95 Mechanisms of Visual Cortex Plasticity during Development

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A prominent feature of the mammalian visual cortex is that its proper development requires visual experience, and that development of its synapses, neurons, and circuits is highly influenced by electrical activity. This makes the visual cortex an attractive model system for studying the role of sensory experience in refining cortical circuits and function. Ocular dominance (OD) plasticity is a classic form of experience-dependent plasticity that refers to changes in visual cortical circuitry due to unbalanced inputs from the two eyes. Hubel and Wiesel first demonstrated almost 50 years ago that altering visual inputs from one eye by eyelid closure during development changes responses of cells located in the primary visual cortex (V1) of cats; responses to the deprived (closed) eye are weakened while responses to the nondeprived (open) eye are strengthened (Wiesel & Hubel, 1963). This paradigm, called monocular deprivation (MD), induces OD plasticity during a specific developmental time window termed the critical period (Gordon & Stryker, 1996; Hubel & Wiesel, 1970). In rodents, however, the definition of the critical period is controversial due to the observation that plasticity still exists outside a classically defined developmental window, leading to a consensus view of the critical period as a particularly sensitive period of development during which even a brief alteration in visual experience induces significant cortical plasticity. In recent decades, many discoveries have revealed a surprisingly rich variety of molecular and cellular mechanisms that underlie OD plasticity, which have, somewhat surprisingly, propelled an understanding of mechanisms underlying a variety of developmental brain disorders. The purpose of this review is to organize these findings into a coherent conceptual framework and suggest areas of further research.

TWO ASPECTS OF PLASTICITY: FEEDFORWARD (HEBBIAN) AND FEEDBACK (HOMEOSTATIC)

The V1 of rodents contains a binocular region that receives inputs from both eyes, with the contralateral eye providing a much greater number and larger extent of projections compared to the ipsilateral eye, leading to a contralateral bias in visual responses. Various recording techniques, such as visually evoked potentials (VEPs), intrinsic signal optical imaging, single-unit recording, and two-photon calcium imaging, have been employed to measure OD plasticity of single neurons and neuronal populations—importantly from the contralateral toward the ipsilateral eye following MD of the contralateral eye. Strengthening and weakening of responses from each eye are measured according to the technique used; for example, VEP recordings measure summed synaptic currents of thalamocortical input to layer 4 while optical and calcium imaging are limited to layer 2/3 neurons located less than 500 μm of the cortical surface and measure intrinsic activities of a population of cells or calcium transients in single cells, respectively (Smith, Heynen & Bear, 2009). Using these techniques, it is now clear that a shift in OD is observed after brief (3 days of) MD, which is mediated by weakening of deprived-eye responses whereas a longer duration (5–7 days) of MD induces an additional OD shift due to strengthening of open-eye responses (Frenkel & Bear, 2004; Kaneko et al., 2008). The framework of feedforward and feedback regulation was developed to understand these two components of plasticity, namely the initial weakening of deprived-eye responses and later strengthening of open-eye responses, respectively (Tropea, Van Wart, & Sur, 2009b). It is suggested that feedforward regulation is mediated by synapse-specific Hebbian forms of plasticity while feedback regulation is mediated by cell-wide global homeostatic mechanisms, which together comprise mechanisms underlying OD plasticity (see figure 95.1).

MECHANISMS OF FEEDFORWARD PLASTICITY

The idea that the initial weakening of deprived-eye responses is mediated by Hebbian, feedforward plasticity comes from the observation that molecular and cellular changes of the deprived eye follow mechanisms similar to homosynaptic long-term depression (LTD), which is induced by decorrelated firing of pre- and

