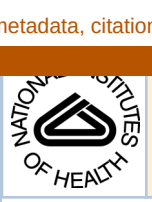

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Activity-Regulated Genes as Mediators of Neural Circuit Plasticity

Jennifer H. Leslie

Department of Biology Picower Institute for Learning and Memory Massachusetts Institute of Technology Phone: 617-258-5241 Fax: 617-452-2249 jhleslie@mit.edu

Elly Nedivi

Departments of Biology, and Brain and Cognitive Sciences Picower Institute for Learning and Memory Massachusetts Institute of Technology Phone: 617-253-2344 Fax: 617-452-2249 nedivi@mit.edu

Abstract

Modifications of neuronal circuits allow the brain to adapt and change with experience. This plasticity manifests during development and throughout life, and can be remarkably long lasting. Many electrophysiological and molecular mechanisms are common to the seemingly diverse types of activity-dependent functional adaptation that take place during developmental critical periods, learning and memory, and alterations to sensory map representations in the adult. Experience-dependent plasticity is triggered when neuronal excitation activates cellular signaling pathways from the synapse to the nucleus that initiate new programs of gene expression. The protein products of activity-regulated genes then work via a diverse array of cellular mechanisms to modify neuronal functional properties. They fine-tune brain circuits by strengthening or weakening synaptic connections or by altering synapse numbers. Their effects are further modulated by posttranscriptional regulatory mechanisms, often also dependent on activity, that control activity-regulated gene transcript and protein function. Thus, the cellular response to neuronal activity integrates multiple tightly coordinated mechanisms to precisely orchestrate long-lasting, functional and structural changes in brain circuits.

1. Introduction

The adult brain had long been considered hardwired, incapable of the structural remodeling seen during development. Synapses, the points of communication between neurons, were though to be stable structures that transmit a stereotyped postsynaptic response following quantal presynaptic release of neurotransmitter. In the past few decades, these long-held views have gradually shifted to accommodate a tremendous flexibility of neuronal form and function in the adult brain. It is now accepted that neurons and synapses undergo varied forms of structural and functional plasticity, allowing for profound changes to brain circuit wiring. These changes are adaptive, driven by patterns of neuronal activity generated by both external sensory experience and internal sources.

The realization that adult brain circuits can be modified in response to experience emerged in parallel to discoveries in developmental biology indicating that activation of gene expression programs in response to extracellular cues such as growth factors occurs in post-mitotic, terminally differentiated cells. Transcriptional activation in mature cells could be induced by a variety of extrinsic stimuli, including some of the same factors that activate transcription during development. In particular, neurons, as part of an exclusive club of electrically excitable cell types, were shown to alter gene expression in response to depolarizing stimuli. This led to the hypothesis that transcriptional activation might play a part in everyday neuronal function and could be influenced by normal synaptic activity. The observation that neuronal activity controls both adaptive neuronal changes and alterations in gene expression patterns suggested that activity-induced gene transcription might underlie the expression of specific forms of plasticity (Sheng and Greenberg, 1990).

Decades of work have since provided evidence that activity-regulated genes do indeed participate in the long-term circuit modifications required for adaptive changes such as alterations in sensory map representations, as well as long-term memory formation and storage. Research has also linked the same activity-regulated genes to circuit refinement during brain development, suggesting that plasticity at all ages utilizes similar mechanisms and molecular machinery. This review focuses on genes that are regulated by neuronal activity, their identification, and evidence linking them to learning and memory in the adult, as well as circuit refinement during development. We also discuss the cellular mechanisms utilized by activity-regulated genes to implement long-term changes to neuronal circuits.

2. Activity-Dependent Gene Expression

The initiation of gene expression programs in response to synaptic activity is analogous in many ways to the cellular response program to other extracellular stimuli such as growth factors, mitogens, and phorbol esters (Loebrich and Nedivi, 2009). In both cases, the response begins at the cell membrane when extrinsic stimuli activate cell surface receptors. These, in turn, trigger intracellular signaling cascades to the nucleus that initiate a bi-phasic transcriptional response. The first phase is comprised of rapid response genes, termed immediate early genes (IEGs) that do not require protein synthesis for their expression. Many IEGs encode transcription factors that then activate a secondary phase of the activity-dependent transcriptional program, expression of the delayed early genes.

The intracellular signaling pathways triggered by neuronal activity largely overlap with those triggered by other cell surface stimuli. In neurons, however, the activation sites for these pathways are spatially discrete. Unlike growth factors whose receptors are distributed throughout the cell membrane, the bulk of signaling by neuronal activity occurs through synaptically localized receptors. Despite this difference, the elucidation of signaling pathways that couple extracellular growth and differentiation cues with transcription paved the way for understanding of the neuronal response to activity.

2.1. Signaling from the Synapse to Activate Gene Expression

How do synaptic signals at the cell surface propagate to the nucleus to effect changes in gene expression programs? Neurons establish gradients of ions such as Na^+, K^+, and Cl^- across their membranes that are important regulators of membrane excitability. Ca^{2+} in particular, as a potent activator of intracellular signaling cascades, is normally maintained at very low concentrations within the cytoplasm. At glutamatergic synapses, activity leads to Ca^{2+} influx into the postsynaptic cell via activation of Ca^{2+}-permeable α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and N-methyl-D-aspartic acid (NMDA) type glutamate receptors, as well as through voltage sensitive Ca^{2+} channels (Catterall, 1995, Rosen et al., 1995). The various routes of Ca^{2+} entry into the cell activate different,

but overlapping cellular responses. These signaling pathways can have distinct temporal windows of action, but are extensively linked to allow cross talk and mutual modulation. Once Ca^{2+}-activated signaling pathways converge on the nucleus, they target transcriptional activators that initiate gene expression. Targets include the transcription factors CRE-binding protein (CREB), serum response factor, and myocyte enhancer factor 2, among others (Brindle and Montminy, 1992, Sassone-Corsi, 1995, Lonze and Ginty, 2002, Flavell and Greenberg, 2008, Knoll and Nordheim, 2009). These transcription factors are in turn regulated by a multitude of co-factors, proteins that enhance and repress transcription in response to specific upstream signaling pathways (Greer and Greenberg, 2008). Both the Ca^{2+}-activated signaling pathways originating at the cell surface, and the complex ensemble of transcription factors they activate have been previously reviewed in great detail (Brindle and Montminy, 1992, Rosen et al., 1995, Sassone-Corsi, 1995, Lonze and Ginty, 2002, Flavell and Greenberg, 2008, Greer and Greenberg, 2008, Knoll and Nordheim, 2009, Lyons and West, 2011).

Epigenetic modifications of DNA and chromatin additionally regulate transcriptional activation of genes and are important for neuronal plasticity during development as well as for learning and memory in adults (reviewed in Fagiolini et al., 2009, MacDonald and Roskams, 2009, Roth et al., 2010, Zocchi and Sassone-Corsi, 2010). DNA methylation can repress transcription by interfering with transcription factor binding, while histone acetylation generally promotes transcription. Synaptic activity can activate signaling pathways that modulate epigenetic states. Early experiences, such as maternal care and environmental enrichment, can affect epigenetic states as well as plasticity.

Between the spatial restriction of cell surface receptor activation, the varied signaling pathways activated by Ca^{2+}, and the combinatorial potential for transcription factor action, the cellular response to neuronal activity integrates multiple stimuli from synaptic as well as non-synaptic sources to differentially code a nuanced and highly specific program of gene expression (reviewed in Lyons and West, 2011).

2.2. Discovery of Activity-Regulated Genes

The first genes found to be activity-regulated in neurons were initially identified in mitotic cells as responsive to extracellular cues such as growth factors and mitogens. Most were transcription factor IEGs, including c-*fos*, c-*jun*, *jun*-B, and *zif/268* (Morgan and Curran, 1986, Morgan et al., 1987, Saffen et al., 1988), important for activating the secondary transcriptional wave of delayed early genes. Depolarizing stimuli and Ca^{2+} influx through voltage sensitive Ca^{2+} channels were found to elicit c-*fos* induction in cultured PC12 cells (Morgan and Curran, 1986), leading to the examination of c-*fos* expression, as well as that of other transcription factor IEGs such as c-*jun* and *zif/268*, in the brain (Morgan et al., 1987, Saffen et al., 1988). All were found to be robustly activated in seizure paradigms, as well as by more natural, physiological levels of stimulation (Loebrich and Nedivi, 2009).

