriving one eye or the other (so that the two eyes never simultaneously have normal patterned vision) none the less causes the orientation map from each eye to be remarkably similar. Finally, while retinal projections routed to the auditory pathway in ferrets lead to a visual field map and orientation-selective responses in auditory cortex, the details of the orientation columns and horizontal connections remain very different from those in primary visual cortex, indicating that the basic structural substrates in cortex may still remain unique to each cortical area and be modified only to a restricted extent by activity.

Consistent with these observations, many of the brain circuits in the visual pathway that are developmentally dependent on neural activity form before any environmentally driven visual experience by the animal. The formation of eye-specific laminae and ON–OFF sublaminae in the ferret LGN, ocular dominance columns in monkeys, and orientation tuning properties of visual cortical neurons all occur before eye opening.

The patterned neural activity required during this early period of development most likely comes from endogenously generated patterns of activity. Retinal ganglion cells, for example, fire bursts of activity during prenatal life. In the ferret, these bursts form spontaneous waves of neural activity that sweep across the retina during the time that retinal axons are reorganizing the circuits they make with neurons in the LGN. Similarly, in the neonatal rat cortex, spontaneous activity in one cell propagates a calcium wave via gap junctions throughout the local area, activating an entire assembly of neurons. These cell assemblies, which appear to be organized in columns, immediately precede the organization of columnar cortical circuitry. In both the developing retina and the neonatal neocortex, spontaneous, synchronous waves of neural activity provide a temporal coordination of neighbouring cells. Computational models of topographical mapping and ocular dominance column formation predict that the temporal coordination of neighbouring cells is necessary for appropriate circuit formation.

Molecules and Synaptic Strength

We know that blocking neural activity disrupts the normal development of precise connectivity, but it is equally important to specify the mechanisms that transduce activity into patterns of synaptic contact. What are the subsequent links in the chain that translate neural activity into changes in the structure of the nervous system? Candidate molecules in the chain include NMDA receptors, nitric oxide and neurotrophins. These molecules are also involved in most types of long-term potentiation (LTP) of synaptic transmission, a mechanism proposed for altering synaptic strength in the nervous system. Thus, circuit construction and LTP appear to be closely related phenomena.

NMDA receptors

NMDA receptors are one of two types of neurotransmitter receptor that respond to the amino acid glutamate, a major excitatory neurotransmitter in the vertebrate brain. Other receptors do not respond to NMDA, but rather to α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) and are grouped together as the AMPA receptors. The role of the NMDA receptor in plasticity is intriguing because it acts as a type of 'coincidence' detector. That is, both glutamate from the presynaptic terminal and depolarization of the postsynaptic terminal are required simultaneously for Ca^{2+} flux through the associated ion channel.

The existence of coincidence detection at synapses was implied by Donald Hebb in 1949, who proposed (in effect) that a synapse is strengthened in proportion to the product of the activity of its presynaptic and postsynaptic sides. In the early 1970s, Bliss and Lomo discovered that synaptic strengthening could, indeed, be induced in the nervous system. They showed that brief high-frequency stimulation of pathways in the hippocampus, a region critical for learning and memory, produced an increase in synaptic strength that has been termed LTP. A decade later it was discovered that LTP in the CA1 region of the hippocampus could not be induced if the coincidence-detecting NMDA receptors were blocked, thus providing evidence of 'hebbian' synapses in the brain. Subsequent experiments have examined whether NMDA receptors are also involved in activity-dependent development of brain circuits in diverse regions of the brain.

For example, the development of the major postsynaptic targets of retinal axons, the relay cells of the LGN, is perturbed in the ferret when NMDA receptors are blocked. Relay cell dendrites increase in complexity in the weeks after birth, adding branches and small appendages along the branches. This addition of branches and appendages normally pauses during the third postnatal week; however, when a blocker of NMDA receptors is infused into the thalamus during this time, LGN relay cells show an increase in branching and appendage addition.

