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Neuronal Activity–Regulated Gene Transcription in Synapse Development and Cognitive Function

Anne E. West¹ and Michael E. Greenberg²

¹Department of Neurobiology, Duke University Medical Center, Durham, North Carolina 27710

²Department of Neurobiology, Harvard Medical School, Boston, Massachusetts 02115

Correspondence: michael_greenberg@hms.harvard.edu



Activity-dependent plasticity of vertebrate neurons allows the brain to respond to its environment. During brain development, both spontaneous and sensory-driven neural activity are essential for instructively guiding the process of synapse development. These effects of neuronal activity are transduced in part through the concerted regulation of a set of activity-dependent transcription factors that coordinate a program of gene expression required for the formation and maturation of synapses. Here we review the cellular signaling networks that regulate the activity of transcription factors during brain development and discuss the functional roles of specific activity-regulated transcription factors in specific stages of synapse formation, refinement, and maturation. Interestingly, a number of neurodevelopmental disorders have been linked to abnormalities in activity-regulated transcriptional pathways, indicating that these signaling networks are critical for cognitive development and function.

Organismal development is not the sole province of either nature or nurture; rather it is the interactions between genes and the environment that underlie the emergence of differentiated cells, tissues, and individuals. For the vertebrate brain, which continues its maturation long after birth, the interplay between genes and environment ensures that early sensory experiences have a significant influence over the way the brain is assembled and thus can functionally impact the way the mature brain works. Using sensory information to guide brain development is an adaptive way to accommodate behaviors to the environment into which the organism happens to have been born. However, having a flexible and prolonged period of postnatal development renders the

vertebrate brain vulnerable to disruptions in the developmental program that can result in significant cognitive impairment. A substantial body of data indicates that sensory input in early life controls a program of gene expression that is essential for transducing sensory experience into long-lasting changes in brain development and function. Here we review evidence for the roles of these gene expression programs in both normal and aberrant brain development.

Transcription in Activity-Regulated Brain Development

The importance of sensory experience for brain development was elegantly demonstrated in the work of Hubel and Wiesel, who showed that

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vision shapes the synaptic organization of visual cortex during a critical period in postnatal life (Hubel 1982; Wiesel 1982). Although the gross arrangement of axonal projections from the two eyes into alternating ocular dominance columns in the visual cortex is present prior to eye opening (Crowley and Katz 2000), the boundaries of their synaptic target fields are highly dynamic and undergo refinement in the days and weeks after eye opening through a process that is sensitive to visual stimuli (Crair et al. 1998). Similar forms of activity-dependent changes in circuit wiring are found in brainstem nuclei and other sensory cortices (Foeller and Feldman 2004; Kandler 2004), and refinement of synaptic connections during development has also been observed in additional brain regions, including prefrontal cortex (Van den Heuvel and Pasterkamp 2008). These studies suggest that postnatal brain development is highly dependent on input from the environment, and they point toward synapse development as one of the key experience-dependent processes that impacts brain function.

The effects of sensory experience are manifested by the release of neurotransmitter at excitatory synapses where glutamate is the primary neurotransmitter. Glutamate released from the presynaptic terminal binds to its receptors on the postsynaptic neuron and triggers membrane depolarization of the postsynaptic neuron, leading to an activation of calcium channels followed by an influx of calcium into the cytoplasm. This increase in cytoplasmic calcium activates a program of gene expression in the nucleus (Greenberg et al. 1986; Sheng and Greenberg 1990; Corriveau et al. 1998; Lanahan and Worley 1998; Nedivi et al. 1998; Zhang et al. 2007). In addition to classic immediate-early genes (IEGs) such as *Fos* and *Jun*, which are regulated in many cell types by a broad variety of stimuli, the program of synaptic activity-regulated gene transcription includes a large number of neuronally-enriched genes whose products are critical for aspects of synapse development and function. These include the surface membrane-associated protein CPG15, which regulates dendritic arbor formation (Nedivi et al. 1998), the extracellular pentraxin

Narp, which clusters AMPA-type glutamate receptors preferentially on GABAergic interneurons (O'Brien et al. 1999; Chang et al. 2010), and the scaffolding protein Homer, which links neurotransmitter receptors with intracellular signaling pathways (Xiao et al. 2000).

The fact that genes whose products modulate synapses are subject to activity-regulated transcription strongly suggests that transcriptional regulation is a mechanism by which synaptic activity can induce long-lasting changes at synapses. This hypothesis is supported by studies from the developing cortex, where, for example, visual experience induces gene expression during critical periods in early life (Majdan and Shatz 2006; Tropea et al. 2006). Among these gene products is *Arc*, which contributes to the regulated trafficking of AMPA-type glutamate receptors at synapses (Lyford et al. 1995; Tagawa et al. 2005; Tzingounis and Nicoll 2006). Neurons in the visual cortex of *Arc* knockout (KO) mice lack monocular deprivation-induced shifts in ocular dominance (McCurry et al. 2010). Furthermore, these neurons show neither depression of synaptic connections from the visually deprived eye, nor potentiation of inputs from the open eye. These data support the idea that neuronal activity-dependent gene transcription is not only correlated with, but also directly required for, the experience-dependent synaptic changes that underlie the maturation of neural networks.

MECHANISMS OF ACTIVITY-REGULATED TRANSCRIPTION

The first evidence that extracellular signals rapidly induce gene transcription came from studies of quiescent fibroblasts, which were shown to rapidly and robustly up-regulate transcription of the IEG *Fos* when exposed to growth factors (Greenberg and Ziff 1984). The importance of stimulus-dependent regulation of IEG transcription in neuronal cells was first suggested by the observation that nerve growth factor and epidermal growth factor induce *Fos* transcription in the neuroendocrine cell line PC12 (Greenberg et al. 1985). Subsequent studies revealed that activation of nicotinic acetylcholine



or glutamate receptors leads to membrane depolarization and an opening of L-type voltage-sensitive calcium channels (L-VSCCs) thus triggering *Fos* transcription (Greenberg et al. 1986; Morgan and Curran 1986). These initial findings set the stage for a plethora of subsequent studies, which have established that calcium-signaling pathways are of central importance for synaptic activity-regulated transcription in neurons (Ghosh and Greenberg 1995). The up-regulation of *Fos* and other IEGs has been demonstrated in neurons in vivo following seizure, sensory stimulation, and a wide range of other physiologically relevant stimuli that evoke changes in neuronal firing (Hunt et al. 1987; Morgan et al. 1987; Graybiel et al. 1990; Sherin et al. 1996; Herdegen and Leah 1998; Barth et al. 2004; Velho et al. 2005).

Synapse to Nucleus Calcium Signaling

At synapses in the central nervous system (CNS), neurotransmitter reception triggers calcium influx across the plasma membrane through a number of ligand- and voltage-gated calcium channels (Sabatini et al. 2001). Intracellular calcium increases can also be induced by the release of calcium from intracellular stores, although the role of these channels in regulating neuronal transcription is not well understood (Berridge 1998). The route of calcium entry significantly influences the transcriptional consequence of a given calcium signal. For example, although calcium entering through both NMDA-type glutamate receptors (NMDA-Rs) and L-VSCCs can modulate synaptic activity-dependent gene transcription in neurons (Cole et al. 1989; Murphy et al. 1991), the source of synaptic activity and calcium entry leads to the activation of distinct intracellular signaling and transcription factor pathways (Bading et al. 1993; Lerea and McNamara 1993).

