Neuropsychopharmacology REVIEWS (2008) 33, 3–17

Neuroplasticity Mediated by Altered Gene Expression

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Plasticity in the brain is important for learning and memory, and allows us to respond to changes in the environment. Furthermore, long periods of stress can lead to structural and excitatory changes associated with anxiety and depression that can be reversed by pharmacological treatment. Drugs of abuse can also cause long-lasting changes in reward-related circuits, resulting in addiction. Each of these forms of long-term plasticity in the brain requires changes in gene expression. Upon stimulation, second messenger pathways are activated that lead to an enhancement in transcription factor activity at gene promoters. This stimulation results in the expression of new growth factors, ion channels, structural molecules, and other proteins necessary to alter the neuronal circuit. With repeated stimulation, more permanent modifications to transcription factors and chromatin structure are made that result in either sensitization or desensitization of a circuit. Studies are beginning to uncover the molecular mechanisms that lead to these types of long-term changes in the brain. This review summarizes some of the major transcriptional mechanisms that are thought to underlie neuronal and behavioral plasticity.
Neuropsychopharmacology Reviews (2008) **33,** 3–17; doi:10.1038/sj.npp.1301544; published online 29 August 2007

Keywords: addiction; depression; transcription; learning and memory

INTRODUCTION

Neuroplasticity refers to the brain's ability to adapt and change over time. This plasticity underlies all types of memory formation (Barco *et al*, 2006). These can be memories of places, individuals or events. In addition, plasticity occurs in reward- and stress-related centers of the brain, so that one can remember and seek out reinforcing stimuli that are advantageous to survival and avoid potentially dangerous situations. However, drugs of abuse can hijack these circuits and induce abnormally persistent drug reward-related memories and in the extreme addiction (Hyman *et al*, 2006—review of the memory forming processes associated with addiction). Likewise, exposure to physical or emotional stresses can lead to depression or other mood or anxiety disorders (Duman, 2002; Nestler *et al*, 2002). Antidepressants and psychotherapeutic treatments can reverse these stress-related changes, and this is thought to mediate their efficacy. Therefore, long-term plasticity in the brain is highly relevant to both normal learning and memory, and the development and treatment of psychiatric disorders.

Work from diverse fields has suggested that common molecular and cellular mechanisms underlie aspects of all of these types of plasticity, and that long-term plasticity in the brain requires changes in gene expression. The most well-characterized potential cellular mechanisms of plasticity are long-term potentiation (LTP) and long-term depression (LTD) (Malenka and Bear, 2004—a review of what is known about the regulation of LTP and LTD and the role of these events in memory formation). LTP and LTD describe long-lasting changes in the efficiency of synaptic transmission that occur in response to repeated stimulation. The diverse signal transduction pathways implicated in mediating LTP and LTD in different brain regions have been reviewed recently (Malenka and Bear, 2004). Both LTP and LTD appear to be important in the development of all types of memory formation including the reward-related memories associated with drug addiction (Hyman *et al*, 2006). The first indication that new gene expression is required for long-term plasticity came from several studies showing that LTP does not persist when animals are injected with protein synthesis inhibitors (Krug *et al*, 1984; Stanton and Sarvey, 1984—one of the first studies to show that LTP in the hippocampus is dependent on new gene expression; Montarolo *et al*, 1988; Otani *et al*, 1992). These drugs also have severe effects on memory formation, reactivation, and reconsolidation, suggesting that new protein expression is necessary for these processes as well (Davis and Squire, 1984; Rudy *et al*, 2006). Although it has long been thought that protein synthesis was only needed for the induction of the late phase of LTP or LTD, a recent study by Fonseca *et al* (2006) shows that early LTP can also be dependent on protein synthesis when there are high levels of synaptic activation, and that the requirement for new protein synthesis can extend well beyond LTP induction, depending

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Received 23 April 2007; revised 26 June 2007; accepted 22 July 2007

on the degree of synaptic stimulation. Therefore, the regulation of new gene expression in response to stimulation may be important in most aspects of LTP and LTD.

TRANSCRIPTION FACTORS AND PLASTICITY

Gene expression is controlled by a series of DNA-binding proteins known as transcription factors. With cellular stimulation, modifications are made to transcription factors that allow nuclear entry, change protein stability, enhance DNA binding, or allow binding to essential co-factors. Several studies have identified specific transcription factors that are important in the persistence of LTP, LTD, and other forms of neural and behavioral plasticity.

A Role for CREB

The most well-studied transcription factor in the context of neural plasticity is the cAMP response element-binding protein (CREB). CREB binds to the cAMP response element (CRE) in many gene promoters, including several growth factors, enzymes, structural proteins, and other transcription factors (Lonze and Ginty, 2002—an overview of CREB function and CREB family members and how they regulate various processes). CREB can be modified in multiple ways leading to changes in activity or stability of the protein. For example, it can be phosphorylated at multiple sites, acetylated by CREB-binding protein (CBP), ubiquitinated and targeted for degradation, glycosylated, or stabilized through SUMOylation (Johannessen *et al*, 2004). CREB can also interact with at least 30 other proteins, all of which affect the ability of CREB to influence gene expression (Johannessen *et al*, 2004). Upon stimulation, CREB can be activated via phosphorylation at Serine-133 by several signal transduction cascades involving protein kinase A (PKA), Ca^{2+}/calmodulin (CaM)-kinases, and growth-factor related kinases (eg ribosomal S6 kinase, which is downstream of extracellular signal-regulated kinases (ERK)) (Figure 1) (Mayr and Montminy, 2001; Lonze and Ginty, 2002). CREB can also be phosphorylated at Ser-142 by CaMKII, which generally leads to a decrease in activity, however, positive effects of this phosphorylation on transcription have been observed as well (Johannessen *et al*, 2004). In addition, CREB can be phosphorylated at Ser-129 by glycogen synthase kinase β (GSK-3β); the function of this event is still unclear, but it may reduce the activity of CREB at certain gene promoters and enhance activity at others (Salas *et al*, 2003; Hansen *et al*, 2004; Johannessen *et al*, 2004).