Studies of IEGs like c-*fos*, c-*jun*, and *zif/268* were critical to the realization that gene expression is a normal downstream response to neuronal depolarization (Sheng and Greenberg, 1990). However, since transcription factor IEGs are ubiquitously expressed in multiple cell types, their characterization did little to reveal the specific cellular processes implemented by activity-dependent genetic programs in neurons. In the 1990's several large-scale screens were performed to directly identify genes regulated in the brain by neuronal activity (Nedivi et al., 1993, Qian et al., 1993, Yamagata et al., 1993). Using conceptually similar approaches, they utilized a combination of subtractive hybridization and differential screening to select for seizure-induced transcripts in the rat cerebral cortex, or more specifically the hippocampus (Loebrich and Nedivi, 2009).

These first screens identified a significant number of the activity-regulated genes known to date. They provided an estimate of 500–1,000 genes regulated by activity in the brain (Nedivi et al., 1993), and they afforded the first view of the cellular mechanisms likely to take part in activity-dependent plasticity. Along with transcription factors and signal transduction proteins, these screens identified many genes whose products could directly affect neuron form and function such as trophic factors, structural, and synaptic proteins. The number and diversity of activity-regulated genes illustrates the complex, multi-faceted neuronal response to input activity (Nedivi et al., 1993, Hevroni et al., 1998, Lanahan and Worley, 1998).

Many activity-regulated genes have now been characterized in terms of cellular functions. These include the genes we discuss in greater detail later; *rgs2*, *arc/arg3.1*, *cpg2*, *homer1a*, *snk*, *cpg15*, *tPA*, *arcadlin*, *npas4*, *narp*, and *bdnf*. As revealed by their functional characterization, they all work to effect circuit plasticity through various modifications of the synapse. Before discussing the mechanisms utilized by individual genes, we will examine the evidence supporting a role for activity-regulated genes in plasticity.

3. Linking Activity-Regulated Genes to Brain Plasticity

3.1. Long-Term Memory

Pioneering experiments by Flexner, Flexner, and Stellar in 1963 were the first to hint at the importance of protein synthesis for the consolidation and maintenance of long-term memory. Using intracerebral injections of the protein synthesis inhibitor puromycin they were able to erase the memory of a trained task in mice (Flexner et al., 1963). While this remarkable first study may have actually induced amnesia for reasons independent of effects on protein synthesis, it prompted a great deal of research into the link between new protein synthesis and memory formation (Davis and Squire, 1984). There are many difficulties surrounding the interpretation of studies showing the effects of protein synthesis inhibitors on learning and memory. However, in their thoughtful review Davis and Squire (1984) emphasize that useful generalizations can still be drawn from findings that are consistent across multiple behavioral tasks, with different protein synthesis inhibitors, and in many species. First, protein synthesis is necessary for long-term memory retention. Second, learning and short-term memory are unaffected by protein synthesis inhibitors indicating that they work by mechanisms distinct from long-term memory storage. Finally, protein synthesis inhibitors only affect memory when administered circumjacent to the training, either shortly before or after. Moving injections further from the time of training reduces the effect on memory retention indicating that there is a small window of time during which protein synthesis is necessary for the formation of long-term memory.

Studies in the invertebrate sea slug, *Aplysia*, were the first to provide a mechanistic, cellular framework for understanding learning and memory. The gill- and siphon-withdrawal reflexes of *Aplysia* exhibit forms of nondeclarative memory, including sensitization and habituation (Pinsker et al., 1970, Carew et al., 1971). These can be dissociated behaviorally into short- and long-term forms depending on the amount of training. A single training session elicits short-term behavioral changes lasting minutes to hours (Pinsker et al., 1970, Carew et al., 1971) while multiple training sessions induce behavioral modifications lasting days or weeks (Carew et al., 1972, Pinsker et al., 1973). Changes in the strength of the synaptic connections between sensory and motor neurons were shown to underlie these simple behavioral reflexes. Tactile or electrical stimulation of sensory neurons that evoked habituation led to depression of synaptic transmission between sensory and motor neurons (Castellucci et al., 1970, Kupfermann et al., 1970). Similarly, stimuli that induce sensitization facilitate synaptic transmission at these synapses (Castellucci and Kandel, 1976).

Remarkably, these simple forms of non-declarative memory in *Aplysia*, sensitization and habituation, show similar requirements for protein synthesis as more complex forms of learning in vertebrates. Long-term sensitization could be blocked by protein synthesis inhibitors, while short-term sensitization remained unaffected (Castellucci et al., 1989). Synaptic facilitation, which underlies sensitization, was also susceptible to protein synthesis inhibition, with only long-term facilitation disrupted, and short-term facilitation remaining intact (Montarolo et al., 1986). In addition, protein synthesis inhibitors were only effective at disrupting long-term memory formation in *Aplysia* when applied during training (Montarolo et al., 1986, Castellucci et al., 1989). These studies firmly established that the acquisition of new memory occurs in two phases, a short-term, protein synthesis independent phase that lasts only minutes to hours, and a long-term protein synthesis-dependent phase lasting days or more. Long-term facilitation in *Aplysia* could also be blocked by inhibitors of RNA synthesis, suggesting that in addition to new protein synthesis, new gene transcription is also required for forming long-term memories (Montarolo et al., 1986).

The *Aplysia* studies opened the door for the cellular and molecular study of learning and memory by providing a cellular framework for relating long-term behavioral plasticity with the requirement for transcriptional activation. Both short- and long-term sensitization in *Aplysia* are mediated by serotonin, and multiple, spaced applications of serotonin to *Aplysia* sensory neurons *in vitro* can mimic behaviorally induced long-term sensitization (Montarolo et al., 1986). Application of serotonin induces the synthesis of cAMP (Bernier et al., 1982) and activates the cAMP-dependent protein kinase, PKA (Bacskai et al., 1993). Brief application of serotonin activates PKA only in the cytoplasm, however, with longer application, PKA is able to translocate into the nucleus where it may phosphorylate and activate transcription factors (Bacskai et al., 1993). cAMP-mediated gene expression had been previously described for genes containing a cAMP-response element (CRE) that is bound by the nuclear transcription factor CREB (Brindle and Montminy, 1992, Sassone-Corsi, 1995). A CREB-like protein that binds CRE was also identified in *Aplysia*. To test the possible role of CREB in gene transcription underlying long-term memory, Dash and colleagues titrated out *Aplysia* CREB with nuclear injections of excess CRE oligonucleotide into the sensory neurons. This selectively blocked long-term, but not short-term, facilitation (Dash et al., 1990). These studies provided strong evidence that stimuli leading to long-term memory formation are able to signal to the nucleus and initiate gene expression through the activation of transcription factors such as CREB.

Work on *Aplysia* also provided the first evidence that synaptic active zone structural plasticity accompanies long-term memory. The number, size, and vesicle pool of synaptic active zones increased following long-term sensitization and decreased following long-term habituation (Bailey and Chen, 1983). These structural modifications persisted as long as the behavioral readout of long-term memory (Bailey and Chen, 1989), were not observed during short-term memory paradigms (Bailey and Chen, 1988), and were dependent upon new RNA and protein synthesis (Bailey et al., 1992).

3.2. LTP and LTD

It is widely thought that in mammals, the electrophysiological paradigms of long-term potentiation (LTP) and long-term depression (LTD), akin to *Aplysia* facilitation and depression, may be the synaptic basis of learning and memory (Bliss and Collingridge, 1993, Martin et al., 2000, Malinow and Malenka, 2002, Lynch, 2004, Malenka and Bear, 2004). LTP is defined as long-term synaptic strengthening induced by specific patterns of neural activity (Bliss and Lomo, 1973). Conversely, LTD is long-term synaptic weakening in response to specific patterns of neural activity (Artola and Singer, 1993, Kirkwood and Bear, 1994). LTP and LTD have been described in diverse brain regions including the

hippocampus, the locus for declarative memory formation (Bliss and Lomo, 1973, Levy and Steward, 1979).