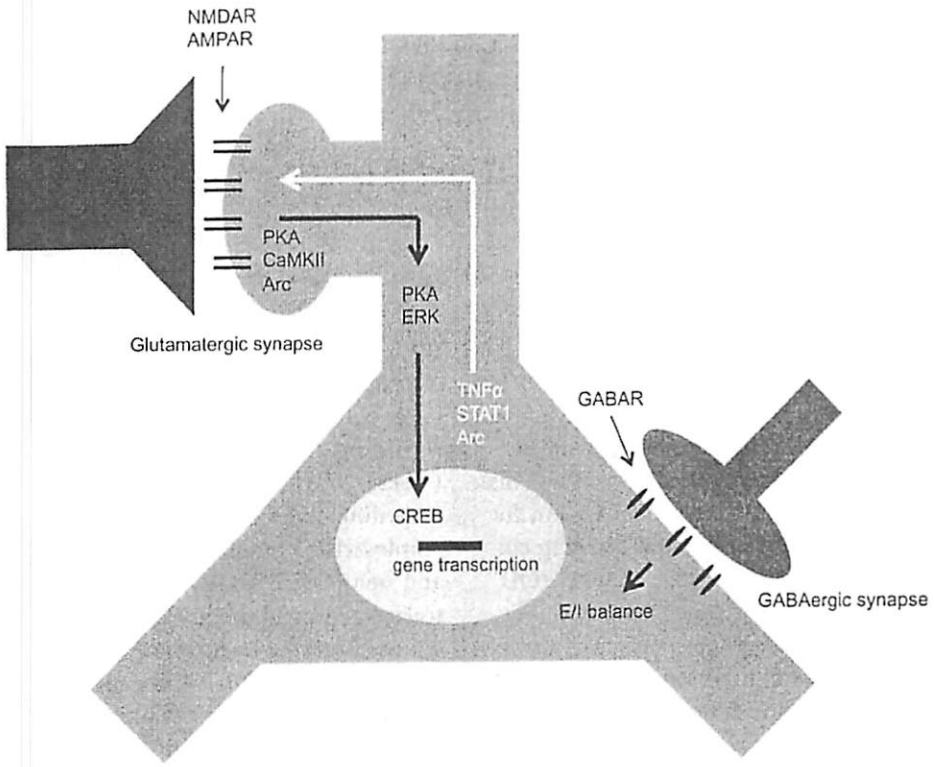

FIGURE 95.1 Schematic of key intracellular molecules that mediate feedforward and feedback plasticity in visual cortex. A pyramidal neuron (middle) receives inputs from an excitatory neuron through a glutamatergic synapse (top left) and from an inhibitory neuron through a gamma-aminobutyric acid-releasing (GABAergic) synapse (bottom right). Feedforward plasticity is shown with thick black arrows; following brief monocular deprivation (MD), *N*-methyl-D-aspartate receptor (NMDAR) activation leads to activation of intracellular kinases such as calcium/calmodulin-dependent protein kinase II (CaMKII), protein kinase A (PKA), and extracellular signal-regulated kinase 1,2 (ERK). PKA may regulate glutamate receptor function at synaptic sites and, together with ERK, also leads to cyclic AMP response element (CRE) mediated gene transcription through CRE-binding protein (CREB). An immediate-early gene, Arc, mediates weakening of deprived-eye responses through alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) internalization at synaptic sites. A balance between excitation (E) and inhibition (I) is maintained at a proper level through modulation of inhibition at GABAergic synaptic sites. Feedback plasticity is shown with a white arrow; following longer duration of MD, molecules of the classic immune system such as tumor necrosis factor alpha (TNF-alpha) and STAT1 regulate strengthening of open-eye responses, possibly through synaptic scaling and increased AMPAR trafficking. Arc may enhance open-eye responses through NMDAR-dependent long-term potentiation and/or synaptic scaling.

postsynaptic neurons leading to synaptic weakening. Brief MD has been reported to induce homosynaptic LTD in visual cortex (Heynen et al., 2003). Several studies have demonstrated involvement of similar molecular machinery as LTD in feedforward plasticity, including requirement for *N*-methyl-D-aspartate receptors (NMDARs) and activation of intracellular calcium signaling. Maintaining a proper balance between excitation and inhibition is a crucial factor in initiating and terminating critical period plasticity, which importantly involves modulation of inhibition. Finally, functional changes in deprived-eye responses are accompanied by structural changes in dendritic spines.

