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Controlling the critical period

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Abstract

Neuronal circuits are shaped by experience during 'critical periods' of early postnatal life. The ability to control the timing, duration, and closure of these heightened levels of brain plasticity has recently become experimentally possible. Two seemingly opposed views of critical period mechanism have emerged: (1) plasticity may be functionally accessed throughout life by appropriately modified stimulation protocols, or (2) plasticity is rigidly limited to early postnatal life by structural modifications. This overview synthesizes both perspectives across a variety of brain regions and species. A deeper understanding of critical periods will form the basis for novel international efforts to ''nurture the brain''.

Keywords: Critical period; BDNF; GABA; LTP; LTD; Protease; Neurite outgrowth; Inhibition

1. Introduction

At no time in life is the brain so easily shaped by experience than in infancy and early childhood (Doupe and Kuhl, 1999; Daw, 1995). It is during these ''critical periods'' that neural circuits acquire language with native fluency, reproduce the courtship song of a parent bird, expand the representation of a stimulated whisker, or eliminate responsiveness to an occluded eye (ocular dominance, OD). Unraveling the mechanisms that limit such dramatic plasticity to early life would pave the way for novel paradigms or therapeutic agents for rehabilitation, recovery from injury, or improved learning in adulthood. Recent results primarily in the visual system indicate we are ever closer to reaching this elusive goal (Linkenhoker and Knudsen, 2002; Pizzorusso et al., 2002).

Essentially two lines of reasoning have been pursued (Fig. 1). In one view, the potential for plasticity is never lost, but merely tempered by an evolving dynamic of neural activation that can effectively tap into the process. One would thus need to identify the correct ''training'' regimen to coax these neural networks out of one stable state into another. It may simply be easier to do so in immature tissue, whose composition of receptors and downstream signaling machinery is actively changing. Alternatively, one may posit that amidst this molecular maelstrom appears a class of factors that are inhibitory to further plasticity, eventually preventing large-scale circuit reorganization and thereby structurally closing the critical period. Evidence has now been presented for both possibilities.

2. Stabilization of network dynamics

The most convincing demonstration that a ''critical period'' for plasticity exists would be the ability to directly manipulate timing of its expression. Remarkably, this has only recently been achieved in the classical model system of primary visual cortex. Converging inputs from the two eyes typically compete for connectivity (OD) with a peak sensitivity to monocular deprivation around 1 month after birth in cats and rodents (Hubel and Wiesel, 1970; Daw, 1995; Fagiolini and Hensch, 2000). Yet, the critical period is not simply age-dependent, but rather a series of events itself controlled in a use-dependent manner. Rearing in complete darkness from birth leaves the cortex in a flexible state that can be altered by sensory perturbation

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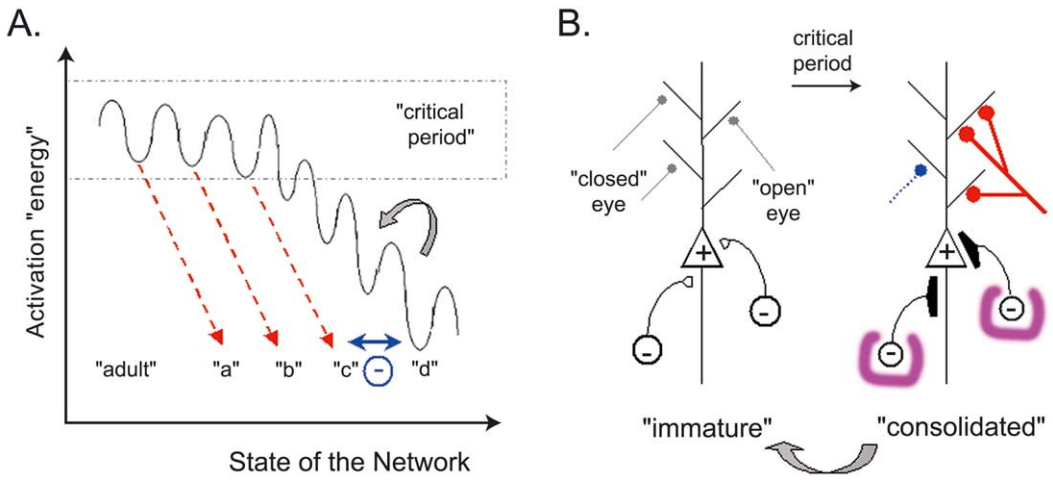