Like memory, LTP in slices and *in vivo* is dissociable into two phases. An early phase (E-LTP) that is independent of protein synthesis, and a late phase (L-LTP) that persists for many hours in slices and up to weeks in the intact animal, and is protein synthesis dependent at the time of induction (Krug et al., 1984, Stanton and Sarvey, 1984, Deadwyler et al., 1987, Frey et al., 1988, Huber et al., 2001, Karachot et al., 2001). The exact timing and length of E-LTP and L-LTP vary depending on the precise induction protocol and the timing of protein synthesis inhibitor application. Forms of hippocampal LTD dependent upon activation of group 1 metabotropic glutamate receptors (mGluRs), and cerebellar LTD at granule cell to purkinje cell synapses also require protein synthesis (Huber et al., 2000, Karachot et al., 2001). Hippocampal mGluR-LTD particularly has been shown to rely on local dendritic translation of mRNAs already present near the synapse (Huber et al., 2000). While in cultured purkinje cells, LTD has been dissociated into an early phase lasting approximately 45 minutes that is independent of translation and a late phase that is protein synthesis dependent (Linden, 1996), in slices the requirement for protein synthesis is acute and necessary for the induction of LTD not just its long-term maintenance (Karachot et al., 2001).

Modulation of synaptic strength by LTP and LTD is generally thought to occur through the trafficking of AMPA receptors to and from the synapse (Isaac et al., 1995, Liao et al., 1995, Carroll et al., 1999, Heynen et al., 2000) from extrasynaptic locations as well as from intracellular pools (reviewed in Malinow and Malenka, 2002). However LTP has also been associated with the growth of new synaptic connections. Induction of LTP *in vivo* and in hippocampal slices using a robust paradigm of repetitive, high frequency stimulation of the Schaffer collateral-commissural projections from CA3 to CA1 results in new synapse formation on dendritic shafts and stubby spines of CA1 neurons as revealed by electron microscopy (Lee et al., 1980, Chang and Greenough, 1984). In slice experiments, LTP that persisted at least 8 hours was accompanied by persistent changes in synapse numbers (Chang and Greenough, 1984) suggesting that L-LTP is accompanied by long-term morphological changes to synapses. Conversely, LTD may be accompanied by synapse loss. Repeated pharmacological induction of LTD in hippocampal slices is accompanied by a loss of synaptic structures (Shinoda et al., 2005, Kamikubo et al., 2006).

LTP and LTD also share signaling pathways with *Aplysia* plasticity paradigms. Both cAMP and PKA activity have been implicated particularly in L-LTP (Frey et al., 1993, Huang and Kandel, 1994, Abel et al., 1997). Transgenic mice with reduced PKA activity show defects in LTP and LTD (Abel et al., 1997, Hensch et al., 1998) as well as in spatial memory (Frey et al., 1993, Bourtchuladze et al., 1994, Abel et al., 1997, Hensch et al., 1998). It has been reported that CREB too plays a role in LTP. Mice lacking the alpha and delta isoforms of CREB exhibit deficits in LTP in the hippocampus and impaired long-term memory (Bourtchuladze et al., 1994), however these findings remain controversial (Gass et al., 1998). Thus, analogous to how *Aplysia* facilitation and depression seem to underlie simple forms of non-declarative memory, mechanisms of LTP and LTD in vertebrates are thought to underlie adult behavioral plasticity related to learning and memory and indeed share similar cellular pathways.

3.3. Developing Circuit Refinement

It is perhaps unsurprising that LTP and LTD are also implicated in experience dependent plasticity that occurs during brain development, when synapses and neuronal branches are selected for stabilization or elimination based on salient activity patterns (Bear and Rittenhouse, 1999, Lynch, 2004, Hensch, 2005, Hofer et al., 2006). During nervous system

development, after axonal outgrowth and the staking out of prospective innervation domains by axonal and dendritic arbors, there is a period when neural activity directs the precision of synaptic connections through selective synapse stabilization or elimination, concomitant with dendritic and axonal arbor elaboration or pruning (Constantine-Paton et al., 1990, Goodman and Shatz, 1993, Katz and Shatz, 1996). In pioneering studies of the developing kitten and monkey visual system, Hubel and Wiesel were the first to demonstrate how sensory experience could influence the structure and function of brain circuits. They showed that occluding vision through one eye during early postnatal development, known as monocular deprivation, caused thalamocortical afferents from the spared eye to commandeer cortical territory normally innervated by projections from the deprived eye (Hubel et al., 1977). Consistent with this altered wiring of the visual cortex, cortical neurons monitored by single unit recordings shifted their responsiveness towards the spared eye (Wiesel and Hubel, 1963, Hubel et al., 1977). These structural changes and functional ocular dominance shifts took place in response to manipulations of the visual environment only during a specific developmental time window, termed the critical period (Wiesel, 1982). The critical period, during which experience provides patterns of activity that direct circuit refinement, has since emerged as a key developmental feature of sensory systems across many species (Hensch, 2004) and is likely relevant to cognitive and social development as well (Blakemore, 2010).

Activity-dependent pruning and selection of functionally appropriate pre- and postsynaptic partners is common in the developing nervous system (Chen and Regehr, 2000, Lichtman and Colman, 2000, Hashimoto and Kano, 2003, Hashimoto and Kano, 2005, Hooks and Chen, 2006). In this context, an appropriate connection is defined as a connection where pre- and postsynaptic activity are correlated, in other words a Hebbian synapse. The Hebbian hypothesis, “Neurons that fire together, wire together” (Katz and Shatz, 1996), provides a theoretical basis for linking plasticity during sensory system development with plasticity in the adult hippocampus and neocortex. In the developing visual system, as well as in the adult cortex, the ability of postsynaptic cells to detect coincident activity derives from the NMDA-type glutamate receptor (Kleinschmidt et al., 1987, Fox et al., 1989, Bear et al., 1990). Due to its Mg^{2+} block at resting potentials, the NMDA receptor has been considered a Hebbian molecular coincidence detector for correlated activity (Malenka and Nicoll, 1993). Its activation by glutamate can occur only with removal of the Mg^{2+} block after neuronal depolarization by synaptic AMPA type glutamate receptors. Thus, it can act as a detector for closely spaced stimuli generated when neighboring fibers are activated synchronously, or the same fiber fires in rapid succession. Consistent with this, the NMDA receptor is required for developmental plasticity (Kleinschmidt et al., 1987, Bear et al., 1990, Fox et al., 1996, Rajan et al., 1999, Iwasato et al., 2000, Sin et al., 2002), as well as for learning and memory (McHugh et al., 1996, Tsien et al., 1996, Nakazawa et al., 2002) and certain forms of LTD and LTP (Kirkwood et al., 1993).

The rodent visual system has been a particularly robust model for studying developmental plasticity. The ocular dominance shift seen in visual cortex cells in response to monocular deprivation during the developmental critical period is characterized by a depression of the deprived eye response followed by a potentiation of the open eye response (Frenkel and Bear, 2004). NMDA-dependent LTP can be elicited in visual cortex slices of the same age using the same stimulation protocols that induce LTP in the CA1 region of a hippocampal slice (Artola and Singer, 1987, Kirkwood et al., 1993, Kirkwood and Bear, 1994). LTD can also be elicited in a visual cortical slice through repetitive low frequency stimulation (Kirkwood and Bear, 1994) and by monocular deprivation *in vivo* in the developing visual cortex (Rittenhouse et al., 1999). Further, LTP and LTD in the visual cortex are most pronounced during the developmental critical period for ocular dominance plasticity, and diminish with age (Kirkwood et al., 1995, Bear and Abraham, 1996, Dudek and Friedlander,

1996). These and additional studies showing that visual experience can enhance or diminish LTP and LTD in visual cortical slices (Kirkwood et al., 1996) have lent support to the theory that the properties of synaptic LTP and LTD can account for many aspects of activity-dependent plasticity in the developing visual cortex (Bear et al., 1987).

Some of the same kinases that signal in pathways upstream of activity-dependent gene expression programs triggered by Ca^{2+} influx through the NMDA receptor during learning and memory or LTD/LTP, such as ERK, PKA, and CAMKIIα, have also been shown to be important mediators of developmental plasticity (Gordon et al., 1996, Di Cristo et al., 2001, Berardi et al., 2003, Taha and Stryker, 2005). CREB, which plays a critical role in learning and memory, and LTP across species (Frank and Greenberg, 1994, Stevens, 1994, Silva et al., 1998), is also involved in developmental plasticity. In the visual system, CREB-mediated gene expression is upregulated in the visual cortex contralateral to the deprived eye in response to monocular deprivation (Pham et al., 1999), and mutant mice with reduced CREB expression are deficient in refinement of retinogeniculate projections (Pham et al., 2001). Expression of a dominant-negative form of CREB has been used to demonstrate that CREB function is essential for ocular dominance plasticity in the visual cortex (Mower et al., 2002). CRE elements that bind CREB have been identified upstream of the CaMKIIα (Olson et al., 1995) and BDNF (Shieh et al., 1998, Tao et al., 1998) genes. Mouse mutants with manipulations in CaMKIIα and BDNF show deficits in visual system developmental plasticity. Approximately half of CaMKIIα mutants exhibit dramatically reduced ocular dominance plasticity in response to monocular deprivation (Gordon et al., 1996). In transgenic mice expressing elevated levels of BDNF, development of GABAergic innervation is accelerated (Huang et al., 1999), resulting in early onset and premature termination of the critical period for ocular dominance plasticity (Hanover et al., 1999, Huang et al., 1999).