Changes in NMDA Receptor Subunit

Modulation of excitatory synaptic drive takes place partly through changes in glutamate receptors such as NMDARs. Several lines of evidence suggest that changes in the composition of NR2A and NR2B subunits of NMDARs are influenced by visual experience during postnatal development. For example, rearing rodents in darkness decreases the level of NR2A and/or increases the level of NR2B depending on the duration of dark rearing, leading to a reduction in the ratio of NR2A/NR2B subunits (Chen & Bear, 2007). This reduction in the NR2A/2B ratio, which normally transitions

from low to high during development (Quinlan, Olstein, & Bear, 1999), may serve as a condition for OD plasticity to occur even during adulthood (He, Hodos, & Quinlan, 2006). NR2A subunits have a reduced calcium influx and shorter NMDA-mediated synaptic currents, while NR2B subunits have high calcium permeability and thus appear to enhance plasticity (Flint et al., 1997). The reduction in the NR2A/2B ratio may be permissive for strengthening open-eye responses since there is a significant reduction in the ratio following 5–7 days (later, homeostatic component) of MD (Chen & Bear, 2007). Taken together, these studies suggest that developmental and experience-dependent changes in NMDA-mediated excitatory transmission can regulate the capacity for OD plasticity.

Intracellular Signaling: PKA, ERK, CREB

NMDAR-dependent LTD in the hippocampus is associated with dephosphorylation of the GluA1 (GluR1) subunit of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) at Ser-845, which is the phosphorylation site for the cyclic AMP (cAMP)-dependent protein kinase (protein kinase A; PKA) (Kameyama et al., 1998). Similarly in the visual cortex, MD induces synaptic depression and dephosphorylation of GluA1 at Ser-845 (Heynen et al., 2003). Moreover, pharmacological blockade of PKA inhibits OD shift in cats (Beaver et al., 2001). These results thus suggest the involvement of PKA and GluA1 in OD plasticity. Extracellular signal-regulated kinase 1,2 (ERK) is another intracellular kinase that is required for OD plasticity (Di Cristo et al., 2001). Following visual stimulation after a brief period of dark rearing, ERK, together with PKA, enhances downstream cAMP response element (CRE)-mediated gene expression (Cancedda et al., 2003). Blocking the function of CRE-binding protein (CREB), which controls CRE-mediated gene expression, prevents an OD shift (Mower et al., 2002). Interestingly, the role of CRE-mediated gene expression following MD seems unique to the open eye; CRE-mediated *lacZ* expression is mostly observed in the areas receiving inputs from the open eye but not the deprived eye in a time course of 1–3 days (Pham et al., 1999), suggesting the involvement of CRE-mediated gene expression in rapid feedback plasticity for the open eye.

Layer-Specific Mechanisms

Metabotropic glutamate receptors (mGluRs) are another type of glutamatergic receptors implicated in visual cortical plasticity (Daw, Reid, & Beaver, 1999). However, the requirement of mGluRs in LTD in visual cortex and OD plasticity depends on specific layers (Daw et al., 2004). It appears that LTD in layers 2/3 and 5 depends on NMDARs but not mGluRs while LTD in layer 6 requires mGluRs but not NMDARs (Rao & Daw, 2004). It had been long thought that the feedforward pathway into and through the V1 is mainly comprised as retina → thalamus → layer 4 → layer 2/3 (superficial layers) → layer 5/6 (deep layers) → extrastriate and subcortical structures. This notion is brought into a question by findings that support the idea that there is a parallel pathway into layer 2/3 directly from thalamus with distinct molecular requirements. For example, LTD induced in layer 2/3 requires an endocannabinoid CB1 receptor whereas LTD induced in layer 4 is independent of CB1 but instead dependent on PKA and AMPAR endocytosis (Crozier et al., 2007).

Modulation by Inhibition

Although many of the earlier findings emphasized the role of excitatory transmission mediated through glutamate receptors, there is growing evidence for the role of inhibition in OD plasticity. A minimal level of inhibition is necessary for initiation of OD plasticity during the critical period, and maturation of cortical inhibitory circuits limits plasticity in adulthood. Mice with genetic deletion of a gamma-aminobutyric acid (GABA)-synthetic enzyme (GAD65 knockout) show lack of OD shift after MD (Hensch et al., 1998). Conversely, manipulations that accelerate GABA circuit function trigger premature plasticity before the critical period (Di Cristo et al., 2007; Sugiyama et al., 2008). Brain-derived neurotrophic factor (BDNF) is a key neurotrophin that triggers maturation of inhibitory circuits, and overexpression of BDNF leads to precocious termination of the critical period for OD plasticity (Huang et al., 1999). Another molecule, Lynx1, which binds to the nicotinic acetylcholine receptor, was discovered as a crucial protein maintaining the balance between excitation and inhibition through cholinergic inhibition, without which plasticity is extended into adulthood (Morishita et al., 2010). It has become increasingly clear that a GABA-releasing (GABAergic) cell type, the parvalbumin (PV)-positive basket cell, is a key player in critical period plasticity. PV cells are the largest class of inhibitory interneuron in the cortex and comprise about 40% of the GABAergic cell population in the mouse visual cortex (Gonchar, Wang, & Burkhalter, 2007). PV cells regulate OD plasticity by sending inputs to $GABA_A$ receptor-α1 subunits in excitatory neurons (Fagiolini et al., 2004). Lynx1 colocalizes with PV cells (Morishita et al., 2010), and molecules such as BDNF and the embryonic homeoprotein Otx2 are suggested