Interestingly, postsynaptic NMDA receptors also play a role in the development of their presynaptic inputs. Early evidence that NMDA receptors might be involved in activity-dependent plasticity of retinal axons came from experiments in which an extra eye was implanted into a frog embryo. The retinal projections from the third eye grow into the optic tectum and must share that space with the projections from one of the normal retinae. Surprisingly, the projections from the two retinae do not intermingle, but rather segregate into rostrocaudally oriented zones that are reminiscent of the ocular dominance columns found in the visual cortex of carnivores and primates. Chronically blocking the NMDA receptors in the optic tectum results in the gradual desegregation of these eye-specific zones. Likewise, in the ferret, blocking NMDA receptors during the third postnatal week disrupts the normal segregation of ON and OFF retinal ganglion cell axon arbours. Retinogeniculate axon arbours terminate in inappropriate areas of the LGN and/or have arbours that are too large. These experiments suggest that NMDA receptor-mediated activity may serve to modulate the size, complexity and location of retinal axons.

NMDA receptors are also involved in the development of the physiological properties of neurons in the visual pathway. When NMDA receptors in visual cortex are chronically blocked during monocular deprivation, more neurons than normal continue to be responsive to both eyes. Not only are NMDA receptors involved in this activity-dependent decoupling of inappropriate inputs, they are also involved in the strengthening of appropriate ones. When kittens are reared in the dark, visual cortical neurons remain unselective for orientation. When, subsequently, one eye receives normal visual experience, neurons develop normal, strong orientation selectivity. Chronic blockade of NMDA receptors during the late period of visual experience, however, blocks that development of orientation selectivity.

Lastly, NMDA receptors are involved in modulating synaptic strength throughout the visual pathway, a modulation hypothesized to play an important role in shaping brain circuitry (see below). In both the LGN and the visual cortex, blocking NMDA receptors during the high-frequency stimulation of input fibres prevents the strengthening of synaptic strength that normally occurs.

In some cases, however, NMDA receptors do not seem to be involved in plasticity. The segregation of retinogeniculate axons into eye-specific laminae does not depend on NMDA receptor activation. Additionally, there is an important caveat to the interpretation of NMDA blockade experiments. NMDA receptors are involved in the normal transmission of patterned visual information, and inhibiting their activation may result simply in a generalized attenuation of postsynaptic responsiveness to stimuli. That is, it may not be the special coincidence detection properties of NMDA receptors that are involved in developmental plasticity, but rather their contribution to normal synaptic transmission. However, recent experiments that reduced the expression of a particular subunit of the NMDA receptor have shown that the ocular dominance shift resulting from monocular deprivation continues to be disrupted, but with minimal effects on the general responsiveness to and selectivity of visual stimuli.

If blocking NMDA receptors (which are found on the postsynaptic membranes of LGN cells, for example) results in the reorganization of presynaptic retinal axons, then there must be a signal that travels back from the postsynaptic to the presynaptic terminal. Nitric oxide is an attractive candidate for the required retrograde messenger: its production requires the presence of Ca^{2+} which enters through NMDA receptors, and it can diffuse out of the postsynaptic terminal and signal the presynaptic terminal.

There is some evidence that nitric oxide plays exactly that role in LTP (see below). Additionally, nitric oxide synthase, the precursor of nitric oxide, is developmentally regulated in the ferret LGN. Between 1 and 5 weeks after birth, nitric oxide synthase is expressed in LGN cells, but not before or after. The peak of expression at 4 weeks is coincident with the segregation of retinogeniculate axons into ON–OFF sublaminae. Indeed, inhibiting nitric oxide synthase during the third and fourth postnatal weeks significantly reduces normal sublamination. Similarly, the expression of nitric oxide synthase peaks in the chick tectum coincidentally with the retraction of an aberrant retinal projection, and its inhibition during this period prevents the retraction.

Long-term potentiation

The type of activity-dependent development of brain circuits described above has components that seem to be shared with LTP. For example, like activity-dependent development, many types of LTP require electrical activity, NMDA receptor activation and production of nitric oxide. Consequently, numerous researchers have suggested that LTP underlies the stabilization of appropriate synapses in developing sensory structures. Conversely, long-term depression (LTD) might underlie the removal of inappropriate synapses.