The level of free calcium in a cell is regulated by hundreds of calcium-binding proteins that are present within neurons (Clapham 2007). The differential localization of these calcium buffers and effectors near the sources of calcium entry may provide an explanation for how distinct intracellular signaling pathways can be

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activated depending on the route of calcium entry into a neuron (Deisseroth et al. 1996; Dolmetsch et al. 2001; Hardingham et al. 2001). However, in addition to cytoplasmic calcium, an elevation of nuclear calcium is required for the expression of a significant subset of activity-regulated genes, implicating local nuclear calcium effectors as well as synaptic calcium signaling proteins in this process (Dolmetsch 2003; Zhang et al. 2009). Whether signaling proteins locally activated at synapses translocate to the nucleus to regulate their targets (Meffert et al. 2003; Jordan et al. 2007), and/or whether action potentials or calcium waves carry the signal from synapse to nucleus (Adams and Dudek 2005), remains an area of active investigation. Overall, the net effect of these actions of calcium in multiple cellular compartments is to provide a robust yet selective link between synaptic stimuli and the gene transcription response.

Molecular Mechanisms of Activity-Regulated Transcription

Activity-dependent signaling pathways regulate gene transcription by modifying the function, localization, or expression of transcriptional regulators in the nucleus (West et al. 2002). In rare cases, calcium may bind directly to a transcription factor, altering its conformation and function (Carrion et al. 1999). More commonly, calcium bound to calmodulin or other calcium sensors activates any of a number of calcium-regulated intracellular signaling cascades, which include kinases of the calcium-calmodulin kinase (CaMK) and Ras/mitogen-activated protein kinase (MAPK) signaling pathways as well as the calcium-regulated phosphatase calcineurin (Bading and Greenberg 1991; Rosen et al. 1994; Deisseroth et al. 2003; Burgoyne 2007; Wayman et al. 2008b). Changes in the activity of these signaling intermediates subsequently alter posttranslational modifications on transcription factors and transcriptional coregulators (Greer and Greenberg 2008).

The most rapid activity-dependent changes in transcription are mediated by nuclear transcription factors that sit prebound and primed

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at their target gene promoters (Kim et al. 2010). Stimulus-induced posttranslational modifications of these transcription factors induce dynamic changes in protein–protein interactions that rapidly recruit RNA polymerase (Chrivia et al. 1993; Shalizi et al. 2006). A second and slower wave of stimulus-dependent transcription is mediated by factors that translocate to the nucleus following stimulation (Hogan et al. 2003; Shrum et al. 2009). These factors may require the recruitment of chromatin-modifying enzymes to their target gene promoters prior to making these genes competent for stimulus-regulated transcription (Hargreaves et al. 2009). Finally, a late wave of gene transcription is mediated by induced expression of immediate-early gene transcription factors that are targets of regulation by the rapidly modified factors (Sheng and Greenberg 1990). Complexes of these transcription factors regulate transcription of late response genes in a cell type and stimulus-specific manner depending on their differential recruitment to distinct sets of gene promoters (Hill and Treisman 1999).

In addition to the activity-dependent regulation of sequence-specific DNA-binding proteins, a growing body of evidence suggests that changes in chromatin structure play an important role in shaping the transcriptional response to neuronal activity (Crosio et al. 2000; Kumar et al. 2005; Qiu and Ghosh 2008; Ma et al. 2009; Kim et al. 2010). The basic repeating unit of chromatin is the nucleosome, which is comprised of 147bp of genomic DNA wrapped around an octamer of histone proteins (two copies each of histones H2A, H2B, H3, and H4). By modulating nucleosome position or higher-order chromatin structures, signaling pathways can change the accessibility of transcriptional regulatory elements to DNA-binding proteins, thus altering transcriptional output.

Both genomic DNA and histone proteins are targets of posttranslational modifications that can be regulated by activity-dependent signaling pathways. In mammals, genomic DNA is subject to methylation at CpG dinucleotides throughout both expressed and nonexpressed regions of the genome (Klose and Bird 2006). Although the specific mechanisms of DNA

demethylation remain controversial, a recent study describes a rapid reduction in methylation of genomic DNA at the *Bdnf* and *Fgf1* loci in postmitotic hippocampal neurons following electroconvulsive seizure, raising the possibility that DNA demethylation may contribute to transcriptional induction of these genes (Ma et al. 2009). A larger body of data implicates histone modifications in the stimulus-dependent regulation of transcription. Histones are subject to multiple posttranslational modifications (e.g., acetylation, methylation, phosphorylation) at specific residues within their flexible amino-terminal tail domains (Strahl and Allis 2000). Many of the enzymes that mediate these modifications are targets of regulation by activity-dependent signaling cascades, and in particular, increases in histone acetylation are highly correlated with transcriptional activation (Tsankova et al. 2004; Roh et al. 2005; Bernstein et al. 2007; Guan et al. 2009). Finally, neuronal activity may also regulate chromatin by modulating ATP-dependent chromatin remodeling complexes, which use the energy from ATP hydrolysis to induce nucleosome sliding, thus revealing or masking transcription factor binding sites. Regulated expression of a neural specific member of the BRG1/BRM family of chromatin remodeling factors (BAF53b) has been implicated in orchestrating the developmental changes in gene expression programs that underlie neurogenesis and dendrite outgrowth (Wu et al. 2007; Yoo et al. 2009). In addition, BRG1 has been shown to contribute to activity-dependent gene transcription through its interactions with the calcium regulated transcriptional coactivator CREST (Qiu and Ghosh 2008).

The *Fos* gene provides a useful model for understanding how the integration of these multiple activity-regulated transcriptional mechanisms at a single promoter may permit the very rapid and robust activity-dependent induction of transcription in neurons (Fig. 1). Even in the absence of neuronal activity, *Fos* is poised for activation. In quiescent cells, the *Fos* promoter is bound by the activity-regulated transcription factors CREB and SRF, histones that bear a transcriptionally permissive posttranslational

