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Synaptically Localized Transcriptional Regulators in Memory Formation

Shusaku Uchida[1] and **Gleb P. Shumyatsky**[2]

[1]Division of Neuropsychiatry, Department of Neuroscience, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan

[2]Department of Genetics, Rutgers University, 145 Bevier Rd., Piscataway, New Jersey 08854, USA

Abstract

At the neuronal cell level, long-term memory formation emerges from interactions between initial activity-dependent molecular changes at the synapse and subsequent regulation of gene transcription in the nucleus. This in turn leads to strengthening of the connections back at the synapse that received the initial signal. However, the mechanisms through which this synapse-to-nucleus molecular exchange occurs remain poorly understood. Here we discuss recent studies that delineate nucleocytoplasmic transport of a special class of synaptically-localized transcriptional regulators that upon receiving initial external signal by the synapse move to the nucleus to modulate gene transcription.

Keywords

Memory; Memory enhancement; Nucleocytoplasmic shuttling; Transcription; CREB; CRTC1; HDAC4; NF-κB

INTRODUCTION

Activity-dependent neuronal plasticity allows organisms to adapt and respond to changes in the environment (West and Greenberg, 2011). Neuronal plasticity includes modifications in synaptic structure and function, and, in particular, long-term modifications require gene transcription (Alberini, 2009; Klann and Dever, 2004; Mayford et al., 2012). To initiate neuronal activity-dependent gene transcription, signals must be relayed from active synapses to the nucleus (Ch'ng and Martin, 2011; Greer and Greenberg, 2008; Panayotis et al., 2015). This article summarizes work on synaptically-localized transcriptional regulators that directly transmit information regarding synaptic activity by moving to the nucleus and regulating transcription (Ch'ng and Martin, 2011; Jordan and Kreutz, 2009). Recent

Correspondence: Gleb P. Shumyatsky, gleb@dls.rutgers.edu.

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publications demonstrate that certain proteins, which function as transcriptional regulators, are initially localized at synapses but can accumulate in the nucleus in response to synaptic plasticity and learning (Ch'ng et al., 2012; Dieterich et al., 2008; Jordan et al., 2007; Lai et al., 2008; Nonaka et al., 2014; Proepper et al., 2007; Uchida et al., 2017).

Neuronal activity-dependent gene transcription typically requires calcium-dependent signaling (Ebert and Greenberg, 2013). Calcium, as a potent activator of intracellular signaling cascade, is normally maintained at very low concentration within the cytoplasm. Neuronal activity leads to calcium influx into the postsynaptic cells either through NMDA receptors or L-type voltage-sensitive calcium channels (Cole et al., 1989; Murphy et al., 1991). Neuronal activity-induced elevation in intracellular calcium activates multiple signaling molecules such as calcium/calmodulin-dependent protein kinases (CaMKII and CaMKIV) and calcium-dependent protein phosphatases (such as calcineurin), which regulate the activity of transcriptional factors by phosphorylating or dephosphorylating them (Takemoto-Kimura et al., 2017).

Neuronal activity not only regulates sequence-specific DNA-binding proteins, but also modifies chromatin structure to control gene transcription (Crosio et al., 2000; Day and Sweatt, 2011; Graff and Tsai, 2013; Kumar et al., 2005; Lopez-Atalaya and Barco, 2014; Peixoto and Abel, 2013; Uchida et al., 2011). In particular, epigenetic processes, such as histone modifications, are important for activity-dependent regulation of transcription (Graff and Tsai, 2013; Lopez-Atalaya and Barco, 2014; Peixoto and Abel, 2013). Moreover, synaptically localized transcription modulators were recently linked to histone modifications that are required for memory enhancement (de la Fuente et al., 2015; Sando et al., 2012; Uchida et al., 2017).

In this review, we will discuss current advances in the field that have shown unique characteristics of the transcription modulators CRTC1, HDAC4 and NF-κB, which are localized at the synapse but, upon neuronal stimulation (such as learning), move to the nucleus to regulate gene transcription, which is essential for synaptic plasticity and memory formation (Fig. 1).

