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Communication Between the Synapse and the Nucleus in Neuronal Development, Plasticity, and Disease

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Abstract

Sensory experience is critical for the proper development and plasticity of the brain throughout life. Successful adaptation to the environment is necessary for the survival of an organism, and this process requires the translation of specific sensory stimuli into changes in the structure and function of relevant neural circuits. Sensory-evoked activity drives synaptic input onto neurons within these behavioral circuits, initiating membrane depolarization and calcium influx into the cytoplasm. Calcium signaling triggers the molecular mechanisms underlying neuronal adaptation, including the activity-dependent transcriptional programs that drive the synthesis of the effector molecules required for long-term changes in neuronal function. Insight into the signaling pathways between the synapse and the nucleus that translate specific stimuli into altered patterns of connectivity within a circuit provides clues as to how activity-dependent programs of gene expression are coordinated and how disruptions in this process may contribute to disorders of cognitive function.

Keywords

activity-dependent transcription; calcium; CREB; MEF2; MeCP2; Bdnf

Experience Shapes the Nervous System

Development of the brain throughout life occurs in concert with exposure to the environment. The perturbation of sensory or psychosocial experience during early childhood may result in the impairment of cognitive function or behavior, as in cases of amblyopia due to congenital cataracts or intellectual impairment following early deprivation. Interventions that limit exposure to impoverished environments and promote exposure to enriched environments can prevent or even reverse the long-term consequences of deprivation on brain development (Maurer et al. 1999, Nelson et al. 2007). Why is early experience so important to cognition? During embryonic development of the central nervous system (CNS), genetically programmed molecular cues control the proliferation, migration, and maturation of neurons, leading to the widespread formation of connections between neurons and the establishment of rudimentary neuronal circuits. Although neuronal activity is not strictly required for the early development of synaptic connections (Verhage et al. 2000), spontaneous activity within the nascent circuits provides modulatory information about the appropriateness of the synapses formed (Katz &

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Shatz 1996). As the CNS starts to receive and interpret environmental stimuli, sensory cues begin to drive synaptic activity. The discovery that blocking visual experience by monocular deprivation in cats during the critical period disrupts the development of ocular dominance columns in the visual cortex (Wiesel & Hubel 1963) suggested that this sensory-evoked neuronal activity may play a crucial role in CNS development. Since then, researchers have shown that experience modulates the cellular mechanisms that underlie the strengthening and stabilization of useful synapses and the weakening or elimination of those that are unnecessary during both postnatal development and in the adult. Thus, following an initial program of widespread synaptogenesis, neuronal activity leads to the refinement of CNS circuitry, reflecting postnatal experience and allowing continued adaptation to the environment.

Synaptic and Nuclear Roles of Activity in Neuronal Development

The initial formation of an excitatory synapse in the CNS depends on contact between the presynaptic axon and the postsynaptic dendrite, the recruitment of pre- and postsynaptic proteins to the site of contact, and stabilization of the axodendritic interaction to initiate the assembly of a functional synapse. A major class of ionotropic glutamate receptors in the CNS, the NMDA (*N*-methyl-D-aspartate) receptor, is recruited early on to the postsynaptic membrane of the nascent synapse (McAllister 2007). Coincident binding of glutamate to the NMDA receptor and postsynaptic membrane depolarization activate the channel, allowing calcium influx to initiate signals that modulate the maturation of the synapse. An important local effect of calcium influx through the NMDA receptor is to regulate the recruitment of a second major class of ionotropic glutamate receptor to the postsynaptic membrane, the AMPA (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptor (Petralia et al. 1999, Shi et al. 1999). AMPA receptors mediate fast excitatory neurotransmission in the brain, and the number of AMPA receptors at a synapse correlates with the size and maturity of the synapse, determining the relative strength of the synaptic response to glutamate stimulation (Bourne & Harris 2008).

The majority of mature glutamatergic synapses in the cortex occur on dendritic spines, actin-rich protrusions from the dendritic shaft that serve to compartmentalize postsynaptic calcium influx in response to synaptic stimulation (Alvarez & Sabatini 2007). Early postnatal development is characterized by an experience-dependent widespread net loss of spines, or pruning, that depends on NMDA receptor activation and local regulation of spine dynamics to maintain the spines of productive synapses, leading to appropriate maturation of cortical circuits (Grutzendler et al. 2002). A major determinant of synapse formation and the integration of neurons into a circuit is the pattern of dendritic arborization receiving the afferent input. As with dendritic spines, development of dendritic morphology depends on sensory-evoked neuronal activation of glutamate receptors to establish and stabilize the precise connections between pre- and postsynaptic neurons (Parrish et al. 2007).

Synaptic activation and subsequent calcium influx into the postsynaptic neuron regulate dendritic branching and outgrowth not only by acting locally at the site of calcium entry but also by inducing changes in transcription within the nucleus. Calcium influx through the NMDA receptor or voltage-sensitive calcium channels (VSCCs) during the development of dendritic arbors can activate a number of signaling pathways, including the calcium/calmodulin-dependent protein kinases (CaMKs), a diverse group of calcium-sensitive signaling enzymes implicated in neuronal function. Activated CaMKII plays an important local role in mediating AMPA receptor number and conductivity at the synapse and in regulating dendritic growth by inducing changes in the actin cytoskeleton (Dillon & Goda 2005). Calcium-dependent CaMK activity in cultured neurons also initiates signaling to the nucleus, where activation of the cAMP response element binding protein (CREB) transcription factor and the induction of gene expression contribute to activity-dependent dendritic development

(Redmond et al. 2002, Wayman et al. 2006). Mice lacking the calcium-responsive transcriptional coactivator CREST have reduced growth and branching of cortical and hippocampal dendrites and overall smaller brains, likely as a result of a specific deficit in calcium-dependent induction of dendritic arborization (Aizawa et al. 2004). Thus, both in vitro and in vivo, neuronal development depends on activity to modulate dendritic growth and morphology by local effects at the synapse and by regulation of nuclear programs of gene expression.

Synaptic and Nuclear Roles of Activity in Neuronal Plasticity

As in development, activity-induced calcium influx into mature neurons affects synaptic function by acting both at the synapse and within the nucleus. Changes in the strength of individual synapses are thought to enable information storage within neuronal circuits and to represent a cellular correlate of learning and memory. The long-term potentiation (LTP) and long-term depression (LTD) of synaptic efficacy elicited by a short period of synaptic stimulation are partially mediated by local effects at the stimulated synapse, including the incorporation or removal of AMPA receptors to modulate synaptic strength (Derkach et al. 2007) and the regulation of dendritic spine turnover (Alvarez & Sabatini 2007). This contributes to the first, immediate phase of LTP, which depends on the rapid modification of synaptic proteins and the actin cytoskeleton and results in alterations of synaptic strength that are of relatively short duration. Lasting changes in synaptic strength in late-LTP involve activity-dependent changes in gene transcription and the synthesis of effector proteins that stably alter neuronal function. These activity-dependent changes in gene expression rely on the faithful report of synaptic activity to the nucleus, coordinated control of transcription within the nucleus, and ultimately the stable alteration of synapses by the newly synthesized gene products.

The Identification of *c-fos*, CREB, and Activity-Dependent Transcriptional Regulation

The realization that extracellular stimuli trigger rapid changes in gene expression to influence cellular behavior came initially from studies of quiescent fibroblasts stimulated with growth factors to reenter the cell cycle, and subsequent studies of calcium influx into neuronal cell lines (Sheng & Greenberg 1990). Induction of the *c-fos* proto-oncogene, rapidly and without new protein synthesis, has come to define the immediate early genes (IEGs). The discovery that sensory-evoked stimuli induce *c-fos* in the CNS suggested that activity-dependent gene products may mediate adaptation of neuronal function (Hunt et al. 1987, Rusak et al. 1990), and *fos*-deficient animals indeed display deficits in synaptic plasticity and behavioral adaptations (Brown et al. 1996, Fleischmann et al. 2003, Hiroi et al. 1997). Identification of a *cis*-acting regulatory element in the *c-fos* promoter, the cAMP response element (CRE), and the transcription factor, CREB, involved in the induction of CRE-dependent transcription has led to the characterization of a prototypical signaling pathway that has yielded great insight into the mechanisms by which extracellular stimuli are transformed into changes in activity-dependent gene expression (Sheng & Greenberg 1990; Sheng et al. 1990, 1991).