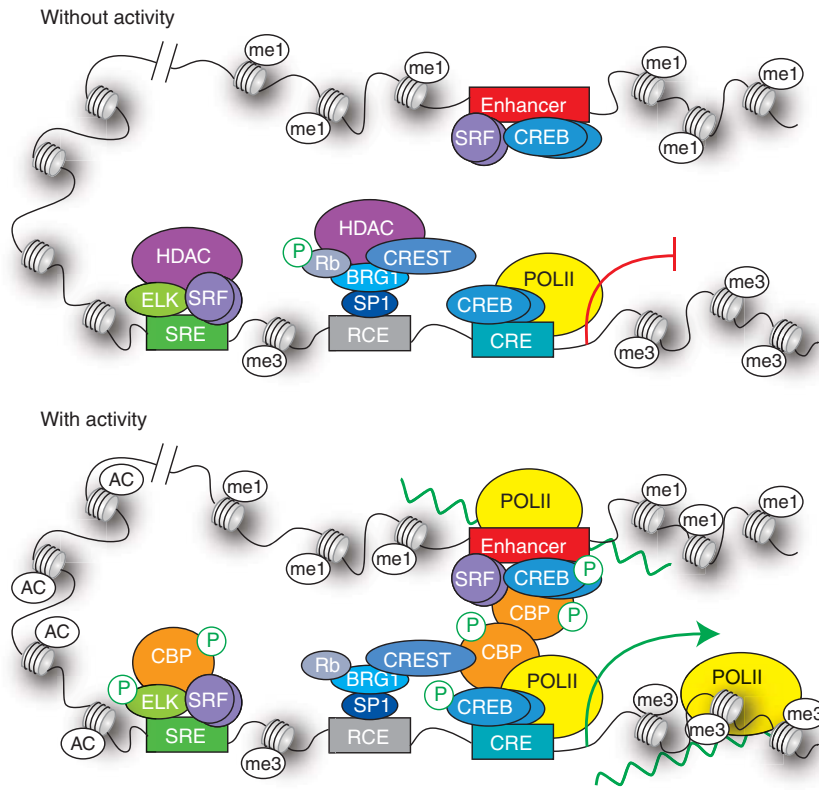


Figure 1. Mechanisms that regulate activity-dependent transcription of *Fos*. The *top* panel represents *Fos* in the absence of activity and the *bottom* panel shows *Fos* following a synaptic stimulus that activates intracellular calcium (Ca²⁺) signaling. In the absence of activity, *Fos* is primed for activation by the association of the transcriptional activators CREB with the cAMP/calcium response element (CRE) and Elk-1/SRF with the serum response element (SRE). The promoter is also bound by RNA polymerase II (POLII), and has the presence of histone H3 lysine 4 trimethylation (me3) at promoter histones. However, the gene is held in a repressed state by the presence of histone deacetylases (HDACs) recruited to Elk-1 and the Retinoblastoma (Rb)-BRG1-CREST complex, which binds the zinc-finger transcription factor Sp1 at the Retinoblastoma control element (RCE). Following activation of calcium-dependent signaling pathways, the histone acetyltransferase CBP is recruited to phosphorylated (P) CREB, inducing local histone acetylation (AC). Calcineurin-dependent dephosphorylation of Rb releases the HDACs, which are then exported from the nucleus in a phosphorylation-dependent manner. RNA polymerase II and CBP are also recruited to histone H3 lysine 4 monomethylated (me1) enhancer regions that are prebound by SRF and CREB and hypothesized to interact with the *Fos* promoter through long-distance looping. Transcription of *Fos* mRNA and of eRNAs is then induced (green wavy lines).

modification (histone H3 lysine 4 trimethylation), and the RNA polymerase II complex (Kim et al. 2010). However, the promoter is held in a repressed state as reflected by the deacetylation of promoter histones, which depends at least in part on the presence of histone deacetylases (HDACs) recruited by the Rb-BRG1-CREST corepressor complex (Qiu and Ghosh 2008). In addition, intragenic

polymerase pause sites have been identified in the *Fos* gene that may provide an additional regulatory step for the production of fully elongated *Fos* transcripts (Lamb et al. 1990; Ryser et al. 2007). Following synaptic activity, multiple calcium-regulated signaling events impact proteins at the *Fos* promoter to relieve this repression. These include (1) the phosphorylation of CREB at Ser133, which facilitates

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recruitment of the histone acetyltransferase CBP to the *Fos* promoter (Sheng et al. 1991; Chrivia et al. 1993); (2) the MAP kinase dependent phosphorylation of Elk-1, which allows Elk to act as a cofactor for SRF-dependent transcription of *Fos* (Marais et al. 1993; Xia et al. 1996); (3) the calcineurin-dependent dephosphorylation of Rb, which releases HDACs from the BRG1-CREST complex (Qiu and Ghosh 2008); and (4) the phosphorylation of the HDACs, which leads to their nuclear export (Chawla et al. 2003). Furthermore, in addition to these local events at the *Fos* promoter, membrane depolarization induces widespread recruitment of CBP and RNA polymerase II to enhancer elements that neighbor *Fos* and other activity-regulated genes (Kim et al. 2010). Similar to promoter regulatory elements, many of these enhancer elements are prebound by activity-regulated transcription factors including SRF, CREB, and MEF2, which may act to recruit CBP (Flavell et al. 2008; Kim et al. 2010). Activity-dependent RNA polymerase II recruitment to enhancers is associated with the induced expression of short noncoding enhancer RNAs (eRNAs) (Kim et al. 2010). Although the functions of eRNAs are not known, they may play a role in recruiting chromatin-modifying enzymes that maintain the chromatin landscape near activity-induced genes in a transcriptionally permissive state.

TRANSCRIPTIONAL CONTRIBUTIONS TO SYNAPSE DEVELOPMENT

Investigation of the mechanisms that mediate activity-dependent transcription of neuronal genes has led to the identification of important transcription factor targets of calcium-signaling pathways that regulate synapse development. The contributions of activity-regulated gene transcription to synapse formation have been demonstrated by disrupting the function and/or modulation of specific transcription factors using a variety of genetic techniques. Here we review this literature and summarize the important contributions of some of the best-studied transcription factors in distinct stages of synapse development.

Synapse development can be divided into roughly four epochs (Fig. 2). First, axons have to find their target cells, and dendrites need to be elaborated to provide target fields for synapse formation. Next, contact between axons and dendrites initiates a period of exuberant synapse formation. This is followed by a period of synapse elimination that refines the accuracy of circuit wiring patterns. Finally, the functional balance between excitatory and inhibitory transmission is modulated through regulation of both synapse number and function. Neuronal activity plays an instructional role at each of these stages, and specific functions of several calcium-regulated transcriptional pathways in each phase of synapse development have been elucidated.

Neurite Outgrowth

Prior to synaptogenesis, spontaneous electrical activity and electrical coupling of neurons drive intracellular calcium ion fluctuations that modulate transcriptional programs and neural development (Spitzer 2006). These calcium transients contribute to key aspects of neuronal differentiation, including neurotransmitter phenotype (Borodinsky et al. 2004), neuronal migration (Kokobu et al. 2009), axon pathfinding (Hanson and Landmesser 2004), dendrite outgrowth (Rajan and Cline 1998), and synapse maturation (Hooks and Chen 2006).