LTP can be induced in visual structures as well as in the hippocampus, where it has been studied most actively. In the LGN, high-frequency stimulation of the optic tract during the period that retinal axons are reorganizing induces LTP. Likewise, LTP can be induced in the visual cortex by way of a number of different stimulating paradigms. The induction of LTP is easier in younger animals, as brain circuits are developing, than in older animals. More specifically, in the rat visual cortex, the ability to induce LTP is correlated tightly with the critical period for developing binocular connections. When the critical period is delayed by rearing rats in the dark, the period during which LTP can be easily induced is also shifted. LTP of inhibitory synapses is also more easily induced in young visual cortex than in old. However, in the mouse visual cortex, the development of ocular dominance columns can proceed normally despite genetically induced defects in several forms of LTP.

If LTP were involved in establishing appropriate synapses early in development, then one would expect synaptic efficacy to be increased after periods of activity-dependent development. Results from studies of the neuromuscular junction indicate that changes in circuitry are, in fact, preceded by changes in synaptic efficacy. However, the increase in synaptic efficacy of one input in parallel with the withdrawal of other inputs in response to normal developmental changes can also be interpreted as a stabilization of total synaptic input. Indeed, in cultures of cortical neurons, blocking activity results in an increase, and increasing activity results in a decrease, in synaptic strength. Similarly, in cultures of hippocampal neurons, synaptic strength is inversely correlated with the amount of input a neuron receives. In addition, synaptic efficacy in the LGN following the activity-dependent reorganization of retinogeniculate axons into ON–OFF sublaminae is not significantly different from synaptic efficacy before sublamination. Even if retinal inputs are examined exclusively, no change in the strength of the connections is observed that would suggest that a subset of synapses is strengthened while another is weakened and retracted over the time period of sublamination. Rather, it is likely that total synaptic input to a neuron is normalized toward some acceptable level and that if LTP is involved in the stabilization of appropriate synapses during development, a subsequent mechanism counteracts its effects. This normalization in the central nervous system appears to be of a different type than that at the neuromuscular junction. Whereas at the neuromuscular junction total input is kept stable by increasing the strength of some synapses while others are removed, stability may be maintained in normally developing central circuits by replacing inappropriate synapses with appropriate ones of the same strength.

Neurotrophins

In the late 1940s Viktor Hamburger and Rita Levi-Montalcini determined that the number of neurons in a structure is modulated by the target to which it sends its output. For example, more neurons survive development in ganglia that innervate larger structures than in those that innervate smaller ones. More specifically, the modulating influence was later discovered to be a molecule released by the target neurons. Since that time, a number of such molecules have been identified and grouped together as the neurotrophins. Neurotrophins mediate growth and survival in a number of systems and may be the mechanism whereby activity is translated into structural changes. For example, the levels of messenger ribonucleic acid that encode a receptor for a particular neurotrophin vary with visual experience in the rat visual cortex. Additionally, neurotrophins are involved in the formation of ocular dominance columns in the cat visual cortex. The expression of trkB, a neurotrophin receptor, is well correlated with the critical periods in visual development, and blocking the neurotrophins that act on trkB prevents ocular dominance column formation. Similarly, neurotrophin expression in the frog retina coincides with the patterning of retinal axons in the tectum. More specifically, neurotrophins have been shown to modulate both axonal and dendritic growth in the visual system. When a particular neurotrophin is injected into the optic tectum of live tadpoles, the branching and complexity of optic axon terminal arbours

is rapidly increased. Localized delivery of neurotrophins to the visual cortex during monocular deprivation rescues geniculocortical axons of the deprived eye from the atrophy that normally results. Neurotrophins also modulate the growth of dendrites in the developing visual cortex. Neurotrophins increase evoked neurotransmitter release during the critical period of plasticity in visual cortex. Lastly, neurotrophins can induce increases in long-term synaptic efficacy that may lead to the stabilization of appropriate inputs.

Regulation of Critical Periods

A key feature of activity-dependent development of brain circuits is their susceptibility to electrical activity during a well-defined, brief, window of time. As mentioned previously, children with cataracts who are not treated in early life have permanent deficits in form perception. However, children who are operated on during infancy develop fully normal vision. Similarly, Hubel and Wiesel found that, after about 6 months of age, blocking visual experience in monkeys has no permanent effect on perception or the anatomical and physiological development of visual cortex that underlies vision. Critical periods have also been identified for the development of language and social behaviour.

