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Promoting neurological recovery of function via metaplasticity

Kathleen KA Cho and
The Picower Institute for Learning & Memory, Howard Hughes Medical Institute, Department of Brain & Cognitive Science, Massachusetts Institute of Technology, 77 Massachusetts Avenue, 46–3301, Cambridge, MA 02139, USA Tel.: +1 617 324 7002 Fax: +1 617 324 7007 kcho@mit.edu

Mark F Bear†
The Picower Institute for Learning & Memory, Howard Hughes Medical Institute, Department of Brain & Cognitive Science, Massachusetts Institute of Technology, 77 Massachusetts Avenue, 46–3301, Cambridge, MA 02139, USA Tel.: +1 617 324 7002 Fax: +1 617 324 7007 mbear@mit.edu

Abstract

The modification of synapses by neural activity has been proposed to be the substrate for experience-dependent brain development, learning, and recovery of visual function after brain injury. The effectiveness or 'strength' of synaptic transmission can be persistently modified in response to defined patterns of pre- and post-synaptic activity. Well-studied examples of this type of synaptic plasticity are long-term potentiation and long-term depression. Can we exploit the current understanding of these mechanisms in order to strengthen brain connections that may have been weakened or impaired by sensory deprivation, disease or injury? Theoretically motivated research in the visual cortex has suggested ways to promote synaptic potentiation. The theoretical concept is that the type and extent of synaptic plasticity caused by patterns of activity depend critically on the recent prior history of synaptic or cellular activity. Studies in visual cortex strongly support this concept, and have suggested a mechanism for 'metaplasticity' – the plasticity of synaptic plasticity – based on activity-dependent modification of NMDA-receptor structure and function. The knowledge gained by these studies suggests ways in which recovery of function can be promoted.

Keywords

long-term depression; long-term potentiation; metaplasticity; monocular deprivation; NMDA receptor; NR2A; NR2B; ocular dominance plasticity; visual cortex

A common neurological consequence of impoverished sensory experience, brain disease and nervous system injury is the loss or weakening of synaptic connections in the brain, leading to impaired function. The best prospects for treating these conditions lie in tapping the potential for synaptic plasticity of connections that remain intact. Long-term potentiation (LTP) is induced at many excitatory synapses in the brain by strong activation of *N*-methyl-D-aspartate receptors (NMDARs) [1,2]. Clearly, one approach to promoting recovery of function is to provide the types of synaptic stimulation that trigger LTP through training and enriched experience. However, this approach is limited by the simple fact that the synapses we wish to

†Author for correspondence: The Picower Institute for Learning & Memory, Howard Hughes Medical Institute, Department of Brain & Cognitive Science, Massachusetts Institute of Technology, 77 Massachusetts Avenue, 46–3301, Cambridge, MA 02139, USA Tel.: +1 617 324 7002 Fax: +1 617 324 7007 mbear@mit.edu .

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strongly activate are often precisely those that have been weakened by sensory deprivation or disease. It may not be possible to strongly activate a feeble synapse enough to realize any gains. An alternative approach would be to systematically change the properties of synaptic plasticity so that even weak stimulation is enough. Are the properties of synaptic plasticity modifiable? Here we review research on the consequences of sensory deprivation in visual cortex that suggest the properties of synaptic plasticity depend on the recent history of cortical activity. A mechanism for this meta-plasticity is the activity-dependent modification of NMDAR structure and function. We suggest that this knowledge can be exploited to enhance recovery of function in humans.

The roles of experience and deprivation on the function of visual cortex have been extensively studied since the pioneering work of Wiesel and Hubel [3]. In species from mouse to man, temporarily closing one eyelid early in postnatal life sets in motion a sequence of synaptic changes in visual cortex. The first response to monocular deprivation (MD) is the loss of responsiveness to the deprived eye, leading to a persistent impairment of vision. A second, slower response is a compensatory increase in responsiveness to the nondeprived eye. These changes have been studied in considerable detail in rodents, and a mechanistic understanding is now emerging [4].