Because of the similarities between the activity-dependent cellular pathways for transcriptional activation in behavioral and electrophysiological paradigms of plasticity, many genes isolated or characterized on the basis of response to activity in the adult have also been investigated in the context of development during critical period plasticity. Indeed most activity-regulated genes show expression patterns that support their participation in multiple forms of plasticity.

3.4. Expression of Activity-Regulated Genes during Plasticity: learning and memory, LTP, and development

Consistent with evidence showing that activity-dependent gene transcription is required for plasticity, many activity-regulated genes are activated concurrent with paradigms of plasticity. Stimuli that induce LTP induce activity-regulated gene expression, suggesting their involvement in learning and memory. Genes activated during LTP include *zif/268*, c-*fos*, c-*jun*, *rgs2*, *arc/arg3.1*, *homer1a*, *snk*, *tPA*, *arcadlin*, *narp*, and *bdnf* (Cole et al., 1989, Wisden et al., 1990, Patterson et al., 1992, Qian et al., 1993, Link et al., 1995, Lyford et al., 1995, Tsui et al., 1996, Brakeman et al., 1997, Hevroni et al., 1998, Ingi et al., 1998, Kauselmann et al., 1999, Yamagata et al., 1999).

Spatial exploration of a novel environment induces expression of the IEGs *arc/arg3.1* and *homer1a* (Guzowski et al., 1999, Vazdarjanova et al., 2002). *arg/arg3.1* in particular has been shown to be induced in distinct but overlapping ensembles of hippocampal neurons after exposure to two separate novel environments, suggesting that *arc/arg3.1* may play a role in spatial coding (Guzowski et al., 1999). Additionally, *arc/arg3.1* induction shows orientation selectivity in the visual cortex as assessed by two-photon imaging of knock-in mice expressing green fluorescent protein from the *arc/arg3.1* locus. Homozygous green fluorescent protein knock-in mice, which completely lack *arc/arg3.1*gene expression, have

broader orientation-tuning curves than their heterozygous counterparts suggesting that *arc/arg3.1* expression may be important for sharpening neuronal responses (Wang et al., 2006).

Many activity-regulated genes also have distinct spatiotemporal developmental expression profiles that correspond to periods of heightened synaptogenesis and activity-dependent circuit refinement. For example, *cpg15* expression in the visual system begins first in the retina, progresses to the lateral geniculate nucleus of the thalamus, and then finally the cortex, as these structures sequentially mature (Nedivi et al., 1996, Corriveau et al., 1999). The peak of *cpg15* expression in the cortex, at postnatal day 28, corresponds to the height of the critical period for visual cortex plasticity (Lee and Nedivi, 2002). Other activity-regulated genes with developmental expression profiles consistent with a role in activity-dependent circuit refinement include the transcription factors *c-fos*, and *zif/268* (Parma et al., 1991, Herms et al., 1994) as well as the effector genes *rgs2*, *arc/arg3.1*, *cpg2*, *homer1a*, *tPA*, *arcadlin*, *npas4*, *narp*, and *bdnf* (Bozzi et al., 1995, Lyford et al., 1995, Nedivi et al., 1996, Tsui et al., 1996, Brakeman et al., 1997, Yamagata et al., 1999, Ingi and Aoki, 2002, Mataga et al., 2002, Lin et al., 2008). Sensory manipulations during development, such as monocular deprivation, alter the expression of activity-regulated genes such as *arc/arg3.1*, *cpg15*, and *bdnf* (Bozzi et al., 1995, Lee and Nedivi, 2002, Tagawa et al., 2005). Monocular deprivation increases *arc/arg3.1* expression in cortex contralateral to the deprived eye, while it decreases *bdnf* and *cpg15* expression suggesting a complex transcriptional response to altered patterns of activity.

Activity-regulated gene expression is also modulated by sensory experience in primary sensory areas of adult cortex, consistent with a role in plasticity of primary sensory map representations. Visual activity in particular has been shown to regulate the adult cortical expression of a number of activity-regulated genes. Manipulating visual activity by intraocular injections of tetrodotoxin, or by dark adaptation followed by light exposure regulates adult expression of the genes *zif/268*, *arc/arg3.1*, *cpg2*, *homer1a*, *cpg15*, *narp*, and *bdnf* (Castren et al., 1992, Lyford et al., 1995, Nedivi et al., 1996, Tsui et al., 1996, Brakeman et al., 1997). As during development, monocular deprivation alters expression of *arc/arg3.1*, and *bdnf* in visual cortex (Bozzi et al., 1995, Tagawa et al., 2005). Other cortical regions also exhibit experience-dependent gene expression. Single whisker experience in the adult increases expression of *cpg15* (Harwell et al., 2005) and c-*fos* (Barth et al., 2004) in the spared whisker barrel, and six hours of whisker stimulation leads to the upregulation of *bdnf* mRNA in contralateral barrel cortex (Rocamora et al., 1996).

Distinct but overlapping activity-regulated gene sets are expressed during learning and memory, LTP, developmental periods of high plasticity, and in correlation with changes to sensory map representations in the adult. These expression patterns provide strong evidence that the induction of gene expression by neuronal activity is a ubiquitous mechanism for effecting long-term change in neuronal circuits throughout life, throughout the brain, and for purposes as diverse as vision and cognition. To understand how gene expression leads to plasticity, it is essential to understand the molecular and cellular function of individual activity-regulated genes. Below we discuss the mechanism of action of some activity-regulated genes characterized thus far and their common purpose in adaptive modification of synaptic structure and function.

4. Cellular Function of Activity-Regulated Genes

4.1. Activity-Regulated Genes that Modulate Synaptic Strength

Modulation of synaptic strength can occur through either the pre- or post-synaptic compartment of the neuron. Presynaptic alterations in neurotransmitter release or postsynaptic modifications to glutamate receptor signaling both have potential to impact the

strength of connections in the neurocircuit. While few activity-regulated genes havebeen localized to the presynapse, *rgs2* is an exception. In contrast, postsynaptic trafficking of AMPA or NMDA type glutamate receptors in and out of the synapse has emerged as an important mechanism of activity-dependent synaptic plasticity, for adjusting individual synaptic strengths as during LTP and LTD (Isaac et al., 1995, Liao et al., 1995, Carroll et al., 1999, Heynen et al., 2000) and for homeostatic adjustment of synaptic transmission across the cell (Turrigiano, 2008). Several of the best-characterized activity-regulated effector genes, *arc/arg3.1*, *cpg2*, and *homer1a*, converge on the post-synaptic machinery that directly regulates glutamate receptor trafficking. Additionally, synaptic strength can be indirectly modulated by regulating synapse size, as is the case for the activity-regulated, intracellular kinase gene *snk*.

4.1.1. regulator of gene signaling 2 (rgs2)—RGS2 is member of a large family of GTPase activating proteins (GAPs), several of which are expressed in the brain, yet it is unique within this family in its rapid regulation by neuronal activity (Ingi et al., 1998). *rgs2* mRNA is expressed in multiple brain regionsincluding the cortex, hippocampus, amgdala, and striatum (Ingi et al., 1998, Grafstein-Dunn et al., 2001). The RGS2 protein modulates intracellular signaling through its role as a GAP. GAPs inhibit signaling of heterotrimeric G-proteins by increasing the rate of hydrolysis of the small nucleotide GTP by the alpha subunit (Koelle, 1997). RGS2 specifically acts on Gqα and Giα subunits (Ingi et al., 1998), and can block Gsα signaling to some adenylate cyclases (Sinnarajah et al., 2001). At the presynapse, Giα signaling can inhibit Ca^{2+} channels. RGS2 affects short-term plasticity by downregulating presynaptic Giα signaling, resulting in increased Ca^{2+} concentrations and enhanced neurotransmitter release probability (Han et al., 2006). Mutant mice lacking the *rgs2* gene display normal behavior in learning and memory tasks. However, their hippocampal CA1 pyramidal neurons exhibit weaker connectivity measured as reduced spine numbers and altered input/output curves (Oliveira-Dos-Santos et al., 2000). The mechanism by which RGS2 may regulate spine, and hence synapse density is not known, and could be due to compensatory adjustments to altered synaptic excitability in these mice (Oliveira-Dos-Santos et al., 2000). *rgs2* mutant mice display increased anxiety and reduced male aggression (Oliveira-Dos-Santos et al., 2000), perhaps related to the regulation of *rgs2* by dopamine (Ingi et al., 1998). While the role of RGS2 in neurons is still far from clear it is likely an important presynaptic player in synaptic plasticity.