Activation of intracellular calcium signaling pathways promotes axonal and dendritic outgrowth, bringing pre- and postsynaptic partner neurons into apposition (Cline 2001; Henley and Poo 2004). Pharmacological and/or genetic inactivation of any one of several calcium-regulated phosphatases, kinases, and transcription factors can interfere with the growth-promoting effects of calcium, suggesting that multiple signaling pathways and transcription factors may contribute to different aspects of activity-dependent neurite outgrowth (Polleux et al. 2007). For example NFAT-dependent transcription is regulated by the calcium-dependent phosphatase calcineurin, which promotes translocation of NFAT from the cytoplasm to the nucleus (Hogan et al. 2003). Triple *Nfatc2/3/4*

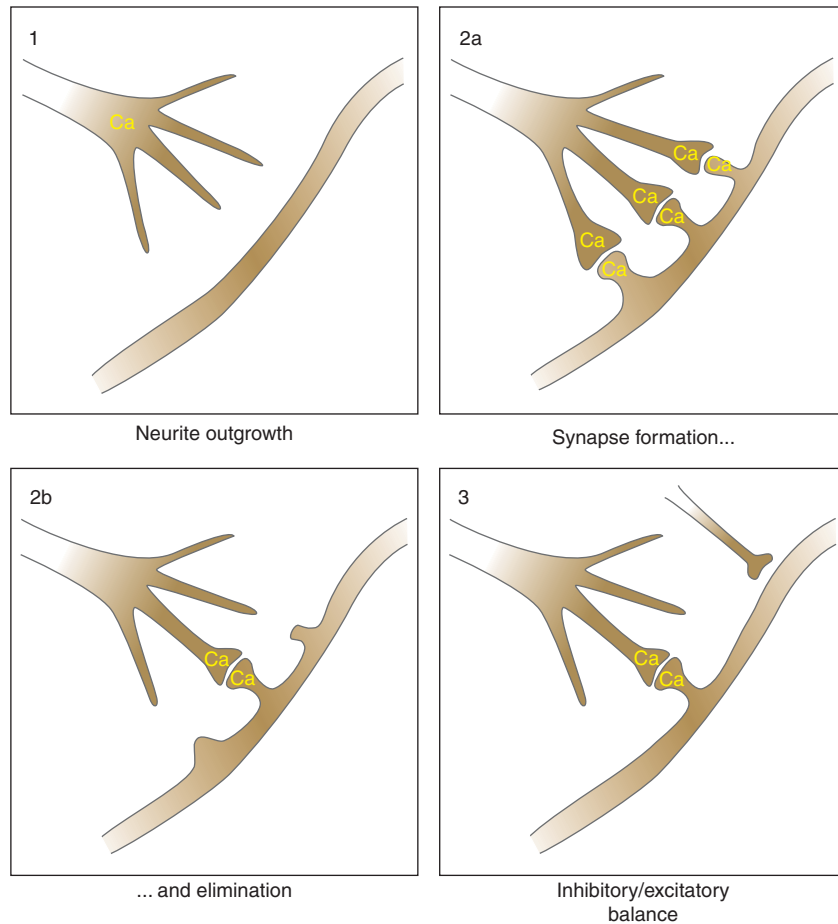


Figure 2. Activity-dependent transcription factor regulation of distinct stages in synapse development. Neurite outgrowth promotes contacts between axons (*left*) and dendrites (*right*) that define potential synaptic target fields. At some of these points of contact, actin-rich dendritic spines develop at sites opposed to axon terminals to form excitatory synapses. These synapses either stabilize and strengthen, or they are eliminated. Finally, excitatory synapses are balanced by the formation of inhibitory synapses (pictured on the dendritic shaft). Calcium signaling (Ca) is involved at each of these steps.

KO mice show severe axon pathfinding defects *in vivo* and fail to display BDNF-dependent neurite outgrowth *in vitro* (Graef et al. 2003). Other calcium-regulated transcription factors appear to have a more selective effect on dendrite outgrowth. In cerebellar granule neurons CaMKII-dependent regulation of NeuroD selectively specifies dendritic morphogenesis while having no effect on axon outgrowth (Gaudilliere et al. 2004). Dendrite development is also impaired by mutations of the calcium-regulated transcriptional coactivator CREST (Aizawa et al. 2004)

and the neural-specific BRG-family chromatin remodeling protein BAF53b (Wu et al. 2007).

At the transcriptional level, calcium-regulated pathways cooperate with activity-independent tyrosine kinase signaling pathways to integrate intrinsic and experience-guided stages of development (Takasu et al. 2002; Pfeifferberger et al. 2005). As a transcription factor that integrates the activation of multiple signaling cascades, including calcium signaling pathways, receptor tyrosine kinases, and G-protein coupled receptors, SRF is particularly well

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poised to contribute to early neural development (Knoll and Nordheim 2009). Loss-of-function studies show that SRF is essential for the regulation of neurite outgrowth. *Srf*-deficient neurons have abnormal growth cones and fail to show growth cone collapse responses to axon guidance cues including ephrins and semaphorins (Knoll et al. 2006). Mice lacking *Srf* in the developing nervous system show impairments of several actin-dependent processes including neural migration, neurite outgrowth, and axon pathfinding (Alberti et al. 2005; Knoll et al. 2006; Wickramasinghe et al. 2008). The growth cone defects of *Srf* knockout neurons are mimicked by overexpression of a dominant-interfering form of the G-actin regulated SRF cofactor Mal (Knoll et al. 2006). These data suggest that SRF is part of an actin-regulated feedback loop for the modulation of neuronal morphology during the earliest steps of axon outgrowth and neuritogenesis.

Synapse Formation and Maturation

Upon reaching their target fields, axons arborize and dendrites branch, increasing the likelihood of cell–cell contact. Many of these contacts are transient; however, a small number become stable adhesive junctions that mature into synapses (Niell et al. 2004). Stabilization of nascent synapses promotes the growth of local dendritic branches, iteratively linking synaptogenesis with dendritic arbor elaboration (Cline and Haas 2008).

Calcium signaling pathways play an important role in coordinating both the local and the cell-wide processes that mediate this stage of synapse formation. Local calcium transients in both dendritic and axonal filopodia are correlated with reduced mobility, which may allow for stabilization of contact sites (Gomez et al. 2001; Lohmann and Bonhoeffer 2008). Contemporaneous activation of calcium-regulated transcription factors triggers the induction of gene expression programs that promote dendrite growth and synaptic maturation (Redmond and Ghosh 2005). Interestingly, the two transcription factors implicated at this stage in synapse formation, NFAT and CREB, have

opposite effects on synapse number, suggesting that striking a balance between these pathways may be important for proper synaptogenesis.

To study the cell-autonomous role of post-synaptic NFAT activity in synapse formation, Schwartz and colleagues transfected *Xenopus* optic tectal neurons with either a genetically encoded calcineurin inhibitor or the peptide N-VIVIT, which is a nuclear localized peptide that blocks the association of calcineurin with its targets including NFAT (Schwartz et al. 2009). Transfected neurons showed increased dendritic branching and had an increased number of miniature excitatory postsynaptic potentials (mEPSPs), suggesting that activation of NFAT normally serves to limit both dendrite arborization and synapse formation. By contrast, CREB activity is positively coupled to excitatory synapse formation. In hippocampal neurons, activation of CaMKI or CaMKIV-dependent phosphorylation of CREB is required for the ability of membrane depolarization or NMDA-receptor activation to promote dendritic arborization (Redmond et al. 2002; Wayman et al. 2006, 2008a). Furthermore, CREB activity drives the formation and enlargement of dendritic spines, which are actin-rich protrusions of dendrites that are the sites of excitatory synapse formation onto many CNS neurons (Murphy and Segal 1997; Marie et al. 2005; Suzuki et al. 2007). One gene target of CREB that may promote spine development is the microRNA miR132, which positively regulates dendritic spine formation through its ability to modulate activity of the p250GAP-Rac1-Pak signaling cascade (Impey et al. 2010). These data suggest that calcium-regulated transcription factors coordinate synaptogenesis by co-regulating both dendrite development and synaptic maturation.