Late-phase LTP at cortical synapses leads to an increase in the Ser-133 phosphorylation of CREB (Hotte *et al*, 2007) and an increase in CREB activity is observed in the hippocampus following training in certain tasks, or memory provoking stimuli (Bito *et al*, 1996; Taubenfeld *et al*, 1999). Furthermore, in hippocampal neuronal cultures, activation of NMDA receptors increases Ser-133 CREB phosphorylation, whereas chronic cellular stimulation by bicuculline further increases this NMDA-dependent phosphorylation of CREB (Ehlers, 2003). There is evidence to suggest that multiple signal transduction cascades are required for full activation of CREB. Consequently, CREB-mediated gene expression can be different depending on the strength of the stimulation (Johannessen *et al*, 2004). In addition, activation of certain signal transduction cascades leads to a prolonged Ser-133 phosphorylation of CREB, producing more long-lasting changes in gene expression, while others produce only a transient phosphorylation (Johannessen *et al*, 2004). This prolonged Ser-133 phosphorylation of CREB is seen with stimulation of the ERK pathway, one that is required for LTP maintenance and normal memory (Atkins *et al*, 1998; Schafe *et al*, 2000; Wu *et al*, 2001; Deisseroth and Tsien, 2002). Expression of a constitutively active form of CREB (VP16-CREB) in the CA1 region of the hippocampus lowers the threshold for eliciting the persistent late-phase LTP (Barco *et al*, 2002; Barco *et al*, 2005),

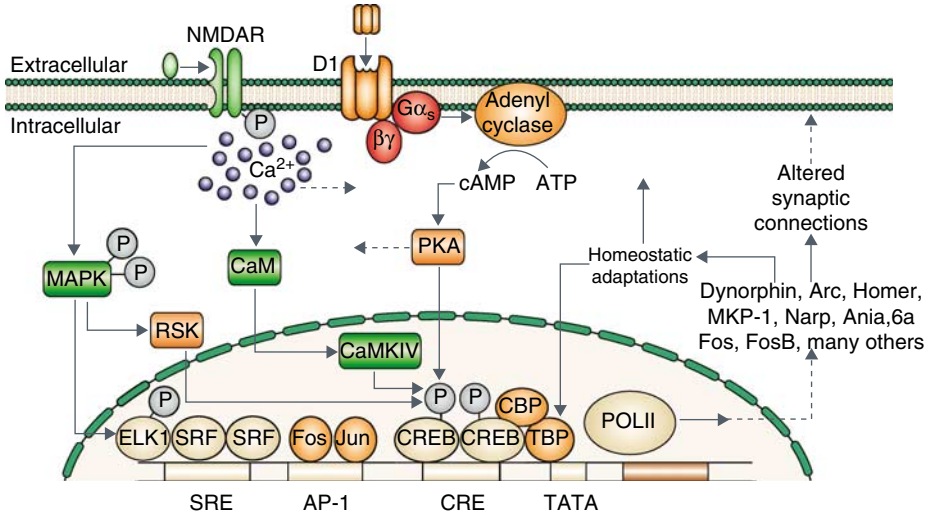

Figure 1 Regulation of CREB activity. Stimulation of D1 dopamine receptors and glutamate receptors on striatal neurons activates several second messenger cascades. Shown in the cell nucleus is a model of binding sites from the *cFos* promoter including a serum response element (SRE), activator protein-1 element (AP-1), and a cyclic AMP (cAMP) response element (CRE). CBP, CREB-binding protein; CREB, cAMP response element binding protein; MAPK, MAP kinase; NMDAR, NMDA receptor; PKA, protein kinase A; TBP, TATA binding protein. Modified from Hyman *et al* (2006).

and promotes NMDA receptor function (Marie *et al*, 2005). Some of these effects are dependent on the CREB target gene, *brain-derived neurotrophic factor (BDNF)* (Barco *et al*, 2005). Moreover, inducible overexpression of CREB in *Drosophila* enhances long-term memory, and overexpression of CREB in the amygdala of rodents leads to enhanced fear memory (Yin *et al*, 1995—one of the original studies implicating CREB in the formation of long-term memory; Josselyn *et al*, 2001; Jasnow *et al*, 2005). Likewise, genetic disruptions of CREB activity in several animal species leads to severe deficits in learning and memory (Yin and Tully, 1996; Mayford and Kandel, 1999; Josselyn *et al*, 2004). Therefore, CREB appears to be central in the formation of long-term memory.

CREB activity is also increased in reward-related areas of the brain following acute or chronic treatment with opiate drugs (such as morphine and heroin) or psychostimulants (such as amphetamine and cocaine) (Konradi *et al*, 1994; Hyman *et al*, 1995; Shaw-Lutchman *et al*, 2002; Shaw-Lutchman *et al*, 2003; Walters *et al*, 2003; Carlezon *et al*, 2005; Olson *et al*, 2005). This induction of CREB activity appears to be involved in regulating reward-related measures associated with addiction. Increasing CREB levels by the use of inducible transgenic mice or viral-mediated gene transfer in the nucleus accumbens (NAc), a crucial brain reward region, decreases the conditioned preference for these drugs, whereas blocking CREB function through expression of a dominant-negative protein has the opposite effect (Carlezon *et al*, 1998; Barrot *et al*, 2002; McClung and Nestler, 2003). Studies of constitutive CREB knockdown mice generally support these findings (Walters and Blendy, 2001). Furthermore, induction of CREB increases the excitability of GABAergic NAc neurons, whereas the dominant-negative CREB (mCREB) decreases neuronal excitability (Dong *et al*, 2006). It is thought that these acute actions of CREB represent a feed-back mechanism in which the increased activation of CREB by drugs of abuse in the NAc induce a decrease in dopaminergic activity, leading to drug tolerance and dependence, as manifested in dysphoria during withdrawal (Figure 2) (Carlezon *et al*, 2005). Indeed, one of the target genes of CREB, *prodynorphin*, encodes a peptide (dynorphin) that is released from NAc neuron projections in the ventral tegmental area (VTA) where it binds to κ opioid receptors on dopaminergic neurons and decreases dopamine release (Cole *et al*, 1995). A recent study by found that inhibition of CREB expression by antisense oligonucleotides in the NAc selectively reduced cocaine self-administration and increased the threshold dose of cocaine needed to reinstate self-administration after a period of withdrawal. These findings suggest that activation of CREB in the NAc, and the downregulation of reward mechanisms, can lead to increased drug self-administration and relapse, perhaps as a result of the associated dysphoria.

CREB activity in other brain regions is also involved in plasticity associated with drug addiction. The actions of CREB in the VTA are complex, in that CREB overexpression in the rostral *vs* caudal subregions of the VTA have opposing effects on opiate and psychostimulant preference (Walters *et al*, 2003; Olson *et al*, 2005). This may be due to differences in the proportion of dopaminergic and GABAergic neurons in these two subregions. CREB in the VTA is also implicated in nicotine reward (Walters *et al*, 2005—an important study that outlines a crucial role for CREB in the ventral tegmental area in nicotine reward). In addition to the VTA, CREB may modulate drug reward through its actions in the lateral hypothalamus (LH). CREB activity is induced in this area following chronic opiate or psychostimulant treatment (Shaw-Lutchman *et al*, 2002; Georgescu *et al*, 2003; Shaw-Lutchman *et al*, 2003; Georgescu *et al*, 2005), and CREB overexpression in the LH increases the conditioned preference for morphine,