to regulate OD plasticity by controlling the maturation of PV cells (Huang et al., 1999; Sugiyama et al., 2008).

Structural Modification

Functional changes in OD plasticity are tightly linked to structural changes at dendritic spines, which can be observed even on a time scale of hours (Yu, Majewska, & Sur, 2011). Degradation of the extracellular matrix (ECM) and increased spine motility are key components of such structural changes (Majewska & Sur, 2003). Brief MD during the critical period increases spine motility and decreases dendritic spines in layer 2/3, which are dependent on degradation of the ECM due to tissue-type plasminogen activator (tPA)/plasmin proteolytic cascade (Mataga, Mizuguchi, & Hensch, 2004; Oray, Majewska, & Sur, 2004), and an OD shift is prevented without tPA (Mataga, Nagai, & Hensch, 2002). Conversely, inducing ECM degradation with chondroitinase-ABC, which selectively degrades chondroitin sulfate proteoglycans (CSPGs) in extracellular perineuronal nets (PNNs, which are components of the ECM), restores OD plasticity in adult animals (Pizzorusso et al., 2002). Proper sulfation of CSPGs in PNNs is particularly required for the accumulation of Otx2 and maturation of PV cells, which controls the termination of the critical period (Miyata et al., 2012).

One important question is whether these structural changes occur at spines receiving input from the deprived or open eye. A recent study addressed this issue using a genetically engineered Förster resonance energy transfer probe for the detection of calcium/calmodulin-dependent protein kinase II (CaMKII) activity in identified spines in vivo (Mower et al., 2011). Brief MD specifically activates CaMKII in spines within deprived-eye regions, and spines that are eliminated receive input from the deprived eye and have low basal CaMKII activity while spines that are preserved show increased CaMKII activation following MD (Mower et al., 2011). These results not only demonstrate the deprived-eye specificity of synapse elimination but also imply a protective role for activated CaMKII against synapse loss following reduction of input drive.

MECHANISMS OF FEEDBACK PLASTICITY

The studies described above strongly suggest that Hebbian-based, feedforward plasticity and its underlying cellular and molecular mechanisms are key for one component of OD plasticity, specifically the rapid weakening of deprived-eye responses. However, several lines of evidence indicate that OD plasticity also includes homeostatic feedback regulation that leads to the later strengthening of open-eye responses; first, strengthening of open-eye responses in the mouse V1 is observed 2–3 days after weakening of deprived-eye responses (Frenkel & Bear, 2004; Kaneko et al., 2008), suggesting a homeostatic-like feedback mechanism in response to initial weakening of deprived-eye responses; and second, even cells responding to the deprived eye can strengthen their responses after longer duration of MD (Mrsic-Flogel et al., 2007), suggesting non-cell-specific, global feedback regulation. Homeostatic feedback regulation may exist to preserve a net visual drive for each neuron through mechanisms such as synaptic scaling and intrinsic excitability.

Synaptic Scaling

Homeostatic regulation is necessary to prevent neural circuits from becoming hyper- or hypoactive, without which Hebbian forms of plasticity such as long-term potentiation (LTP) and LTD could drive neuronal activity toward runaway excitation or total quiescence (Turrigiano & Nelson, 2004). The most studied mechanism for homeostatic plasticity is synaptic scaling, which was first discovered in rat visual cortical culture, where blockade of neuronal activity with tetrodotoxin (TTX) or increasing activity with bicuculline results in an increase or decrease in miniature excitatory postsynaptic currents (mEPSCs) amplitude, respectively (Turrigiano et al., 1998). Synaptic scaling induces a multiplicative change in synaptic weights across the entire neuron, such that the entire distribution of mEPSC amplitudes is scaled up or down proportionally (Turrigiano et al., 1998). Thus, synaptic scaling appears to be a global process involving all synapses in a postsynaptic neuron, which might account for feedback regulation in OD plasticity.

