A Comparison of Experience-Dependent Plasticity in the Visual and Somatosensory Systems

Review

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In the visual and somatosensory systems, maturation of neuronal circuits continues for days to weeks after sensory stimulation occurs. Deprivation of sensory input at various stages of development can induce physiological, and often structural, changes that modify the circuitry of these sensory systems. Recent studies also reveal a surprising degree of plasticity in the mature visual and somatosensory pathways. Here, we compare and contrast the effects of sensory experience on the connectivity and function of these pathways and discuss what is known to date concerning the structural, physiological, and molecular mechanisms underlying their plasticity.

Introduction

Since the classic work of Hubel and Wiesel in the 1960s demonstrating the influence of visual experience on ocular dominance columns, much effort has been focused on determining how experience shapes neuronal architecture and connectivity in ways that impact their physiology and behavior. Technical advances in live-imaging studies and molecular approaches have contributed significantly to our current understanding of developmental plasticity in these sensory systems and also focused our attention on plasticity exhibited by the mature brain.

The visual and somatosensory systems are highly amenable for investigating the role of sensory experience in regulating the development and plasticity of neural circuits. This is because activity along these sensory pathways can be manipulated relatively easily. The role of visual experience has typically been studied by raising animals in the dark and by depriving one (monocular deprivation, MD) or both (binocular deprivation, BD) eyes of patterned vision (Figure 1). In the somatosensory system of rodents, manipulating sensory experience by whisker deprivation is readily achieved. Here, clever ways to deprive one, several, or all whiskers from being stimulated have been used (Figure 1). Based upon these deprivation paradigms, the effects of sensory deprivation on neuronal morphology and connectivity in developing and mature visual and somatosensory systems have been assessed. Furthermore, because much is known about the physiology of neurons in the visual and somatosensory pathways, new studies have probed what aspects of synaptic transmission are responsible for changes in circuitry.

Here, we review recent findings and current ideas about the effects of sensory deprivation on development and processing of information by the visual and somatosensory systems. In particular, we will compare what is known concerning the structural and functional bases of the plasticity observed in these two systems during development and at maturity. We first review how sensory deprivation alters the developmental patterning of axonal and dendritic branching in ways that influence connectivity. Next, we discuss how lack of experience affects developing circuits at the subcellular level by regulating synapse formation and elimination. We will briefly discuss recent findings concerning plasticity in the visual and somatosensory sensory systems in the adolescent and adult brain. We then consider the role of spike timing in synaptic potentiation or depression leading to this plasticity and highlight new findings on the key signaling pathways involved.

Sensory-Dependent Development of Axonal and Dendritic branching Patterns

It is evident that deprivation can lead to dramatic alterations in pre- and postsynaptic structures, especially during development. In recent years, the use of transgenic animals has enabled further assessment of how activity shapes axonal and dendritic architecture in both the visual and somatosensory systems. Furthermore, improvements in optical imaging methods have led to a surge of exciting studies that provide a real-time view of how sensory-evoked activity could impact structural development in vivo.

It is well established that MD during the critical period of development causes shrinkage of thalamic axonal arbors corresponding to the deprived eye (Antonini and Stryker, 1993, 1996; Antonini et al., 1999; Figure 2A). The effects of sensory deprivation on the projection patterns of individual thalamic axons in the somatosensory system are less clear. Lesioning a row of whiskers leads to shrinkage of deprived barrels and expansion of non-deprived neighboring barrels, but as yet, it is not known what effects, if any, peripheral deprivation (whisker trimming) rather than deinnervation have on axonal morphology. Some insight into how sensory drive could influence thalamic axonal projections to S1 is gained by reconstruction of individual thalamic axonal arbors in mice in which cortical excitatory neurons fail to express the NR1 subunit of the NMDA receptor. In these mutant mice (CxNR1KO), barrels form but they are poorly defined, and thalamic axons extend beyond the barrel boundaries (Figure 2A). This axonal branching pattern correlates well with previous physiological studies that showed that thalamic inputs principally representing a single vibrissa spread to neighboring barrels when NMDA receptors are pharmacologically blocked (Fox et al., 1996b). Together, these results underscore the importance of postsynaptic activity in organizing presynaptic morphology, an outcome also apparent in the

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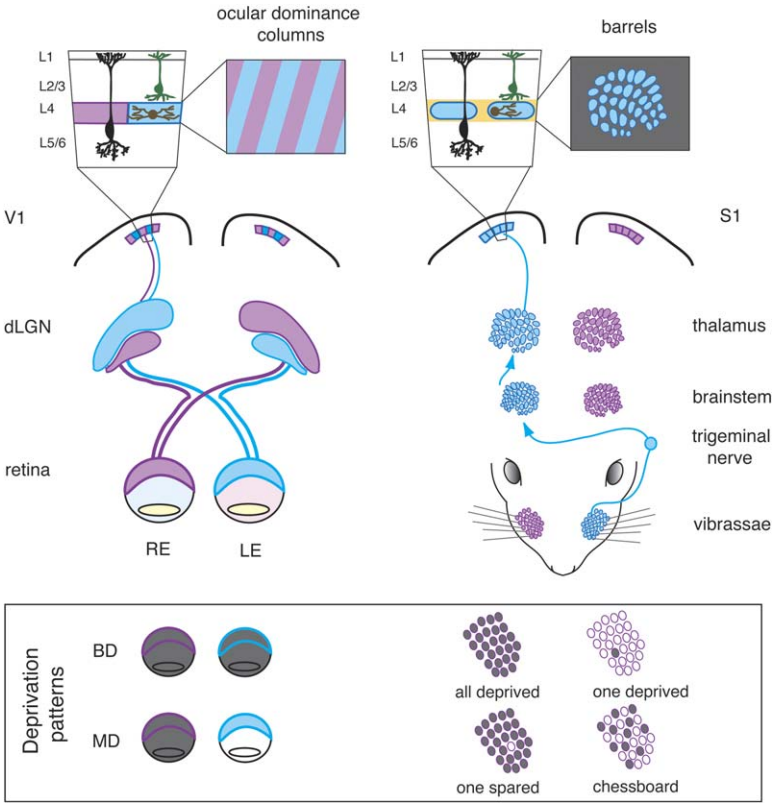

Figure 1. Schematic Showing the Basic Arrangement of the Visual and Somatosensory Pathways in Mammals

Various sensory-deprivation paradigms have been used to determine the role of sensory experience in plasticity exhibited in both these systems. BD, binocular deprivation; MD, monocular deprivation; V1, primary visual cortex; S1, primary somatosensory cortex.

visual system when V1 neurons are inhibited during MD (Hata and Stryker, 1994; Hata et al., 1999).

What about intracortical projections? It was recently established that sensory stimulation is not required for attaining precise topographic projections from layer IV to layers II/III in S1 (Bender et al., 2003), even though whisker trimming significantly reorganizes synaptic drive between these cortical layers (Stern et al., 2001; Shepherd et al., 2003). How layer IV axonal projections to layers II/III in V1 might be altered by visual deprivation is not known, but it is clear that connectivity between layers II/III neurons is readily affected by visual deprivation (Trachtenberg and Stryker, 2000). Combined electrophysiological recordings and morphological studies are needed to more directly correlate anatomical and functional responses to sensory deprivation. Recent in vivo approaches are likely to help facilitate such studies, as they can provide a real-time view of how axons behave dynamically in the cortex during the deprivation period. Although not yet completed in mammals, such studies are well underway in lower vertebrates (Alsina et al., 2001; Ruthazer et al., 2003; Hua et al., 2005).