Fig. 1. Two views of critical period closure and reactivation. (A) Stabilization of network dynamics. In this view, neural networks can operate in any number of potential states. Each well represents an ''attractor'' state of local 'energy' minimum. During the ''critical period'' (shaded region) any path (red arrows) toward a final, stable state (''a'' to ''d'') is equally accessible once triggered by an optimal excitatory-inhibitory balance (Fagiolini and Hensch, 2000). Eventually, only one ''adult'' network configuration (''d'') is attained from which it is difficult to escape. Incremental training (gray arrow) may allow gradual step-wise reversion to intermediate states even in adulthood (Linkenhoker and Knudsen, 2002). If multiple, alternative paths had been etched previously during the juvenile period (''a'', ''b'', ''c''), more drastic and rapid switching to those latent maps is possible by disinhibition (blue arrows) in adulthood (Knudsen et al., 2000). (B) Structural consolidation of neural circuits. Large-scale anatomical reorganization accompanies critical period plasticity (e.g. ''closed'' vs. ''open'' eye inputs). Eventually, ECM components such as myelin and perineuronal nets (pink) may actively inhibit further growth and synapse formation. These factors can be degraded by proteases (gray arrow) to reactivate plasticity in adulthood (Pizzorusso et al., 2002).

even in adulthood (Cynader and Mitchell, 1980; Mower, 1991; Daw, 1995; Fagiolini et al., 2003).

Focus on cortical inhibition by γ-aminobutyric acid (GABA) has recently provided major cellular insight into the critical period (Hensch et al., 1998). When the maturation of inhibitory transmission is prevented by targeted deletion of a synaptic isoform of GABA-synthetic enzyme, glutamic acid decarboxylase (GAD65), plasticity is delayed indefinitely until restored locally within cortex by GABAergic modulators (diazepam). Likewise, natural critical period onset can be prematurely opened (and then closed) by drug treatment of wild-type animals (Fagiolini and Hensch, 2000), or indirectly by transgenic over-expression of growth factors for GABAergic interneurons, such as brain-derived neurotrophic factor, BDNF (Huang et al., 1999).

Clearly then, the onset of plasticity is not a result of peripheral maturation, but rather depends upon processes within the brain. Inhibitory connections increase in strength leading up to the critical period, which is recapitulated when animals raised in complete darkness to delay its onset are placed into the light (Morales et al., 2002). Developmental peaks in GABA cell number have also been observed in key motor nuclei (RA) of male zebra finches in correlation with their acquisition of song (Sakaguchi, 1996). The maturation of inhibition may establish patterns of neural activity that enable plasticity. Ultimately, these patterns may themselves serve to close it, i.e. the developmental dynamics approaches a stable ''attractor'' that remains stable under subsequent perturbations of activity (Fig. 1A).

Faced with fluctuating excitatory-inhibitory balance during development, neurons will scale their synaptic inputs to help retain their basic response properties. It has now been shown that scaling occurs in response to sensory deprivation in the visual cortex in vivo to keep neuronal firing rates within an optimal range for information processing (Desai et al., 2002). Importantly, these homeostatic processes also exhibit a critical period by cortical layer. The data indicate that scaling in upper layers may contribute to the onset of OD plasticity, while layer 4 cannot as it is regulated earlier upon eye-opening.

Dynamic reconfiguration of circuit behavior with development would suggest that the same stimuli effective in producing plasticity early in life may be less than optimal in adulthood. The new work by Linkenhoker and Knudsen (2002) takes this into consideration. In the tectum of the barn owl, two superimposed maps are normally aligned to appropriately match the auditory and visual space (Knudsen et al., 2000). This coordination must be learned during a critical period when visual manipulation can adjust the auditory map.

Although large-scale recalibration is no longer effective in adult birds, gradually shifting the visual scene in several small steps produced a much greater degree of adaptive change than previously believed possible (Fig. 1A). This could then be reproduced by subsequent

exposure to a single large prismatic displacement. Similar success in training Japanese adults to discriminate 'r' from 'l' has been based on a knowledge of what works in infants (Y. Wang and P. Kuhl, personal communication). Incremental training can, thus, tap into ever-present plasticity mechanisms and challenges us to be more precise in defining what is meant by a critical period.