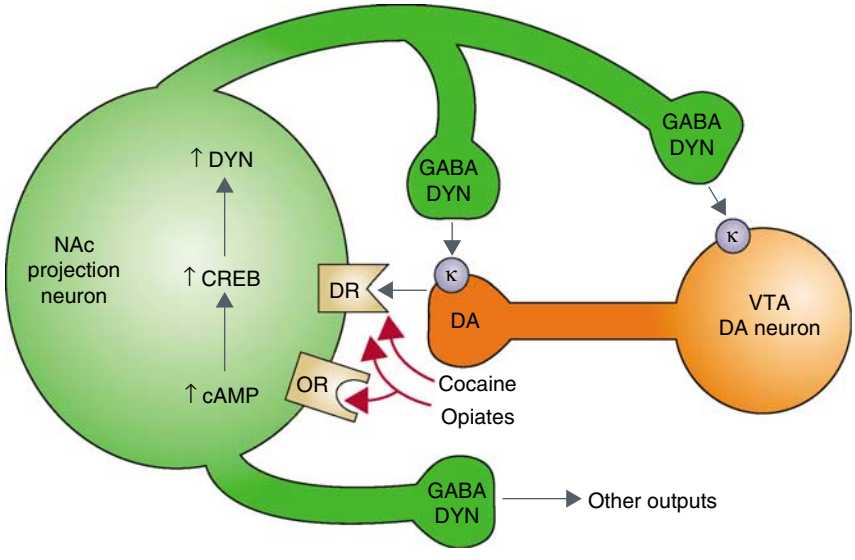

Figure 2 Feedback between the NAc and VTA via CREB activation. Cocaine and amphetamine have been shown to activate *prodynorphin* gene expression in the nucleus accumbens (NAc) and dorsal striatum via D1 dopamine receptor stimulation, the cyclic AMP pathway, and the phosphorylation of CREB. The resulting dynorphin peptides are transported to presynaptic terminals including terminals found on recurrent collateral axons that feedback on dopaminergic neurons. Dynorphin peptides are agonists at inhibitory κ opiate receptors, resulting in decreased dopamine release. Modified from Hyman *et al* (2006).

whereas expression of a dominant-negative CREB decreases morphine preference (Olson *et al*, 2007). Together, these results show that CREB is involved in regulating drug-induced plasticity in multiple brain regions.

CREB also appears to be involved in the development and treatment of mood and anxiety disorders. However, studies showing the effects of stress on CREB activity are highly dependent on the method and duration of stress and brain region examined. For example, CREB activity is increased in the NAc following stress associated with short-term foot shock, restraint, and unfamiliar social interactions, whereas long-term social isolation decreases CREB activity in the NAc (Barrot *et al*, 2002; Barrot *et al*, 2005). Chronic, unpredictable stress also decreases Ser-133 CREB phosphorylation in the dentate gyrus of the hippocampus and the frontal cortex (Gronli *et al*, 2006; Xu *et al*, 2006). However, restraint stress increases CREB activity in the frontal cortex with no effects on the hippocampus (Miller *et al*, 2006).

Induction of CREB causes very different functional effects—either antidepressant-like or pro-depression-like effects—depending on the brain region involved (Duman, 2002; Blendy, 2006; Nestler and Carlezon, 2006). Selective overexpression of CREB in the dentate gyrus of the hippocampus has an antidepressant effect in multiple behavioral measures (Chen *et al*, 2001a). In contrast, overexpression of CREB in the amygdala or NAc has a prodepressant effect, whereas dominant-negative CREB (mCREB) expression results in an antidepressant-like response in several behavioral measures (Pliakas *et al*, 2001; Newton *et al*, 2002; Wallace *et al*, 2004). These results highlight the importance of CREB in this type of plasticity, and how the changes evoked from these types of stimuli differ throughout the brain.

Other CREB family members act as modulators of CRE-mediated transcription and contribute to the regulation of neuronal plasticity. The actions of CREB can be inhibited by the inducible cAMP early repressor (ICER) proteins, which are protein products of the *CRE modulator* gene (*Crem*) (Mioduszewska *et al*, 2003). Although overexpression of CREB in the hippocampus of older rats (15 months old) leads to an improvement in long-term memory over wild-type animals, overexpression of an ICER protein decreases long-term memory in spatial-navigation and passive avoidance tasks (Mouravlev *et al*, 2006). Furthermore, reported recently that acute exposure to either stress or psychostimulants induces ICER proteins in the NAc, and overexpression of an ICER protein in this region through viral-mediated gene transfer, like overexpression of the artificial dominant-negative mCREB, enhances responses to drugs of abuse and natural rewards, and induces an antidepressant-like effect. These results suggest that natural inhibitors of CREB are involved in modulating neural plasticity relevant to drug addiction and stress-related disorders.

A Role for ΔFosB

The Fos family of transcription factors, including cFos, FosB, ΔFosB, Fos-related antigen 1 (Fra1), and Fra2, dimerize with Jun proteins to form an AP-1 transcription factor complex (Hess *et al*, 2004). LTP stimulation in the dentate gyrus leads to an increase in AP-1 DNA binding, 4 h after stimulation, suggesting that this enhanced binding is associated with late-phase LTP and long-term plasticity (Williams *et al*, 2000). All Fos family proteins are induced rapidly in many brain regions following various types of acute stimulation. With more chronic treatments, this induction becomes less and less prominent. However, ΔFosB, a splice variant of the *FosB* gene, is an unusually stable protein that accumulates with chronic treatments (McClung *et al*, 2004—a recent review of the actions and regulation of DeltaFosB). As this protein is so persistent, it is thought that it is important in the induction and maintenance of long-term plasticity. Indeed, ΔFosB is induced by a wide range of chronic stimuli, including repeated exposure to many types of drugs of abuse or stress, in specific brain regions (McClung *et al*, 2004; Perrotti *et al*, 2004). ΔFosB also appears to have different functions over time, in that, it acts much like a transcriptional repressor at AP-1 sites with short-term treatments, but then functions as a transcriptional activator, as it accumulates with more chronic treatments (McClung and Nestler, 2003).

When the FosB gene is knocked out, resulting in the absence of both FosB and ΔFosB, mice have behavioral abnormalities in response to drugs of abuse, and in measures of anxiety and depression, that are more pronounced when mice are stressed, suggesting that this gene is important in the regulation of these responses (Zhu *et al*, 2007). Long-term overexpression specifically of ΔFosB in the NAc mimics an overall addiction-like phenotype seen in response to drugs of abuse (Kelz *et al*, 1999; Colby *et al*, 2003; Zachariou *et al*, 2006). Conversely, the expression of a dominant-negative c-Jun, termed Δc-Jun, which acts as a repressor of AP-1 activity, in NAc opposes this addiction-like phenotype (Peakman *et al*, 2003; Zachariou *et al*, 2006). Long-term ΔFosB expression in the NAc also leads to enhanced food-reinforced instrumental performance and an increase in voluntary wheel running, suggesting that it is important in the response to natural as well as drug rewards (Werme *et al*, 2002; Olausson *et al*, 2006). Recently, found that ΔFosB is phosphorylated by casein kinase 2 (CK2) at Serine 27, and that this phosphorylation opposes protein degradation, contributing to ΔFosB's unusual stability. Furthermore, this phosphorylation event increases the transcriptional activity of ΔFosB (Ulery and Nestler, 2007). As it has been shown that LTP induction rapidly increases the activity of CK2 in the hippocampus (Charriaut-Marlangue *et al*, 1991), it is possible that this provides a mechanism by which the activity of ΔFosB is increased and stabilized following chronic stimulation, leading to some of the long-term gene expression changes responsible for plasticity. ΔFosB's unusual stability is also due to the fact that it lacks two degron domains present in the C-terminus of full-length FosB and all other Fos family proteins, which target these proteins for rapid degradation (Carle *et al*, 2007).