It should be noted that although the functional consequences of brief and prolonged deprivation are similar, their structural underpinnings can be different. The earliest changes are best described as ultrastructural–manifest, for example, as a modification in the glutamate-receptor content of the postsynaptic membrane. Later changes (as first described by Hubel and Wiesel and later retold in countless textbooks; e.g., [5]) can include gross modifications of thalamocortical axon arbors. Despite these differences, however, the first step in structural plasticity at any scale is the modification of synapses. Put another way, structural plasticity is sequential, and the first step is the m odification of the strength of synaptic transmission.

Of particular interest in the current context is the process of open-eye potentiation. Closing one eyelid has no effect on the qualities of visual experience through the nondeprived eye. Yet, after a few days of MD, the open-eye responses potentiate [6,7]. This increase in visual responsiveness requires activation of NMDARs in the cortex, and may use the same mechanisms as LTP induced by electrical stimulation [8-10].

The idea that the threshold for LTP is variable and depends on the history of cortical activity originates with the Bienenstock–Cooper–Munro (BCM) theory [11]. According to this theory, active synapses potentiate when the concurrent level of integrated postsynaptic response exceeds a ‘modification threshold’ (see Figure 1A). However, the modification threshold is not fixed, but adjusts up and down with the time-average of integrated neuronal firing. Thus, when neurons are quieted by deprivation of one eye, the threshold slides down and enables potentiation of active inputs from the other eye [12,13]. The general concept that the properties of synaptic plasticity depend on the history of cellular and synaptic activity is captured by the term ‘meta-plasticity’ – the plasticity of synaptic plasticity [14]. There is widespread evidence that meta-plasticity is a fundamental property of synapses in the brain [15].

Experimental tests of the assumptions of the BCM theory have repeatedly demonstrated that the threshold for LTP induction in slices of visual cortex *ex vivo* varies according to the history of prior sensory experience *in vivo* [16-18]. If rats or mice are kept in the dark for a few days, LTP can be induced with a lower stimulation frequency than if they are kept in the light. Conversely, re-exposure of deprived animals to light raises the LTP threshold in just a few hours (Figure 1B).

Since LTP [2] and open-eye potentiation [8-10] require activation of postsynaptic NMDARs, there has been interest in the hypothesis that activity-dependent changes in NMDAR-mediated

synaptic transmission are important mechanisms for metaplasticity in visual cortex. In support of this idea, the reduction in the LTP threshold caused in visual cortex by total light deprivation can be reversed acutely with low concentrations of a competitive NMDAR antagonist [17].

While there are many ways to modulate NMDAR effectiveness, one appealing mechanism is the activity-dependent regulation of NMDAR structure and function. NMDARs consist of the obligatory NR1 subunit in combination with NR2A-D and NR3A-B subunits [19]. NR2A and NR2B subunits, which predominate in postnatal cortex [20-22], exhibit several important differences that can influence NMDAR-mediated plasticity. First, NR2B-containing NMDARs have longer current durations than NR2A-containing receptors, due to a higher affinity for glutamate and slower rates of desensitization [23-26]. Second, NR2B-containing NMDARs carry more calcium charge per unit of current than NR2A subtypes [27]. Third, NR2A and NR2B subunits have distinct intracellular binding partners [28-34].

Biochemical experiments demonstrate that NR2B-containing NMDARs predominate in light-deprived visual cortex, whereas NR2A-containing NMDARs predominate in visual cortex following light exposure [35,36]. NMDAR current durations reflect the changes in NMDAR subunit composition, such that the current durations are longer in animals that have been light deprived than in animals that are light-reared [18,37]. It has therefore been hypothesized that the LTP threshold is raised by increases, and lowered by decreases, in the NR2A:NR2B ratio [38]. In strong support of this hypothesis, genetic deletion of NR2A abrogates the effects of visual deprivation on NMDAR currents and prevents metaplasticity of LTP in visual cortex [18]. Recent work suggests that this mechanism for metaplasticity also generalizes to hippocampal as well as cortical synapses [39].