4.1.2. activity-regulated cytoskeleton-associated (arc/arg3.1)—*arc/arg3.1* mRNA is somatodendritically localized (Link et al., 1995, Lyford et al., 1995) where it is locally translated in response to synaptic activity (Steward et al., 1998). This spatial and temporal coupling allows for an additional level of activity-dependent control, with local activity regulating mRNA translation at specific synapses or dendritic segments (Huang, 1999). The cellular function of the Arc/Arg3.1 protein was neatly laid out in a recent set of complementary studies (Chowdhury et al., 2006, Plath et al., 2006, Rial Verde et al., 2006, Shepherd et al., 2006). Arc/Arg3.1 interacts with components of the postsynaptic endocytic machinery, Endophilin A2 & A3 and Dynamin (Chowdhury et al., 2006). Endophilins regulate Clathrin-mediated endocytosis through interactions with dynamin and other components of the endocytic machinery (Conner and Schmid, 2003). Dynamin is a large GTPase that aids in pinching off endosomes from the plasma membrane during Clathrin-mediated endocytosis (Praefcke and McMahon, 2004, Roux et al., 2006). In the presence of Arc/Arg3.1, glutamate receptor endocytosis is enhanced, reducing cell surface levels of AMPA receptors (Chowdhury et al., 2006) and consequently, synaptic transmission (Rial Verde et al., 2006). Binding of the AMPA receptor subunit GluR2 C-terminal tail to the Clathrin adaptor complex AP2 is required for glutamate receptor endocytosis during LTD (Lee et al., 2002) and for downregulation of synaptic transmission by Arc/Arg3.1.

Overexpression of Arc/Arg3.1 precludes the expression of LTD, suggesting that they utilize common molecular machinery (Rial Verde et al., 2006), and that patterns of activity that initiate synaptic weakening by LTD could act through Arc/Arg3.1.

Arc/Arg3.1's function is also consistent with a role in regulating synaptic homeostasis (Rial Verde et al., 2006, Shepherd et al., 2006, Gao et al., 2010). In order to ensure that synaptic responses do not become saturated by repeated potentiation or depression, synaptic strength is scaled up or down across all synapses while the relative difference between individual synapses is maintained (Turrigiano, 2008). Thus, activity regulated genes can act to implement forms of plasticity that serve to weaken as well as strengthen synapses.

While gross organization of the visual cortex in mice lacking the *arc/arg3.1* gene appears normal, they have abnormal cortical responses to visual stimuli and reduced ocular dominance plasticity during the critical period, indicating that *arc/arg3.1* may also be required developmentally for proper connectivity (McCurry et al., 2010).

4.1.3. candidate plasticity gene 2 (cpg2)—CPG2 is also involved in the endocytosis of synaptic glutamate receptors, however, unlike Arc/Arg3.1, CPG2 regulates the trafficking of both AMPA and NMDA type receptors. There are two *cpg2* transcripts that are brain-specific splice variants of the *syne-1* gene expressed in the hippocampus, cerebral cortex, striatum, and cerebellum (Cottrell et al., 2004). Other transcripts from the *syne-1* gene encode proteins with different cellular and tissue specificity. CPG2 protein is found postsynaptically, exclusively at excitatory synapses on excitatory neurons, and therefore mostly in dendritic spines. Electron microscopy studies show that CPG2 in spines is situated below and lateral to the postsynaptic density (PSD), localized to an endocytic zone containing Clathrin-coated pits and vesicles (Cottrell et al., 2004). The spine endocytic zone has been proposed to be an important site of constitutive as well as activity-dependent glutamate receptor internalization (Racz et al., 2004). RNAi-mediated *cpg2* knockdown in cultured neurons leads to a decrease in glutamate receptor endocytosis, by both constitutive and activity-dependent processes. Although there is also a corresponding decrease in receptor insertion, overall knockdown leads to an accumulation of receptors on the membrane, suggesting that CPG2 is important for regulating rapid receptor turnover. Activity-dependent regulation of *cpg2* levels could be a mechanism for modulating rates of Clathrin-mediated endocytosis, thus modifying the strength of developing synapses and influencing their selection for stabilization versus elimination during activity-dependent circuit refinement (Cottrell et al., 2004).

4.1.4. homer homolog 1a (homer1a)—The activity-regulated gene *homer1a* acts to regulate synaptic strength through its interaction with elements of the postsynaptic protein scaffold. Homer1a belongs to the Homer family of proteins, encoded by splice variants of three Homer genes, Homer1–3. Homer1a is unique in several ways among Homer family members. It is transcriptionally regulated by activity, unlike all other constitutively expressed Homer proteins (Xiao et al., 1998). Additionally, all Homer proteins except Homer1a have a C-terminal coiled-coil domain through which they can oligomerize with each other leaving their N-terminal EVH1 (Ena/vasodilator-stimulated phosphoprotein homology 1) domain free to interact with other proteins such as the type 1 mGluR and the inositol triphosphate receptor (Brakeman et al., 1997, Xiao et al., 1998). Type I mGluRs are G-proteins coupled receptors that modulate synaptic transmission (Niswender and Conn, 2010). They act by signaling through phosphatidylinositol, which in turn activates the inositol triphosphate receptor and induces Ca^{2+} release from intracellular stores. This signaling pathway is important for regulating surface expression of AMPA and NMDA receptors in some forms of LTP and LTD (Snyder et al., 2001, Xiao et al., 2001). Homer proteins bind type I mGluRs as well as the inositol triphosphate receptor, bringing them

together to form multimeric signaling complexes. Homer1a, due to its lack of a coiled-coil domain, can interact with Homer binding partners, but not other Homer proteins. Thus, it acts as a natural, inducible dominant negative that disrupts Homer-mediated scaffolding and hence signaling complex formation (Xiao et al., 1998).

Activity-independent, long-tailed Homer proteins also provide a physical bridge between the PSD and the endocytic zone (Lu et al., 2007) by interacting both with Shank, a member of the PSD-95 postsynaptic complex, and Dynamin-3, which anchors the Clathrin-mediated endocytic machinery (Tu et al., 1998, Gray et al., 2003, Lu et al., 2007). By breaking this link, Homer1a untethers the endocytic zone from the PSD. Without the endocytic zone, rapid glutamate receptor cycling is disrupted, and synaptic transmission is decreased (Lu et al., 2007). Homer1a also reduces the size of the spine and the PSD, presumably through disruption of synaptic scaffolding, a phenomenon that goes hand in hand with synaptic weakening (Sala et al., 2003). Like Arc/Arg3.1, Homer1a may work in a negative feedback loop that acts to down-regulate synaptic transmission after synaptic activation in order to homeostatically reset synaptic strength to pre-stimulation levels (Sala et al., 2003, Van Keuren-Jensen and Cline, 2006).

4.1.5. serum-induced kinase (snk)—Intracellular signaling also plays a major role in the regulation of synaptic strength. *snk*, also known as *pololike kinase 2* is expressed at low basal levels in the neocortex, hippocampus, and amygdala, among other brain regions (Kauselmann et al., 1999). In response to activity, SNK protein accumulates in the cell bodies and dendrites of CA1 pyramidal neurons (Kauselmann et al., 1999), as well as in dendritic spines (Pak and Sheng, 2003). SNK regulates synaptic strength through phosphorylation of the PDZ domain containing protein SPAR (spine-associated RAS GTPase activating protein). PDZ domains mediate modular protein-protein interactions that allow for PDZ containing proteins to form large multi-molecular complexes. The PSD of the synapse is composed of a protein scaffold consisting of multiple PDZ containing proteins that also interact with other synaptic and spine proteins such as receptors and the cytoskeleton. SPAR is one such scaffolding component of the PSD (Kim and Sheng, 2004) that interacts with PSD-95 to promote spine growth. Once phosphorylated, SPAR is targeted for ubiquitination and degradation leading to synaptic weakening and potentially synapse and spine elimination (Pak and Sheng, 2003, Ang et al., 2008). SNK's ability to weaken synapses has been shown to regulate synaptic scaling and membrane excitability (Seeburg et al., 2008, Seeburg and Sheng, 2008) suggesting that, like the other postsynaptic activity-regulated genes discussed above, it may be important for mediating homeostatic synaptic plasticity.