In *Xenopus*, the tectum is normally innervated only by the contralateral eye. Surgically forcing the tectum on one side to be innervated by projections from both eyes leads to segregation of axonal terminals into eye-specific stripes (Law and Constantine-Paton, 1980). Time-lapse imaging of retinal axons now reveals that this enforced segregation into eye-specific territories is due to selective stabilization, rather than biased growth, of axonal branches within their appropriate eye territory (Ruthazer et al., 2003). Whether under normal developmental conditions retinal axons behave in this way in order to occupy their appropriate postsynaptic territories is unclear, but a new study in zebrafish demonstrates that, if so, activity is likely to be involved. In zebrafish, suppressing retinal ganglion cell activity by expression of a dominant-negative vesicle-associated membrane protein (VAMP) or the inward rectifier potassium channel, Kir 2.1, leads to a reduction in branch complexity and size of the axonal terminal (Figure 2B). Importantly, if activity-depressed axons have neighbors that are also suppressed, axonal arbors appear normal (Hua et al., 2005; Figure 2B). Tetrodotoxin injection into the eye does not affect axonal morphology and in fact restored branching patterns of ganglion cells expressing dominant-negative VAMP or Kir 2.1 to control levels. These results suggest that changes in axonal terminal structure depend on the "activity levels" of potential competitors. These insights gained from imaging axonal behaviors in lower vertebrates may help explain the effects of MD on thalamic axons in mammals (Antonini and Stryker, 1993, 1996; Antonini et al., 1999). However, future in vivo studies directly visualizing the effects of MD on thalamic axons in mice or other mammals are very much needed. Such studies will especially be rewarding if individual axonal terminals can be followed over short- and long-term deprivation, as well as during recovery from deprivation within the critical period. These observations could help distinguish whether reduced arbor size and branching of deprived axons, as observed in MD, are due to a failure of growth or alterations in the stability of newly generated branches. Comparisons between V1 and S1 will also further illuminate similarities or differences in how thalamic axons in these two systems behave under conditions of sensory deprivation.

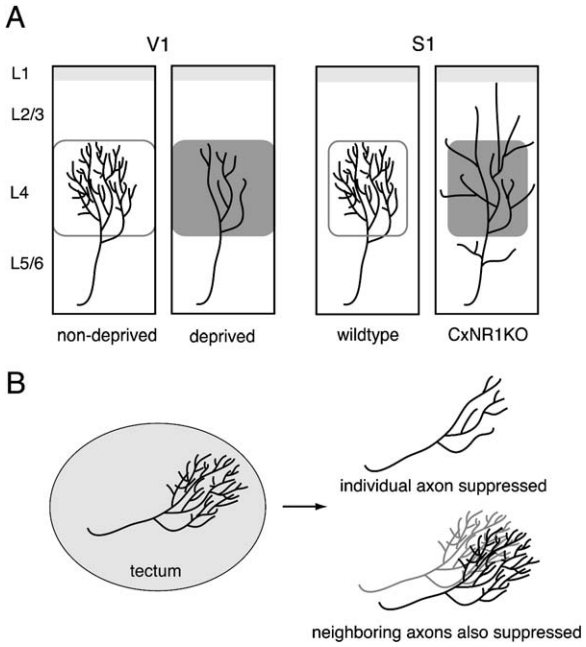

Figure 2. Neuronal Activity Influences Axonal Branching Patterns in the Visual and Somatosensory Systems

(A) Thalamocortical projections in visual cortex (V1) and barrel cortex (S1) in normal versus activity-perturbed conditions. In V1, axonal branching is reduced after MD during the critical period (adapted from Antonini et al., 1999). In S1, axonal branches overshoot the primary barrel and layer IV in a mutant animal in which the NR1 subunit of the NMDA receptor is knocked out in the cortex (Datwani et al., 2002; Lee et al., 2005).

(B) Axonal terminal patterns of retinal ganglion cell projecting to the tectum in developing zebrafish are influenced by neurotransmission (adapted from Hua et al., 2005).

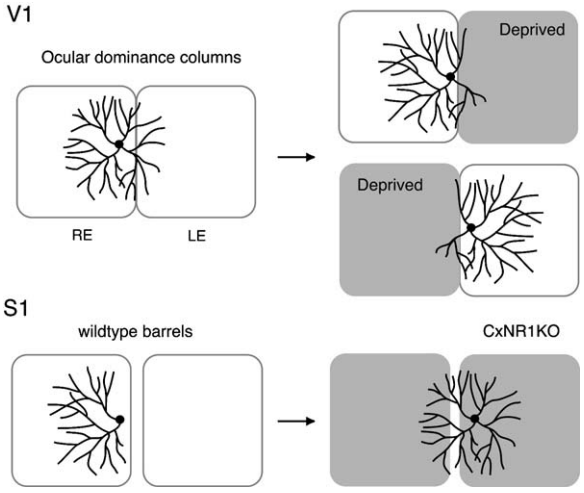

Figure 3. Neuronal Activity Regulates Dendritic Branching Patterns of Layer IV Neurons in V1 and S1

V1 neurons near the borders of ocular dominance columns in normal and monocularly deprived cats (after Kossel et al., 1995). S1 neurons in wild-type or mutant mice lacking the NR1 subunit of the NMDA receptor (CxNR1KO; see Datwani et al., 2002).

Although initial studies seeking to understand how experience regulates sensory development have largely focused on axons, in recent years, dendrites also have received much attention. Dendritic arbors of neurons possess several features that are pertinent to their connectivity and information processing. The branching patterns of neurons are thought to influence dendritic processing and connectivity (Yuste and Bonhoeffer, 2004). How sensory stimulation influences the development or maintenance of dendrites has come under intense investigation, largely because these structures can now be visualized in vivo.

Neurons in V1 and S1 share common features in their dendritic organization (Figure 1). Pyramidal cells with apical and basal dendrites are localized to all layers, whereas stellate neurons are found in layer IV (Staiger et al., 2004). Sensory deprivation does not have a dramatic effect on dendritic branching or field size of cortical layer III pyramidal cells in V1 or S1 (Tieman et al., 1995; Maravall et al., 2004). In contrast, in both cortical areas, dendritic patterning of layer IV stellate neurons, the immediate postsynaptic targets of thalamic neurons, is more readily affected by changes in activity. In V1, layer IV cells near the border of ocular dominance columns show a slight orientation bias away from the border between columns. In MD, these cells show an even more pronounced orientation away from the deprived-eye column and toward columns representing the open eye (Kossel et al., 1995; Figure 3). Mature layer IV stellate neurons in S1 located near barrel boundaries exhibit a highly biased orientation of their dendrites away from the boundaries and toward the center of the barrel. This arrangement is established by reorientation of the arbor during development and requires NMDA receptor activation because it does not occur in the CxNR1KO (Datwani et al., 2002; Figure 3). Whether depriving a single whisker of stimulation prevents this dendritic reorientation in S1 during development has not been explored. What is evident, however, is that the effects of deprivation on dendritic branching patterns of cortical neurons even within a single sensory area vary with cell type.