Indeed, 2 days of MD scale up the amplitude of mEPSCs onto monocular pyramidal neurons in a layer- and age-dependent manner (Desai et al., 2002). Scaling up of mEPSC amplitude by MD or dark rearing starts to take place at the opening of the critical period and persists throughout adulthood in layer 2/3 while mEPSCs in layer 4 pyramidal neurons can be scaled up at an earlier postnatal age P14–16 but is unaffected during the critical period (Desai et al., 2002; Goel & Lee, 2007), suggesting developmental regulation of synaptic scaling in different layers. It is also interesting to note that synaptic scaling in adult mice in layer 2/3 is not multiplicative in nature, that is, not all the synapses are scaled up (Goel & Lee, 2007). This raises an important question of whether a given postsynaptic neuron can preferentially scale one type of synapse while leaving others unaffected.

Another line of evidence that synaptic scaling underlies the homeostatic component of OD plasticity comes from studies that use genetically modified mice for a molecule that is important for synaptic scaling. Tumor necrosis factor alpha (TNF-alpha) is a proinflammatory cytokine that is released by glial cells and acts on neurons through its receptor, TNFR1 (Stellwagen et al., 2005; Stellwagen & Malenka, 2006). In optical imaging recording, mice lacking TNF-alpha show impairment in open-eye responses (i.e., no increase in the responses following 5–6 days of MD) while deprived-eye responses are left intact (i.e., normal decrease in the responses) (Kaneko et al., 2008). These mice show normal LTP in the visual cortex but lack synaptic scaling induced by activity blockade (Kaneko et al., 2008). While the downstream molecular mechanism of TNF-alpha regulation of the homeostatic component of OD plasticity is not clear, one possibility is that it occurs through increased surface insertion of the GluA1 subunit of AMPARs (Stellwagen et al., 2005).

An interesting interaction was suggested between TNF-alpha and signal transducer and activator of transcription1 (STAT1). Using optical imaging, STAT1 was found to negatively regulate the homeostatic component of OD plasticity by inhibiting TNF-alpha signaling; STAT1 knockout mice show accelerated increase of open-eye responses following 4 days of MD, which is reversed with cortical infusion of a TNF-alpha inhibitor (Nagakura et al., 2012). STAT1 might regulate OD plasticity through trafficking of AMPARs since accelerated increase of open-eye responses in STAT1 knockout mice is accompanied by increased surface levels of GluA1 AMPARs (Nagakura et al., 2012).

Scaling of Intrinsic Excitability

Relatively unexplored but potentially just as important as synaptic scaling for homeostatic OD plasticity is scaling of intrinsic excitability. Changes in intrinsic excitability affect neuronal circuit plasticity through alterations of a neuron's input–output function without changing synaptic weights (Turrigiano, 2011). In visual cortical cultures, activity blockade by TTX enhances intrinsic excitability by increasing sodium currents and lowering the threshold for action potentials, so that neurons fire more to the same synaptic input (Desai, Rutherford, & Turrigiano, 1999). Interestingly, MD by lid suture does not scale up mEPSC amplitude in layer 2/3 pyramidal neurons while intraocular activity blockade by TTX does (Desai et al., 2002; Maffei & Turrigiano, 2008). Instead, lid suture increases homeostatic plasticity through an increase in intrinsic excitability in layer 2/3 neurons (Maffei & Turrigiano, 2008). It is suggested that lid suture induces stronger decorrelation of sensory drive to cortex (Linden et al., 2009), which drives strong synaptic depression in layer 2/3 (Maffei & Turrigiano, 2008), and this depression exceeds the ability of synaptic scaling to compensate and instead triggers intrinsic homeostatic plasticity (Turrigiano, 2011). Consistently, when synaptic scaling normally takes place in layer 4, intrinsic excitability is not affected (Maffei, Nelson, & Turrigiano, 2004).