Open-eye potentiation *in vivo* occurs 3–7 days after the onset of MD in juvenile mice [7]. Biochemical experiments were therefore conducted to determine if changes in NR2A and/or NR2B expression occur in this time window. These studies reveal an increase in neuronal surface expression of NR2B following 3 days of MD, and a subsequent decrease in NR2A expression after 7 days of MD. Taken together, the data suggest a hypothesis that the reduction in overall cortical activity caused by MD leads to a gradual decrease in the NR2A:NR2B ratio that lowers the LTP threshold, and that this change is permissive for open-eye potentiation.

In order to test the idea that the lowered threshold for LTP caused by reduction of the NR2A:NR2B ratio enables open-eye potentiation *in vivo*, we studied the effect of NR2A gene dosage on the response of visual cortex to 3 days of MD. In both NR2A-knockouts (KOs)and heterozygotes (in which expression of NR1 and NR2B is unchanged), we observed a precocious increase in open-eye responses and reduced depression of deprived-eye synapses following MD [9]. These findings strongly support the hypothesis that the NR2A:NR2B ratio specifies the value of the synaptic modification threshold that controls the bidirectional cortical response to MD.

A number of questions remain to be answered. First, we do not understand how activity regulates NMDAR-subunit composition. An appealing idea is that transcription of NR2A is proportional to the average activity of the neuron. When activity falls, so would the availability of NR2A mRNA. Such a mechanism could account for the slow reduction in the LTP threshold, since the modified NMDAR-subunit composition would manifest only as fast as the rate of receptor turnover.

An additional mechanism is suggested by experiments performed on cultured cortical neurons. When signaling through NR2B-containing NMDARs is inhibited (by treatment with tetrodotoxin, 2-amino-5-phosphonovalerate, or ifenprodil), there is a selective increase in NR2B protein expression within 24 h. This increase in NR2B requires mRNA translation, but not transcription [40]. These findings suggest an interesting model in which signaling through

NR2B normally suppresses the synthesis of NR2B protein. Relief from this suppression caused by deprivation leads to a rapid increase in expression of this subunit and a corresponding decrease in the NR2A:NR2B ratio of synaptic NMDARs.

Another puzzle concerns how changing the NR2A:NR2B ratio actually enables open-eye potentiation. If the threshold was simply determined by the subunit ratio, then we would expect that open-eye responses in the NR2A KO would have nowhere to go after MD – that is, if the animal grows up with the threshold genetically fixed at a low value, why is there any role for deprivation in triggering the additional increase in visual responsiveness? The data are better described by a model in which the rate of threshold adjustment is constrained by the NR2A:NR2B ratio, which of course is faster in the NR2A-mutant mice. However, this leaves open the question of what the threshold actually is in biophysical or biochemical terms.

Finally, it is important to emphasize that although the evidence is now very strong that supports that changes in the NR2A:NR2B ratio is a mechanism for metaplasticity and for regulating the LTP threshold, this is almost certainly not the only mechanism. Some obvious additional possibilities include changes in inhibitory tone, the number of NMDARs, postsynaptic calcium ion buffering and diffusion, and calcium-dependent biochemical reactions. Indeed, recent studies *in vivo* have demonstrated that dark exposure can shift the LTP threshold in visual cortex within a few hours, which is faster than the NMDAR subunit changes observed so far [41].

Conclusion

The possibility of additional mechanisms notwithstanding, available data strongly suggest that lowering the NR2A:NR2B ratio provides a permissive milieu for strengthening weak cortical inputs. An exciting possibility is that manipulation of this ratio, either experienti ally or pharmacologically, could be exploited therapeutically to promote synaptic rewiring after sensory deprivation, brain injury or disease.