How does sensory experience dynamically regulate dendritic branching? In vivo time-lapse imaging studies in *Xenopus* have clearly demonstrated that light stimulation promotes dendritic branching in tectal neurons, a process that also requires NMDA receptor-mediated transmission (Sin et al., 2002). By combining labeling of postsynaptic densities with dendritic labels, tectal dendritic development and synaptic maturation can now be monitored over time in the intact animal. Niell et al. (2004) proposed that dendritic branches are stabilized by synaptic contact. Whether it is visually evoked activity at nascent synapses that acts to locally stabilize dendrites has not yet been assessed directly, but the tools needed for such a study are in place.

Surprisingly, visual deprivation also induces significant changes in dendritic branching patterns in the retina. In the turtle retina, dark rearing results in an expanded dendritic territory in retinal ganglion cells (Sernagor and Grzywacz, 1996). Recently, visual deprivation in mice showed that there are more bistratified retinal ganglion cells in dark-reared compared to light-reared animals (Tian and Copenhagen, 2003). Bistratified cells respond to both an onset (ON) and offset (OFF) of light, in contrast to monostratified cells that

are either ON or OFF responsive (Wässle, 2004). The effect of visual deprivation was attributed to the maintenance of a greater proportion of bistratified cells in the mouse retina. Because retinal ganglion cell numbers are largely unchanged after eye opening, the increased bistratified cell population is thought to arise from a failure to eliminate dendrites in the ON or OFF synaptic sublamina. The anatomical perturbation by light deprivation is supported by physiological recordings showing a similar increase in the incidence of ON-OFF retinal ganglion cells in dark-reared animals. Visual stimulation therefore acts in various ways to shape the dendritic organization and light responses of the retinal ganglion cells. It is not yet apparent why maturing retinal circuits should be fine tuned by visual stimulation, but this plasticity may represent a strategy by which the animal can adapt to novel visual environments if the need arises. However, these observations of vision-dependent dendritic plasticity in the retina underscore the need to consider the developmental effects of sensory stimulation at all levels of the visual pathway and raise the possibility that some physiological changes in the cortex may be due to alterations of retinal circuitry.

In summary, recent studies provide further support for the notion that the maturation of neuronal architecture in the visual and somatosensory systems is influenced by sensory stimulation. However, drawing parallels between S1 and V1 with regard to the mechanisms underlying their structural development has not been straightforward. In part, this is because, unlike the visual system, relatively little is known with regard to how sensory deprivation affects axonal and dendritic development in different parts of the somatosensory pathway, especially at the single-cell level. Clearly, the findings from perturbation of neurotransmission by pharmacological methods or in mutant animals support the importance of activity, but it remains unclear how sensory stimulation itself alters neuronal morphology in S1 during development. Determining whether sensory-evoked activity acts uniformly across the visual and somatosensory systems to shape axonal and dendritic structure thus awaits further experimentation. Future comparisons will also require that effects at similar ages be compared, but with the awareness that the developmental time course of structural and functional maturation of these two sensory systems may not be identical. Certainly, unraveling the detailed connectivity patterns, unique to these two systems, is essential to help us interpret how sensory signals influence their structural maturation.

Regulation of Synapse Formation and Elimination by Sensory Experience

Although the gross patterning of axonal or dendritic arbors may not be affected in some instances by sensory deprivation, circuitry may still be altered at the synaptic level. One way to determine whether synapses are gained or lost upon deprivation is to ascertain the effects on dendritic spines. Cortical neurons bear numerous spines that are postsynaptic to glutamatergic inputs, although in some cells, a small fraction of spines are coinnervated by GABAergic inputs. Changes in spine number or density have been attributed to changes in connectivity, and alterations to spine morphology have been linked to modifications in synaptic strength (Yuste and Bonhoeffer, 2004). Spine motility and turnover are thought to represent synapse formation, stability, or elimination. Sensory deprivation during development affects some, but not all, features of dendritic spines in V1 and S1 (summarized in Figure 4).

Early studies by Valverde (1967, 1971) have long suggested that spine density of layer V cortical neurons is decreased by dark rearing. More recently, Mataga et al. (2004) discovered a significant and rapid spine loss in the apical and basal dendrites of layer III pyramidal cells in V1 within 4 days of MD in mice. Likewise, MD in rats also causes a loss of spines as well as changes in spine shape in the basal dendrites of layer III cells (Wallace and Bear, 2004). In S1, the basal processes of developing layer II/III pyramidal cells within barrels receiving deprived input exhibit normal spine density, length, and shape even though receptive field tunings of these cells were altered, suggesting that functional changes are not always necessarily accompanied by alterations to these spine parameters (Lendvai et al., 2000). But, the normal developmental loss of spines on apical dendrites of S1 layer V cells in juvenile mice is prevented by long-term whisker trimming (Zuo et al., 2005b). Sensory deprivation thus appears to have varied effects on spine density of V1 or S1 cortical neurons, depending on cell type and stage of development.

Although spine motility as well as spine turnover decreases with age in both S1 and V1 (Lendvai et al., 2000; Majewska and Sur, 2003; Konur and Yuste, 2004), the effects of deprivation on spine motility during development differ somewhat in these two sensory regions (Figure 4). In S1, spine motility of layer II/III neurons is reduced by whisker deprivation within a narrow window (postnatal days P11–P13) corresponding to the period of rapid synaptogenesis (Lendvai et al., 2000). In contrast, binocular deprivation enhances spine motility of layer V cells in V1 at the peak of the critical period (P28) (Majewska and Sur, 2003). Examination of motility at different cortical depths revealed the novel finding that motility of layer V apical dendrites induced by monocular deprivation is lamina specific (Oray et al., 2004). This lamina-specific change is attributed to the localized action of the tissue plasminogen activator (tPA) that facilitates proteolysis of the extracellular matrix (ECM) (Mataga et al., 2004; Oray et al., 2004). Thus, even for a single neuron, connectivity may be altered locally and differentially across the dendritic arbor by sensory stimuli.

Another means of exploring how experience affects synapses is by mapping the distribution of pre- or postsynaptic markers. Eye opening in rats has been observed to rapidly induce dendritic localization of PSD-95, a major glutamate receptor scaffolding protein, in the central targets of retinal ganglion cells, the superior colliculus and the dorsal lateral geniculate nucleus (dLGN), as well as the visual cortex (Yoshii et al., 2003). By controlling the time of eye opening with eye-lid suture, it was further determined that localization of PSD-95 in the dendrites of dLGN neurons is greater in the open-eye territory compared to the closed-eye territory. No differences are observed when both eye lids are opened at the same time. Visual experience may therefore act as a trigger for rapid organization of synapses