MOLECULES AND PATHWAYS THAT LINK FEEDFORWARD AND FEEDBACK PLASTICITY

Although mechanisms for feedforward and feedback plasticity appear to be distinct and seemingly independent processes, they are not totally separable. Signaling cascades inside cells and even individual molecules are likely to be involved in the coordinated regulation of feedforward and feedback plasticity. Gene expression analyses in V1 during the critical period, and following variable periods of visual deprivation, provide a comprehensive picture of cortical changes during normal development and experience-dependent plasticity. The critical period in mice is accompanied by a distinct transcriptional profile that includes a relative abundance of genes involving the actin cytoskeleton, G protein signaling, transcription, and myelination, and MD until around P28, the peak of the critical period, reverses the expression pattern of the majority of these genes (Lyckman et al., 2008), suggesting that a surprisingly large number of genes and molecules have a role in feedback regulation. Another microarray study revealed that dark rearing and MD both activate feedforward and feedback mechanisms, and MD specifically activates sets of genes that comprise molecular pathways related to growth factors and neuronal degeneration (Tropea et al., 2006). In particular, expression of a binding protein of insulin-like growth factor-1 (IGF1) is highly up-regulated after MD whereas IGF1 and components of its downstream phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway are down-regulated. Exogenous application of IGF1 up-regulates these signals and prevents OD plasticity in vivo (Tropea et al., 2006).

A good example of a single molecule that appears to coregulate feedforward and feedback plasticity is an immediate-early gene, Arc (Arg3.1). Arc has diverse roles in activity-dependent plasticity, both in Hebbian and homeostatic forms of plasticity, through regulation of AMPAR trafficking (Shepherd & Bear, 2011). A study using Arc knockout mice demonstrated that OD plasticity is completely blocked, where both deprived- and open-eye responses are unaffected following *MD*

(McCurry et al., 2010). Weakening of deprived-eye responses, measured as decreased intrinsic signal in optical imaging and synaptic depression in VEP recordings, is suggested to be blocked by the lack of a LTD-like mechanism that requires internalization of AMPARs since AMPAR internalization is impaired in these mice. The lack of subsequent strengthening of open-eye responses, that is, increased intrinsic signal and synaptic potentiation, could be due to one of two reasons, which are not mutually exclusive. Visual deprivation may cause a metaplastic adjustment of the properties of NMDAR-dependent LTP (the threshold for LTP lowered by induction of NMDAR-dependent LTD) that enables open-eye potentiation, which is impaired without Arc (McCurry et al., 2010). Alternatively, Arc may be required for strengthening of open-eye responses through mechanisms of synaptic scaling. While these possibilities are difficult to test because Arc has a role in both LTP and synaptic scaling, they point to crucial mechanisms that link multiple forms of plasticity.

Despite the plethora of protein-coding genes shown to influence OD plasticity, very little is known about the potential role of noncoding RNAs in modulating experience-dependent plasticity in the visual cortex. Noncoding RNAs are abundantly expressed in the brain and have recently emerged as novel molecular regulators of various cellular processes inside the nervous system (Qureshi & Mehler, 2011). Moreover, a type of evolutionarily conserved small noncoding RNAs, known as microRNAs (miRNAs), have already been shown to be a critical component of brain development, maturation, and synaptic plasticity (Mellios & Sur, 2012). Two pivotal studies have recently demonstrated the involvement of an activity-dependent miRNA, miR-132, in the modulation of the critical period and OD plasticity. In one study, virus-mediated inhibition of miR-132 function in the visual cortex during the critical period resulted in increases in GTPase p250GAP (Mellios et al., 2011), which is a bona fide target of miR-132 capable of inhibiting dendritic spine growth by blocking Rac activation (Vo et al., 2005; Wayman et al., 2008) (see also figure 95.2). As a result, dendritic spine number is reduced and synaptic maturation is delayed (Mellios et al., 2011). In the second study, infusion of a miR-132 mimic through an osmotic minipump resulted in an opposite shift in dendritic spine morphology toward increased maturation (Tognini et al., 2011). Intriguingly, both in vivo manipulations of miR-132 expression abrogate OD plasticity, suggesting that an optimum level of miR-132 is required to maintain the appropriate timing of synaptic maturation necessary for visual cortical plasticity. Furthermore, these findings suggest the possibility that miR-132 is important for the onset and termination of the critical period. It is known that miR-132 can interact with NMDA and neurotrophin signaling (Miller et al., 2012; Remenyi et al., 2010), and its expression can be robustly activated by CREB (Remenyi et al., 2010; Vo et al., 2005) (see also figure 95.2). Moreover, miR-132 can indirectly increase the expression of BDNF (Klein et al., 2007), a known enhancer of miR-132 transcription (Remenyi et al., 2010). Such a complex feedback loop may allow the regulation of both Hebbian and homeostatic parameters of cortical plasticity through miR-132.