Role of Activity-Dependent Gene Expression

For experience to shape the CNS, an individual neuron must process thousands of synaptic inputs and translate them into the appropriate changes in function. Synaptic activity initiates calcium-dependent signaling events that regulate the expression of a group of genes involved in various aspects of neuronal function from metabolism to synaptic function, the modulation of which allows the cell to respond to extracellular stimuli (Figure 1). In-depth study of several

such genes in the CNS, including *c-fos* (see side bar) and *brain derived neurotrophic factor* (*bdnf*) (see below), has yielded insight into the signaling pathways, transcriptional effectors, and activity-dependent gene products important for experience-dependent neuronal development and plasticity. As the mechanisms underlying neuronal adaptation have become better understood, mutations in many of the molecules involved in activity-dependent gene regulation have been implicated in human disorders of cognitive function. Behaviors that require environmental input for development, such as verbal communication, or that depend on environmental adaptation, such as learning, are often disrupted in neurodevelopmental and psychiatric disorders, suggesting that dys-regulation of experience-dependent neuronal adaptation may contribute to the pathogenesis of these human diseases. Understanding how the synapse and nucleus communicate with one another to coordinate activity-dependent gene expression may thus provide insight into both normal development and plasticity of the brain, as well as the etiology of disorders of cognitive function.

Communication from the Synapse to the Nucleus

Because an individual neuron must process a diverse array of extracellular stimuli, received by hundreds of individual synapses, and coordinate a functional response, neuronal adaptation presents a significant signaling challenge. Since the discovery that stimulus-induced calcium influx into neuronal cell lines is required for the induction of immediate early gene (IEG) expression, the role of calcium in the biochemical transduction of signals from the synapse to the nucleus has been a topic of great interest. Neurons actively maintain low levels of intracellular calcium through the uptake of calcium into internal stores and the extrusion of calcium into the extracellular space. By thus limiting baseline calcium noise, the cell can quickly sense and respond to calcium influx. There are several possible routes of calcium entry into the cytoplasm of the postsynaptic neuron: Extracellular calcium can enter through the NMDA or AMPA glutamate receptors or through VSCCs, or calcium can be released from intracellular stores (Figure 2).

The AMPA Receptor: Calcium Signaling in Synaptic Development or Plasticity?

Recent evidence suggests that AMPA receptors may play a direct role in calcium signaling to the nucleus during CNS development and synaptic plasticity. Early in development cortical pyramidal neurons express calcium-permeable, GluR2 subunit-lacking AMPA receptors. During postnatal development these neurons undergo a switch in the subunit composition of AMPA receptors, expressing instead GluR2-containing, calcium-impermeable AMPA receptors (Kumar et al. 2002). However, even at the mature synapse, the initiation of LTP can induce the rapid and transient incorporation of GluR2-lacking AMPA receptors into activated synapses, allowing a brief period of calcium flux through the AMPA receptor before the calcium-permeable channels are replaced (Liu & Cull-Candy 2000, Plant et al. 2006). Thus, both early in development and during synaptic plasticity, calcium influx through AMPA receptors may regulate activity-dependent gene expression. Although AMPA receptors may initiate signals to the nucleus (Perkinton et al. 1999, Rao et al. 2006), whether the regulated expression of calcium-permeable AMPA receptors can drive activity-dependent changes in gene expression remains an outstanding question.

As the result of the developmental switch in AMPA receptor subunit expression, mature glutamatergic synapses in the CNS primarily express calcium-impermeable AMPA receptors (Derkach et al. 2007), and AMPA receptor activation at these synapses contributes to calcium signaling by mediating the postsynaptic membrane depolarization that is required to activate the NMDA receptor and VSCC. Thus, studies of the induction of activity-dependent gene expression have largely focused on calcium influx through the NMDA receptor and the VSCC.

The NMDA Receptor: Local and Transcriptional Responses to Activity

Calcium influx through the NMDA receptor and the subsequent initiation of signaling pathways have a well-established role in activity-dependent neuronal development and plasticity. Activation of NMDA receptors within an individual dendritic spine by glutamate and postsynaptic membrane depolarization leads to rapid, restricted accumulation of calcium within the spine, allowing for synapse-specific induction of signaling. NMDA receptors are heteromeric channels composed of NR1 and NR2 subunits, with alternative splicing of the NR1 subunit, multiple NR2 isoforms, and developmental regulation of subunit incorporation providing complex regulation of channel composition (Lau & Zukin 2007). Regulation of NMDA receptor subunit incorporation affects the kinetics of calcium influx through the channel and the cytoplasmic coupling to downstream effectors, influencing both the local and transcriptional consequences of NMDA receptor activation.

Over the course of cortical development, NR2B-containing NMDA receptors are replaced by NR2A-containing receptors that have a shortened duration of calcium influx (Carmignoto & Vicini 1992). This developmental regulation of NMDA receptor expression may have implications for synaptic adaptation to activity. Recent work suggests that early in development the presence of NR2B-containing NMDA receptors may inhibit synaptic AMPA receptor accumulation, whereas the activation of mature, NR2A-containing synapses recruits AMPA receptors to the postsynaptic membrane (Hall et al. 2007). Activity-dependent signaling to the nucleus may also be affected by the developmental regulation of the NMDA receptor subunit composition. Sensory experience in visual cortex drives age-specific programs of gene expression (Majdan & Shatz 2006), and NMDA receptor-dependent alterations in both synaptic function and calcium signaling may mediate the developmental regulation of specific activity-dependent transcriptional programs. In support of this idea, the ability of the NMDA receptor to activate the transcription factor CREB by phosphorylation of CREB at serine-133 (discussed below) depends on the age of the hippocampal neurons. Whereas NMDA stimulation in immature neurons initiates a lasting phosphorylation of CREB serine-133, stimulation of more mature cultures induces only a transient phosphorylation as the result of coincident activation of a CREB phosphatase (Sala et al. 2000). This developmental effect on CREB regulation is unique to NMDA receptor-dependent signaling; depolarization of postsynaptic membranes to induce VSCC activation does not result in such a developmental transition.

Studies of Eph receptor tyrosine kinase modulation of NMDA channel function provide further support for the conclusion that alterations in calcium influx through the NMDA receptor can directly affect activity-dependent gene expression. The EphB subfamily of receptor tyrosine kinases has been implicated in dendritic spine development both in vitro and in vivo (Pasquale 2005). During synaptic maturation in cultured cortical neurons, activation of EphB in the postsynaptic membrane by its presynaptic ligand, ephrinB, induces the extracellular association of EphB with the NR1 subunit of the NMDA receptor, promoting rapid clustering of the NMDA receptor with EphB and inducing synapse formation (Dalva et al. 2000). In the adult brain, the NR1-interacting extracellular domain of EphB is required for NMDA receptor-dependent induction of LTP and LTD, suggesting that EphB may regulate the NMDA receptor during synaptic plasticity as well as in synaptic development (Grunwald et al. 2001, Henderson et al. 2001). Although the EphB kinase domain is not required for the interaction of EphB with the NMDA receptor (Dalva et al. 2000, Grunwald et al. 2001, Henderson et al. 2001), ephrinB stimulation of EphB induces the activity of the nonreceptor tyrosine kinase Src (Grunwald et al. 2001, Takasu et al. 2002). Src-dependent tyrosine phosphorylation of the NR2B subunit of the NMDA receptor increases calcium influx through the NMDA receptor in response to glutamate activation and, as a result, leads to the upregulation of activity-dependent gene expression (Takasu et al. 2002). Although it remains possible that ephrinB/EphB-dependent

phosphorylation of the NMDA receptor also regulates its association with downstream signaling molecules, these findings suggest that changes in the magnitude of NMDA receptor-dependent calcium influx are able to modulate nuclear gene expression.