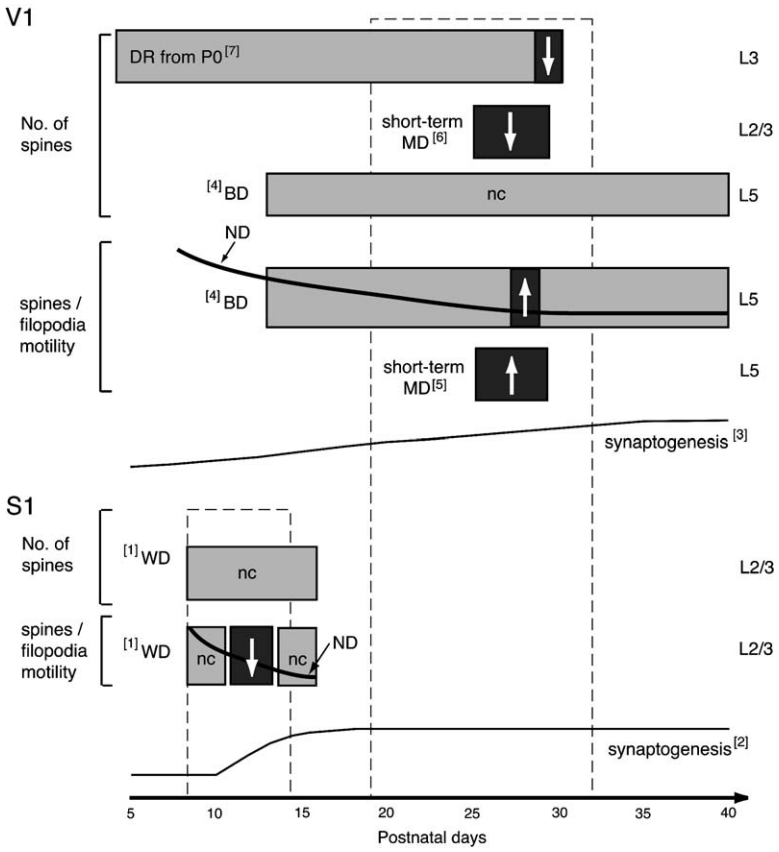

Figure 4. Summary of the Effects of Sensory Deprivation on Spines of Layers II/III or V Pyramidal Neurons in Developing V1 and S1

Dashed boxes indicate the critical period for functional reorganization in layers II/III and V (V1 in mice, Gordon and Stryker (1996); S1 in rat, Stern et al., 2001). Gray boxes indicate period of deprivation, dark boxes indicate at which age effects were measured or observed. Arrows within the dark boxes: up = increase, down = decrease; nc = no change. ND = normal developmental loss of spine/filopodial motility. BD, binocular deprivation; MD, monocular deprivation; DR, dark rearing; WD, whisker deprivation. Adapted from [1] Lendvai et al., 2000; [2] Micheva and Beaulieu (1996); [3] De Felipe et al., 1997; [4] Majewska and Sur, 2003; [5] Oray et al., 2004; [6] Mataga et al., 2004; [7] Wallace and Bear, 2004.

in the visual pathway. Is visual stimulation required to maintain an appropriate synaptic density in the cortex? Interestingly, neither the densities of excitatory nor inhibitory presynaptic sites in V1 as assessed by immunolabeling approaches appear to be altered upon MD at times when physiological changes have already occurred (Silver and Stryker, 2000). Thus, rapid changes in physiological response may reflect changes in synaptic transmission rather than alterations in synaptic density. As yet, it has not been determined how sensory stimulation dynamically influences excitatory and inhibitory synapse maturation and maintenance in the somatosensory pathway using markers of synaptic proteins.

Although tracking pre- or postsynaptic structures by light microscopy is informative, synapses are perhaps best defined at the ultrastructural level. In fact, in contrast to light microscopy studies, EM studies of V1 and S1 recently revealed that the development of inhibitory synapses is affected by sensory stimulation. For example, the developmental increase in GABAergic synaptic density in V1 is retarded by visual deprivation (Benevento et al., 1995; Morales et al., 2002). Also, the number and density of GABAergic synapses is significantly decreased in layer IV of deprived S1 (Micheva and Beaulieu, 1995). Intriguingly, this is due to a selective reduction in GABAergic innervation of spines. Conversely, there is an increased number of spines and postsynaptic surface in layer IV ipsilateral to the deprived side, perhaps due to enhanced usage of whiskers on the intact contralateral facial pad (Vees et al., 1998). Together, these results suggest that experience regulates the development of V1 and S1 not only by modifying excitatory synapses but also by modifying the arrangement of inhibitory synapses. It would be useful in the future to determine whether experience-dependent changes in GABAergic innervation of layer IV spines reflects plasticity in the projections of specific subsets of GABAergic interneurons. Furthermore, addressing how changes in neurotransmission leads to spatially selective alterations in inhibitory inputs could provide more clues as to why some synapses are "plastic" and others are not.

The Nature of Adult Plasticity in Visual and Somatosensory Systems

It has been known for some time that plasticity is possible in adult somatosensory cortex. The groundbreaking work of Merzenich and colleagues in the early 1980s showed that peripheral nerve lesions can lead to changes in cortical mapping of the neighboring innervated areas (Merzenich et al., 1983). Similarly changes in the way a monkey uses its fingers also leads to receptive field changes in adult monkey somatosensory cortex (Clark et al., 1988). It has also been known for some time that adult plasticity involves potentiation of the spared peripheral input rather than depression of the deprived sensory input (Glazewski et al., 1996). Deprivation of whiskers in mice and rats up to the age of about 2 months causes depression of the deprived whisker input in the cortex but not the thalamus (Fox et al., 2002; Glazewski et al., 1996). However, deprivation at 6 months of age does not produce any depression, only potentiation of the spared whisker input to

the cortex. Again this effect is cortex specific (Wallace et al., 2001).

Interestingly, evidence is now coming to the fore that the same is true in the visual cortex (Sawtell et al., 2003). Using chronic in vivo recording and visually evoked potentials (VEPs), it has been shown that MD for a period of 5 days can cause shifts in ocular dominance in animals as old as P90 (age of groups studied = P60–P90). The shifts at the older ages are due almost entirely to potentiation of the open or experienced eye. The period of deprivation is important because potentiation of the open-eye input occurs far more slowly than depression of the closed-eye input (Frenkel and Bear, 2004; Mioche and Singer, 1989). Therefore, a deprivation period of 3 days is insufficient to cause significant open-eye potentiation, while 5 days is sufficient.

Again these properties are shared between visual and somatosensory cortex. Whisker deprivation in animals starting at 1 month of age will cause depression of deprived whisker input before potentiation of spared whisker input. If a single whisker is spared, depression occurs within 7 days and potentiation within 20. If a chessboard pattern of deprivation is used, potentiation can occur far more quickly (within 7 days) and presumably depression as well, though this has not been explicitly tested. The difference in time course is affected by the action of competition, which is inherently present in the MD paradigm but can be varied in barrel cortex by varying the whisker deprivation pattern (Wallace and Fox, 1999). One further similarity exists with the somatosensory literature in that the potentiation is mainly seen in supragranular layers of visual cortex.

It is not known in the visual cortex at present whether the ability to potentiate open-eye inputs persists to greater ages. Certainly, longer periods of deprivation cause changes in ocular dominance plasticity in extragranular layers of cat visual cortex up to 1 year of age (Daw et al., 1992) and in monkey visual cortex up to 2 years of age (LeVay et al., 1980). It is therefore possible that these ocular dominance shifts are due to potentiation mechanisms rather than depression mechanisms too.