3. Relevance of synaptic plasticity rules

Taken together, these findings argue against a primary role for turning on and off excitatory synaptic plasticity rules to establish a critical period. Enhancing inhibition enables plasticity in visual cortex in vivo (Fagiolini and Hensch, 2000), but suppresses long-term potentiation (LTP) induced by high-frequency stimulation in vitro (Huang et al., 1999). Likewise, long-term depression (LTD) is reportedly most robust in young wild-type mice before the critical period, when OD plasticity is low (Choi et al., 2002). In fact, direct targeting of the homosynaptic LTD induction mechanism in neocortex (mGluR2 deletion) has no effect upon monocular deprivation in vivo (Renger et al., 2002). Conversely, LTD is unimpaired (Hensch et al., 1998), input-specific, and saturable in GAD65 knockout mice (Atapour and Hensch, 2002) at ages when OD plasticity remains absent in this animal model (Fagiolini and Hensch, 2000).

Nearly 100 molecules have been implicated in LTP (Sanes and Lichtman, 1999), but critical period plasticity in vivo is resistant to disrupting many of them. One example is the *N*-methyl-D-aspartate (NMDA) type glutamate receptor, whose cortical disruption influences barrel formation but not plasticity (Iwasato et al., 2000; Datwani et al., 2002). The duration of currents through this all-important trigger for synaptic plasticity is developmentally regulated by NR2A subunit expression in many brain regions, curtailing calcium influx. Yet, in its absence whisker barrel rearrangement (Lu et al., 2001) and sensitivity to monocular deprivation occurs normally at the usual ages (Fagiolini et al., 2003). Another example is the neurotrophin BDNF, for which it was originally thought axons might compete to produce OD changes (Katz and Shatz, 1996). Endogenous physiological levels of BDNF limit LTD induction by low-frequency stimuli (Kinoshita et al., 1999), predicting that BDNF over-expression should fully block the loss of deprived-eye input. But visual plasticity is intact in mice over-expressing BDNF, if only shifted in time (Huang et al., 1999).

Although it is phenomeonologically appealing to think of "potentiation" of stimulated inputs and "depression" of deprived connections, classical induction protocols relying on changes in mean firing rate in slices are clearly artificial and possibly misleading about critical period mechanism. Spike timing-dependent plasticity has recently emerged as an attractive alternative based on natural, realistic, millisecond-scale sequences in the temporal order of pre- and postsynaptic action potentials (Bi and Poo, 2001; Froemke and Dan, 2002). Importantly, such models are sensitive to dynamic changes in excitatory-inhibitory balance at critical period onset (Feldman, 2000).

For example, inhibition situated at the axon initial segment or soma may optimally control either spike initiation or back-propagation required for synaptic plasticity in the dendritic arbor. Synaptic scaling is another means to produce competitive plasticity during development, by weakening all inputs that are not potentiated through Hebbian mechanisms or vice versa. Further research into the cellular/molecular basis and potential contribution of these forms of plasticity in vivo at different ages will be fruitful.

4. Structural consolidation of circuits

A different view of critical period closure is an anatomical one (Fig. 1B). For instance, in barrel cortex the critical period refers to the capacity for anatomical expansion or contraction of individual whisker representations just after birth (Van der Loos and Woolsey, 1973; Lu et al., 2001; Datwani et al., 2002). If a row of whiskers is removed (cauterized) just after birth, barrels serving the deprived whiskers shrink while neighboring barrels from the intact whiskers expand. The degree of "filling in" or plasticity becomes progressively smaller the later the deprivation is started. By around postnatal day 6 or 7, whisker cautery has little obvious effect on barrel cytoarchitectonic structure, marking the end of the critical period for barrel development.

More recently, a peak in dendritic spine motility observed by two-photon imaging in vivo predicted a novel, later critical period for somatosensory receptive field plasticity that is very brief (Stern et al., 2001). Activity-dependent elimination of multiple, climbing fiber inputs onto single Purkinje cells in the cerebellum is also strictly limited to a 2-day critical period (Kakizawa et al., 2001). Instead, in other brain regions where neurogenesis is possible throughout life such as the olfactory bulb or hippocampus (see Gage, 2002), continuous circuit reorganization may enhance learning into adulthood (Rochefort et al., 2002; Shors et al., 2001). Many of the molecules implicated in LTP models (Sanes and Lichtman, 1999) could just as well underlie morphological mechanisms.

Perhaps the best-described structural change accompanying critical period plasticity is the expansion or shrinkage of geniculo-cortical afferents serving the two eyes in visual cortex (Fig. 1B; Antonini and Stryker,

1993). More recently, the motility of target dendritic spines has been found to stabilize with the end of the critical period (Grutzendler et al., 2002). Proteolytic activity (tPA) and protein synthesis are now known to be required for even rapid monocular deprivation effects (Mataga et al., 2002; Taha and Stryker, 2002), consistent with a role for navigating the extracellular matrix (ECM). Sensitivity to sensory experience may then disappear as neuronal substrates "consolidate" by actively inhibiting further growth.