PLASTICITY MECHANISMS THAT REVEAL MECHANISMS OF DEVELOPMENTAL BRAIN DISORDERS

Disorders of human brain development such as autism appear to be related significantly to abnormal development of synapses and, potentially, to abnormal plasticity of synapses and circuits. OD plasticity in mice, a classic model of how experience modifies synapses and circuits in cortex throughout development, can thus be a useful window into mechanisms of developmental brain disorders. It is particularly useful for exploring the role of genes in cortical plasticity, and mice with a deletion of a particular gene that is nonfunctional in these disorders give us an important insight into the underlying mechanisms causing developmental deficits. Mechanisms and even therapeutics emerging from understanding OD plasticity have already made a clinical impact on disorders such as Rett syndrome (RTT) and fragile X syndrome (FXS).

Rett Syndrome

RTT is a subset of autism and an X-linked neurodevelopmental disorder affecting approximately 1 in 10,000 girls, mostly caused by mutations in the gene *MECP2* encoding X-linked methyl-CpG-binding protein 2 (MeCP2) (Amir et al., 1999). MeCP2 is a transcriptional repressor involved in chromatin remodeling and modulation of RNA splicing, aberrations of which result in neuropathophysiology underlying RTT symptoms such as loss of speech, repetitive hand movements, and cognitive symptoms (Chahrour & Zoghbi, 2007). Expression of MeCP2 is regulated in a manner that correlates with neuronal maturation (Cohen et al., 2003), and mice lacking MeCP2 show RTT-like symptoms, which are rescued by postnatal expression of MeCP2 (Giacometti et al., 2007; Guy et al., 2007). This reversible feature of RTT supports the idea that neuronal circuits are not atrophic but rather remain in a labile, immature state, and activation of MeCp2 even at a later stage of the