Activity-Dependent Excitatory Synapse Elimination

The sheer exuberance of synapse growth during brain development presents a challenge to the specificity of neural circuit construction. In vivo, synaptic density reaches its peak very early in postnatal life, long before brain development



is complete (Rakic et al. 1986). A key step in the refinement of synaptic connections during late stages of postnatal brain patterning is mediated by the activity-dependent elimination of synapses (Purves and Lichtman 1980).

Synapse elimination has been particularly well studied at the neuromuscular junction (NMJ), as the accessibility of these synapses to both visualization and cell type-specific genetic manipulation has facilitated molecular understanding of the elimination process (Sanes and Lichtman 2001). Initially, multiple motor neurons innervate a single muscle fiber. However, during postnatal development all but one of the motor axons lose their synapses and retract from the muscle while synapses from the single remaining axon become stronger and larger. Inhibiting neurotransmitter synthesis in the presynaptic motor neurons prevents elimination, suggesting that it is actively mediated by neurotransmission (Misgeld et al. 2002). In the brain, a similar developmental transition from multiple weak inputs to a single strong input occurs in the cerebellum for climbing fiber innervation of Purkinje cells (Rabacchi et al. 1992) and for retinal ganglion cell (RGC) innervation of neurons in the lateral geniculate nucleus (LGN) of the thalamus (Chen and Regehr 2000). At the RGC-LGN synapse, synapse elimination is initiated by spontaneous activity of the RGC neurons, whereas later stages of synapse strengthening and maintenance require sensory-driven synaptic activity (Hooks and Chen 2006). Further understanding of the molecular processes underlying the stages of synapse development may help to explain the differential role of these forms of neural activity in the refinement of synaptic connections.

Possible insight into the molecular mechanisms by which activity-dependent transcription factors may regulate synapse elimination has emerged from studies on the role of MEF2. In hippocampal neurons, genetic manipulations that decrease MEF2 expression are associated with increased numbers of glutamatergic synapses (Flavell et al. 2006; Barbosa et al. 2008), whereas conditional overexpression of a constitutively active MEF2-VP16 fusion

protein is sufficient to acutely reduce excitatory synapse number (Flavell et al. 2006). Furthermore, in granule neurons of the cerebellum, MEF2-dependent transcription negatively regulates differentiation of specialized postsynaptic structures termed dendritic claws (Shalizi et al. 2006). The ability of MEF2 to regulate synapse number in both of these neuronal types is dependent on calcium signaling pathways, suggesting that MEF2 may participate in a negative feedback loop that links synaptic activity with the control of excitatory synapse number. A genome-level analysis of the MEF2-dependent transcriptional program in hippocampal neurons identified hundreds of activity-dependent MEF2 target genes that contribute to a variety of different aspects of synaptic function (Flavell et al. 2008). Among these targets, *Arc* (Chowdhury et al. 2006) and *Homer1* stand out for their roles in regulating synaptic AMPA-type glutamate receptor content (Sala et al. 2003). Another MEF2 target gene, *Bdnf*, not only modulates the strength of both excitatory and inhibitory synapses (Poo 2001) but is also tightly linked to control of GABAergic synapse numbers (Huang et al. 1999; Hong et al. 2008). These data suggest that by coordinating the expression of a broad program of gene expression, MEF2 may regulate multiple processes at synapses that act in concert to restrict excitatory synaptic transmission.

Inhibition/Excitation Balance

In vivo, neuronal firing depends not only the strength of excitatory inputs but also on the number, location, and strength of inhibitory inputs (Mann and Paulsen 2007). The development of inhibitory synapses is sensitive to sensory experience (Morales et al. 2002), and the functional maturation of local inhibitory connections in the cortex is thought to trigger closure of the critical period of cortical plasticity (Hensch 2005). Disruption of excitatory/inhibitory balance has been associated with several developmental neuropsychiatric disorders including autism, schizophrenia, and Rett Syndrome (Rubenstein and Merzenich 2003; Levitt et al. 2004; Dani et al. 2005).

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One transcription factor that plays a role in inhibitory/excitatory synapse balance is *Npas4*. Expression of *Npas4* is robustly induced by the activation of calcium signaling pathways following membrane depolarization or synaptic NMDA-type glutamate receptor activation in vitro, and following sensory stimuli in vivo (Lin et al. 2008; Zhang et al. 2009). Acute RNAi-mediated knockdown of *Npas4* during synaptogenesis in cultured hippocampal neurons reduces GABAergic synapse numbers while overexpression of *Npas4* selectively increases GABAergic synapses (Lin et al. 2008). By contrast these manipulations have no effect on the number of glutamatergic synapses, indicating a selective role for *Npas4* in regulating GABAergic synapse development. Within intact circuits, homeostatic plasticity mechanisms compensate for changes in inhibition by inducing compensatory changes in the number or strength of excitatory synapses (Turrigiano and Nelson 2004). Consistent with role for *Npas4* in regulation of this excitatory/inhibitory balance, manipulating *Npas4* expression in a single pyramidal neuron within an organotypic hippocampal slice preparation induces a compensatory change in the number and/or strength of the excitatory connections onto the transfected cell that oppose the change in GABAergic synapse number (Lin et al. 2008). Overall these data indicate that activity-induced *Npas4* expression acts to increase inhibition, and suggest that one important function of *Npas4* is to maintain the excitation/inhibition balance in the face of changing patterns of neural activity.

Over 270 unique genes are differentially regulated by knockdown of *Npas4*, and a large percentage of these are also activity-regulated transcripts, including the gene encoding the neurotrophin BDNF (Lin et al. 2008). The identification of *Bdnf* as an *Npas4* target is of particular interest because expression of BDNF has been tightly associated with GABAergic synapse formation (Huang et al. 1999; Kohara et al. 2007; Sakata et al. 2009). Consistent with the idea that activity-dependent regulation of *Bdnf* is important for its effects on inhibition, mutation of the CREB-binding site in *Bdnf* promoter IV selectively eliminates the activity-inducible

component of *Bdnf* exon IV expression, yet still results in significantly reduced GABAergic synapse numbers (Hong et al. 2008). Notably, the transcription factor CaRF is another of the transcriptional regulators that contributes to *Bdnf* exon IV expression (Tao et al. 2002), and knock-out of this factor is also associated with selective alterations in GABAergic but not glutamatergic synapse development (McDowell et al. 2010). Taken together these data suggest that regulation of *Bdnf* may be a common mechanism for transcriptional control of GABAergic synapse numbers.