A Role for NF-κB

The transcription factor, NF-κB, can exist as a latent form or a constitutively active form in neurons (Kaltschmidt *et al*, 2005). Although the constitutive form is located in the nucleus, the latent form is held in the cytoplasm through an

interaction with inhibitory kappaB (IκB). Upon stimulation by numerous factors, IκB is degraded, allowing NF-κB to enter the nucleus. In addition, the RelA subunit of NF-κB can be acetylated upon stimulation and this prevents its interaction with IκBα (Chen *et al*, 2001b). RelA can subsequently be deacetylated by histone deacetylase 3 (HDAC3), and this promotes nuclear export and IκBα binding (Chen *et al*, 2001b). This reversible acetylation contributes to the duration of NF-κB activity in the nucleus. NF-κB is activated in response to neurodegeneration, cellular stress, or trauma, and through its regulation of antiapoptotic genes, it promotes neuronal survival (Mattson, 2005). NF-κB activity is also induced following LTP in the hippocampus and after fear conditioning in the amygdala (Yeh *et al*, 2002; Romano *et al*, 2006). Studies have found that the administration of a competing decoy κB can prevent LTD and severely impair LTP in both the hippocampus and amygdala (Albensi and Mattson, 2000; Yeh *et al*, 2002). In addition, members of the NF-κB family, p50, p65, and c-Rel, show an increase in DNA binding in the hippocampus following glutamate receptor stimulation, and mice lacking c-Rel have a deficit specifically in the late-phase of LTD (O'Riordan *et al*, 2006). Furthermore, animals that overexpress a 'super repressor' IκB-AA in neurons selectively using a bitransgenic system have defects in learning and memory (Kaltschmidt *et al*, 2006). The late phase of hippocampal LTP in these mice is also compromised and LTD can not be induced (Kaltschmidt *et al*, 2006). Interestingly, this study identified the PKA catalytic α-subunit as a transcriptional target for NF-κB, and the loss of NF-κB function reduces PKA-mediated CREB phosphorylation (Kaltschmidt *et al*, 2006). Thus, the plasticity and memory defects in the IκB-AA overexpressing mice may come from a lack of activated CREB.

In addition to the effects on memory, NF-κB is also induced by chronic cocaine in the NAc, where it may be a transcriptional target of ΔFosB (Ang *et al*, 2001). Therefore, NF-κB may also be involved in the plasticity associated with addiction, a possibility, which now requires further investigation.

A Role for Circadian Transcription Factors

Recent studies have implicated the transcription factors that make up the circadian clock in neural plasticity. Circadian rhythms, or 24-h cycles, occur in many bodily functions, including sleep/wake, body temperature, and hormone levels. Circadian rhythms are largely regulated by a transcriptional feed-back loop located in the suprachiasmatic nucleus (SCN) in the hypothalamus. However, the genes that make up the clock are expressed throughout the brain and other organs, and can form SCN-independent oscillators that respond to many types of external stimuli (King and Takahashi, 2000—a review of the circadian clock and rhythms in mammals; Abe *et al*, 2001; Reppert and Weaver, 2001; Stokkan *et al*, 2001; Iijima *et al*, 2002; Granados-Fuentes *et al*, 2006; McDearmon *et al*, 2006; Mieda *et al*, 2006). In fact, it is estimated that >10% of all mammalian messenger RNA (mRNA) transcripts are regulated in a circadian manner (Akhtar *et al*, 2002; Duffield *et al*, 2002).

The major transcriptional activator consists of a dimer between the Circadian Locomotor Output Cycles Kaput Protein (CLOCK) and Brain and Muscle ARNT-like Protein 1 (BMAL1, also known as ARNTL or MOP3). This complex binds to E-box sequences in the promoters of many genes, including the *Period (Per)* and *Cryptochrome (Cry)* genes. The PER and CRY proteins are translated in the cytoplasm, and are phosphorylated by casein kinase I ε and δ (CK1) and GSK3β, leading to changes in their stability, association, and nuclear entry (Harms *et al*, 2003; Iitaka *et al*, 2005; Knippschild *et al*, 2005; Kurabayashi *et al*, 2006). These proteins can then repress the actions of CLOCK:BMAL1, which creates a precisely timed transcriptional feedback loop, the molecular basis of circadian rhythms. In addition, there is an adjoining loop in which CLOCK:BMAL1 activates the transcription of *Rev-erbα* and *Rorα* (Sato *et al*, 2004; Guillaumond *et al*, 2005). These proteins can bind to the promoter of the *Bmal1* gene and both positively and negatively regulate its transcription. Selectively in forebrain regions, Neuronal PAS Domain Protein 2 (NPAS2), a protein very similar to CLOCK, can bind BMAL1 and induce *Per* and *Cry* gene expression independent of CLOCK (Reick *et al*, 2001). NPAS2 may also function in the place of CLOCK in the SCN, if the CLOCK protein is abolished (Debruyne *et al*, 2006).

It is thought that sleep contributes strongly to the process of memory formation and consolidation (Walker and Stickgold, 2006). In addition, phase shifting of circadian rhythms or chronic disruption of circadian rhythms can impair long-term memory and working memory in both rodents and humans (Cho *et al*, 2000; Devan *et al*, 2001). Several studies have found differences in learning and memory when experiments are performed during the light cycle *vs* the dark cycle. For example, snails display a diurnal regulation of conditioned taste aversion (Wagatsuma *et al*, 2004). Rodents also show diurnal differences in contextual fear conditioning and performance in the Morris water maze (Chaudhury and Colwell, 2002; Valentinuzzi *et al*, 2004). In addition, the magnitude of hippocampal LTP is greater and the decay of LTP is slower during the night in nocturnal mice, even when the mice are kept in constant darkness, suggesting that an endogenous circadian oscillator regulates hippocampal plasticity (Chaudhury *et al*, 2005). Studies in *Aplysia* found that long-term memory formation in response to electrical stimulation or 5-HT is suppressed in diurnal animals that were trained during the night (Fernandez *et al*, 2003; Lyons *et al*, 2005, 2006). This reduction in memory formation during the night was correlated with a circadian rhythm in the induction of the memory-related proteins, phosphorylated ERK, and CCAAT/enhancer-binding protein, such that a greater induction of these proteins was seen when training was performed during the day than at night (Lyons *et al*, 2006). Long-term memory formation at night could be restored to day-time levels when animals were treated with agents that activate ERK and another transcriptional activator together, but not individually, indicating that both ERK phosphorylation and general gene transcription are necessary for normal memory formation, and that both are inhibited by the circadian clock during the night.