The VSCC: Activity-Dependent Regulation of Gene Expression

In neurons the dihydropyridine-sensitive L-type VSCCs (L-VSCCs), $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$, are concentrated in the basal dendrites and cell soma, where they are well-positioned to respond to the cumulative activation of many synapses and transduce calcium-regulated signaling events to the nucleus (Westenbroek et al. 1998). Indeed, although pharmacological blockade of the L-VSCCs has a relatively minor effect on the rise in cytoplasmic calcium in response to synaptic activity, blockade of L-VSCCs results in a disproportionate disruption of IEG induction (Murphy et al. 1991), consistent with a key role for the L-VSCC in the communication of synaptic activity to the nucleus (Bading et al. 1993). Mice with specific deletion of $\text{Ca}_v1.2$ L-type channels in the hippocampus and cortex display deficits in protein synthesis-dependent LTP and spatial learning tasks (Moosmang et al. 2005), suggesting a requirement for L-VSCC-dependent calcium influx in cellular and behavioral adaptation to experience.

As with the NMDA receptor, precise regulation of calcium influx through the voltage-gated calcium channel is required for appropriate CNS development and function. This is illustrated by mutations in an alternatively spliced exon of $\text{Ca}_v1.2$ that give rise to Timothy syndrome, a disorder characterized by severe cardiac arrhythmias and generalized cognitive dysfunction with autistic features (Splawski et al. 2004). The tissues affected express a $\text{Ca}_v1.2$ splice variant containing exon 8A, which has a relatively limited expression pattern in the brain. Mutation of $\text{Ca}_v1.2$ exon 8A in Timothy syndrome results in inappropriately sustained calcium currents upon channel opening and, despite its limited expression, gives rise to the phenotypes described above (Barrett & Tsien 2008, Erxleben et al. 2006, Splawski et al. 2004). A mutation affecting the same amino acid in the pore of the more widely expressed $\text{Ca}_v1.2$ exon 8 splice variant, and thus predicted to give rise to sustained calcium currents throughout the brain, was identified in individuals with severe mental retardation (Splawski et al. 2005), supporting the correlation between the expression of the dysfunctional channel and cognitive impairment. Similar mutations in the $\text{Ca}_v1.4$ pore-forming subunit of an L-type channel associated with congenital stationary night blindness also disrupt channel inactivation, giving rise to sustained calcium currents upon activation, and are likewise associated with intellectual impairment (Hemara-Wahanui et al. 2005, Hope et al. 2005, Splawski et al. 2006). That these abnormalities result from defects in the regulation of calcium influx through voltage-gated calcium channels, rather than a loss of channel expression, suggests that dysregulated activation of downstream activity-dependent gene expression may contribute to the pathogenesis of these disorders.

Input-Specific Calcium Signaling to the Nucleus

As illustrated by studies of the NMDA receptor and L-VSCC, the downstream consequences of synaptic activity are dependent on the precise regulation of calcium influx through the various channels. Moreover, the specific route of calcium entry into the postsynaptic neuron, whether through the NMDA receptor or the VSCC, can determine the effect on activity-dependent transcriptional regulation (Bading et al. 1993). How is such input-specific translation of synaptic activity accomplished? Although localized microdomains of high calcium concentration arise near the mouths of open calcium channels, neuronal activity can also trigger more widespread calcium transients throughout the neuronal cytoplasm and nucleus via the spread of membrane depolarization and the triggered release of calcium from intracellular stores.

Experimental evidence confirms that sub-membranous calcium, cytoplasmic calcium, and nuclear calcium are each capable of regulating gene expression. However, the study of calcium channel-associated complexes suggests that the physical association of signaling molecules with calcium channels is particularly important in coupling calcium influx to activity-dependent transcriptional changes. The use of calcium chelators that specifically inhibit the signaling capacities of either submembranous or cytoplasmic calcium demonstrates that local calcium influx restricted to the channel mouth can be sufficient to induce signaling to the nucleus (Deisseroth et al. 1996, Hardingham et al. 2001). As calcium ions flow through the channel into the postsynaptic cell, they encounter a complex of calcium sensors and signaling enzymes physically associated with the cytoplasmic portion of the calcium channel. The identity of the molecules within this complex determines the functional consequences of channel activation.

The cytoplasmic protein complex associated with the NMDA receptor determines both the local synaptic effects of NMDA receptor activation as well as the consequences for changes in activity-dependent gene expression. Association of the NR2 subunit of the NMDA receptor with members of the MAGUK family of scaffolding proteins localizes the receptor to the postsynaptic density (PSD) of glutamatergic synapses (Sheng & Hoogenraad 2007). Clustered within the PSD are hundreds of proteins involved in functions as diverse as neurotransmission, cell adhesion, intracellular signaling, and cytoskeletal rearrangements. The NMDA receptor associates directly or indirectly with a number of these effector molecules, many of which, such as CaMKII, are activated upon calcium influx through the NMDA receptor. As a result, the protein composition of the PSD can determine the signaling properties of the channel.

The subunit composition of the NMDA receptor itself also contributes to downstream signaling by determining which proteins can interact with the NMDA receptor cytoplasmic domain. Mice lacking the cytoplasmic C terminus of the NR2B subunit die perinatally, whereas *in vivo* loss of the NR2A C terminus results in deficits of synaptic function and behavioral defects in learning and memory (Sprengel et al. 1998), suggesting unique roles for the cytoplasmic portion of the various NR2 subunits in mediating NMDA receptor function. Likewise, alternative splicing of the NR1 subunit regulates the expression of the C1 C-terminal domain, resulting in differential effects on gene expression without altering calcium current through the channel (Bradley et al. 2006).

Regulated association with distinct signaling complexes, for instance, during CNS development or in the mature nervous system in response to sensory experience, may allow the NMDA receptor to activate specific programs of gene expression and mediate particular biological responses. Recent evidence suggests that NMDA receptor context indeed determines the transcriptional response elicited by calcium influx. The NMDA receptor moves laterally in and out of the synapse (Groc et al. 2004, Tovar & Westbrook 2002), raising the possibility that extrasynaptic NMDA receptors may not associate with the synaptic PSD protein complex and may therefore initiate distinct signaling. Stimulation paradigms designed to specifically activate either synaptic or extrasynaptic NMDA receptors are able to induce transcriptional programs with opposite effects on neuronal survival (Hardingham et al. 2002, Zhang et al. 2007). This finding may be explained by altered subunit composition in synaptic versus extrasynaptic NMDA receptors (Groc et al. 2006) or by differential association with distinct cytoplasmic signaling complexes. Although further work is required to elucidate the underlying mechanisms, it is clear that NMDA receptor context can have a significant effect on the transcriptional consequences of NMDA receptor activation.

Like the NMDA receptor, the L-type channel associates with scaffolding proteins that cluster signaling molecules in close proximity to one another. A theme emerging from the study of these anchored signaling complexes is that calcium plays a dual role, regulating both L-type

channel function and nuclear signaling. Activation of the calcium sensor calmodulin (CaM), which is bound to the L-type channel via the L-VSCC C-terminal IQ domain, can initiate Ras/MAPK signaling to the nucleus, leading to the induction of activity-dependent gene expression (Dolmetsch et al. 2001). In addition, the stable association of CaM with the L-type channel mediates both facilitation and inactivation of the L-type channel, resulting in feedback autoregulation of the channel that alters calcium influx and thereby has consequences for subsequent activity-dependent changes in gene expression (Peterson et al. 1999, Zuhlke et al. 1999). Likewise, the cAMP-dependent protein kinase (PKA), which phosphorylates the L-type channel to facilitate calcium influx, is present at the mouth of the channel in association with other activating or inhibitory signaling molecules such as G protein-coupled receptors and protein phosphatases (Davare et al. 2001). A-kinase anchoring proteins (AKAPs) often anchor PKA to its targets, and one such AKAP, AKAP79/150, mediates the effect of calcium influx through the L-VSCC by recruiting both PKA and calcineurin, a protein phosphatase that antagonizes PKA facilitation (Oliveria et al. 2007). Importantly, AKAP79/150 is required for L-type channel-dependent activation of the transcription factor NFAT (nuclear factor of activated T cells), an activity-dependent transcriptional regulator that has recently been implicated in the pathogenesis of Down syndrome (DS) (discussed below). Thus, the establishment of signaling microdomains, through direct interaction of proteins with calcium channels or via localization of the channels within larger scaffolding complexes, allows for input-specific control of channel function, local modification of synaptic components, and nuclear signaling.