4.2. Activity-Regulated Genes that Act in Synapse Addition and Elimination

Modulating synaptic strength is one strategy towards the lasting circuit modifications underlying activity-dependent processes. During developing circuit refinement and likely during adult learning and memory, these functional synapticadjustments are often accompanied by structural changes that effectively alter synapse numbers. The activity-regulated gene *cpg15* has been implicated in arbor-wide structural remodeling of axons, dendrites, and spines. Other genes such as *tPA* and *arcadlin*, seem to specifically effect dendritic spines.

While much work has focused on elucidating the mechanisms underlying excitatory circuit plasticity, recent studies have begun to shed light on the activity-dependent mechanisms underlying inhibitory synapse plasticity. This is a highly significant area of study given the key role that inhibitory circuit maturation plays in critical period onset and closure (Hensch, 2004), and the potential role of inhibition in regulating plasticity in the adult brain (Maya

Vetencourt et al., 2008, Spolidoro et al., 2009). Two activity-regulated genes have been described that regulate the inhibitory circuit. *npas4* controls inhibitory synapse numbers, and *narp* may modulate inhibitory drive by selectively controlling the number of excitatory synapses on inhibitory neurons in the central nervous system. It is important to keep in mind that changes in synaptic strength and number can be tightly coupled, interdependent processes. During activity-regulated synapse formation and elimination, synapses are often strengthened prior to further synapse addition, or they are weakened and then lost.

4.2.1. candidate plasticity gene 15 (cpg15)—*cpg15* (also termed *neuritin*) is a highly conserved gene involved in dendritic and axonal arbor remodeling. CPG15 protein is secreted and attached to the extracellular surface of the cell through a glyosyl-phosphatidylinositol anchor that can be cleaved to release CPG15 extracellularly (Naeve et al., 1997, Putz et al., 2005). The CPG15 protein is targeted to projection axons (Nedivi et al., 2001), and can be trafficked from intracellular vesicles to the cell surface of axons in response to neuronal activity (Cantallops and Cline, 2008). This suggests that CPG15 expressed presynaptically may act as an intercellular signal to promote postsynaptic arbor remodeling.

Overexpression of *cpg15* in the *Xenopus* optic tectum *in vivo* has profound non-cell autonomous effects on the maturation of both synapses and arbors. Elevated CPG15 levels result in increased dendritic and axonal arbor size and complexity (Nedivi et al., 1998, Cantallops et al., 2000) at the same time promoting the acceleration of synapse maturation through insertion of AMPA-type glutamate receptors into NMDA-only silent synapses (Cantallops et al., 2000). CPG15 also affects the structural maturation of mammalian neurons. *In vitro*, neurite outgrowth and branching increase in the presence of exogenous CPG15 protein (Naeve et al., 1997, Fujino et al., 2008). Similar to neurotrophins, CPG15 can promote neuronal survival as well as differentiation (Putz et al., 2005).

4.2.2. tissue-type plasminogen activator (tPA)—Central nervous system neurons are embedded in an extracellular environment composed of a complex and dense glycoprotein scaffold known as the extracellular matrix (ECM). This matrix and the adhesive proteins within it must first be degraded for structural rearrangements to occur, such as process growth and extension or formation and dismantling of synaptic connections. Proteolysis is required for ECM degradation, but it may also play a role in structural and synaptic plasticity by converting proteins to their active forms and cleaving signaling molecules (Lee et al., 2008). The gene encoding a secreted serine protease, *tPA*, is an IEG regulated by neuronal activity in the brain (Qian et al., 1993). Proteolysis by tPA is important both very early in development and throughout adulthood. Early in neuronal development, tPA can be released from growth cones of neurites extending from cultured neuroblastoma cells (Krystosek and Seeds, 1981). In hippocampal cultures, tPA activity leads to increased axon elongation and the formation of putative synapses (Baranes et al., 1998). During the critical period of visual cortex development, tPA proteolysis is necessary for the rapid pruning of dendritic spines in response to monocular deprivation during ocular dominance plasticity. tPA contributes to synaptic refinement by enabling pruning during postnatal development. Presumably the pruned spines reflect the loss of connections specific to inputs from the deprived eye (Mataga et al., 2004). This is consistent with *in vivo* imaging studies showing elevated tPA proteolytic activity concurrent with enhanced spine motility after 2 days of monocular deprivation (Mataga et al., 2002, Oray et al., 2004). *tPA* knockout mice develop apparently normal visual responses during the critical period. However, upon monocular deprivation they show virtually no ocular dominance plasticity even with prolonged deprivation, suggesting that *tPA* is essential for visual cortex plasticity during this period (Mataga et al., 2002). Perhaps due to its role in structurally modulating synaptic connections, *tPA* is also important for L-LTP in the hippocampus (Huang et al., 1996),

suggesting a role for *tPA* that may extend beyond development to mediate plasticity in the mature brain.

4.2.3. activity-regulated cadherin-like protein (arcadlin)—An additional regulator of spine numbers is the transmembrane cadherin encoding gene *arcadlin*, also known as *paraxial protocadherin* (*PAPC*) in mice. Cell adhesion molecules, particularly N-cadherin which is abundant at excitatory synapses in the hippocampus, have been implicated in paradigms of synaptic plasticity such as LTP (Tang et al., 1998, Bozdagi et al., 2000, Tanaka et al., 2000). However, *arcadlin* is the only cadherin known to be transcriptionaly regulated by activity. *arcadlin* is expressed in many brain regions including the hippocampus, limbic structures, the thalamus, and the amygdala (Yamagata et al., 1999). Arcadlin protein is found in neuronal cell bodies and dendrites and is also localized to synapses (Yamagata et al., 1999, Yasuda et al., 2007). In the presence of Ca^{2+}, Arcadlin binds homophilically via its extracellular domains (Yamagata et al., 1999) and can also bind N-cadherin (Yasuda et al., 2007). In response to neuronal activity, Arcadlin is transiently expressed in hippocampal neurons (Yamagata et al., 1999). This leads to temporary increases in synaptic levels of Arcadlin, increasing homophilic Arcadlin interactions. Homophilic binding triggers an intracellular signaling cascade, activating the MAP kinase kinase kinase, TAO2β, which binds the intracellular domain of Arcadlin. TAO2β signaling activates the p38 MAPK that then feeds back to phosphorylate TAO2β, leading to the internalization of Arcadlin and N-cadherin complexes. Cultured neurons from mutant mice lacking the *arcadlin* gene have more spines than wild-type neurons, suggesting that *arcadlin* expression may ultimately lead to spine and synapse loss (Yasuda et al., 2007). Arcadlin's function as a negative regulator of synapse numbers suggests it plays a role in balancing synapse formation with synaptic pruning and elimination during activity-dependent plasticity.

4.2.4 neuronal PAS domain protein 4 (npas4)—The recently identified, activity-regulated transcription factor, Npas4, specifically regulates inhibitory synapse development (Lin et al., 2008). Npas4 was discovered using a DNA microarray screen for genes specifically upregulated by activity during periods of inhibitory synapse development in cortical neurons. RNAi knockdown of *npas4* mRNA *in vitro* reduces the number of inhibitory synapses formed, shifting the balance of inhibition and excitation. Mutant mice lacking *npas4* expression exhibit increased anxiety, hyperactivity, and susceptibility to seizures, consistent with a defect in inhibitory circuit function. While electrophysiological recordings in acute hippocampal slices from global *npas4* mutant mice show no defect in inhibitory synapse function, acute deletion of *npas4* in hippocampal slices does lead to a pronounced decrease in the frequency of miniature inhibitory postsynaptic potentials, suggesting that fewer functional inhibitory synapses are formed. Conversely the ectopic introduction of excess copies of the *npas4* gene results in the formation of more and stronger inhibitory synapses. As a transcription factor, Npas4 works to regulate inhibitory synapse number through the transcriptional control of effector genes. Understanding the functions of Npas4 transcriptional targets will provide further insight into the mechanisms that regulate inhibitory synapse function.