Additional studies have implicated individual members of the circadian clock or clock-controlled hormones in

learning and memory. *Drosophila* that carry a mutation in the *Per* gene are defective in long-term memory associated with experience-dependent courtship, whereas overexpression of *Per* enhanced memory formation in this paradigm (Sakai *et al*, 2004). Interestingly, mutations in other circadian genes including *Clock* and *Cycle* did not affect memory formation in this task, suggesting an independent role for *Per* outside of the central clock (Sakai *et al*, 2004). Somewhat surprisingly, mice that lack functional *Per1* or *Per2* show normal spatial and contextual learning in hippocampal-dependent tasks (Zueger *et al*, 2006), however, mice lacking both genes have not been tested. The circadian hormone, melatonin, which is released at night in response to signals from the SCN, can inhibit hippocampal LTP (Wang *et al*, 2005). As well, expression of the circadian-controlled transcription factor, albumin D-element-binding protein (DBP), is suppressed by hippocampal activation of a protein associated with increased learning, glucagon-like peptide-1 receptor, and viral-mediated overexpression of DBP in the hippocampus leads to an inhibition of spatial learning (Klugmann *et al*, 2006). Moreover, induction of LTP leads to the phosphorylation and inhibition of the circadian modulator, GSK-3β in the hippocampus (Hooper *et al*, 2007) LTP is impaired in mice that conditionally overexpress GSK-3β and the deficits can be rescued by treatment with the GSK-3β inhibitor, lithium (Hooper *et al*, 2007). These results suggest that certain components of the molecular clock are involved in learning and memory.

Several mood and substance abuse disorders have also been strongly linked to the circadian clock (Bunney and Bunney, 2000; Mansour *et al*, 2005; Yuferov *et al*, 2005; Wirz-Justice, 2006). Indeed, some of the most pronounced symptoms of diseases like major depressive disorder (MDD) and bipolar disorder (BPD) are abnormal sleep/wake, appetite, and social rhythms (Boivin, 2000; Bunney and Bunney, 2000; Lenox *et al*, 2002; Grandin *et al*, 2006). In addition, nearly all of the successful treatments for mood disorders affect circadian rhythms, and it appears that the shifts, resetting, and stabilization of these rhythms, produced by these treatments, are important for their therapeutic efficacy (McClung, 2007). Interestingly, a recent study found that the circadian genes, *Clock*, *Npas2*, and *Bmal1*, are all strongly induced in the mouse hippocampus after chronic, but not acute, treatment with the antidepressant, fluoxetine (Uz *et al*, 2005). This suggests that these genes may be involved in the plasticity that occurs in this region with chronic antidepressant treatment. In addition, chronic treatment with the mood stabilizer, valproate, decreased the expression of *CK1*δ and *Cry2* in the amygdala (Ogden *et al*, 2004). These changes did not occur when mice were co-treated with methamphetamine, which was given to induce manic-like symptoms, suggesting that these genes may be involved in the treatment of mania (Ogden *et al*, 2004).

Researchers have begun to examine the roles of individual members of the circadian clock in the regulation of mood and drug addiction. Transgenic mice that overexpress GSK-3β are hyperactive, have reduced immobility in the forced swim test (interpreted as lower depression-like behavior), and an increased startle response (Prickaerts *et al*, 2006). These behaviors are reminiscent of those of bipolar patients in the manic state. This is perhaps not surprising, as GSK-3β is inhibited by the mood stabilizer, lithium (Jope and Roh, 2006). Recently, Roybal *et al* (2007)—the authors report a mania-like phenotype, and its reversal by chronic lithium treatment, in mice lacking functional Clock protein—found that mice harboring a mutation in the *Clock* gene also display a behavioral profile that is strikingly similar to human mania. These mice have a point mutation in the *Clock* gene that results in the expression of a dominant-negative protein (King *et al*, 1997). These mice are extremely hyperactive in response to novelty and throughout the light/dark cycle, they have reduced depression-like behavior in the forced swim and learned helplessness tests, reduced anxiety or increased risk-taking behavior in several measures, and an increase in the reward value of cocaine, sucrose, and intracranial self-stimulation (McClung *et al*, 2005; Roybal *et al*, 2007). In addition, other groups have found that these mice sleep less and have increased exploratory activity, adding to their overall manic-like phenotype (Naylor *et al*, 2000; Easton *et al*, 2003). Interestingly, when these mice were treated chronically with lithium, the majority of their behavioral responses return to wild-type levels (Roybal *et al*, 2007). As the midbrain dopaminergic system has been widely implicated in the development of mania, we performed *in vivo* recordings from the dopaminergic neurons of the VTA in the *Clock* mutant mice, and found an overall increase in dopamine cell firing and bursting (McClung *et al*, 2005; Nestler, 2005; Nestler and Carlezon, 2006). CLOCK is expressed in the VTA, where it regulates several genes that are important in dopaminergic transmission (McClung *et al*, 2005). Therefore, we used viral-mediated gene transfer to express a functional CLOCK protein specifically in the VTA of the mutant mice, and found that this treatment returned several of their behavioral phenotypes to wild-type levels (Roybal *et al*, 2007). These results suggest that CLOCK is important in the development of mania, and that at least a portion of the behavioral and mood-related phenotypes seen in the mutant mice are due to the loss of CLOCK function in the VTA.

As mentioned above, one of the phenotypes of the *Clock* mutant mice is an increase in the reward value for cocaine. This was measured both by conditioned place preference and by levels of intracranial self-stimulation following cocaine treatment (McClung *et al*, 2005; Roybal *et al*, 2007). Other members of the circadian clock have also been implicated in drug reward and addiction. The original studies implicating circadian genes in drug-induced plasticity found that *Drosophila* lacking *Per*, *Clock*, *Cycle*, or *Doubletime* all fail to sensitize to cocaine (Andretic *et al*, 1999—this is the first study to demonstrate a role for the genes that control circadian rhythms in the regulation of cocaine responsiveness). Since then, several studies have found changes in the expression of multiple circadian genes in various brain regions of rodents treated with drugs of abuse (Nikaido *et al*, 2001; Ammon *et al*, 2003; Yuferov *et al*, 2003, 2005; McClung *et al*, 2005; Uz *et al*, 2005; Manev and Uz, 2006). In addition, mice that lack a functional *Per1* gene show reduced behavioral responses to cocaine (Abarca *et al*, 2002). Reduction in the expression of *Per1* by DNAzyme targeting likewise leads to a reduction in the conditioned preference for morphine (Liu *et al*, 2005). However, mice lacking *Per1* show normal levels of alcohol

self-administration and reinstatement of alcohol-seeking behavior, suggesting that *Per1* is perhaps not involved in alcohol reinforcement (Zghoul *et al*, 2007). Interestingly, mice lacking *Per2* show an enhanced sensitization to cocaine, but normal levels of conditioned preference for cocaine (Abarca *et al*, 2002). They also show an increase in alcohol self-administration and enhanced incentive motivation for alcohol (Spanagel *et al*, 2005). These results suggest that *Per1* and *Per2* may serve different functions in response to treatment with drugs of abuse.