Activity-Dependent Transcriptional Regulation

Integration of the calcium-regulated signaling networks at the synapse, within the cytoplasm, and in the nucleus allows for the coordinated regulation of nuclear transcription factors in response to a variety of extracellular stimuli. In the nucleus, calcium-regulated transcription factors cooperate to control the expression of hundreds of activity-dependent genes, orchestrating the experience-dependent development and plasticity of neuronal function. The mechanisms underlying these activity-dependent transcriptional events, and the nature of the gene expression programs they induce, have been the subject of intense investigation and have led to the identification of a number of activity-regulated transcription factors. Studies of a subset of these factors have begun to yield insight into the role of experience in CNS development and human disorders of cognition.

CREB-Dependent Transcription and Cognitive Function

The transcription factor CREB often serves as the prototype for calcium-dependent regulators of transcription. A reporter gene that contains multiple CREB binding sites (CREs) within its promoter is driven by stimuli that induce cortical plasticity during postnatal development, by LTP, and by hippocampus-dependent learning and memory, suggesting that CREB can regulate experience-dependent gene expression (Lonze & Ginty 2002). A diverse array of extracellular stimuli are converted into changes in gene expression via the regulation of CREB activity, and insight into the mechanisms by which a single stimulus-inducible factor such as CREB can coordinate the expression of specific activity-dependent genes in response to a host of signaling cues has begun to emerge.

CREB was initially identified as a factor that bound to (a) the CRE within the *somatostatin* proximal promoter responsible for cAMP-dependent induction of *somatostatin* gene expression (Montminy & Bilezikjian 1987) and (b) the calcium response element (CaRE) required for calcium-dependent *c-fos* activation (Sheng et al. 1990). The identification of a cAMP- and calcium-inducible phosphorylation event at CREB serine-133 that is required for CRE/CaRE-dependent transcriptional activation (Dash et al. 1991, Gonzalez & Montminy 1989, Sheng et al. 1991), and the ability to identify the kinases that trigger CREB activation

using a phospho-specific antibody to CREB phosphorylated at serine-133 (Ginty et al. 1993), enabled the identification of the upstream signaling pathways that promote CREB-dependent transcriptional activation. A number of signal transduction cascades initiated by either cytoplasmic or nuclear calcium have since been shown to mediate CREB serine-133 phosphorylation in various neuronal cell lines and primary neuronal cultures. These pathways ultimately result in the activation of CREB kinases such as the CaMKs (Dash et al. 1991, Kang et al. 2001, Sheng et al. 1991, West et al. 2001) and the Ras/ERK-dependent kinases ribosomal S6 kinases (RSKs) and mitogen- and stress-activated protein kinases (MSKs) (Ginty et al. 1994, Impey et al. 1998, Rosen et al. 1994, Xing et al. 1996) (Figure 3).

The prevailing view of CREB-dependent transcriptional activation proposes that in the unstimulated cell, CREB binds CREs within the promoters of CREB-regulated genes and recruits components of the basal transcriptional machinery. In the absence of extracellular stimuli, the presence of transcriptional repressors and a relatively condensed chromatin conformation result in low levels of CRE-driven transcription from these promoters. Cellular stimuli that result in the phosphorylation of CREB at serine-133 recruit CREB-binding protein (CBP) or its paralog p300, multifunctional proteins that increase the transcriptional activity of the CREB transcriptional complex (Chrivia et al. 1993). CBP possesses endogenous histone acetyltransferase (HAT) activity and catalyzes the acetylation of promoter-associated histones, disrupting the histone-DNA interactions and making the chromatin surrounding the transcriptional start site accessible to the transcriptional machinery (Bannister & Kouzarides 1996). CBP may also promote transcription by binding and stabilizing the preinitiation complex that forms at the promoters of CREB target genes (Kwok et al. 1994).

CREB serine-133 phosphorylation is a reasonable correlate for CREB activation and has proven useful in identifying CREB kinases and transcriptional coactivators. However, clues that CREB phosphorylation and transcriptional activation are not a simple ON-OFF switch came from studies of the relationship between CREB serine-133 phosphorylation and target gene expression. Although various stimuli that increase cAMP or calcium, such as neurotransmission and growth factor treatment, are able to induce CREB serine-133 phosphorylation, they do not always induce target gene activation (Bonni et al. 1995). The duration of CREB serine-133 phosphorylation varies depending on which CREB kinase is activated, and may reflect the duration or nature of the synaptic stimulus (Wu et al. 2001). In addition, the timing of target gene induction does not necessarily coincide with the onset or duration of CREB serine-133 phosphorylation, suggesting that additional modifications are required for CREB activation or that CREB cooperates with other regulatory factors at some target genes (Tao et al. 1998). Studies have since demonstrated that, depending on the nature of the stimulus and the cell type, CREB-dependent transcription is regulated by a number of additional mechanisms. These include additional CREB phosphorylation sites (Gau et al. 2002, Kornhauser et al. 2002, Parker et al. 1998), stimulus-dependent CREB dephosphorylation (Bito et al. 1996, Hardingham et al. 2002, Sala et al. 2000), inducible binding of CREB to the regulatory elements of target genes (Riccio et al. 2006), and the association of CREB with novel transcriptional coactivators (Conkright et al. 2003, Iourgenko et al. 2003). Each of these mechanisms is likely involved in the regulation of only a subset of CREB targets, suggesting that a number of signaling pathways may converge to promote a stimulus-specific transcriptional outcome.

The phosphorylation of CREB at serine-142 and -143, in addition to serine-133, is required for maximal, calcium-specific CREB-dependent gene expression in cortical neurons (Kornhauser et al. 2002). Surprisingly, these additional phosphorylation sites prevent CREB-CBP interactions, implying that CREB may be able to initiate gene expression without recruiting CBP (Kornhauser et al. 2002, Parker et al. 1998). Both CREB serine-142 phosphorylation and serine-133 phosphorylation are induced in the brain in response to light

stimulation (Gau et al. 2002, Ginty et al. 1993). Mutation of CREB serine-142 to alanine in mice prevents calcium-specific phosphorylation at this site in response to visual experience, resulting in impaired activity-dependent gene induction in the suprachiasmatic nucleus and a consequent behavioral defect in circadian entrainment (Gau et al. 2002). Together these findings suggest that CBP-independent CREB function is required for stimulus-dependent behavioral adaptations under some circumstances.

A better understanding of the context in which CREB-CBP interactions are required may reveal how this aspect of CREB function determines the induction of target genes and specific biological outcomes, and may yield insight into the etiology of some human cognitive disorders that affect the activity-dependent signaling pathways important for CREB-dependent gene expression. Mutations of the CREB kinase, RSK2, have been identified in Coffin-Lowry syndrome (CLS), a severe mental retardation disorder (Trivier et al. 1996), and mutations in CBP and p300 cause the neurodevelopmental disorder Rubenstein-Taybi syndrome (RTS) (Petrij et al. 1995, Roelfsema et al. 2005). Although disruption of CREB function may play a role in the etiology of RTS and CLS, mutations in RSK2 and CBP do not conclusively implicate CREB in these disorders. RSK2 likely has other activity-dependent functions in neurons and may play a role in the phosphorylation of histone H3 as part of the modification of chromatin structure thought to contribute to the activation of the promoters of inducible genes (Sassone-Corsi et al. 1999). Although CREB and CBP cooperate to regulate certain target genes, each likely functions independently of the other as well. CBP itself is posttranslationally modified in response to extracellular stimuli (Impey et al. 2002, Xu et al. 2001) and can interact with sequence-specific transcription factors other than CREB. Thus, CLS and RTS are likely the consequence of disruption of signaling involving a number of transcription factors, including CREB. Nevertheless, elucidation of the mechanisms underlying stimulus-dependent CREB activation has begun to identify the complex interplay among signaling pathways, transcription factors, and the chromatin structure required for the coordinated regulation of activity-dependent programs of gene expression. The fact that CREB, together with its transcriptional coactivator CBP and its upstream regulatory pathways, may play a role in synaptic development, plasticity, and the pathogenesis of human disorders suggests that regulation of these activity-dependent genes underlies cognitive development and function.