4.2.5. neuronal activity-regulated pentraxin (narp)—Another effector of synapse number is Narp, a member of the pentraxin family. Pentraxin proteins are secreted Ca^{2+} binding lectins with a variety of functions. Narp protein facilitates synaptogenesis and regulates synaptic strength through the clustering of postsynaptic AMPA receptors (O'Brien et al., 1999, Chang et al., 2010). Interestingly, Narp selectively aggregates AMPA receptors on aspiny neurons. On excitatory cells, excitatory synapses occur primarily on dendritic spines while on inhibitory aspiny neurons excitatory synapses occur on the dendritic shaft.

Narp protein is located both pre- and postsynaptically in axons of excitatory neurons and dendrites of aspiny neurons, clustering at excitatory synapses on dendritic shafts (O'Brien et al., 1999). Single axons can form synapses on both dendritic shafts and spines, but Narp secretion is selectively restricted to shaft synapses (Mi et al., 2002). Further, Narp immunostaining is seen preferentially at excitatory synapses of a specific subtype of interneurons, the Parvalbumin expressing interneurons. These interneurons are surrounded by a perineuronal net that seems to play a key role in the synaptic localization of Narp (Chang et al., 2010).

Narp works by forming large complexes with itself and a non-activity regulated neuronal pentraxin, NP1, through N-terminal coiled-coil domains (Xu et al., 2003). This leaves the C-terminal pentraxin domains of Narp and NP1 free to interact with AMPA receptors and mediate their aggregation (O'Brien et al., 1999, Xu et al., 2003). In response to activity, cellular levels of Narp rise, increasing the incorporation of Narp into Narp-NP1 complexes, and greatly enhancing both pentraxins' effects on AMPA receptor clustering. This suggests that activity-induced expression of Narp may facilitate the effects of constitutively expressed NP1 on synaptogenesis (Xu et al., 2003). In culture, Narp can also homeostatically regulate GluR4 AMPA receptor content at excitatory synapses on Parvalbumin positive interneurons in response to alterations in activity levels. Tetrodotoxin treatment leads to an increase in GluR4 and miniature excitatory postsynaptic current (mEPSC) amplitude at these synapses, while bicuculline treatment decreases GluR4 incorporation as well as mEPSC amplitude. Cultures from mutant mice without the *narp* gene do not show differences in GluR4 synaptic content and very little change in mEPSC amplitude in response to alterations in activity levels (Chang et al., 2010).

4.3. Pleiotropic Effectors

4.3.1. brain-derived neurotrophic factor (bdnf)—Due to its multifaceted role in neuronal plasticity and development *bdnf* may be the most well studied and extensively characterized activity-regulated gene. It was also one of the first non-transcription factor effector genes found to be regulated by neuronal activity. *bdnf* mRNA expression was shown to be expressed in hippocampus *in vivo* in response to kainate-induced seizures (Zafra et al., 1990) prior to large-scale screens for activity-regulated genes utilizing seizure paradigms (Nedivi et al., 1993, Qian et al., 1993, Yamagata et al., 1993). Transcription of *bdnf* mRNA can be driven from multiple promoters (Timmusk et al., 1993, Aid et al., 2007) which are differentially regulated (Tongiorgi et al., 2006) *bdnf* mRNA also has two alternative sites of polyadenylation (Timmusk et al., 1993). The long version of the transcript is targeted to dendrites where it undergoes local translation, while the short version remains in the soma (An et al., 2008). BNDF is a secreted neurotrophin that binds and signals through the TrkB receptor (Klein et al., 1991, Soppet et al., 1991, Squinto et al., 1991), which is also expressed in the brain (Klein et al., 1989).

Consistent with its identification as a neurotrophin, BDNF regulates the growth of developing axonal and dendritic arbors (McAllister et al., 1995, Cohen-Cory, 1999, Cohen-Cory et al., 2010) in an activity-dependent manner (McAllister et al., 1996, Cohen-Cory, 1999). In addition to its structural effects, BDNF also regulates synaptic transmission at both excitatory (Kang and Schuman, 1995, Carmignoto et al., 1997, Rutherford et al., 1998), and inhibitory synapses (Rutherford et al., 1997). BDNF can also modulate synaptic plasticity, and is important for the induction and maintenance of LTP. Mutant mice lacking the *bdnf* gene display reduced hippocampal LTP (Korte et al., 1995) which can be rescued by application of exogenous BDNF protein (Patterson et al., 1996). In developing mouse hippocampus, application of BDNF to wild-type slices can also induce LTP using a tetanic stimulus that normally elicits only short-term potentiation (Figurov et al., 1996).

In the developing circuit, BDNF is an important mediator of critical period plasticity. In the visual system, transgenic mice overexpressing BDNF under the control of the CaMKIIα promoter exhibit a precocious critical period in the visual cortex (Hanover et al., 1999, Huang et al., 1999). This is due to the effect of BDNF on inhibitory circuit maturation. During development, the balance between excitatory and inhibitory circuit maturation regulates the extent and duration of critical period plasticity (Hensch, 2004). In rodents raised in darkness, inhibitory circuit maturation is delayed (Blue and Parnavelas, 1983b, Blue and Parnavelas, 1983a, Benevento et al., 1992, Benevento et al., 1995) and the critical period is prolonged (Cynader and Mitchell, 1980, Mower, 1991, Fagiolini et al., 1994). BDNF overexpression tips the balance in favor of inhibitory circuit maturation, increasing inhibitory synaptic transmission and the density of GAD65 positive puncta, a marker of putative inhibitory synapses (Huang et al., 1999).

Perhaps key to the multifarious role of BDNF in neuronal plasticity is its ability to regulate other activity-regulated genes. Many activity-regulated genes can be induced in response to extracellular stimuli other than neuronal activity, including neurotrophins like BDNF. Infusion of BDNF into the dentate gyrus of rats leads to a long-lasting form of LTP that requires new gene transcription (Messaoudi et al., 2002). Induced genes include the activity-regulated genes *arc/arg3.1*, *narp*, and *cpg15* (Wibrand et al., 2006). BDNF application to cultured neurons can also induce expression of *tPA* (Fiumelli et al., 1999).

5. Posttranscriptional Regulation

Activity-induced gene products are often dynamically regulated at multiple levels, underscoring the importance of their precise, coordinated activation. Additional layers of activity-dependent regulation include the trafficking of mRNA to dendrites and axons, local dendritic translation induced by synaptic activity, activity-dependent secretion of extracellular proteins, and regulated mRNA degradation.

Many mRNAs can be trafficked to neuronal dendrites where they may undergo local translation (Steward and Schuman, 2001, Bramham and Wells, 2007). These mRNA species often encode proteins important for modifying synapses. Included among these are activity-regulated mRNAs such as *arc*/*arg3.1*, *tPA*, *bdnf* (Steward et al., 1998, Shin et al., 2004, An et al., 2008) and likely many more. mRNAs are largely transported to the dendrites as part of heterogenous RNA-protein complexes (ribonucleoprotein particles). The translocation of ribonucleoprotein particles into dendrites, including those containing *arc/arg3.1* mRNA, can be regulated by neuronal activity (Steward and Schuman, 2001). Certain mRNAs are also trafficked to axons (Taylor et al., 2009) for local translation (Gumy et al., 2010). These mRNAs are thought to be particularly important during development (Lin and Holt, 2007) and after axonal injury (Willis and Twiss, 2006, Taylor et al., 2009, Gumy et al., 2010). *cpg15* mRNA is known to be transported to axons of the peripheral nervous system (Willis et al., 2007, Karamoysoyli et al., 2008) consistent with its role in neurite outgrowth as well as axonal regeneration. It is not clear whether neuronal activity can regulate mRNA trafficking in axons directly. However, the activity-regulated neurotrophin BDNF can affect axonal transport of some mRNAs (Willis et al., 2007).

Once the mRNA is localized to axons or dendrites, translation into protein is also activity-regulated. Local translation allows the spatial and temporal restriction of synapse modifying proteins to regions near activated synapses. One important regulator of dendritic mRNA translation is the cytoplasmic-polyadenylation-element-binding protein (CPEB). There are four CPEB family members that are all thought to regulate translation, but CPEB1 has been most extensively studied. CPEB binds regulatory sites called cytoplasmic-polyadenylation elements (CPEs) in the 3′-untranslated regions of its target mRNAs (Wells et al., 2000). The

Aurora kinase A and CamKIIα can phosphorylate and activate CPEB1 in response to NMDA or mGluR receptor stimulation, pathways also utilized for activity-dependent gene transcription. Unphosphorylated CPEB1 binds to an inhibitor of mRNA polyadenylation, poly(A)-specific ribonuclease (PARN). However, once phosphorylated PARN is released, mRNA polyadenylation and translation can be resumed (Steward and Schuman, 2001, Bramham and Wells, 2007). Activity-induced CPEB1 has been shown to regulate dendritic translation of *tPA* transcripts (Shin et al., 2004).

