P102

Experience Dependent Plasticity in Visual Cortex

Se-Young Choi

Department of Physiology, College of Dentistry, Seoul National Univeristy, Seoul 110-749

Sensory experience during the postnatal certain time range, 'critical period', is essential for the normal maturation of visual cortical circuits and function. Shortly after birth, the visual cortex enters into a brief critical period of enhanced plasticity. At this stage, a simple alteration of visual experience, such as monocular deprivation, selectively weakens the deprived inputs, shifting the eye preference of cortical cells toward the nondeprived eye. However, the nature of critical period is not yet fully understood. One hypothesis is that the maturation of inhibitory circuits plays an important role in timing the critical period for the modifications of excitatory connections. The experience in critical period induces the synaptic reorganization in sensory cortex by the modulation of synaptic plasticity. It is widely believed that NMDA receptor-dependent forms of synaptic modification, such as long-term potentiation (LTP) and long-term depression (LTD), are essential for developmental plasticity in the visual and other sensory cortices. In the context of this idea, it has been proposed that the critical period results from the delayed maturation of the GABAergic inhibitory neuronal system. The recruitment of GABAergic synaptic inhibition restricts the induction of synaptic plasticity; hence, its late maturation would provide a window of opportunity for plasticity to occur studied the role of sensory experience in the maturation of GABAergic circuits in the rat visual cortex. Between the time at which the eyes first open and the end of the critical period for experience-dependent plasticity, the total GABAergic input converging into layer II/III pyramidal cells increases threefold. I propose that this increase reflects changes in the number of quanta released by presynaptic axons. I show that the developmental increase in GABAergic input is prevented in animals deprived of light since birth but not in animals deprived of light after a period of normal experience. Thus, sensory experience appears to play a permissive role in the maturation of intracortical GABAergic circuits. In this mechanism, especially, long-term depression (LTD) is widely considered a mechanism for experience-induced synaptic weakening in the brain. Recent in vivo studies on glutamic acid decarboxylase [GAD 65 (-/-)] knock-out mice indicates that GABAergic synaptic inhibition is also required for the normal weakening of deprived inputs in the visual cortex. To better understand how GABAergic inhibition might control plasticity, I assessed the status of synaptic inhibition and LTD in visual cortical slices of GAD 65 knock-out mice. I found the following: (1) the efficacy of GABAergic synapses during repetitive activation is reduced in GAD 65 (-/-) mice; (2) the induction of LTD is impaired in the visual cortex of GAD 65 (-/-) mice; and (3) chronic, but not acute, treatment with the benzodiazepine agonist diazepam restores LTD in GAD 65 (-/-) mice. These results suggest that a certain inhibitory tone is required for the induction of LTD in visual cortex. I propose that the lack of visual cortical LTD in GAD 65 (-/-) may account for the lack of experience-dependent plasticity in these mice. Previous in vivo study suggests that not only the sensory input but also modulatory inputs are critical for the synaptic reorganization and synaptic plasiticity. The cutting of inputs from basal forebrain complex and locues coeruleus block the effect of monoocular deprivation and the result implies synaptic reorganization in critical period is also regulated by adrenergic and cholinergic inputs. I propose that the induction of LTD also requires the activation of receptors coupled to the PLC pathway. Antagonists of the PLC-coupled receptors:1 adrenergic, M1 muscarinic and mGluR5 glutamatergic block the induction of LTD regardless of the induction protocol used (LFS: 1 Hz, 15 min; pairing: 1 Hz, 2 min + postsynaptic depolarization). However, the antagonists blocked LTD only if administered together: when any one of them was omitted, LTD was fully induced. In a complementary set of experiments we immunolesioned the structures supplying cholinergic and adrenergic inputs to the cortex. In slices prepared from these "agonist-depleted" animals, mGluR5 antagonists blocked LTD, yet supplying exogenous cholinergic agonists restored LTD. Taken together, these results underscore the importance of PLC-linked neurotransmitters in the induction of LTD. Consistent with this idea, the induction of LTD is impaired by intracellular application of a PLC blocker, and it is severely reduced in mice lacking PLC-beta1, the predominant isoform in the forebrain. I propose that a minimal level of PLC activity is required to support LTD in visual cortex. This essential requirement places PLC-linked receptors in a unique position to control the induction of LTD, thus providing a mechanism for regulating visual cortical plasticity by extra-retinal inputs.