CHROMATIN MODIFICATIONS THAT UNDERLIE PLASTICITY

Modifications to Histones

Long-term modifications to chromatin may underlie some of the changes in gene expression that lead to neural plasticity. DNA is tightly packed around octamers of the histone proteins H2A, H2B, H3, and H4, linked together by histone H1 (Berger, 2001). Histone proteins can be modified to allow the DNA to unwind and permit transcription factor binding and gene activation (Figure 3). In turn, other modifications to histone proteins can inhibit transcription factor binding. Several studies have found that gene activation is associated with histone acetylation (Cheung *et al*, 2000). This acetylation is catalyzed by a histone acetyltransferase (HAT) enzyme, such as CBP/p300 or many others, which serve as transcriptional co-activators. In addition, some transcription factors appear to have their own HAT domain that may allow histone acetylation. For example, the CLOCK protein has recently been shown to contain an active HAT domain that is enhanced by BMAL1 binding (Doi *et al*, 2006). HDAC proteins reduce gene expression at these promoters through histone deacetylation. Histone phosphorylation is also generally associated with an increase in transcription, and phosphorylation has been associated with immediate early gene activation in response to growth factor treatment (Mahadevan *et al*, 1991; Sassone-Corsi *et al*, 1999).

Histones H3 and H4 can also be methylated at arginine or lysine residues, which can lead to gene activation or repression depending on the residue undergoing methylation (Beaujean, 2002). The arginine methyltransferase, co-activator-associated arginine methyltransferase-1, can co-activate myogenic transcription factor-mediated gene expression (Chen *et al*, 2002). However, methylation of histone H3 on lysine residues K9 or K27 is associated with stretches of transcriptional repression and inert heterochromatin (Beaujean, 2002). Finally, ubiquitination, SUMOylation, and ADP-ribosylation of histones have been observed, and these processes influence gene transcription as well (Huletsky *et al*, 1985; Davie and Murphy, 1990; Beaujean, 2002; Nathan *et al*, 2003).

HAT and HDAC proteins can associate with transcription factors, and this association often occurs in response to second messenger stimulation. For example, CREB binds CBP after phosphorylation at Ser-133 (Johannessen *et al*, 2004). Mice that lack full CBP function through various genetic methods have defects in late-phase LTP, spatial learning, and fear conditioning (Alarcon *et al*, 2004; Korzus *et al*, 2004; Wood *et al*, 2005). Furthermore, studies have found that the induction of LTP in hippocampal slices using high-frequency stimulation is enhanced by treatment with the nonspecific HDAC inhibitors, trichostatin A and sodium butyrate (Levenson *et al*, 2004). Trichostatin A also enhanced forskolin-induced LTP in the amygdala (Yeh *et al*, 2004). These results suggest that HDAC inhibition and transcriptional activation may improve the plasticity associated with memory formation.

Long-term modifications to histone proteins have been seen in response to chronic stimuli, where they contribute to neuronal plasticity. Early studies in *Aplysia* found that acetylation of histone H4 at the ApC/EBP promoter was increased following 5-HT-induced long-term facilitation,

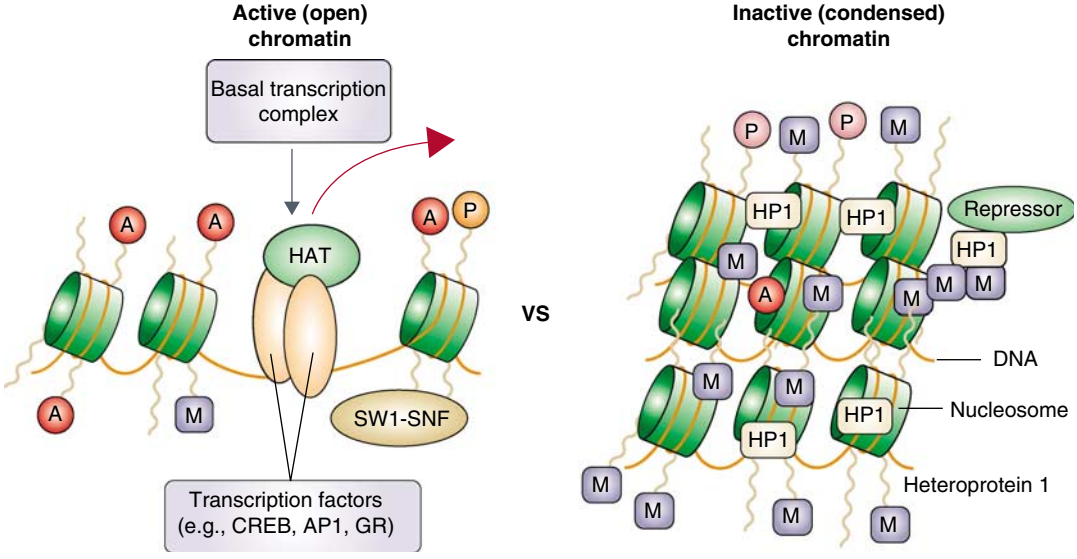

Figure 3 Differential states of chromatin. Chromatin can either be open (ie active, allowing gene expression) or condensed (ie inactive, repressing gene expression). This change in state is mediated by the modifications to core histone proteins. Histone acetylation (A) is associated with chromatin relaxation and the binding of transcription factors and co-activators, such as HATs (histone acetyl transferases) and SWI-SNF proteins that mediate the movement of nucleosomes along a strand of DNA. Histone methylation (M) results in condensed chromatin and transcriptional repression (REP).

and acetylation was decreased following FMRFamide-induced LTD through the recruitment of HDAC5 (Guan *et al*, 2002). Later, it was found that multiple signaling pathways modify histones in the rodent hippocampus, including an increase in H3 acetylation following the activation of NMDA receptors and the ERK pathways associated with LTP (Crosio *et al*, 2003—an important paper that delineates some of the intracellular messenger pathways that lead to regulation of histone acetylation; Levenson *et al*, 2004). In studies of depression, the HDAC inhibitor, sodium butyrate, has an antidepressant-like effect in mice that correlates with hyperacetylation at the *Bdnf* promoter in the frontal cortex (Schroeder *et al*, 2006; Tsankova *et al*, 2006—this is the first study to implicate histone modifications in depression- and antidepressant-like behavior). In agreement with these findings, our studies found that a chronic electroconvulsive seizure paradigm, which is antidepressant in humans, changes the acetylation of specific histones at the *Bdnf*, *Creb*, and *c-Fos* promoters in the hippocampus, and these changes correlate with sustained increases or decreases in levels of expression of these genes (Tsankova *et al*, 2004). Furthermore, a chronic social defeat stress paradigm, which produces a depression-like state (Berton *et al*, 2006), decreases the expression of *Bdnf* in the hippocampus (Tsankova *et al*, 2006). The prolonged reduction in *Bdnf* expression was correlated with an increase in repressive histone methylation at the gene promoter (Tsankova *et al*, 2006). The antidepressant, imipramine reversed the depression-associated behavior and increased histone acetylation at the *Bdnf* promoter and increased *Bdnf* expression (Tsankova *et al*, 2006). Furthermore, this increase in histone acetylation with imipramine treatment involves the downregulation of HDAC5, and overexpression of HDAC5 in the hippocampus blocks the ability of imipramine to reverse the depression-like behavior (Tsankova *et al*, 2006). Together, these studies highlight the importance of long-term histone modifications in the plasticity associated with depression and antidepressant treatment.