ACTIVITY-DEPENDENT NUCLEOCYTOPLASMIC SHUTTLING OF CRTC1 IS REQUIRED FOR MEMORY FORMATION

CREB-dependent gene expression is essential for synaptic plasticity, learning and memory (Bito et al., 1996; Bourtchuladze et al., 1994; Deisseroth et al., 1996; Impey et al., 1998; Josselyn et al., 2004; Kida et al., 2002; Kida and Serita, 2014; Mayford et al., 2012; Silva et al., 1998; Suzuki et al., 2011). Membrane depolarization or an increase in cAMP induces CREB phosphorylation at serine amino acid 133 (Ser133), and the mutation from serine to alanine (Ser133Ala) blocks the induction of CREB-dependent transcription (West et al., 2002). Various kinases phosphorylate CREB at Ser133; however, specific kinases were found to be responsible for its phosphorylation in response to a certain stimulus (Mayr and Montminy, 2001). The nuclear protein kinase CaMKIV is crucial for rapid activity-dependent phosphorylation of CREB at Ser133 in neurons (Ho et al., 2000; Ribar et al., 2000). Eventually, calcium influx leads to CREB dephosphorylation at Ser133 through

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calcium-dependent activation of the protein phosphatases PP1 and PP2A (Lonze and Ginty, 2002). Although CREB-mediated transcription requires CREB phosphorylation, the latter is not a reliable predictor of target gene activation; additional regulatory processes are required for the engagement of transcriptional promoter elements. For instance, histone acetyltransferase CBP is critical, and the CBP paralog p300 also enhances CREB functionality, resulting in upregulation of plasticity-related genes such as *Bdnf* and *Arc* (Impey and Goodman, 2001; Patterson et al., 2001).

Genetic disruption of CREB function leads to a decrease in long-term potentiation (LTP), a form of synaptic plasticity, and long-term memory in mice (Bourtchuladze et al., 1994; Kida et al., 2002; Pittenger et al., 2002). Conversely, genetic enhancement of CREB activity in forebrain increases both LTP and long-term memory through the activation of *Bdnf* gene expression (Barco et al., 2002; Barco et al., 2005; Suzuki et al., 2011). Moreover, viral-mediated acute increase in CREB function locally in the dentate gyrus leads to memory enhancement (Sekeres et al., 2012). Importantly, neurons overexpressing CREB by viral-mediated gene transfer in the lateral amygdala are recruited selectively into the trace of cued fear memory (Han et al., 2007). Thus, activity-dependent CREB activation plays a key role in memory enhancement by participating in memory trace (Kida and Serita, 2014).

While CREB phosphorylation is essential it is not sufficient for CREB-dependent gene transcription (Impey et al., 1996; Mayr and Montminy, 2001). Thus, neuronal activity-dependent CREB-mediated gene regulation could be controlled by additional mechanisms, such as the coactivators that can modulate CREB activity (Bito et al., 1996; Lonze and Ginty, 2002; Zhang et al., 2005). The CREB-mediated transcriptional coactivators (CRTCs, also known as TORCs; Fig. 2) may potentiate the interaction of CREB with CBP/p300 (Xu et al., 2007) and dramatically increase CREB transcriptional activity independently of Ser133 phosphorylation (Conkright et al., 2003; Iourgenko et al., 2003). Importantly, CRTC1 is translocated from synapses/dendrites to the nucleus in response to neural activity and learning (summarized in Table 1) (Ch'ng et al., 2012; Kovacs et al., 2007; Li et al., 2009; Nonaka et al., 2014; Parra-Damas et al., 2017; Uchida et al., 2017). Nuclear-cytoplasmic redistribution of CRTCs is known to be dependent on its activity-regulated phosphorylation status (Altarejos and Montminy, 2011). Calcium signals promote nuclear translocation of CRTC1 via activation of calcineurin, which directly dephosphorylates CRTC1 at Ser151 (Bittinger et al., 2004; Ch'ng et al., 2012; Screaton et al., 2004). Indeed, a CRTC1 mutant lacking two calcineurin binding sites was confined to the cytoplasm following neuronal stimulation (Nonaka et al., 2014; Uchida et al., 2017). In addition, dephosphorylation of CRTC1 at Ser151 and Ser167 by salt-inducible kinases is required for cytoplasm-to-nucleus translocation of CRTC1 (Bittinger et al., 2004; Ch'ng et al., 2012; Li et al., 2009; Sasaki et al., 2011; Screaton et al., 2004). Both CRTC1 Ser151Ala and CRTC1 Ser151Ala/Ser167Ala mutants were localized to the cytoplasm, but were transported to the nucleus when neurons were stimulated (Ch'ng et al., 2012; Uchida et al., 2017). Thus, dephosphorylation of CRTC1 at Ser151 and Ser167 may not be necessary for the initial translocation of CRTC1 to the nucleus. Indeed, a recent report has shown that two phosphorylation sites (S151 and S245) contribute to nuclear import of CRTC1 (Nonaka et al., 2014).