ACTIVITY-REGULATED TRANSCRIPTION IN COGNITIVE DISORDERS

A subset of cognitive disorders is characterized by symptoms that first appear during early postnatal life. These include nonsyndromic forms of mental retardation, Down syndrome, Fragile-X syndrome, Angelman syndrome, Duchenne muscular dystrophy, autism spectrum disorders, Rett syndrome, and other rare genetic diseases (Volpe 2008). At the time of birth, neurogenesis is largely complete and most axons have reached their target destinations. However, synapse formation and elimination, as well as glial proliferation and differentiation, are still ongoing and thus represent strong candidate processes to contribute to the pathogenesis of these disorders. Consistent with the evidence that activity-regulated transcriptional pathways contribute to postnatal synapse development, advances in human genetics have revealed that a subset of these disorders are caused by mutations in sequence-specific DNA-binding transcription factors, transcriptional cofactors, or the signaling pathway components that couple transcription to synaptic activity (Hong et al. 2005).

Rett Syndrome

Rett Syndrome (RTT; OMIM 312750) is a severe neurodevelopmental disorder that occurs almost exclusively in females. RTT is characterized by arrested development that is clinically apparent by 6 to 18 months of age, regression



of acquired skills, loss of speech, stereotypical hand wringing movements, microcephaly, seizures, and mental retardation (Bienvenu and Chelly 2006; Chahrour and Zoghbi 2007). More than 90% of clinically diagnosed cases of RTT are caused by loss-of-function mutations in the X-chromosome gene encoding Methyl-CpG binding protein 2 (*MECP2*) (Amir et al. 1999).

MeCP2 is an abundant, nuclear methyl-DNA-binding protein that regulates transcription by recruiting chromatin-modifying enzymes onto methylated regions of genomic DNA (Boyes and Bird 1991; Nan et al. 1998; Fuks et al. 2003; Kimura and Shiota 2003). Despite the general nature of MeCP2's DNA-binding activity and its broad tissue distribution, the deleterious effects of *MECP2* mutations in RTT are largely limited to the nervous system (Chahrour and Zoghbi 2007). MeCP2 expression is significantly higher in neurons than in other cell types, and loss of MeCP2 has selective effects on neuronal chromatin. Specifically, deficiency of MeCP2 in neurons is associated with genome-wide elevation of acetylated histone H3 and increased expression of histone H1 (Skene et al. 2010). Unlike the other histones, which are incorporated into nucleosomes, histone H1 binds to the linker DNA between nucleosomes and is thought to play a role in stabilizing the structure of chromatin fibers (Wolffe et al. 1997). If the enhanced expression of histone H1 in *Mecp2* null neurons is compensatory, this could imply that MeCP2 has a similar structural role. Nonetheless, these global chromatin changes in *Mecp2* null neurons are associated with surprisingly subtle, and potentially selective, changes in gene expression (Tudor et al. 2002; Chahrour et al. 2008; Skene et al. 2010). It is possible that even a subtle change in the amplitude or timing of gene expression in *Mecp2* mutant neurons is sufficient to disrupt functionally important and normally tightly regulated neuronal processes. One potential target of MeCP2 is BDNF. Both transcription of *Bdnf* mRNA and the secretion of BDNF protein are dysregulated in *Mecp2* null mice (Chen et al. 2003; Wang et al. 2006). Regardless of whether these changes in BDNF

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expression are causative for RTT, enhancing BDNF expression ameliorates some of the synaptic, locomotor, and respiratory symptoms in *Mecp2* mutant mice, suggesting potential for the development of future RTT therapies targeting this growth factor (Chang et al. 2006; Ogier et al. 2007; Kline et al. 2010).

Several lines of evidence suggest that defects in both synapse development and function are involved in the pathophysiology of RTT. The onset of RTT symptoms during postnatal life coincides with the peak of synapse formation (Chahrour and Zoghbi 2007). Consistent with the hypothesis that RTT arises as a disorder of development, autopsy studies have found reduced dendritic branching and increased cell packing density in RTT brains, in the absence of evidence for neurodegeneration or inflammation (Armstrong 2005). The functions of MeCP2 in synapse development have been addressed experimentally in *Mecp2* loss-of-function mouse models. Among the excitatory synaptic defects that have been detected are reductions in dendritic spine density (Belichenko et al. 2009; Tropea et al. 2009), decreased glutamatergic synapse numbers (Chao et al. 2007), decreased presynaptic glutamatergic vesicle release (Nelson et al. 2006), and reduced excitatory synaptic amplitudes (Chao et al. 2007; Dani and Nelson 2009; Tropea et al. 2009; Wood et al. 2009). Changes in the strength and/or number of GABAergic synapses have also been observed (Medrihan et al. 2008; Deng et al. 2010; Zhang et al. 2010). Although long-term potentiation and depression (LTP and LTD, respectively) can be induced in slices from *Mecp2* mutant animals (Dani and Nelson 2009), other forms of circuit plasticity are altered in the mutant mice in vivo. For example, acute monocular deprivation induces an ocular dominance shift in adult female *Mecp2* heterozygous mice long after brain maturation has closed the critical period for this form of plasticity in their wild-type littermates (Tropea et al. 2009). Interestingly, MeCP2 is rapidly phosphorylated at Ser421 in response to synaptic activity in vivo, and NMDA-receptor activation or membrane depolarization in vitro, suggesting a potential mechanism through which the

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function of MeCP2 may be directly regulated by neural activity (Zhou et al. 2006). These data raise the possibility that loss of *Mecp2* may impair the normal activity-dependent process of synapse maturation, trapping the brain in an immature state. An important corollary of these findings is the possibility that uncovering strategies to reawaken brain maturation could offer prospective therapies to treat the debilitating symptoms of RTT.

Angelman Syndrome

Angelman syndrome (AS; OMIM 105830) is a developmental disorder characterized by mental retardation, movement or balance disturbances, characteristic abnormal behaviors, and severe limitations in speech and language. Most cases are caused by maternally inherited deletions of the imprinted region on chromosome 15q11-q13, whereas paternal deletion of the same chromosomal region causes the clinically distinct Prader-Willi Syndrome (Jiang et al. 1998a). The key maternally expressed gene within this region is *Ube3a*, and failure to inherit a functional maternal *Ube3a* accounts for 85%–95% of AS cases (Matsuura et al. 1997).

Targeted genetic inactivation of *Ube3a* in mice recapitulates many of the neurological symptoms of AS, offering a model system to investigate the pathophysiology of this disorder (Jiang et al. 1998b). Mice that inherit mutant *Ube3a* through the maternal lineage show impaired motor function, audiogenic seizures, and reduced context-dependent learning (Jiang et al. 1998b). During very early postnatal development of the visual cortex, glutamatergic transmission is normal in *Ube3a* mutant mice (Yashiro et al. 2009). However after eye opening, wild type mice show a visual stimulus–dependent increase in the number of functional glutamatergic connections, whereas this change is absent in maternally deficient *Ube3a* mice (Yashiro et al. 2009). Moreover, these mice fail to show rapid ocular dominance column plasticity upon monocular deprivation (Sato and Stryker 2010). These observations suggest that activity-dependent mechanisms of

glutamatergic synaptic plasticity may be abnormal in *Ube3a* mutant mice. Consistent with this hypothesis, maternally deficient *Ube3a* mice show impairments in both LTP and LTD relative to their wild-type littermates in slice preparations from cortex and hippocampus (Jiang et al. 1998b; Yashiro et al. 2009).