Future perspective

It is now well established that the polarity and magnitude of activity-dependent synaptic plasticity in the cerebral cortex varies as a function of the prior history of cortical activation. Although most of the early experimental support was obtained in rodent model systems, particularly the mouse visual cortex, the phenomenon of metaplasticity has now been demonstrated in human subjects [42-44]. Metaplasticity appears to be a fundamental property of cortical synapses and must be taken into account if we are to harness the therapeutic potential of activity-dependent synaptic modifications [45].

The data reviewed in this article suggest that reducing the NR2A:NR2B ratio will promote the synaptic changes that support recovery of function after deprivation. Support for this idea has come from studies in visual cortex of adult rats that have undergone long-term MD. Normally, opening the deprived eye in an adult will not lead to a substantial recovery of vision through this eye [46]. This outcome is changed considerably if both eyes are deprived of vision 7 days prior to eye opening [47]. The total light deprivation causes (among other things) a decrease in the NR2A:NR2B ratio in visual cortex at the time of eye opening. It remains to be determined whether the adjustment of NMDAR composition and function is responsible for the enhanced recovery of function in these experiments. Regardless, these findings lend support to the concept of a sliding modification threshold that can be lowered by a period of deprivation to enhance subsequent synaptic potentiation in response to sensory experience. A regimen of total deprivation followed by enhanced experience might be useful in clinical practice to p romote recovery of function.

Another approach that could have promise is to pharmacologically control signaling through NMDARs. Genetic experiments suggest that NR2A has a 'dominant negative' influence on synaptic potentiation in response to NMDAR activation and, conversely, that NR2B has a negative influence on synaptic depression. An NR2A-selective NMDAR antagonist might pheno copy the effects of reduced genetic expression of NR2A to promote synaptic potentiation, with greater temporal control. Alternatively, drugs that promote signaling via NR2B-containing NMDARs might have the same effect.

Executive summary

- Metaplasticity is an important phenomenon that describes how the activation history of synapses modifies their potential reaction to subsequent experience. Targeting the threshold that underlies metaplasticity may serve as a means to promote synaptic potentiation in response to experience.
- Experience-dependent increases in NR2A, which change the NR2A:NR2B ratio of NMDARs, normally raise the stimulation threshold that must be exceeded to strengthen synaptic inputs.
- A reduction in NR2A results in a lowered threshold, which might serve as a potential therapy for reversing effects of deprivation in adults.