Another way to regulate protein levels post-transcriptionally is through mRNA turnover, limiting the availability of transcripts for translation. For example, there are translation-dependent mRNA decay mechanisms such as nonsense-mediated decay, whereby mRNA is quickly degraded following a round of translation. If coupled to activity-dependent local translation, this leads to a short spurt of protein synthesis. Nonsense-mediated decay has been shown to regulate the *arc/arg3.1* transcript (Bramham et al., 2008). Another way to modulate transcript abundance is by regulating the stability of the transcript. Many IEG transcripts, such as *arc/arg3.*1, *homer1a*, *cpg15*, and *narp* have long 3′-untranslated regions rich in AU sequences that include the consensus motif AUUUA (Yamagata et al., 1993, Link et al., 1995, Lyford et al., 1995, Tsui et al., 1996, Brakeman et al., 1997, Wang et al., 2011), implicated in mRNA instability and thought to facilitate transient expression of important messages (Shaw and Kamen, 1986).

All of these mechanisms provide tight regulatory control over gene products that mediate cellular plasticity. Some of these mechanisms may also serve to spatially restrict the effects of activity-regulated gene products. Local protein synthesis may be selectively turned on at activated synapses, allowing for synapse-specific plasticity. Other mechanisms, such as mRNA degradation, may instead regulate global availability of these proteins to temporally tune homeostatic cell-wide responses.

6. Conclusions

Experience in the outside world, relayed to the brain by neuronal activity, drives lasting, adaptive changes in neurocircuits. While these changes occur on the grandest scale during development, they do not cease in the adult. Brain plasticity continues throughout life, underlying important brain functions including learning and memory. Neuronal activity at the synapse signals to the nucleus in the form of intracellular signaling pathways that activate a complex transcriptional response. Activity-induced genes then act to further modulate gene expression or to directly affect neuronal properties. Activity-regulated effector genes work via a diverse array of mechanisms to modify synaptic strength or number, ultimately leading to changes in the connectivity of neuronal circuits.

Only a small fraction of the hundreds of known activity-regulated genes have been characterized to date. Despite the slow progress, several important insights are beginning to emerge regarding how these genes work to effect synaptic change. First, multiple activity-regulated genes, including *arc/arg3.1*, *cpg2*, *homer1a*, *snk*, *arcadlin*, and *narp*, encode proteins that impact postsynaptic mechanisms. It is too early to say that the presynaptic compartment is less amenable to activity-dependent regulation since further characterization may reveal additional presynaptic players. It is also important to note the tight coordination and communication between the pre- and postsynaptic compartments, which does not rule out secondary effects by postsynaptically localized proteins on the presynapse. Second, while these genes are all expressed in response to changes in synaptic activity, many function to downregulate synaptic strength and prune synapses. In Hebbian forms of plasticity positive feedback loops are important for strengthening synapses that are highly utilized, however activity-dependent mechanisms are also important for weakening and

pruning inappropriate synapses. *tPA* and *arcadlin* both play a role in synaptic pruning. Additionally, *arc/arg3.1*, *homer1a*, *snk*, and *narp* have all been implicated in synaptic homeostasis (Sala et al., 2003, Rial Verde et al., 2006, Shepherd et al., 2006, Van Keuren-Jensen and Cline, 2006, Seeburg et al., 2008, Seeburg and Sheng, 2008, Chang et al., 2010, Gao et al., 2010), a form of neuronal gain control in which global synaptic weights can be adjusted up or down while relative differences are maintained (Turrigiano, 2008). Finally, many activity-regulated genes modulate inhibitory circuit function including *npas4*, *narp*, and *bdnf*, consistent with studies showing the importance of the balance of inhibition and excitation in regulating plasticity (Hensch, 2004).

It is interesting to note that multiple genes initially identified based on their activity-dependent expression have been independently identified in human genetic screens for susceptibility loci associated with neuropsychiatric disorders. Single nucleotide polymorphisms in *rgs2* have been linked to anxiety disorders (Leygraf et al., 2006, Smoller et al., 2008). The rat *arcadlin* gene is homologous to human *protocadherin 8* (*PCDH8*), in which polymorphisms have been associated with susceptibility to schizophrenia (Bray et al., 2002), as is also the case for *cpg15* (Chandler et al., 2010). Genetic studies have linked *bdnf* to depression (reviewed in Watanabe et al., 2010). Additionally, several other human cognitive disorders have been linked to mutations in genes involved in regulating activity-dependent transcription. These include Rett syndrome, Rubinstein-Taybi syndrome, Coffin-Lowry syndrome, and some forms of autism (Hong et al., 2005, Greer et al., 2009). These findings are consistent with a newly emerging view that many diseases of the brain including mood disorders and cognitive disorders may be related to deficits in brain plasticity (Coyle and Duman, 2003, Zarate et al., 2003, Ramocki and Zoghbi, 2008, Greer et al., 2009). Thus elucidation of activity-regulated gene function and pathways for their regulation may provide insight not only into mechanisms of normal circuit plasticity, but also into circuit dysfunction that occurs during disease.

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List of Abbreviations

RGS2	regulator of gene signaling 2
Arc/Arg3.1	activity-regulated cytoskeleton-associated
CPG2	candidate plasticity gene 2
Homer1a	homer homolog 1a
SNK	serum-induced kinase
CPG15	candidate plasticity gene 15
tPA	tissue-type plasminogen activator
Arcadlin	activity-regulated cadherin-like protein
Npas4	neuronal PAS domain protein 4
Narp	neuronal activity-regulated pentraxin
BDNF	brain-derived neurotrophic factor

IEG	immediate early gene
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
NMDA	N-methyl-D-aspartic acid
GABA	γ-Aminobutyric acid
CaMK	Ca^{2+}-calmodulin-dependent protein kinase
cAMP	cyclic AMP
PKA	protein kinase A
ERK	extracellular related MAP kinase
CREB	CRE-binding protein
CRE	cAMP-response element
LTP	long-term potentiation
LTD	long-term depression
E-LTP	early long-term potentiation
L-LTP	long-lasting long-term potentiation
GAP	GTPase activating protein
mGluR	metabotropic glutamate receptor
PSD	postsynaptic density
EVH1	Ena/vasodilator-stimulated phosphoprotein homology 1
SPAR	spine-associated RAS GTPase activating protein
ECM	extracellular matrix
PAPC	paraxial protocadherin
MAPK	mitogen activated protein kinase
NP1	neuronal pentraxin 1
mEPSC	miniature postsynaptic current
TrkB	receptor tyrosine kinase B
CPEB	cytoplasmic-polyadenylation-element-binding protein
CPE	cytoplasmic-polyadenylation elements
PARN	polyadenylation, poly(A)-specific ribonuclease

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Table 1

Regulation of activity-regulated gene expression

Cellular function	Gene	LTP	Development	Sensory manipulation (juvenile)	Sensory manipulation (adult)
Modulate synaptic strength	*rgs2*	Ingi et al., 1998	Ingi and Aoki, 2002	—	—
	arc/arg3.1	Lyford et al., 1995; Link et al., 1995	Lyford et al., 1995	Tagawa et al., 2005	Lyford et al., 1995
	cpg2	Not regulated by LTP Hevroni et al., 1998	Nedivi et al., 1996	—	Nedivi et al., 1996; Harwell et al., 2005
	homer1a	Brakeman et al., 1997	Brakeman et al., 1997	—	Brakeman et al., 1997
	snk	Kauselmann et al., 1999	—	—	—
Synapse addition and elimination	*cpg15*	—	Nedivi et al., 1996; Corriveau et al., 1999; Lee and Nedivi, 2002	Lee and Nedivi, 2002	Nedivi et al., 1996
	tPA	Qian et al., 1993	Mataga et al., 2002	—	—
	arcadlin	Yamagata et al., 1999	Yamagata et al., 1999	—	—
	npas4	—	Lin et al., 2008	Lin et al., 2008	—
	narp	Tsui et al., 1996	Tsui et al., 1996	—	Tsui et al., 1996
Pleiotropic	*bdnf*	Patterson et al., 1992	Bozzi et al., 1995	Bozzi et al., 1995	Castren et al., 1992; Bozzi et al., 1995; Rocamora et al., 1996; Tagawa et al., 2005