Ube3a is a member of the E3 family of ubiquitin ligases, which direct the addition of ubiquitin to specific target proteins, often resulting in their degradation (Yi and Ehlers 2005). Imprinting of *Ube3a* is restricted to neurons, suggesting that the neurological selectivity of symptoms in AS may arise from abnormal turnover of neuronal proteins (Dindot et al. 2008). One target of *Ube3a*-dependent regulation that may contribute to the synaptic plasticity defects in *Ube3a* mutant mice is the AMPA-type glutamate receptor trafficking protein *Arc* (Greer et al. 2010). *Ube3a* binds and ubiquitinates *Arc*, and in the hippocampus of *Ube3a*-mutant mice, following kainate-induced seizure *Arc* protein levels are elevated relative to wild-type controls. Previous studies have shown that reducing *Arc* expression increases the surface expression of AMPA-type glutamate receptors whereas increasing *Arc* expression drives AMPA receptor endocytosis (Chowdhury et al. 2006; Rial Verde et al. 2006; Shepherd et al. 2006). Surface synaptic GluA1 expression is reduced in *Ube3a*-deficient neurons, and overexpression of *Ube3a* rescues the synaptic defects in a manner that requires its ubiquitin ligase domain (Greer et al. 2010). Synaptic GluA1 expression can be rescued in *Ube3a*-deficient neurons by RNAi-mediated knockdown of *Arc*. Interestingly, excitatory synaptic defects fail to appear in visual cortical slices made from *Ube3a* mutant mice reared in the dark a condition under which *Arc* levels would be expected to be low in both wild-type and *Ube3a*-deficient mice. By contrast, deficiencies in synaptic plasticity are rapidly induced in these *Ube3a*-mutant mice following a short period of light exposure that may trigger abnormally high levels of *Arc* induction in the absence of *Ube3a* (Yashiro et al. 2009). *Arc* transcription is robustly induced by neural activity, but notably expression of *Ube3a* is also induced by

membrane depolarization in a MEF2-dependent manner (Greer et al. 2010), facilitating increased Ube3a-mediated Arc protein degradation and thus fine-tuning the level of Arc protein. These data raise the possibility that finely tuned regulation of Arc protein levels is essential for activity-dependent synapse maturation, and that dysregulation of activity-dependent synaptic protein expression may contribute to neurodevelopmental abnormalities in AS (Fig. 3).

Autism

Autism spectrum disorders (ASD; OMIM 209850) are a collection of disorders that share the core symptom triad of limited or absent verbal communication, impaired social interactions, and restricted or repetitive behaviors and interests. There is a strong genetic component to autism and numerous loci have been linked to the disorder, some or all of which may contribute to the phenotype. The most common cytogenetic abnormality associated with autism is maternally derived duplication of chromosome 15q11-13 (Schanen 2006), a region that contains the *UBE3A* gene linked to Angelman Syndrome as described above. These data raise the possibility that synaptic regulatory pathways similar to those implicated in AS could contribute to neural circuit dysfunction in autism. However, no single gene has been pinpointed as the cause of autism in the vast majority of cases.

Like RTT and AS, the symptoms of ASDs tend to appear during early postnatal life, suggesting the hypothesis that the disorder may arise as a result of disrupted synapse development or refinement (Bourgeron 2009). Indeed several of the loci that have been linked to autism in genetic studies are known to play important roles in synaptogenesis. Rare Mendelian transmission of autism has been linked to mutations in the neuroligins *NLGN3* and *NLGN4* (Jamain et al. 2003). Neuroligins form adhesive complexes across the synaptic cleft with members of the neurexin family (Ichtchenko et al. 1995) and have been suggested by genetic studies to regulate either the number (Chih et al. 2005) or the function of synapses

(Varoqueaux et al. 2006). One of the strongest genetic associations identified for ASDs is with the *SHANK3* locus (Durand et al. 2007). Shank3 is a scaffolding protein that links together multiple components of glutamatergic synapses and is thought to be important for controlling the growth and maturation of excitatory synapses (Sheng and Kim 2000). Finally, a large genome-wide association study recently linked autism risk to single nucleotide polymorphisms near *SEMA5A*, which encodes an axon guidance molecule (Kantor et al. 2004; Weiss et al. 2009). Although the specific functions of semaphorin 5A at CNS synapses remain to be determined, other members of the semaphorin family have been implicated in control of glutamatergic and/or GABAergic synapse numbers (Paradis et al. 2007).

Additional rare inherited autosomal recessive risk alleles for ASDs have been identified by mapping regions of homozygosity in families with shared ancestry (Morrow et al. 2008). A subset of the regions linked with autism risk contain large rare inherited deletions, suggesting they could be causative mutations. Interestingly, the three genes within or closest to the two largest deletions are target genes of activity-regulated transcription factors. These genes include the uncharacterized transcript *C3orf58* and the protocadherin family member *PCDH10*, which are transcriptionally induced by membrane depolarization of cultured hippocampal neurons and are targets of regulation by MEF2 (Flavell et al. 2008). The third gene, *NHE9* (*SLC9A9*) is a sodium–hydrogen exchanger localized to recycling endosomes that has also been linked to other neuropsychiatric disorders (de Silva et al. 2003; Markunas et al. 2010). Levels of *NHE9* mRNA are not acutely altered in cultured hippocampal neurons by elevation of extracellular KCl; however, this gene may be a target of transcriptional regulation by the activity-inducible transcription factor Npas4 (Lin et al. 2008). Although the functional consequences of the mutations identified in the study of Morrow et al. remain to be tested, these data raise the possibility that disruption of activity-regulated transcription may be a pathophysiological mechanism that