In follow-up experiments, it was discovered that the critical period could be delayed if animals were reared in the dark after birth. More recent experiments have shown that inhibiting visual activity in early development can delay the maturity of the mechanisms that are hypothesized to be involved in circuit construction. As described in the previous section, high-frequency stimulation of the thalamic inputs in the rat results in LTP in the upper layers of the visual cortex. The ability to induce that potentiation decreases in early development until very little potentiation can be induced at all. That decrease in plasticity can be delayed if the rats are reared in the dark and is mirrored by a delay in the critical period for the formation of binocular connections. In a number of species, the duration of NMDA receptor-mediated responses decreases significantly as the animal matures. More specifically, one particular subunit of the receptor is replaced by another. This shift in subunits during early development occurs in both rats and ferrets just after the period of heightened plasticity. In ferrets, blocking retinal activity with chronic tetrodotoxin application delays the subunit shift, as does the dark-rearing of rats. In the case of rats, once the animals have been exposed to light, the shift to the mature form of subunit happens rapidly.

Providing the biochemical environment that patterned visual activity normally produces can both rescue circuits from the effects of dark-rearing and accelerate normal development. Thus, if Schwann cells, which produce neurotrophins, are injected into the lateral ventricles of dark-reared rats, orientation selectivity and receptive-field size are almost normal and certainly better than they would have been had neurotrophin production not been increased during dark-rearing. In mice that overexpress brain-derived neurotrophic factor, inhibitory circuitry develops more quickly than in normal mice. Concomitantly, the normal, gradual reduction in LTP magnitude is accelerated.

Conclusion

One of the most pressing questions in developmental neurobiology is how the extremely complex circuitry of the nervous system forms with the exquisite precision that is characteristic of the normal animal. Research over the past three decades has provided clear evidence that neural activity is required during critical periods in early development for the appropriate development of brain circuits.

A great deal of the research on the role of neural activity in circuit construction has focused on the visual system. The visual system lends itself well to manipulation, but more importantly it has well defined, distinct, anatomical and physiological properties that can be used to assay the effects of those manipulations and the mechanisms that underlie connectivity (**Figure 1**). Dramatically disrupting the formation of ON–OFF sublaminae with tetrodotoxin injections in the ferret retina, for example, provides an opportunity to measure the components (e.g. the duration of NMDA receptor-mediated current) that are suspected of being modulated by neural activity and involved in circuit construction.

Patterned neural activity can arise from stimuli in the environment or, in some cases, can be generated endogenously very early in development. In either case, particular patterns of neural activity can lead to the modification of synaptic strengths and trigger the activation of a cascade of important molecules. Neurotrophins are growth factors that may act as the bridge between patterns of neural activity and changes in brain circuitry. Activity-dependent development employs mechanisms that may be similar to those used for long-term increases in synaptic strength in the mature brain. NMDA receptors, nitric oxide and neurotrophins play critical roles in both phenomena. However, there are more than just a few cases of both types of events that do not rely on these three components. It is likely that many mechanisms exist for the crucial purpose of mediating plasticity in the nervous system.

Particular periods during early development are especially sensitive to inappropriate patterns of neural activity. If an eye is deprived of normal vision or if all neural activity in the retinae is blocked with tetrodotoxin, the normal patterns of brain circuitry are disrupted. Rearing animals

in total darkness or providing the nervous system with the biochemical milieu that is normally achieved with patterned neural activity can regulate these periods.

One major question is whether, during the refinement of connections, activity is instructive or permissive. In the adult, neural activity involved in learning and memory must, at some level, be instructive and experiments suggest that the quality as well as the quantity of visual input is important. One model that emerges from these considerations is that neural activity is exploited by the nervous system at different stages of development for progressively more precise manipulations. At the earliest stages of development axons find their targets without the aid of activity. Subsequently, spontaneous (but patterned) activity is generated by the nervous system itself to guide the refinement of connectivity within the target. Later, stimulus-driven activity is required dynamically to maintain the complex and precise synaptic relationships that mediate sophisticated perceptual and cognitive processing. Lastly, after sufficient wiring has been established, activity instructs specific changes in synaptic connectivity that result in learning and memory.

Further Reading

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