The findings of adult plasticity do not negate the existence of a critical period for plasticity. In the visual cortex much stronger shifts in ocular dominance occur in response to monocular deprivation at P23 but far less at P30 (Fagiolini et al., 1994; Gordon and Stryker, 1996; Sawtell et al., 2003). The difference between plasticity in the critical period and in adulthood, however, is that it is due not only to potentiation of open-eye input but critically on depression of the closed-eye input. Only during the critical period can alterations in experience through the eye lead to a decrease in response once the eye is reopened. Again the results are strikingly similar to the findings in the somatosensory cortex that depression of deprived whisker input only occurs in the first 2 months of age (Glazewski and Fox, 1996).

These findings are important for a number of reasons. First, they suggest that because the plasticity mechanisms are similar between visual and somatosensory cortex that they may represent fundamental cortical properties that are not just peculiar to one area or another. Second, because the molecular bases of potentiation and depression mechanisms are different, their prevalence at different ages allows them to be distinguished more easily. This was always the case for somatosensory cortex but is now possible in visual cortex too. For example, as pointed out later (molecular pathway section) the role of α-CaMKII appears to be restricted to potentiation in the somatosensory cortex and plays little or no part in depression. So far, the potentiation and depression states have not been separated in visual cortical experiments on CaMKII mutants, which could account for the variable effect of the mutation on plasticity during the critical period.

Is there evidence for structural plasticity in adult somatosensory cortex? Both axons and dendrites are affected in barrel cortex following follicle ablation or denervation. Cells located in barrel columns which have their principle whisker input spared tend to project their axons further than cells located in deprived barrels (Kossut and Juliano, 1999). Furthermore, whereas layer III barrel neurons tend to have their dendrites oriented in toward the center of their "home" barrel, after 8.5 weeks of follicle ablation, they lose their orientation and send dendrites in all directions (Tailby et al., 2005). This is evidence of new dendritic growth in adult animals, because the neurons would have started with a lack of dendrites projecting away from the barrel center and ended with dendrites oriented in all directions. Such large-scale reorganization of dendrites has not been seen in response to whisker deprivation, and it is not clear whether this is because of a difference between experience-dependent plasticity and lesion-induced plasticity or due to the longer time scales at which the lesion-induced plasticity has been studied thus far.

At the synaptic level, it is generally agreed from in vivo imaging studies that spines become more stable with maturation in V1 and S1. However, the quantitative extent to which spines turn over in the mature V1 and S1 and the issue of whether spines are more stable in V1 compared to S1 are still highly debated (Grutzendler et al., 2002; Trachtenberg et al., 2002; Holtmaat et al., 2005; Zuo et al., 2005a). Nevertheless, it is evident that spine turnover in the 1- to 2-month-old cortex is increased by whisker deprivation over a period of 4 days (Trachtenberg et al., 2002) and that spine elimination that continues during adolescence is regulated by experience (Zuo et al., 2005b). Also, as in development, inhibitory synapses are plastic in the adult barrel cortex; whisker stimulation in adult rats surprisingly increases coinnervation of layer IV spines by GABAergic and glutamatergic inputs (Knott et al., 2002).

How do the physiological measures of plasticity in adult animals relate to structural changes we have been describing for developmental plasticity? One point noted earlier in the review is that the experience-dependent changes in spine motility and resultant loss of spines following MD only occur during the critical period and not in adult animals (Mataga et al., 2004). This finding is consistent with the observation that depression of closed-eye responses only occurs during the critical period and not in adult animals as discussed above. It has recently been noted that even follicle ablation does not lead to a decrease in spine density in deprived barrel columns in adult animals (Tailby et al., 2005). It is an open question as to what limits loss of spines in adult animals. It may be that the ECM limits spine loss by stabilizing

spines, which would explain why dissolving the ECM increases plasticity in adult animals (Pizzorusso et al., 2002). Alternatively, it may be that a vital component of the synaptic-depression mechanism is absent in adult animals.

In conclusion, some progress has been made toward understanding plasticity in adult animals, most notably that potentiation of synaptic responses remains possible in adults as in younger animals. Experience-dependent potentiation is possible in adult rat and mouse somatosensory cortex beyond 1 year of age, and it will be important to test visual cortex at similar ages. It is important to know that depression does not occur at these older ages, and it will be of interest to see if this is related to a greater persistence of spines in adult animals. From a functional viewpoint it is not clear whether the function of the neuron can change purely as a result of potentiation. The newer experience-dependent changes are presumably superimposed on the previously existing representation. Is this sufficient to allow recovery from amblyopia, for example, or do erroneous connections need to be eliminated for a full functional recovery? It is conceivable that current methods for prolonging the critical period or reopening it are preserving or reinstating depression mechanisms into later life.

The Role of Spike Timing in Plasticity

How do neurons distinguish between neuronal activity that drives plasticity and activity that simply conveys information to be processed within the neuronal circuit? Patterns of activity that induce plasticity need to be sufficiently different from patterns solely conveying information to avoid perpetual and inappropriate change. Work on LTP induction in the hippocampus originally hinted that the difference between information processing and plasticity induction might be the difference between high and low frequencies of neuronal activity because high-frequency stimulation produced potentiation of synapses while low-frequency stimulation produced no change. However, the problem with this idea is that in many neural systems, including the somatosensory and visual systems, similarly high or low frequencies of neuronal firing often occur within the normal range of information processing with little or no apparent change in the properties of the neurons concerned. For example, a firing rate of 100 Hz can induce LTP in the hippocampus and yet similar rates can be recorded in anesthetized or awake visual cortex in response to visual stimuli (Carandini and Ferster, 2000; Hubel, 1959). Conversely, plasticity can be induced by manipulations that produce practically no change in firing rate at all. For example, whisker deprivation decreases layer IV neuron firing rates from 4 to 2 Hz during exploratory whisking (Celikel et al., 2004). While this form of deprivation causes plasticity, the rate changes are not sufficiently different to drive plasticity at the cellular level. The resolution of this issue may be that changes in plasticity state are conveyed not by a reserved set of plasticity frequencies but by the relative phase of firing between neurons.

At the systems level, there is an abundance of evidence that relative action potential (spike) timing is important for plasticity. In the visual system, correlated neuronal firing can drive the development of particular receptive field properties and maps (Maffei and Galli-Resta, 1990). In the somatosensory system, correlated activity can produce receptive field plasticity even in adult animals (Clark et al., 1988). At the cellular level, the finding that the relative phase of pre- and postsynaptic spikes can produce either depression or potentiation provided that they occur within a 10 ms time window provides a plausible cellular mechanism for such systems-level observations (Bi and Poo, 1998; Markram and Tsodyks, 1996). This method of producing plasticity in a neuron has been called spike timing-dependent plasticity (STDP) and produces potentiation when the presynaptic spike occurs approximately 10 ms before the postsynaptic spike and depression when the presynaptic spike occurs approximately 10 ms after the presynaptic spike. Specific evidence linking the cellular mechanism to a role at the system levels has been difficult to obtain. However, a number of recent studies have shown that it is at least plausible that STDP may operate in both the visual and somatosensory systems.

