Growth through learning
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Connections between neurons in the brain are thought to be made, broken and adjusted in strength both during learning in adult life and during development. Specific cellular changes called long-term potentiation and depression (LTP and LTD) seem to be responsible, at least in large part, for an important form of learning. Are similar mechanisms involved in the refinement of neural connections in development? Papers on pages 325 and 326 of this issue show correlational evidence that they are.

Unlike a computer, in which a circuit diagram specifies the connections in advance, the brain must wire itself at least in primary sensory cortical areas, the brain refines its connections to a state of high precision during a critical period in early life, in a form of unsupervised learning. During this critical period, but not before or after, synaptic connections between neurons are highly plastic and respond dramatically to alterations in the pattern of neural activity.

Cellular mechanisms of neural plasticity have been worked out in greatest detail in the hippocampus, where the study of LTP and LTD has become a growth industry. The use of the slice preparation allows a specific class of synapses to be manipulated and studied directly in vitro, and a great deal has been learned about the cellular events that underlie the changes in the strength of these synapses.

The question, again, is whether plasticity in cortical synapses during the critical period is carried out by the same cellular machinery responsible for LTP in the hippocampus. Many features of the synapses are similar, and the same neurotransmitters and receptors seem to be involved. If we were confident that the mechanisms were indeed the same, then work on cortical development could piggy-back on the hippocampal story.

One way of tackling the question is to look for correlations between the occurrence of LTP and manipulations known to affect developmental cortical plasticity in vitro. The most prominent feature of such plasticity is the critical period. Crair and Malenka and Kirkwood et al. take advantage of it by comparing LTP in slices from animals of different ages, and both find forms of LTP during the critical period that are smaller or absent thereafter. In addition, Kirkwood et al. raise animals in darkness, which appears to extend the critical period in vivo, and they find that susceptibility to one sort of LTP is also extended. The findings are consistent with the notion that LTP in vitro involves the same mechanisms that organize neuronal connections in development.

An understanding in cellular and molecular terms of the mechanisms responsible for properly connecting up synapses in the cortex would not only be tremendously satisfying on intellectual grounds, it would also have valuable implications for further experiments and for attempts at therapy. The power of LTP in vitro is that, unlike most experimental means that can be carried out on developing in vivo, the particular synapses that change can be identified, and their properties can be examined susceptible to pharmacological and biochemical analysis. Crair and Malenka's study on somatic sensory cortex realizes this promise. Their slice preparation allows them to find the synapses (at the earliest or input stage of cortical processing) at which changes take place, and further cellular studies of this synapse in this system can only enrich our understanding of the mechanisms that control cortical plasticity in development. Kirkwood and colleagues' findings on visual cortex present a more complicated picture. These authors study the aggregate activity produced in the upper layers (which constitute the second stage of cortical processing) by the whole visual cortical circuit, monitored by extracellular recordings. They find that one form of LTP, evoked by stimulation of layer IV (electrode S1 in the figure), is of similar magnitude no matter what the age of the slice, while a second form of LTP, evoked by stimulation of white matter (electrode S2), disappears after the critical period (confirming earlier findings). Because of the complex nature of the circuitry activated by S2, the change in synaptic efficacy responsible for the plasticity during the critical period could occur at any of synapses A-E shown in the figure. The authors' hypothesis to explain the end of the critical period could equally result not from a loss of plasticity at the originally plastic site but from compensatory changes at any of these loci. Indeed, the authors' hypothesis to explain the end of the plasticity in vitro is an increase in inhibitory postsynaptic currents such as can be seen in the figure, rather than some decrement in a synaptic mechanism of plasticity. This
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exploration may well be correct, but it is not clear what we have gained in simplicity by taking the system in vitro. It is certainly not yet clear from these findings whether changes in the actual cellular mechanisms of plasticity at the input synapse could account for the end of the critical period in rodent visual cortex, as Crair and Malska have now shown evidence for in somatic sensory cortex.

'Long-term potentiation' is often taken to refer to a cellular mechanism. But it actually denotes a wide variety of phenomena, for only a few of which is there any understanding in cellular terms. One hopes that the unity of biology will triumph in the end and that common mechanisms will be found to operate in all neocortical areas as well as in hippocampus. For now, however, optimism we may be the promise of a cellular understanding of visual cortical plasticity, we must continue to seek it.

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