MEF2-Dependent Transcription Mediates Activity-Dependent Synaptic Remodeling

Like CREB, the myocyte enhancer factor 2 (MEF2) family of transcription factors is regulated by a number of extracellular stimuli, including those that can induce calcium-dependent signaling pathways. As with CREB, activation of the transcriptional targets of MEF2 likely depends on the coordinate regulation of chromatin structure and transcription factor function. Calcium-dependent modulation of MEF2 function in myocytes has been well-characterized, and similar mechanisms likely play a role in neuronal cells in which MEF2 controls the activity-dependent regulation of synapse number (Flavell et al. 2006, Shalizi et al. 2006).

The MEF2 proteins appear to be constitutively bound to target genes and to act as either transcriptional activators or repressors, depending on their posttranslational modification state (Figure 4). In the unstimulated cell, MEF2 is phosphorylated at serine-408, is sumoylated at lysine-403 (Flavell et al. 2006, Shalizi et al. 2006), and associates with the class II histone deacetylases (HDACs) (McKinsey et al. 2000), resulting in repression of MEF2-dependent transcription at target promoters. In response to calcium influx, calcineurin, a protein phosphatase, dephosphorylates MEF2 at serine-408, lysine-403 is desumoylated and subsequently acetylated, and the association of MEF2 with the class II HDACs is disrupted. The resultant activation of MEF2-dependent transcription restricts synapse number in developing neuronal cultures (Flavell et al. 2006, Shalizi et al. 2006).

Although the *in vivo* role of MEF2 in the nervous system is not known, its function in primary neurons *in vitro*, together with the finding that activity controls MEF2-dependent transcription, suggests that MEF2 family members may mediate experience-dependent neuronal development and plasticity. In support of this hypothesis, the stimulus-dependent nuclear export of the class II HDACs, a process correlated with MEF2 activation, has recently been implicated in behavioral adaptation to cocaine and stress (Renthal et al. 2007).

The Control of NFAT-Dependent Transcription and Down Syndrome

Studies in other cell types raise the possibility that in neurons MEF2 may interact with additional transcription factors to control activity-dependent synapse development. Consistent with this hypothesis, activation of calcineurin in neurons not only dephosphorylates MEF2 but also dephosphorylates and activates nuclear factor of activated T cells (NFAT) (Graef et al. 1999) (Figure 5). Prior to synaptic activity, NFAT transcription factors are maintained in the cytoplasm by kinases that phosphorylate a series of NFAT residues. The subsequent dephosphorylation of NFAT induces a conformational change in the transcription factor that exposes its nuclear localization signal (NLS) and leads to NFAT transport into the nucleus. Once in the nucleus, NFAT proteins require the cooperative binding of a nuclear factor to initiate transcription, and MEF2 is one of many transcription factors that can serve this function in nonneuronal cells (Olson & Williams 2000). One possibility is that NFAT activates MEF2 target genes by bringing calcineurin in close proximity to MEF2, promoting MEF2 dephosphorylation and transcriptional activation. Within the nucleus, NFAT is subject to regulation by kinases, such as glycogen synthase kinase-3 (GSK-3) (Graef et al. 1999), that promote the export of NFAT back into the cytoplasm, thereby inhibiting the transcription of NFAT target genes.

Although NFAT is known to regulate neuronal survival and axonal outgrowth (Benedito et al. 2005, Graef et al. 2003), NFAT's role in experience-dependent synaptic development and plasticity is largely unexplored. However, recent work suggests that the dysregulation of calcium-dependent NFAT signaling may be involved in the etiology of Down syndrome (DS), a neurodevelopmental disorder caused by trisomy of chromosome 21 and characterized by cognitive impairment. Mice with a homozygous deletion in the genes for two NFAT family members, *Nfat2* and *Nfat4*, have characteristic craniofacial skeletal structure reminiscent of previous DS mouse models, and abnormalities in social- and anxiety-related behaviors consistent with a DS-like phenotype (Arron et al. 2006). This observation, and findings from a screen for upstream regulators of calcium-dependent NFAT translocation in *Drosophila* (Gwack et al. 2006), led to the identification of gene products encoded by the human Down syndrome critical region (DSCR) as negative regulators of NFAT transcriptional activity. These include DSCR1, an inhibitor of calcineurin (Arron et al. 2006, Rothermel et al. 2000), and DYRK1A [dual-specificity tyrosine (Y) phosphorylation-regulated kinase 1A], a serine/threonine kinase that primes substrates for phosphorylation by GSK-3 (Arron et al. 2006, Gwack et al. 2006). Duplication of the DSCR in DS results in overexpression of DSCR1 and DYRK1A, both of which are predicted to prevent NFAT activation in response to calcium (Figure 5), supporting a model whereby increased gene dosage of two negative regulators of NFAT in the DSCR decreases calcium-dependent NFAT activation. Experimental disruption of NFAT signaling during CNS development and postnatal plasticity may shed light on the nature of the intellectual impairment that characterizes DS, and the identification of NFAT transcriptional targets may provide new insight into experience-dependent gene programs in neuronal development.

Activity-Dependent Regulation of MeCP2 and Rett Syndrome

Although studies of activity-dependent transcriptional regulation have focused on transcription factors, such as CREB and MEF2, that bind specific sequences within target promoters,

available evidence suggests that stimulus-dependent gene expression relies on the coordinated control of a range of transcriptional effectors that form regulated complexes at the promoters of target genes. It is now becoming clear that many nuclear proteins once thought to bind statically to DNA in neurons are actually dynamically regulated by extracellular stimuli and contribute to the activity-dependent programs of gene expression relevant to synaptic development and plasticity.

One such protein is the methyl-CpG-binding protein 2 (MeCP2), a transcriptional regulator initially identified on the basis of its ability to bind singly methylated CpGs in the genome (Meehan et al. 1992). MeCP2 is thought to play a role in the structural conformation of stably repressed chromatin. Once bound to methylated DNA, MeCP2 recruits a complex of chromatin-remodeling enzymes that help to condense and silence the DNA surrounding the MeCP2 binding site (Chahrour & Zoghbi 2007). When mutations in MeCP2 were identified as the cause of Rett syndrome, a severe neurodevelopmental disorder, significant effort was aimed at identifying the target genes upregulated upon loss of function of this transcriptional repressor. However, initial attempts to identify altered gene expression profiles in the brains of MeCP2 mutant mice yielded only subtle defects (Tudor et al. 2002), and further studies in specific neuronal cell types have identified only a few dysregulated MeCP2 target genes in MeCP2-deficient mice (Chahrour & Zoghbi 2007).

Recent work suggests that the limited effect of the loss of MeCP2 on gene expression reflects additional, unknown functions for MeCP2. A clue regarding these uncharacterized functions of MeCP2 came from experiments demonstrating that synaptic activity, both in cultured neurons and in the brain, induces the phosphorylation of MeCP2 at serine-421 (Chen et al. 2003a, Zhou et al. 2006). Phosphorylation of MeCP2 serine-421 occurs with a time course that suggests that this phosphorylation event may play a role in activity-dependent transcription, and MeCP2 binds to the promoter of *Bdnf*, an activity-regulated gene important for neuronal development and plasticity (Chen et al. 2003a, Martinowich et al. 2003). MeCP2 serine-421 phosphorylation appears to be required for activity-dependent *Bdnf* transcription: Mutation of MeCP2 serine-421 to alanine blocks serine-421 phosphorylation and disrupts *Bdnf* induction in response to membrane depolarization (Zhou et al. 2006). Importantly, phosphorylation of MeCP2 serine-421 is enriched in the brain relative to other tissues and regulates dendritic branching and spine development, providing insight into how mutations in MeCP2 that prevent its role in activity-dependent gene regulation may contribute to neuronal dysfunction and therefore may be relevant to Rett syndrome.