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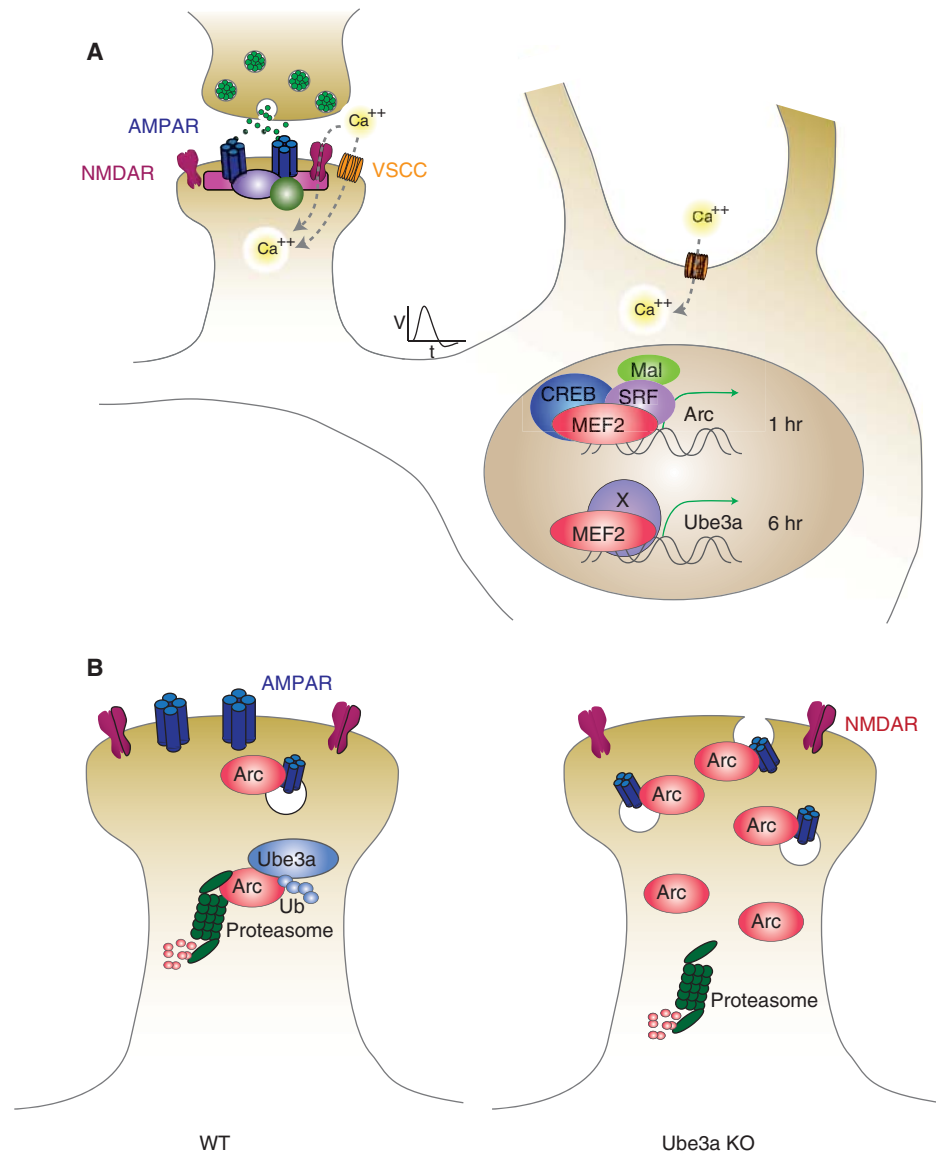


Figure 3. Ube3a/Arc-dependent dysregulation of activity-induced AMPA-type glutamate receptor trafficking in Angelman syndrome. (A) Synaptic activation of AMPA-type (AMPA) and NMDA-type (NMDAR) glutamate receptors induces the rapid MEF2-dependent transcription of *Arc* and the slower MEF2-dependent transcription of *Ube3a* in the nucleus. Transcriptional regulation of *Arc* is initiated by calcium influx through both NMDARs and voltage-sensitive calcium channels (VSCCs). This plasma membrane signal is transmitted to the nucleus through the calcium-dependent activation of multiple intracellular signaling intermediates, including the MAP kinase cascade and actin signaling pathways that subsequently modulate nuclear transcription factor function. The *Arc* promoter is coregulated by multiple activity-responsive transcription factors including MEF2, CREB, SRF, and the SRF cofactor Mal. Other transcription factors that contribute to regulation of *Ube3a* remain to be identified (X). (B) At synapses, Arc protein contributes to endocytosis of AMPA-type glutamate receptors from the cell surface. In wild-type (WT) neurons, Arc levels are kept in check by Ube3A-dependent proteosomal degradation. In *Ube3a* knockout neurons, elevated levels of Arc lead to abnormally high levels of AMPA-type glutamate receptor internalization, impairing synaptic strength.

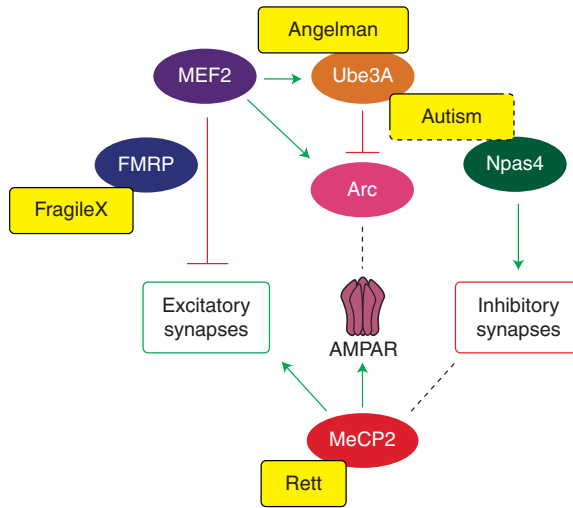


Figure 4. Model for a common activity-regulated transcriptional network underlying synapse dysfunction in neurodevelopmental diseases. The yellow boxes show four neurodevelopmental diseases associated with disrupted synapse development: Angelman syndrome, Fragile X syndrome (OMIM 300624), Rett syndrome, and autism. Each disease is shown next to a gene product implicated in disease pathogenesis. The dotted line around Autism depicts the hypothetical nature of the link between autism and Npas4 as discussed in the text. Green arrows show positive relationships between proteins or processes in the model; the red bars show inhibitory relationships. The dotted black lines indicate more complex relationships. For example Arc is implicated in endocytosis of AMPA-type glutamate receptors (AMPA) from the plasma membrane, suggesting a negative relationship between these two proteins (Chowdhury et al. 2006); however, Arc is also required for some forms of LTP (McCurry et al. 2010), during which AMPARs are added to the synapse. The dotted line between MeCP2 and inhibitory synapses represents the observation that GABAergic synapse numbers are increased in some brain regions of *Mecp2* mutant mice but decreased in others (Deng et al. 2010; Zhang et al. 2010). The ability of MEF2 overexpression to drive excitatory synapse elimination is impaired in mice lacking Fragile X mental retardation protein (FMRP) (Pfeiffer et al. 2010), suggesting a mechanistic link between the synaptic pathologies in Fragile X syndrome and the transcriptional pathways discussed here.

is common to genetically heterogeneous causes of autism.

CONCLUSIONS

A substantial body of evidence indicates that activity-regulated transcriptional networks are essential for the accurate development and maturation of synapses during postnatal life. Dysregulation of these transcriptional regulatory pathways has been associated with a number of neurodevelopmental diseases, suggesting that abnormalities of activity-regulated synapse development may be a common mechanism underlying neuropsychiatric and neurological impairments (Fig. 4). One of the striking findings is that some of these disorders appear to result in the brain being trapped in an immature

state of synaptic development, such that later interventions that reawaken the developmental program may permit improved cognition. Thus, a further understanding of the signaling networks by which experience mediates synapse development may suggest new ideas for therapies for treating these disorders.

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