For instance, CNS myelination—notoriously refractory to neurite elongation (Schwab and Caroni, 1988)—has been correlated with the end of the critical period in cortex (Schoop et al., 1997; Daw, 1995). Conversely, injection of immature astrocytes can reintroduce plasticity into adult cats (Muller and Best, 1989), perhaps by providing a permissive substrate or otherwise creating a favorable environment for growth. Indeed, among many potential secreted substances, nerve growth factor is reported to have similar rejuvenating power in adult cortex (Gu et al., 1994). Taken together, such evidence would indicate that the refractoriness of mature tissue to change lies in its extracellular milieu.

Along these lines, Maffei and colleagues have now successfully disrupted the ECM in adult visual cortex to reactivate OD plasticity (Pizzorusso et al., 2002). Chondroitin sulfate proteoglycans (e.g. neurocan, CAT-301 antigen) are key components that inhibit axonal sprouting and condense around neuronal somata and dendrites in the form of perineuronal nets near the end of the critical period (Fig. 1B). The encapsulation of mature neurons may impede growth and formation of new synaptic contacts due to potent inhibitory ECM components (Celio et al., 1998) or may create microenvironments for buffering extracellular cations (Hartig et al., 1999). Degradation of these nets by repeated local injection of chondroitinase revealed OD shifts toward the open eye following monocular deprivation in adult rats. As chondroitin sulfate proteoglycans are found throughout the mature CNS, these results offer a potentially general strategy for pharmacologically improving local recovery from injury.

5. Future directions

So, does the critical period permanently hard-wire our brains or can we enjoy massive plasticity throughout life by finding the right stimulation protocols? As is common in biology, both views are likely to be correct. Curiously, perineuronal nets mainly surround fast-spiking, parvalbumin-positive interneurons (Fig. 1B), whose function may be particularly sensitive to extracellular ionic balance (Hartig et al., 1999). This raises the possibility that Maffei and colleagues re-opened the critical period by manipulating its original GABAergic trigger in a cell-specific manner. Despite striking parallels to earlier development, however, it is by no means clear whether the same strategies are employed even within one system during newfound adult plasticity. An important principle is that critical periods progress through multiple stages (Doupe and Kuhl, 1999), and it remains to be elucidated to which level protease infusion resets the adult brain.

Conversely, the degree of functional plasticity in the barn owl tectum is limited by structure, the physical extent of axonal branching. Learning during a juvenile period can lay down multiple, persistent neuroanatomical substrates that expand the range of adaptive changes possible in the adult (Fig. 1A; Knudsen, 1998). Interestingly, when several maps co-exist (perhaps as in native polyglots), irrelevant ones are actively suppressed by novel GABA circuits and can be unmasked rapidly and directly as needed (Fig. 1A; Knudsen et al., 2000). Otherwise, incremental training may be required to step along the constrained retinotopic span of individual neurites, yielding a more gradual, progressive change over days and weeks of experience (Fig. 1A).

We are of course all capable of learning new languages beyond childhood (Doupe and Kuhl, 1999). The important issue is to what extent change is possible, and neither of the two new studies consistently produces the same degree of plasticity seen earlier in life. Perhaps some combination of both strategies (Fig. 1) would be more effective. For example, would diazepam treatment complete the OD shifts observed by Pizzorusso et al.; or similarly could protease infusion further improve plasticity in adult barn owls? Intriguingly, the decline of brain function that accompanies old age may result from specific degradation of intracortical inhibition and can be reversed by GABA agonists (Leventhal et al., 2003). What these studies collectively tell us is that the potential for lifelong learning has yet to be fully explored.

Certainly, we must proceed cautiously considering the biological, clinical and ethical hazards of manipulating the critical period. Pharmacologically accelerating neuronal circuit maturation with benzodiazepines (Fagiolini and Hensch, 2000) or nicotine (Maggi et al., 2003) may have deleterious side-effects by disrupting the normal sequence of developmental events. Hyper-stimulation of a young visual system with immature inhibitory circuits may lead to photic seizures (Porciatti et al., 2000), while environmental noise can retard auditory cortical development (Chang and Merzenich, 2003). Understanding the principle of critical periods and how they may be tapped effectively is of utmost social importance. It is already drawing worldwide attention in the form of a major Organization for Economic Cooperation and Development (OECD) initiative to link "Brain Science and Education" over the next several years (http://www.oecd.org). Success by these international (and

domestic) efforts to apply basic neuroscience will empower us to nurture the brain properly across the lifespan.

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