In the somatosensory system, a form of whisker deprivation that induces receptive field plasticity in layers II/III of the barrel cortex can occlude LTD in layer II/III neurons (Allen et al., 2003) and produce a change in the short-term dynamics of connections between columns reminiscent of STDP (Finnerty et al., 1999). The imprint of the deprived experience on the cortical synapses has been observed using two distinct methods: the short-term dynamics of the synapse have been studied following whisker deprivation, and the ability to produce LTD has been investigated in deprived cortical columns. Remarkably, the synaptic plasticity produced in the cortex during deprivation survives the trauma of preparing a cortical slice. For the first method, multipulse stimuli can be used to study the short-term dynamics of the synapse. Short-term dynamics can either be naturally facilitating between excitatory cells in the cortex, such that in response to a train of pulses delivered at 20 Hz, the EPSP to the second stimulus is greater than to the first, or depressing, such that the response to the second pulse is less than to the first. However, following deprivation the short-term dynamics become more depressing than in controls (Finnerty et al., 1999). Specifically, projections to cells located in deprived columns from cells located in spared columns depressed more than projections within deprived columns. This change in short-term dynamics is indicative of an increase in synaptic release and is also produced during STDP in vitro (Markram and Tsodyks, 1996). The second observation is that LTD induced in connections within the column running from layer IV to layer II/III is smaller once deprivation has been induced (Allen et al., 2003). This is a specific effect on the column that has been deprived of its principal whisker input and does not occur, for example, in the neighboring columns of the same slice that did not have their principal whisker deprived.

As mentioned above, whisker deprivation can reverse the spike timing that normally occurs within the barrel cortex circuitry in response to whisker stimulation (Figure 5A). In an undeprived animal, stimulation of several whiskers at a time causes layer II neurons to fire action potentials a few milliseconds after the neurons in layer IV within the columns that lie presynaptic to them. However, stimulation of several whiskers excluding the

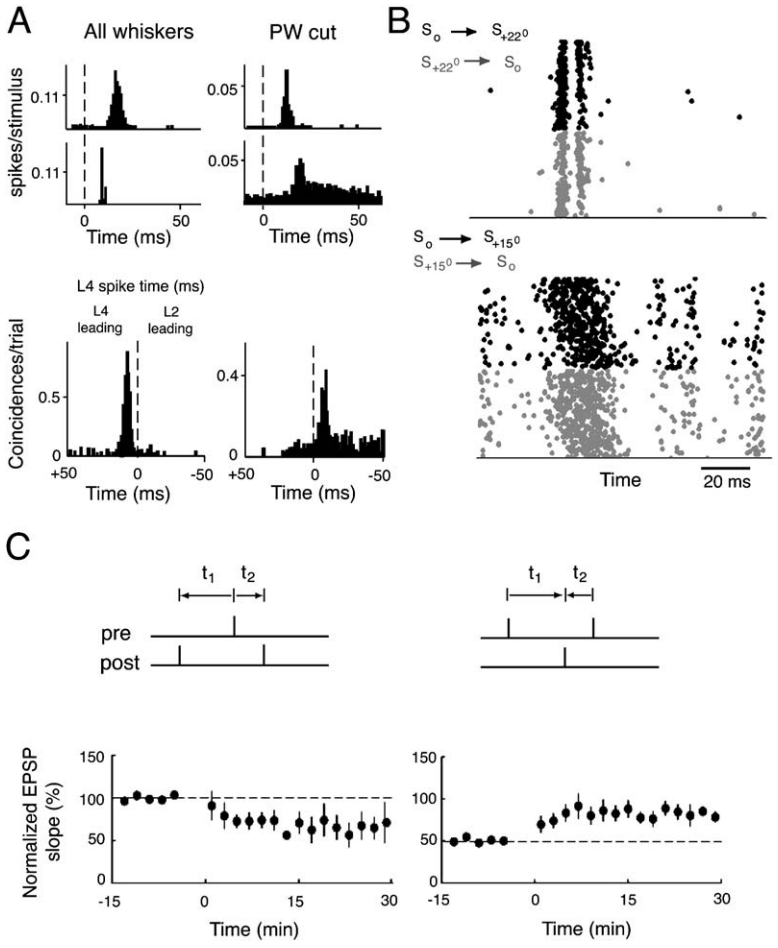

Figure 5. The Relationship between Experience-Dependent Plasticity and STDP

(A) (Left column) All whiskers: Stimulation of the whiskers normally produces a brief response in barrel cortex neurons. PSTHs show that layer IV neurons respond first (bottom PSTH), followed by the layer II neurons (upper PSTH) to which they project. (Lower) Cross-correlation analysis shows that layer IV leads layer II. (Right column) PW: if the principal whisker is cut and the remaining whisker stimulated, then layer II cells respond before layer IV cells (top, PSTH layer II; bottom, layer IV). (Lower) Now the cross-correlation shows layer II cell responses leading layer IV cell responses. (Adapted by permission from MacMillan Publishers LTD: Nature Neuroscience, Celikel et al., 2004).

(B) In the visual cortex, two brief flashes of orientated stimuli timed 8.3 ms apart produce responses in visual cortical neurons. (Top) The raster plots of successive stimuli produce temporally distinct responses in some cells. (Lower) In most cells, the response to the first stimulus merges with the response to the second. Note that the bottom half of each graph shows the effect of reversing the timing of the stimulus orientation, i.e., the top shows S_o then S_{+22}, while the bottom half shows S_{+22} preceding S_o, where S_o is the optimal orientation and S_{+22} is 22 degrees rotated away from optimum. (Adapted from Yao et al., 2004, copyright 2004 National Academy of Sciences, U.S.A.).

(C) Effect of consecutive pairs of intervals on the direction of plasticity. (Left) The top trace represents the timing of the presynaptic spike and the lower the postsynaptic spike. The first interval t_1 represents post before pre, and would on its own lead to LTD, but the second interval t_2 would normally lead to LTP. The experimentally observed result is that these intervals produce LTD (lower trace). (Right) Reversing the contingencies so that t_1 is pre before post, changes the direction of plasticity despite t_2 being a depressing interval. (Adapted by permission from MacMillan Publishers LTD: Nature, Froemke and Dan, 2002).

whisker that principally projects to the barrel column causes the layer IV neurons to fire action potentials a few milliseconds after the layer II neurons, a condition that if replicated in an in vitro slice preparation of somatosensory cortex causes LTD. So, for the somatosensory cortex, there is a good deal of correlation between the effect of STDP at the cellular level and the systems level. The effect of whisker deprivation is not only to cause firing patterns that would cause STDP in vitro but also to occlude and mimic the effects of those forms of STDP in vitro.

The types of firing patterns that occur in somatosensory cortex are typically briefer than those that occur in the visual system. So, while it is plausible that barrel cortex neurons can decode the timing of pre- and postsynaptic spikes to produce the appropriate plasticity, it is not immediately clear how visual cortical neurons can do the same, as they tend to fire long trains of spikes in response to even a brief visual stimulus. This effect is exacerbated by the fact that most visual cortical neurons respond preferentially to moving stimuli, which would naturally tend to produce time lags across neighboring retinotopic cortical columns without necessarily requiring plastic changes. Is it then feasible that spike timing is involved here, or is perhaps a rate code for plasticity more likely?