Chromatin remodeling through histone modification also appears to play a role in drug addiction. One of the key features of addiction is that it is more persistent if drug use begins at an early age, indicating long-lasting changes in brain function. Interestingly, a recent study found that the administration of ascending doses of cocaine to adolescent rats resulted in an increased response to cocaine in adulthood, and an overall decrease in histone H3 methylation at lysines 4 and 27 in the medial pre-frontal cortex (Black *et al*, 2006). Furthermore, acute cocaine leads to a transient increase in histone acetylation at the *c-Fos* promoter in striatal regions, consistent with its transient increase in expression following this treatment (Kumar *et al*, 2005). However, chronic cocaine treatment selectively increases *Bdnf* and *Cdk5* gene expression in these regions, and these increases are associated with hyperacetylation at their promoters (Kumar *et al*, 2005). Kumar *et al* provided several lines of evidence indicating that induction of the *Cdk5* gene is mediated via ΔFosB. Cocaine also increases CBP-mediated acetylation of histone H4 at the *FosB* promoter, and mice lacking one allele of CBP have less accumulation of ΔFosB, and are less sensitive to chronic cocaine (Levine *et al*, 2005). Furthermore, administration of the HDAC inhibitor, TSA, increases the conditioned place preference for cocaine, whereas viral-mediated overexpression of HDAC4 in the NAc decreases cocaine preference (Kumar *et al*, 2005). These results suggest that chronic cocaine treatment leads to a hyperacetylation at several gene promoters, which increases the reward value for cocaine.

DNA Methylation

DNA (cytosine-5) methylation occurs at methyl CpG islands within a gene sequence, and it was once thought to be a permanent way by which certain genes are silenced. This silencing occurs during X-chromosome inactivation, and several cell-fate determination processes throughout development (Morgan *et al*, 2005). Recent studies, however, show that changes in DNA methylation may be more transient, and underlie certain types of long-term plasticity. For example, DNA methylation can occur in response to stimuli experienced during development or early childhood, and this can lead to lasting changes into adulthood. A recent study by Weaver *et al* (2004)—one of the first studies to show that DNA methylation patterns can be influenced during adolescence and that these patterns affect adult behavior—found that patterns of DNA methylation in the *glucocorticoid receptor* gene were determined during early life based on the quality of maternal care experienced. These patterns or 'memories' remained until adulthood, and influenced levels of anxiety and nurturing behavior in the rats as adults. These results suggest that the methylation patterns that occur during early childhood result in long-lasting changes in gene expression that affect adult behavior. Interestingly, these changes in adult behavior were reversible. Infusion of adult rats with the amino-acid L-methionine, a precursor to *S*-adenosyl-methionine that acts as the donor of methyl groups for DNA methylation, reverses the effect of maternal behavior on DNA methylation and the behavioral response to stress (Weaver *et al*, 2005). This shows that the DNA methylation changes that occur during adolescence are not permanent. Another study, by Zhang *et al* (2007) found that maternal cocaine use induces persistent DNA methylation of the *Pkcε* gene in the heart of the fetus. It is possible that similar changes could occur in the brain, leading to a propensity for drug addiction later in life.

Studies aimed at determining whether or not DNA methylation is involved in more short-term learning and memory are just beginning. Interestingly, a protein that binds methylated cytosines and represses transcription, MeCP2, has been associated with memory formation. Loss of function mutations in this protein cause Rett syndrome, a developmental disorder that severely affects cognitive and motor abilities (Williamson and Christodoulou, 2006). These behavioral abnormalities are associated with impairments in presynaptic release of glutamate (Nelson *et al*, 2006—an important study that demonstrates abnormal presynaptic function in mice lacking MeCP2). Surprisingly, overexpression of MeCP2 enhances hippocampal LTP and long-term memory formation transiently before animals develop seizures, severe hypoactivity, and other ailments (Collins *et al*, 2004). This suggests that the proper balance of MeCP2 is needed for memory function. In addition, studies by Chen *et al* (2003)—one of the first studies to

demonstrate regulation of the Bdnf gene by DNA methylation mechanisms—and Martinowich *et al* (2003) found that MeCP2 binds to the *Bdnf* promoter III and inhibits *Bdnf* transcription through CpG methylation. Membrane depolarization leads to a calcium-dependent phosphorylation of MeCP2 that dissociates the MeCP2-HDAC-mSin3A complex from the promoter, allowing *Bdnf* transcription (Chen *et al*, 2003; Martinowich *et al*, 2003). Furthermore, recent studies by Sweatt and co-workers found that the enzymes that catalyze the methylation of cytosine residues, DNA methyltransferases (DNMTs), are important regulators of memory in the hippocampus (Levenson *et al*, 2006; Miller and Sweatt, 2007—a recent study implicating DNA methylation in the formation of long-term memory). Inhibition of DNMT through treatment with phorbol-12,13-diacetate altered the methylation at the *reelin* and *Bdnf* promoters, and blocked the induction of LTP (Levenson *et al*, 2006). Furthermore, DNMT expression is upregulated in the hippocampus with contextual fear conditioning, and DNMT inhibition leads to deficits in memory formation (Miller and Sweatt, 2007). DNMT is involved in the silencing of the memory suppressor gene, *Pp1*, and this gene is rapidly inactivated via DNA methylation following fear conditioning (Miller and Sweatt, 2007). These studies suggest that DNA methylation is far more dynamic than previously described and could be an important mechanism that contributes to long-term neuronal plasticity.

POSTTRANSCRIPTIONAL MODIFICATIONS THAT UNDERLIE PLASTICITY

Polyadenylation Factors

In addition to the long-term modifications to transcription factors and DNA that govern neuronal plasticity, post-transcriptional mechanisms also appear to be involved. Many mRNAs are transported to synapses where they are locally translated, and participate in synaptic remodeling at those locations. Several studies have identified mRNA-binding proteins, such as the cytoplasmic polyadenylation element-binding protein (CPEB) and cleavage and polyadenylation specificity factor that regulate mRNA translation at the synapse (Wu *et al*, 1998). *Drosophila* carrying a mutation in *orb*, a CPEB homologue, lack long-term memory (Dubnau *et al*, 2003). Furthermore, NMDA receptor stimulation induces the phosphorylation of CPEB by Aurora kinase, and disrupts its association with a repressor protein, Maskin, thereby allowing CPEB to interact with the translation initiation factors, eIF4G and eIF4E at target mRNAs (Huang *et al*, 2002; Si *et al*, 2003—a study showing the importance of postranscriptional regulation by CPEB in plasticity). This action can stabilize synaptic changes at these sites associated with plasticity. Interestingly, the *Aplysia* CPEB was reported to have prion-like properties in that, it is modular and transferable, and it is capable of conferring a change in state to other proteins (Si *et al*, 2003). The prion-like, aggregated state is the active state of CPEB, and it is possible that this conformational change comes about through chronic stimulation, leading to long-lasting, local synaptic changes.