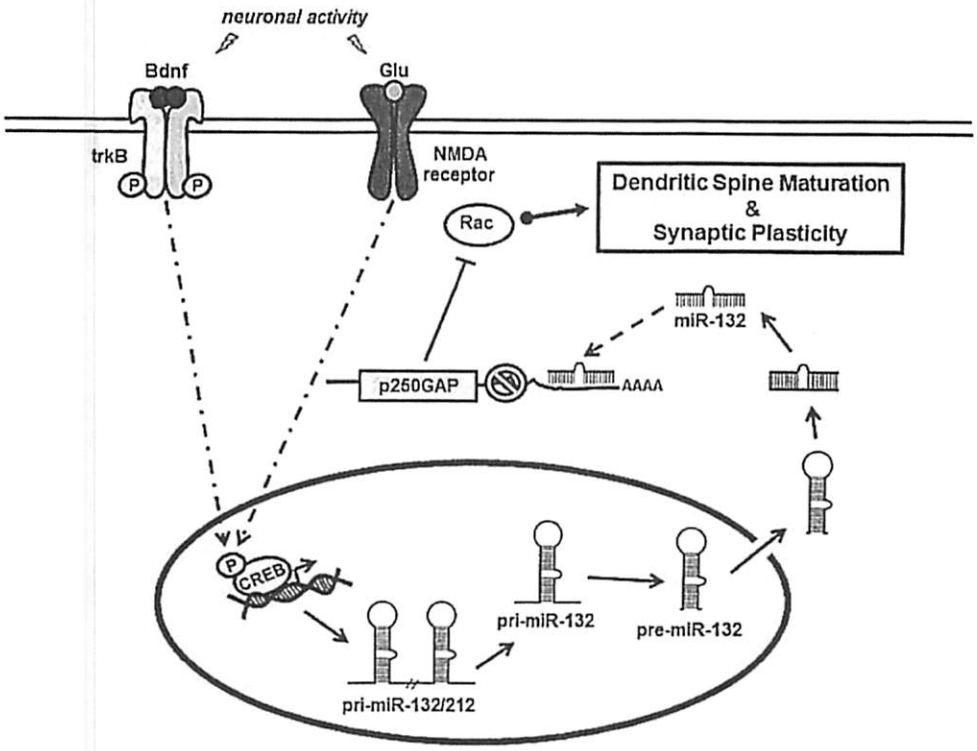

FIGURE 95.2 Neuronal activity-induced microRNA miR-132 expression regulates synaptic plasticity. Following neuronal activation, brain-derived neurotrophic factor (Bdnf) and Glutamate (Glu) activate trkB and *N*-methyl-D-aspartate (NMDA) receptors, respectively, which phosphorylate cyclic AMP response element binding protein (CREB). Phosphorylated (P) CREB then binds to the promoter of miR-132/miR-212, leading to the transcription of a multicistronic primary transcript containing both miRNAs (pri-miR-132/212). Pri-miR-132 is then cleaved to produce pre-miR-132, which translocates to the cytoplasm, where it is further cleaved to generate a miRNA duplex intermediate, which is finally unwound so as to produce mature miR-132. Mature miR-132 then inhibits its target p250GAP, by binding to its 3′ untranslated region, and p250GAP in turn inhibits Rac, a molecule known to promote dendritic spine growth and synaptic plasticity.

disorder can repair the symptoms through subsequent maturation (Tropea et al., 2009a).

MeCP2 null mice show extended OD plasticity into adulthood, presumably because of immature cortical circuits. As mentioned above, decreased IGF1 signaling is correlated with OD plasticity following MD (Tropea et al., 2006), and IGF1 application prevents the effects of MD, suggesting that IGF1 treatment might reverse the synaptic and circuit effects of MeCP2 loss in MeCP2 null mice. Indeed, systemic administration of IGF1 causes a partial to complete reversal of a wide range of symptoms in MeCP2 null mice, including improvements in organismal measures such as lifespan, breathing and heart rate, levels of signaling and synaptic molecules, and closure of the abnormally long critical period for OD plasticity in these mice (Castro et al., 2011; Tropea et al., 2009a). These studies using OD plasticity as a model for cortical maturation identify IGF1 and its molecular pathway as an attractive therapeutic target for RTT, and clinical trials treating RTT patients with IGF1 are currently ongoing.

Fragile X Syndrome

FXS is the most common form of inherited mental retardation and the leading identified cause of autism, accounting for around 4% in the autism population. FXS is caused by silencing of the gene *FMR1* that codes for the fragile X mental retardation protein (FMRP), an RNA-binding protein normally produced in response to activation of group-1 mGluRs (Belmonte & Bourgeron, 2006). *Fmr1* mutant mice exhibit acceleration of OD plasticity following 3 days of MD, suggesting excessive plasticity without FMRP (Dolen et al., 2007). This phenotype is reversed with 50% reduction in group-1 mGluR5 in these mice, indicating mGluR5 as a significant contributor for the pathogenesis of FXS (Dolen et al., 2007). In the visual cortex, group-1 mGluR signaling is highest during the critical period (Dudek & Bear, 1989), suggesting that developmental down-regulation of mGluR signaling may be important for normal synaptic and circuit maturation (Dolen & Bear, 2008). It is proposed that both mGluR5 and FMRP

regulate protein synthesis but in opposite directions; mGluR5 activation initiates protein synthesis while FMRP suppresses it, and without FMRP, mGluR5 activation leads to excessive protein synthesis that might underlie clinical features of FXS (Dolen & Bear, 2008). Treatments for FXS using antagonists to mGluR5 are also undergoing clinical trials.

CONCLUSION

Significant advances have been made in the past decades toward understanding molecular and cellular mechanisms of OD plasticity, in particular, for revealing feedforward components underlying weakening of deprived-eye responses. However, the list of potential mechanisms that impact feedback components of OD plasticity is growing rapidly as well. The importance of understanding mechanisms behind a simple but very robust form of cortical plasticity extends far beyond just OD plasticity alone, as already demonstrated by the fascinating insights these mechanisms have provided into pathological conditions that afflict normal brain development.

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