A number of recent studies suggest that STDP could indeed be involved in some forms of visual cortical plasticity. For example, stimulating the cortex 65 ms after presenting a brief orthogonally oriented visual stimulus increased the response to the paired orientation (Schuett et al., 2001). Furthermore, shifts in the orientation tuning of visual cortical cells can be produced by presenting the stimulus orientation to be conditioned closely before the optimal orientation. The conditioned stimulus may be 15 degrees of rotation off the optimal stimulus and initially fire the cell somewhat variably. The second stimulus in the pair is optimal and therefore fires the cell reliably. The time delay of some 8 ms between stimuli has been found to cause a shift of the optimal orientation toward the conditioned orientation when the pairing is repeated 1600 times (Yao et al.,

2004). The shift in orientation can be mapped not only by presenting stimuli to the eye used for conditioning but also through the other eye, which suggests that the effect must be cortical in origin, as this is the first stage in the visual pathway for binocular effects. These types of stimulus cause a temporally discrete neuronal response in some cells, so that the response to the first stimulus finishes before the second. However, in the majority of cells, the temporal precision of the response is insufficient and the two responses merge (Figure 5B).

To understand fully which spike patterns are set up by this form of stimulation one would need to know the firing patterns of the cells projecting to the cortical cells produced by these stimuli, which is intrinsically difficult to ascertain if they are distributed within the geniculate nucleus (according to the Hubel and Wiesel model of orientation tuning [Hubel and Wiesel, 1962]). On the other hand, if they are located in the cortex, the problem may be tractable. In studies where direct cortical stimuli are paired with visual stimuli to alter orientation preference, the effect is transferable from one eye to the other, demonstrating that intracortical pathways can undergo this form of plasticity (Schuett et al., 2001). Furthermore, plasticity effects occurred in extragranular layers rather than layer IV, suggesting that thalamocortical inputs may be less plastic for this type of input activity.

Given the lack of temporal precision in the first and second response of the postsynaptic cell, it is likely that the presynaptic cells produce trains of spikes to the conditioning stimulus which therefore produce some spikes before the postsynaptic cell (potentially producing potentiation by a STDP rule) and some after (potentially causing depression). Therefore, the question arises of whether an STDP rule could cause the changes in receptive field seen in the visual cortex. In a modeling study that looked at the orientation tuning of cortical cells receiving modifiable intracortical connections, it was found that STDP plasticity could account for shifts in orientation tuning driven by stimuli oriented 15 degrees apart separated in time by 8 ms (Shen et al., 2005). It was found that despite their temporal overlap the asymmetry in the spike times caused by the time lag was sufficient to drive plasticity toward the conditioning stimulus. This model takes all pairs of spikes into account equally in the STDP modification rule. Some spike pairs will cause depression and others potentiation, but overall the time lag causes potentiation to dominate.

A slightly different conclusion was reached by Froemke and Dan (2002) when they investigated the effects of simple spike trains on STDP in vitro in visual cortex. Starting with one presynaptic spike and two postsynaptic spikes, they found that the first spike pair caused a dominant effect over subsequent spike-pair timings (Figure 5C). So, for example, if a postsynaptic spike preceded a presynaptic spike, depression would ensue even if a second postsynaptic spike occurred directly after the presynaptic spike. The effect could be modeled by a STDP modification rule plus a suppression function that followed the preceding spike in each neuron and suppressed plasticity most just after it occurred (Froemke and Dan, 2002). Spike responses to natural stimuli were also recorded in visual cortex in vivo and played into pairs of neurons recorded in vitro. The responses were recorded from two cells with spatially overlapping receptive fields. It was found that the natural spike trains could cause STDP in vitro but that the strength of connection that resulted was predicted more accurately by a model that assumed that the first spike in a train was dominant in controlling the direction of synaptic change.

A number of conclusions and, perhaps inevitably, fresh questions arise from these studies. First, it appears that STDP can account for receptive field plasticity in vivo in both the somatosensory system and the visual system despite the very different temporal precision of the two systems. The case for STDP is stronger for the somatosensory cortex at present because the sensory deprivation that drives experience-dependent plasticity in vivo simultaneously occludes the same direction of STDP in vitro, which has not yet been demonstrated for the visual cortex. However, in the visual cortex, low-frequency induction of LTD is affected by MD (Heynen et al., 2003). Second, questions remain both for experimenters studying the basic cellular mechanisms underlying STDP and those studying the applicability of STDP at the systems level. The cellular mechanism underlying the very tight time window involved in STDP is not properly understood. The time dependence of the mechanism is shorter than the duration of the NMDA-receptor currents, for example. However, there is evidence for surpralinear calcium signals in spines during depolarization by back propagating, which may be involved in restricting the time dependence (Waters et al., 2003). Third, the suppression mechanism proposed by Froemke and Dan (2002) that allows the first spike in a train to dominate is not understood. A number of possibilities exist, including a refractory period for postsynaptic molecules involved in the signaling and expression of plasticity. Fourth, at the systems level, a question that remains is whether it is possible to modify spike timing in a controlled manner and observe a predictable effect on the experience-dependent plasticity. Some experimenters have looked at the effect of stimulus timing on production of binocular cells in the visual cortex in the past (for example, Altmann et al., 1987), but the experiments have not been designed with the narrow time constraints of STDP in mind.

Key Molecular Pathways Involved in Plasticity

The molecular mechanisms driven by STDP and perhaps other forms of neuronal activity have been the subject of intense investigation for a number of years. Recently, studies on this topic have begun to make progress in linking the mechanisms discovered at the cellular level to those driven in the whole animal by altered experience. There is little doubt that kinases and phosphatases are among the most important controls on the early signaling processes. Here we review progress on the role of PKA and CaMKII in visual and somatosensory plasticity first and then further discuss new evidence implicating tPA in the mediation of structural changes.

MD during the critical period leads to a decreased response of visual cortical neurons to the closed eye. LTD is a candidate mechanism for decreasing synaptic transmission, and while structural changes clearly result from MD (Antonini and Stryker, 1993), it is at least likely that structural changes are preceded by earlier synaptic

changes that either cause them or run in parallel with them. Many of the earliest changes that occur during synaptic plasticity are mediated by kinases and phosphatases. Indeed, in a recent screen of gene regulation, kinases and phosphatases were conspicuously upregulated during the critical period for MD (Ossipow et al., 2004).

It has been demonstrated that MD causes a modest but significant 10%–12% decrease in the level of phosphorylation of the S-845 site on the AMPA channel (Heynen et al., 2003). It is known that LTD induced by low-frequency stimulation also causes the same dephosphorylation effect, implying that MD sets in motion the same mechanisms operated on by low-frequency stimulation in vitro. Further evidence in favor of this hypothesis comes from occlusion experiments. In the same way that whisker deprivation occludes LTD in the barrel cortex, it has been shown that MD also occludes LTD in the visual cortex (Heynen et al., 2003). These studies imply an important role for phosphatases in LTD and experience-dependent depression. It is therefore of interest that the Ca^{2+}/calmodulin-induced phosphatase calcineurin can be overexpressed in the visual cortex in a manner that prevents ocular dominance plasticity in this structure (Yang et al., 2005). Together with the data from Heynen et al. (2003) this might lead to the conclusion that calcineurin was required for dephosphorylation of the PKA site on the AMPA channel, a point that has not been explicitly tested as yet. The effect of calcineurin overexpression might also then lead to a decrease in cortical LTD. One further point that is not yet clear is whether calcineurin normally acts in the PSD where the AMPA receptor is located, as PP1 appears to be the dominant phosphatase in this subsynaptic location (Lisman et al., 2002; Strack et al., 1997).