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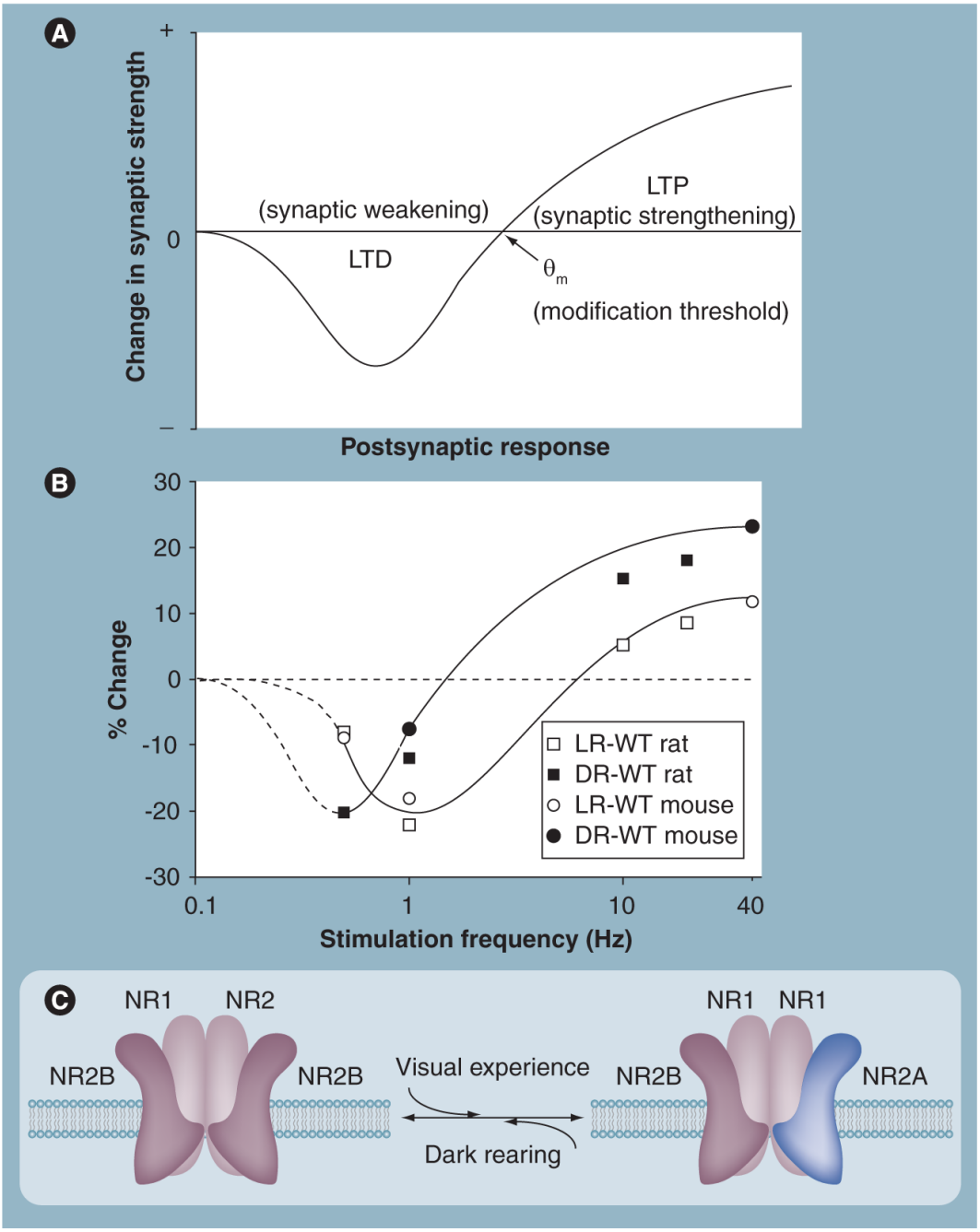

Figure 1. The Bienenstock–Cooper–Munro model

(A) The contribution of bidirectional synaptic modifications to ocular dominance plasticity in visual cortex can be modeled by a learning rule where low levels of postsynaptic activation induce LTD and high levels induce LTP [11]. This model suggests that the magnitude of the postsynaptic response determines the modification of synaptic weight. The crossover from LTD to LTP is termed the modification threshold (θ_m). Importantly, the value of θ_m is not fixed; rather, it 'slides' as a function of the history of postsynaptic activation. The direction the modification threshold slides is determined by the history of postsynaptic activity. **(B)** Semischematic model for frequency-response function in light-reared (LR)-WT and dark-reared (DR)-WT rats and mice. Experimental data points are plotted on a logarithmic scale and

the LR/DR curves are extrapolated from previous studies. The Bienenstock–Cooper–Munro model has been validated experimentally by the observations that LTP is enhanced and LTD reduced in slices of visual cortex from light-deprived rats [16,17] and mice [18]. **(C)** Experience-dependent regulation of NMDA-receptor subunit composition. The NMDA receptor is a heteromer that contains an obligatory NR1 subunit and NR2 subunits that determine receptor properties. Visual experience bidirectionally regulates the composition and function of NMDA receptors in visual cortex. In the absence of visual experience, the NR2B subunit is predominant. With the introduction of visual experience as brief as 2 h of light exposure, the expression of NR2A-containing NMDA receptors increases. Conversely, placing light-reared rats in the dark for 3–4 days causes the levels of NR2A to decrease, switching back to an 'immature state' [35].

DR: Dark-reared; LR: Light-reared; LTD: Long-term depression; LTP: Long-term potentiation; NMDA: *N*-methyl-D-aspartate; WT: Wild-type.