Rett syndrome is an autism spectrum disorder characterized by relatively normal development during the first year of life, followed by a period of regression accompanied by the loss of acquired skills and cognitive impairment (Chahrour & Zoghbi 2007). Although CNS development in Rett syndrome is grossly normal, small neuronal soma size (Chen et al. 2001, Guy et al. 2001), simplified cortical dendritic morphology (Kishi & Macklis 2004), and deficits in glutamatergic function (Chao et al. 2007, Dani et al. 2005, Nelson et al. 2006) occur.

These findings and other lines of evidence suggest that Rett syndrome may be a disorder of experience-dependent synaptic maturation and plasticity. MeCP2 levels increase in the CNS throughout neuronal development (Kishi & Macklis 2004), and mutation of MeCP2 results in a predominantly neurological phenotype despite the fact that MeCP2 is expressed in most tissues. Rett syndrome-like symptoms manifest during postnatal development in both humans and mice (Chahrour & Zoghbi 2007), and the phenotypes and synaptic deficits in MeCP2-null mice can be rescued by the reintroduction of MeCP2 in animals that have already begun to display severe neurological symptoms (Guy et al. 2007). These data suggest that MeCP2 has a critical role in regulating mature neuronal function rather than in survival or early development. Insight into the activity-dependent transcriptional functions of MeCP2 may

reveal mechanisms by which disruptions in experience-dependent neuronal adaptation contribute to the pathogenesis of Rett syndrome and other cognitive disorders.

Communication from the Nucleus to the Synapse

Although stimulus-dependent transcription factors are now known to control specific cellular responses to synaptic activity, the genetic programs that they regulate in response to sensory experience are still poorly defined. Some progress has been made in the identification of the direct transcriptional targets of CREB in neuronal cell lines (Impey et al. 2004). However, genome-wide characterization of the transcriptional targets that are induced by activity-regulated transcription factors in addition to CREB (e.g., MEF2, NFAT, MeCP2, CREST, and others) will be necessary to understand how these transcriptional regulators coordinate context-dependent neuronal function. To date much effort has been made toward elucidating the mechanisms by which individual CREB target genes, such as *c-fos* and *Bdnf*, and an MEF2 target gene, *Arc* (*activity-regulated cytoskeletal-associated protein*), are regulated in a coordinated manner downstream of particular stimuli. Studies of the functions of these target genes suggest that the induction of activity-dependent programs of gene expression in response to synaptic activity allows the nucleus to communicate instructions for functional change back to the synapse (Figure 1).

Coordinated Activity-Dependent Regulation of *Bdnf*

One of the best-studied activity-regulated genes encodes BDNF, a neurotrophin that plays a key role in nervous system development and plasticity. The *Bdnf* gene is composed of at least nine distinct exons, many with unique promoters that drive the synthesis of mRNA transcripts containing distinct 5' untranslated regions (UTRs), a common coding exon, and either of two distinct 3' UTRs that differ in length because of the presence of two distinct sites of polyadenylation (Aid et al. 2007). This complex locus gives rise to the production of at least 18 distinct *Bdnf* transcripts that all encode an identical protein (Aid et al. 2007, Timmusk et al. 1993). Synaptic activity and calcium influx into the postsynaptic neuron lead to the induction of *Bdnf* transcription (Ghosh et al. 1994, Tao et al. 1998, Timmusk et al. 1993, Zafra et al. 1990), and which *Bdnf* transcripts are produced depends on the nature of the stimulus and the signaling pathways that are activated.

Investigation of the mechanisms by which activity induces promoter-specific transcription of the *Bdnf* gene has led to the identification of distinct signaling mechanisms that regulate the different *Bdnf* promoters. The regulation of two of the *Bdnf* promoters, I and IV, both of which are transcribed in a calcium-dependent manner, has been relatively well-characterized. Deletion analysis identified two CaREs in *Bdnf* promoter I and three CaREs in *Bdnf* promoter IV that contribute to the activity dependence of these promoters. CREB and upstream stimulatory factors (USFs) mediate the activity-dependent regulation of both *Bdnf* promoters I and IV (Chen et al. 2003b, Shieh et al. 1998, Tabuchi et al. 2002, Tao et al. 1998). Regulation of promoter IV is also dependent on additional transcription factors that are involved in the activity-dependent transcriptional response, including a novel transcription factor, calcium response factor (CaRF) (Tao et al. 2002), and MeCP2 (Chen et al. 2003a, Zhou et al. 2006). Consistent with the idea that transcriptional activation requires the coordinate regulation of transcription factors and chromatin structure at the promoters of activity-dependent genes, changes in synaptic activity and experience affect not only the activity of transcription factors but also the modification of the histones at the activity-dependent promoters of *Bdnf* (Chen et al. 2003a, Martinowich et al. 2003). Perturbations in the level of BDNF expression have been associated with human psychiatric disorders, and recent reports of altered patterns of *Bdnf* chromatin modifications in mouse models of depression and stress suggest that dysregulation of *Bdnf* transcription plays a role in these disorders of neuronal adaptation (Tsankova et al. 2007).

Although the transcriptional regulation of *Bdnf* in response to experience has been partially characterized, how the different *Bdnf* transcripts relate to the different functions of the BDNF protein remains poorly understood. The production of distinct *Bdnf* transcripts suggests that transcriptional initiation from a particular promoter, or inclusion of a particular UTR in the transcript produced, may determine the localization or translational fate of a *Bdnf* transcript and, as a consequence, the function of the BDNF protein produced from that mRNA transcript. Alternatively, specific stimuli or signaling cascades may drive transcription from particular promoters, regulating the stimulus dependence and amount of BDNF produced. At the present time, our understanding of the consequences of this type of regulation is rudimentary. Additional work is required to reveal how regulated transcripts initiated at different promoters contribute to the specificity of BDNF function.

***Bdnf* in Synapse Development and Plasticity**

Bdnf mRNA transcripts initiated at any of the BDNF promoters are translated into an identical BDNF precursor, proBDNF, that is packaged into vesicles of the constitutive and regulated secretory pathways. Proteolytic cleavage of proBDNF and the secretion of mature BDNF occur in an activity-dependent manner in response to calcium influx (Hartmann et al. 2001). Once released, BDNF binds the tyrosine kinase receptor B (trkB), a neurotrophin receptor located both pre- and postsynaptically. Because of the regulated processing and secretion of BDNF, its functional roles have been difficult to ascertain in vitro, but experiments using bath application of BDNF have implicated BDNF in the regulation of dendritic arborization; the growth of dendritic spines; and the potentiation of activated synapses, as in LTP (Horch et al. 1999, McAllister et al. 1995, Patterson et al. 1996).

In vivo, BDNF is involved in the experience-dependent maturation and maintenance of cortical circuits. Forebrain-specific deletion of BDNF using a conditional knockout mouse revealed that the initial dendritic formation and branching of cortical neurons occur normally through the first few weeks of postnatal development (Gorski et al. 2003). However, BDNF-deficient cortical neurons exhibit reductions in dendritic complexity and soma size by five weeks of age. In addition, mice heterozygous for deletion of the BDNF gene were unable to appropriately modify the number and morphology of dendritic spines in the somatosensory barrel cortex in response to whisker stimulation (Genoud et al. 2004). Another mouse model, with an accelerated increase in postnatal BDNF levels, undergoes premature closure of the critical period for ocular dominance plasticity in the visual cortex (Huang et al. 1999). These in vivo consequences of the disruption of BDNF expression likely result from defective experience-dependent modulation of neuronal circuits, supporting the conclusion that BDNF plays a role in this aspect of activity-dependent synaptic development and plasticity.

In humans, a common single-nucleotide polymorphism (SNP) in the *Bdnf* gene results in the substitution of methionine for valine at codon 66 (Val66Met) in the BDNF prodomain. The presence of this SNP correlates with poor performance on memory tasks and may contribute to the pathogenesis of depression and anxiety disorders (Bath & Lee 2006, Egan et al. 2003). Mice harboring the Val66Met mutation show normal constitutive secretion of BDNF, but activity-regulated secretion of BDNF is perturbed (Chen et al. 2006, Egan et al. 2003). This defect in the regulated secretion of BDNF may reflect a role for the prodomain of BDNF in interactions with sortilin, a protein that is involved in sorting BDNF into the regulated secretory pathway (Chen et al. 2005). Val66Met mice show dendritic arborization defects in the hippocampus and reduced hippocampal volume similar to those seen in mice heterozygous for BDNF. These anatomical defects in mice are consistent with the reduced hippocampal volume observed in human subjects with the Val66Met SNP (Bath & Lee 2006, Chen et al. 2006). Importantly, the Val66Met mice display defects in learning and memory tasks as well as

anxiety-related behaviors, suggesting that abnormalities in activity-dependent secretion of BDNF may underlie some aspects of the human disorders associated with the Val66Met SNP.