It has recently been shown that PKA is required for ocular dominance plasticity and LTD in the visual cortex. In studies where the RII-β subunit of PKA is knocked out (and therefore presumably replaced in the holoenzyme by one of the other three regulatory subunit isoforms), LTD induced by low-frequency stimulation is lost in layers II/III of visual cortex, and ocular dominance plasticity is practically absent (Fischer et al., 2004). The effect is specific to the RII-β isoform because knocking out RII-α has no effect on LTD (Rao et al., 2004) nor RI-β on ocular dominance plasticity (Hensch et al., 1998). The property that makes RII-β remains to be determined but could depend on its ability to associate with postsynaptic density proteins AKAPs and Yotiao.

It might seem contradictory that PKA activity is necessary for LTD and ocular dominance plasticity in the visual cortex when evidence exists for a role of dephosphorylation of the AMPA channel at the PKA phosphorylation site. However, since RII-β is missing in the knockout throughout development, it is possible that the S-845 site is not adequately phosphorylated by PKA prior to MD and therefore dephosphorylation during MD is not possible. One way to test this would be to measure GluR-1 S845 phosphorylation in the RII-β KOs.

In the somatosensory system, more studies exist on the role of α-CaMKII in experience-dependent plasticity than PKA at present. It has been known for some time that α-CaMKII is required for experience-dependent plasticity induced whisker deprivation (Glazewski et al., 1996). It has recently become clear that this requires α-CaMKII autophosphorylation at the T286 site and specifically affects potentiation processes and not depression. One of the advantages of studying experience-dependent plasticity in the barrel system is that depression and potentiation mechanisms can be distinguished relatively easily because they occur for different whisker inputs into the deprived barrels. The deprived and spared barrels can be distinguished relatively easily because the barrel pattern precisely matches the whisker pattern. In this way, it can be shown that the spared whisker potentiation that normally occurs in the barrels deprived of their principal whisker input is absent in animals in which the T286 site is mutated to an alanine and therefore cannot be phosphorylated (Glazewski et al., 2000).

It has also been shown that the way the mutation affects plasticity is by preventing potentiation of EPSPs in the barrel cortex. When field EPSPs (fEPSPs) are recorded in the deprived barrels, the spared whisker inputs show potentiated fEPSP in whisker-deprived animals. In contrast, there is no potentiation of fEPSPs in CaMKII-t286a point mutants (Hardingham et al., 2003). LTP is also abolished by the same mutation in the layer IV-II/III pathway between barrel columns, suggesting that synaptic potentiation may well underlie the experience-dependent mutation driven by whisker deprivation (Hardingham et al., 2003). This is consistent with the finding that LTP is affected in visual cortex if α-CaMKII is knocked out (Kirkwood et al., 1997).

Earlier studies in the visual cortex have concluded that MD in α-CaMKII knockouts was partly blocked in some animals and more completely in others (Gordon et al., 1996). Given that CaMKII mutations affect potentiation rather than depression (Fox et al., 1996a; Glazewski et al., 2000) and given the prominent role of depression mechanisms in MD, this suggests that potentiation processes may have been abolished in the visual cortex and that the residual plasticity measured as an ocular dominance shift was due to depression mechanisms. The two components of experience-dependent plasticity are not as easy to distinguish in visual cortex compared to somatosensory cortex, although it can be done by chronic recording or by reverse-suture studies (Gordon and Stryker, 1996), which could resolve this question.

In conclusion, recent studies have revealed a degree of consensus on some of the signaling molecules that occur early in the pathways that lead to synaptic plasticity in the somatosensory and visual cortex. It is now clear that phosphorylation and dephosphorylation events play an important role in controlling the early stages of synaptic plasticity and experience-dependent plasticity and that one of their main sites of action are the subunits of the AMPA channels.

A question that remains for the future is how these early changes in synaptic plasticity are related to the structural changes that occur during plasticity. One possibility is that mechanisms controlling the efficacy of synaptic transmission play a role in selection of synapses that, as a population, are forming and retracting all the time. One indication of the potential turnover of synapses is spine motility. Spine motility may in turn be affected by a variety of factors, including the composition of the ECM. As discussed earlier, it is of interest

that recent studies have implicated tPA in experience-dependent plasticity in the visual system. tPA is upregulated rapidly by MD during the critical period (Mataga et al., 2004), coinciding with an increase in spine dynamics produced by MD (Oray et al., 2004). The net effect of a short period of MD is loss of spines overall (Mataga et al., 2004). Therefore, tPA may modify the ECM to allow increased spine motility, and the rapid plasticity mechanisms discussed above then allow reselection of synapses; in the case of short-term MD, synaptic depression would on average lead to loss of synapses. In favor of this idea, the spine loss associated with MD does not occur in tPA KO mice (Mataga et al., 2004), and plasticity is reduced in the same animals (Mataga et al., 2002). A further action of tPA is to cleave proBDNF to the mature form of BDNF, which is also known to affect spine density and dendrite morphology (Ji et al., 2005; McAllister et al., 1995). It remains to be determined which mechanism, if either, has the predominant effect on cortical plasticity or whether they act as part of a single synergistic mechanism.

Conclusions and Future Directions

One of the major advances in the work on plasticity during the past few years has been the ability to study the structural changes that accompany various forms of development and plasticity. In particular, the ability to view the same spines and dendrites over a period of time has lead us to a far more dynamic view of synaptic behavior in the developing and adult brain. At present it is not entirely clear what some of the measures of spine behavior might mean; for example, what is the significance of an increase or decrease in spine motility? The fact that spine motility is greatest during synaptogenesis is consistent, however, with the idea that spines protract and retract as they search for presynaptic partners. The spike-timing plasticity and molecular mechanisms associated with potentiation and depression we describe above may then be important for selecting which synapses persist and which are eliminated. While this view is consistent with the evidence, it will be important to test this idea more directly in the future. One of the technical advances that will be important in this endeavor is to be able to see the presynaptic terminals as well as the spines.

Another advance we have noted is a start on defining the molecular pathways involved in translating changes in neuronal activity into changes in structure. We have reviewed some of the recent work on tPA in this regard. It is likely that the list of factors and the molecules controlling structure will grow in the near future, given our past experience with factors controlling synaptic potentiation and depression.

We have compared plasticity in the visual and somatosensory systems and found a number of similarities. Perhaps this is not so surprising, because the plasticity in both systems relies on properties at the cellular level that are similar in both systems. However, the type of activity driving plasticity in the two systems is somewhat different, and it is therefore surprising that evidence on STDP is consistent with a role in plasticity in both visual and somatosensory cortex. Finding similarities across systems and even between different levels in the same pathway is important, as it gives us insights into general principles, in this case, of development and plasticity. The similarities between somatosensory and visual cortex we have described here include the critical period for depression, the persistence of potentiation mechanisms in adults, the slower time course of potentiation, greater spine motility during synaptogenesis, and changes in spine motility following sensory deprivation. Given the recent progress, it is likely that we can anticipate a unified theory of development and plasticity in the near future.

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