MicroRNAs

Recently, a class of non-coding, micro RNAs (miRNA) has been described that influence the translation of mRNA by sequence-specific pairing with 3′-untranslated regions (Presutti *et al*, 2006). It is predicted that 40–50% of mRNAs are regulated by miRNAs (Presutti *et al*, 2006). A number of these miRNAs appear to be brain specific, and they have been implicated in neuronal development and differentia-

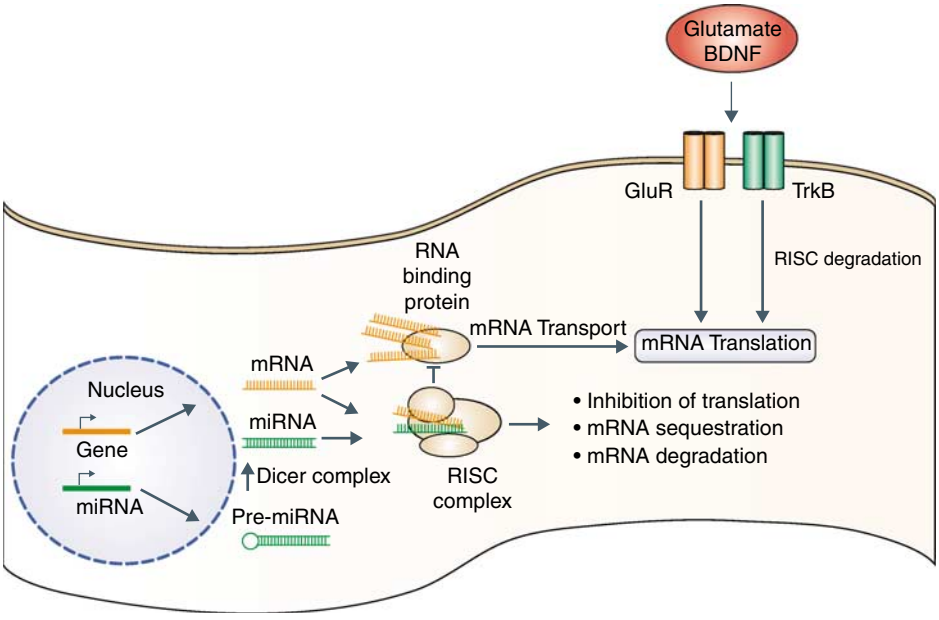

Figure 4 Regulation of mRNA translation by miRNAs. The ability of mRNAs to be locally translated and participate in synaptic plasticity can be altered by miRNAs. This interaction between the miRNA, mRNA, and the RISC complex can lead to the inhibition of translation, mRNA degradation, or the sequestering of the mRNA away from the synapse. Stimulation by glutamate, or growth factors such as BDNF, can lead to the degradation of components of the RISC complex and allow mRNA translation.

tion (Presutti *et al*, 2006). These miRNAs also undergo tissue-specific RNA editing, adding another level of potential regulation to their function (Kawahara *et al*, 2007). It is possible that miRNAs are involved in regulating the local translation of mRNAs at synapses that are involved in plasticity (Figure 4). Many of the structural changes that are thought to underlie synaptic plasticity occur at dendritic spines and branches (Schratt *et al*, 2006—an important study demonstrating the regulation of dendritic spine growth by a microRNA). miRNAs might be involved in repressing translation of proteins at these synapses under normal conditions, with this repression being abolished following stimulation. Indeed, in the hippocampus, a brain-specific miRNA, *miR-134* is localized to the synapto-dendritic compartment of neurons where it decreases the size of dendritic spines through its repressive actions at the *LIM-domain kinase 1* (*Limk1*) mRNA (Schratt *et al*, 2006). Neuronal stimulation by BDNF relieves the repression of *Limk1* by *miR-134*, allowing spine growth (Schratt *et al*, 2006). Another recent study in *Drosophila* found that local protein synthesis occurs at synapses when animals are exposed to an odor paired with an electric shock (Ashraf *et al*, 2006). A component of the RNA-silencing complex (RISC), Armitage, that couples with miRNAs is located at these synapses, where it normally silences mRNAs (Ashraf and Kunes, 2006; Ashraf *et al*, 2006; Chekanova and Belostotsky, 2006). Upon stimulation, Armitage is degraded, and the mRNA is now translated. Some of the key proteins involved in plasticity are targets of this pathway, including CaMKII and Staufen (Ashraf and Kunes, 2006; Ashraf *et al*, 2006). Therefore, the RISC complex may play a key role in synaptic plasticity.

Total expression levels of the miRNAs may contribute to the maintenance of long-lasting plasticity. Interestingly, genome-wide screens of transcription factor binding found that CREB may regulate the expression of individual brain-specific miRNAs (33 had identifiable CRE regulatory sequences), and *MiR-132*, a miRNA expressed predominantly in the hippocampus, was identified as a direct target of CREB (Vo *et al*, 2005; Wu and Xie, 2006; Lukiw, 2007). Furthermore, the transcriptional repressor RE1-silencing transcription factor (also known as neuron-restrictive silencer factor), appears to convey long-term repression of some of the miRNAs by recruiting MeCP2 and HDACs to their regulatory regions (Wu and Xie, 2006). Therefore, long-term treatments could change the expression level of these miRNAs through manipulation of these transcription factors, which would result in more or less local translation of proteins that are involved in altering synaptic connections.

FUTURE RESEARCH DIRECTIONS

Although it is clear that transcriptional and post-transcriptional changes are necessary for the development of neuroplasticity, the mechanisms that underlie these changes are complex, and we are only beginning to understand how these changes are mediated. In addition, many of the transcriptional target genes that are involved in long-term plasticity have yet to be identified. Therefore, future research into the stimulus-dependent regulation of transcription factors, chromatin structure, and mRNA processing are important in our understanding of how long-term changes are facilitated in the brain. The use of new technologies such as chromatin immunoprecipitation (ChIP) followed by microarray analysis (ie ChIP on chip) or DNA methylation arrays will allow us to study chromatin modifications that occur following various treatments, and identify a range of direct transcriptional targets of many transcription factors involved in plasticity. In addition, the study of miRNAs not only allows us to determine their importance in plasticity but also provides a technique that is now being utilized to knock down the expression of specific genes in individual brain regions of adult animals to determine their function in these long-term adaptations.

CLINICAL IMPLICATIONS

This research will undoubtedly lead to new, more targeted, treatments for memory disorders, as well as drug addiction, depression, and other psychiatric conditions. Through better understanding of the mechanisms that underlie long-term plasticity, it might be possible to either enhance or block specific aspects of a form of plasticity depending upon the condition. For example, it may be possible to reverse the chromatin modifications that occur in response to chronic exposure to drugs of abuse by modulating the transcription factors or enzymes necessary to facilitate this process. As all forms of plasticity appear to be mediated via a finite number of basic molecular processes, the large task ahead is to determine the specific molecules, changes, and circuits that are involved in the formation of normal memories, as opposed to drug addiction or depression. It is likely, therefore, that future treatments for these disorders will have to be highly targeted toward specific adaptations.

DISCLOSURE

The authors state that they have no conflicts of interest.

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