Targeting of Activity-Dependent Gene Products to the Synapse

The changes in synaptic weight that underlie neuronal adaptation are input specific and are typically limited spatially to the vicinity of the activated synapse (Harvey & Svoboda 2007). However, early experiments demonstrated that the regulation of transcription (and the subsequent synthesis of activity-induced gene products) is required for long-term changes in synaptic function. Late-LTP induction is prevented when hippocampal dendrites are severed from the neuronal cell body, suggesting a requirement for new gene expression (Frey et al. 1989). Late-LTP also requires protein synthesis: An initial, strong, late-LTP-inducing stimulus at one set of inputs allows the subsequent weak stimulation of a separate synapse—one that, if given on its own, would normally not induce late-LTP—to induce late-LTP at the second synapse (Frey & Morris 1997). This reduction of the LTP threshold for the weak second stimulation requires protein synthesis within a 2–3-h time window surrounding the first stimulation, implying that activity-dependent transcription and protein synthesis in the cell body initiated by the first synaptic stimulus may function in the potentiation of the second synapse.

Elucidating the mechanism by which the correct synapses are modulated in response to nuclear gene expression has been the subject of major effort. One clue comes from a transgenic mouse model expressing a constitutively active form of CREB (VP16-CREB) in the hippocampus under the control of an inducible promoter (Barco et al. 2002). In this mouse model, transcription of VP16-CREB target genes was sufficient to reduce the stimulus threshold required for the induction of late-LTP, much in the same way that an earlier LTP-inducing stimulus elsewhere on a neuron reduces the LTP threshold. Analysis of gene expression in the hippocampus of this VP16 transgenic mouse demonstrated that several genes, including *Bdnf*, are upregulated with VP16-CREB induction (Barco et al. 2005). Further analysis of late-LTP in the VP16-CREB mouse as well as in the *Bdnf* heterozygous mice confirmed a role for BDNF in promoting LTP through both pre- and postsynaptic actions (Barco et al. 2005). Thus, synaptic activity induces the transcription of genes, such as *Bdnf*, whose mRNA or protein products are produced and trafficked to synapses throughout the cell, where they are able to modulate neuronal function in response to subsequent stimuli. Once secreted from the dendrite, BDNF is believed to act both pre- and postsynaptically, facilitating presynaptic neurotransmitter release and increasing the local translation of proteins required within the postsynaptic dendrite (Kang & Schuman 1995, 1996).

Arc in Activity-Dependent Synaptic Plasticity

Some of the best evidence for the role of activity-dependent genes in synaptic function comes from the study of *Arc*, an activity-dependent MEF2 target gene (Flavell et al. 2006) that encodes a cytoskeleton-interacting protein found in the PSD of glutamatergic neurons. A variety of different external stimuli, including visual stimulation, induce *Arc* transcription in the brain (Steward & Worley 2001b, Tagawa et al. 2005, Wang et al. 2006). During development, *Arc* expression is first detected postnatally at day 12 and increases to a maximal and stable level at postnatal day 21 (Lyford et al. 1995), consistent with a role in experience-dependent synaptic plasticity. Animals lacking *Arc* show no gross abnormalities in neuronal development but show impaired late-LTP, impaired long-term memory in behavioral tasks, and a disruption of experience-dependent development of orientation selectivity in the visual cortex (Plath et al. 2006, Wang et al. 2006). Recent experiments have implicated *Arc* in the postsynaptic endocytosis of the AMPA receptor through interactions with the endocytic machinery (Chowdhury et al. 2006, Rial Verde et al. 2006, Shepherd et al. 2006), suggesting a direct function for *Arc* in the modulation of synaptic strength.

Arc transcripts are produced in the nucleus and trafficked specifically to active synapses, where the *Arc* mRNA is translated (Steward et al. 1998). NMDA receptor activation can induce the transcription of *Arc* within 2 min of synaptic stimulation, the processed *Arc* mRNA is exported to the cell body within 15 min, and the synaptically localized *Arc* mRNA is translated within 30 min (Guzowski et al. 1999). Studies using electroconvulsive shock (ECS), a nonphysiological inducer of massive glutamate release at synapses, confirmed that newly synthesized *Arc* mRNA is transported throughout the dendritic tree of activated neurons. Subsequent synaptic activation of a specific set of inputs initiates the redistribution of *Arc* message specifically to the stimulated inputs, suggesting that active synapses can recruit activity-dependent effectors or proteins (Steward & Worley 2001a,b).

This regulation of activity-dependent gene products suggests a model for communication from the nucleus to the synapse. Synaptic activity induces the transcription of genes such as *Arc* or *Bdnf* in the nucleus, and the mRNA transcripts and/or proteins that are produced are trafficked into the dendritic arbor of the neuron. The presence of these activity-dependent gene products allows the synapse to respond differently to subsequent stimulation events by modifying synaptic function. For instance, *Arc* protein produced within the dendritic tree may interact with other activity-dependent gene products and local signaling molecules to mediate AMPA receptor expression at the synapse. Through this type of mechanism, activity-dependent gene expression in the nucleus can influence adaptive changes at the appropriate synapses. The full complement of synaptic effectors that, like *Arc* and *Bdnf*, may contribute to processes of neuronal development and plasticity remains to be defined and is the subject of ongoing research.

Conclusion

The ability to adapt to and learn from the environment requires long-term changes in brain function in response to input from the environment. Sensory experience drives activity within neuronal circuits, and as the individual neurons within these circuits receive and respond to extracellular cues, cellular changes that modulate the strength of synaptic connections drive changes in circuit function. Synaptic activity is required for many aspects of postnatal neuronal development, including dendritic patterning, synapse formation, and synapse elimination, and plays a major role in synaptic plasticity in the adult. The signaling mechanisms that operate within neurons to relay the effect of synaptic stimulation to the nucleus, and the gene products produced as a result, allow the synapse and the nucleus to communicate with one another. Integration of these pathways at the synapse, within the cytoplasm, and in the nucleus allows the neuron to coordinate adaptive responses to a wide range of extracellular cues. Mutations that affect components of the activity-regulated signaling network have been identified and shown to result in deregulation of communication between the synapse and the nucleus and therefore to contribute to the disruption of experience-dependent development and plasticity in human disorders of cognitive function (Figure 6).

As we learn more about the individual molecules involved in the bidirectional signaling between the synapse and the nucleus, many unanswered questions arise. Particular patterns of sensory experience induce synaptic activity in only a subset of neurons within a circuit—each individual neuron must then interpret hundreds of synaptic inputs to generate an appropriate response. How is this specificity of signaling accomplished? Future studies of the regulation and function of activity-dependent gene expression will be required to reveal more fully the mechanisms by which synaptic activity generates structural and functional changes in neural circuits, the importance of experience in shaping brain function, and how disruption in these processes gives rise to human cognitive disorders.

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Glossary

Amblyopia

poor vision through an eye that is otherwise healthy due to disruption of transmission of the visual image to the brain

Synapses

specialized chemical junctions between neurons that transmit electrical activity from the presynaptic to the postsynaptic cell via neurotransmitter release

Critical period

a time window during development in which experience provides information that is essential for normal brain function

Ocular dominance columns

functional columns within primary visual cortex in which neurons respond predominantly to visual inputs from one eye or the other

Glutamate

the primary neurotransmitter released at excitatory synapses in the brain

NMDA

N-methyl-D-aspartate

AMPA

α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid

VSCC

voltage-sensitive calcium channel

CREB

cAMP response element binding protein

LTP

long-term potentiation

LTD

long-term depression

Immediate early gene (IEG)

a gene, such as *c-fos*, that is induced rapidly and transiently in the absence of de novo protein synthesis

Calcium microdomain

a cytoplasmic region limited to the immediate vicinity of a calcium channel in which the concentration of calcium can rise dramatically

Chromatin

a complex of DNA, histones, and nonhistone proteins that controls the accessibility of the DNA to the transcriptional machinery

HAT

histone acetyltransferase

Circadian entrainment

the synchronization of physiology and behavior to extracellular cues by a clock mechanism in the suprachiasmatic nucleus of the brain

HDAC

histone deacetylase

BDNF

brain derived neurotrophic factor

Barrel cortex

a region of somatosensory cortex in the rodent in which each barrel receives sensory input from a single whisker follicle

Figure 1.

Bidirectional communication between the synapse and the nucleus mediates neuronal development and plasticity. Calcium influx into the postsynaptic cell in response to sensory experience modulates neuronal function both by direct actions at the activated synapse and through communication to the nucleus to affect activity-dependent transcriptional programs. (a) Synaptic activity induces glutamate release into the synaptic cleft and activation of the postsynaptic NMDA receptor (NMDAR). Calcium influx into the dendritic spine through the NMDA receptor regulates dendritic patterning and synapse morphology through local effects on the actin cytoskeleton. NMDA receptor activation also regulates the recruitment of AMPA receptors to the synapse in processes important for synaptic maturation and plasticity. (b)

Synaptic activity is communicated to the nucleus to regulate activity-dependent gene expression. Calcium influx through both NMDA receptors and L-type voltage-sensitive calcium channels (L-VSCCs) acts as a second messenger in the cytoplasm to initiate signaling to the nucleus, where the modulation of transcription factors results in activity-dependent changes in gene expression. (c) The mRNA and protein products of activity-dependent genes regulate a range of neuronal functions in response to extracellular stimuli. During processes important for neuronal development and plasticity, the activity of these gene products throughout the cell provides a mechanism by which the nucleus is able to communicate to the synapse the functional changes required for adaptive response.

Figure 2.

Mechanisms to increase calcium levels in the postsynaptic cell. Calcium plays a well-defined role in the biochemical transduction of signals from the synapse to the nucleus. In response to synaptic activity and neurotransmitter release, extracellular calcium flows into the postsynaptic cell through synaptic and extrasynaptic ligand- and voltage-gated calcium channels. Major routes of entry with well-established effects on nuclear gene expression are the NMDA receptor (NMDAR) and the L-type voltage-sensitive calcium channel (L-VSCC). Calcium-permeable AMPA receptors (AMPA) may play a role at developing synapses or after the induction of synaptic plasticity. Calcium signals can also be amplified by calcium-induced release of calcium from intracellular stores, triggered by activation of ryanodine receptors (RyR). Calcium at the mouth of the channel, in the cytoplasm, or within the nucleus can signal to activity-dependent transcription factors. Alterations in calcium influx into the postsynaptic cell during development or as a result of mutation modulate the induction of gene expression in response to neuronal activity. ER denotes endoplasmic reticulum.

Figure 3.

Model of calcium-dependent phosphorylation of CREB (cAMP response element binding protein). Phosphorylation of CREB at serine-133 in response to a diverse array of extracellular stimuli results in CREB transcriptional activation. The signal transduction cascades initiated by these stimuli ultimately result in the activation of a CREB kinase, including protein kinase A (PKA), calcium/calmodulin-dependent kinases II and IV (CaMKII and CaMKIV), and Ras/ERK-dependent kinases such as RSK. Activation of CREB-dependent transcription at particular target genes depends on additional events including other sites of CREB phosphorylation and the recruitment of transcriptional cofactors. CaMKK, CaMK kinase.

Figure 4.

Model of calcium-dependent regulation of myocyte enhancer factor 2 (MEF2) transcriptional activity. MEF2 proteins bound to their target genes can act as either transcriptional activators or repressors, depending on the stimulation state of the cell. (a) In the unstimulated cell, the class II histone deacetylases (HDACs), which repress transcription by removing acetyl groups from histones and transcription factors, associate with MEF2. Under these conditions, MEF2 is also phosphorylated at a number of sites. Both basal phosphorylation of MEF2 at serine-408 and its association with HDACs contribute to MEF2 transcriptional repression, in part by promoting the sumoylation (Su) of MEF2 at lysine-403, a modification that represses MEF2-dependent transcription. (b) In response to synaptic activity, two calcium-dependent signaling pathways convert MEF2 from a repressor to an activator of transcription. Calcium/calmodulin-dependent protein kinase (CaMK) activation leads to the phosphorylation of the class II HDACs, initiating their binding to the 14-3-3 chaperone proteins and subsequent nuclear export. As a result, MEF2 is able to interact with the transcription-activating histone

acetyltransferases (HATs), which likely increases histone acetylation at MEF2 target genes, promoting transcription, and may also contribute to the acetylation of MEF2 itself. In addition, activation of calcineurin (CaN), a calcium-dependent protein phosphatase, dephosphorylates MEF2 at serine-408. Serine-408 dephosphorylation of MEF2 promotes the desumoylation and subsequent acetylation of MEF2 lysine-403, contributing to MEF2 transcriptional activation.

Figure 5.

Model of calcium-dependent nuclear factor of activated T cells (NFAT) activation. In the unstimulated cell, NFAT transcription factors are maintained in the cytoplasm by kinases that phosphorylate a number of NFAT phosphorylation sites. Calcineurin (CaN) docking and the subsequent dephosphorylation of NFAT induce a conformational change in the transcription factor that exposes its nuclear localization signal (NLS) and leads to NFAT transport into the nucleus. Within the nucleus, NFAT is subject to regulation by kinases that promote the export of NFAT back into the cytoplasm, thereby resulting in the shutoff of NFAT target genes. The exportin protein Crm1 shuttles NFAT back into the cytoplasm and interacts with the same region of NFAT as does calcineurin, competing with calcineurin for binding to NFAT. Nuclear NFAT kinases that phosphorylate NFAT, such as glycogen synthase kinase-3 (GSK-3), may trigger the release of calcineurin from NFAT to promote NFAT export from the nucleus. When overexpressed in Down syndrome as the result of duplication of the Down syndrome critical region (DSCR), both DSCR1 and DYRK1A [dual-specificity tyrosine (Y) phosphorylation-regulated kinase 1A] are predicted to prevent NFAT activation in response to calcium. Increased DSCR1 activity may block calcineurin-dependent NFAT dephosphorylation and translocation to the nucleus, whereas overexpression of DYRK1A may promote premature GSK3-dependent export of NFAT from the nucleus, inhibiting NFAT transcriptional activity.

Figure 6.

Human diseases of cognitive function disrupt communication between the synapse and the nucleus. The signaling mechanisms that operate within neurons to relay the effect of synaptic stimulation to the nucleus, and the gene products produced as a result, allow communication between the synapse and the nucleus. Mutations in components of these activity-dependent signaling networks have been identified and shown to disrupt experience-dependent neuronal development and plasticity. These include mutations in the L-VSCC in Timothy syndrome, RSK2 in Coffin-Lowry syndrome, CBP in Rubenstein-Taybi syndrome, and MeCP2 in Rett syndrome. Duplications in DSCR1 and DYRK1A may contribute to the etiology of Down syndrome. Disruptions of the activity-dependent genes and their products may contribute to disorders of adaptive behavior, including depression, anxiety, and addiction. These and other mutations suggest that further insight into the programs of activity-dependent gene expression and their regulation may aid in our understanding of CNS development and function as well as of human disorders of cognitive function. Abbreviations used: CaN, calcineurin; CREB, cAMP response element binding protein; CBP, CREB-binding protein; DSCR1, Down syndrome critical region 1; DYRK1A, dual-specificity tyrosine (Y) phosphorylation-regulated kinase 1A; GSK-3, glycogen synthase kinase-3; L-VSCC, L-type voltage-sensitive calcium channel; NFAT, nuclear factor of activated T cells; MeCP2, methyl-CpG-binding protein 2; MEF2, myocyte enhancer factor 2; RSK2, ribosomal S6 kinase 2.