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Several lines of evidence have shown recently that CRTC1 plays a key role in synaptic plasticity and memory formation in rodents (Nonaka et al., 2014; Sekeres et al., 2012; Uchida et al., 2017; Zhou et al., 2006). The phosphorylation of CRTC1 in the hippocampus is decreased following contextual fear conditioning (Parra-Damas et al., 2017) and nuclear transport of CRTC1 is observed in the CA1 and CA3 pyramidal neurons, but not in the dentate gyrus granule neurons, of the hippocampus following contextual fear conditioning, novel object location task and Morris water maze task (Parra-Damas et al., 2017; Uchida et al., 2017). This learning-dependent nuclear translocation of CRTC1 also occurs in the basolateral amygdala following contextual fear conditioning (Nonaka et al., 2014). Viral-mediated enhancement of CRTC1 activity in the dentate gyrus (Sekeres et al., 2012) and CA area of the hippocampus (Nonaka et al., 2014; Uchida et al., 2017) increases contextual fear. Conversely, shRNA-mediated knockdown of CRTC1 in the CA region of the hippocampus (Uchida et al., 2017) or basolateral amygdala (Nonaka et al., 2014) leads to decreased contextual fear along with decreased CREB-mediated gene transcription. Furthermore, increased CRTC1 function promoted spine enlargement in the CA1 pyramidal cells (Nonaka et al., 2014) and the loss-of-function CRTC1 disrupted LTP in CA1 (Uchida et al., 2017; Zhou et al., 2006), strongly suggesting that CRTC1 is involved in structural and synaptic plasticity.

EMERGING ROLE OF LEARNING-DEPENDENT NUCLEAR TRANSLOCATION OF CRTC1 IN MEMORY ENHANCEMENT

Activity-dependent synapse-to-nucleus translocation of transcription regulators is believed to be an important regulation of synaptic function and memory, but the exact mechanisms of this translocation remain unclear. As mentioned above, the studies of CRTC1 have largely focused on the role of its nuclear translocation in memory processing. CRTC1 is transported from the synapses/dendrites to the nucleus following learning (Fig. 2), but how the strength of activity that reaches the synapse can be transmitted to the nucleus and be involved in epigenetic regulation of gene transcription is unknown. To this end, a recent study has found that hippocampus-dependent learning induces calcineurin-dependent transport of CRTC1 into the nucleus of excitatory neurons of the hippocampal CA subregion (Uchida et al., 2017). CRTC1 nuclear translocation in the CA1 and CA3 areas is more prominent in mice that received strong training (3 footshocks) compared to weak training (1 footshock) in contextual fear conditioning (Fig. 3). Moreover, this translocation is dependent on microtubules, as it is disrupted by microtubule destabilizer drug nocodazole, in agreement with the observations showing key role of microtubule dynamics in synaptic plasticity and memory (Dent, 2017; Jaworski et al., 2009; Martel et al., 2016; Uchida et al., 2014; Uchida and Shumyatsky, 2015). Genetic enhancement of CRTC1 activity in the CA area strengthened both contextual fear memory and object location memory even following weak training. Conversely, viral-mediated knockdown of CRTC1 with shRNA against *Crtc1* in the CA area weakened long-term memory following strong training and this impairment was reversed by overexpression of shRNA-resistant CRTC1, but not by mutant CRTC1 that has constitutive cytosolic localization, suggesting that nuclear transport of CRTC1 plays a key role in memory enhancement. The phosphorylated form of CREB at Ser133 occupied the *Fgf1b* promoter following both weak and strong training in contextual fear and the

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recruitment of CRTC1 and CBP enhanced the acetylation of H3K14, which is one of the substrates of CBP (Peixoto and Abel, 2013), leading to *Fgf1b* gene transcription. This molecular events were transient, because the occupancies of the phosphorylated CREB and CBP on the *Fgf1b* gene promoter were no longer observed 1 h following weak training (Fig. 3). Interestingly, sustained CRTC1 recruitment on *Fgf1b* gene promoter (up to 2 hours) following strong training was associated with long-lasting upregulation of H4K12 acetylation, which was not observed in weak training condition. This sustained transcription following strong training is mediated at least in part by substitution of histone acetyltransferase KAT5 for CBP in a CRTC1-dependent manner. Strong training maintains upregulation of *Fgf1b* transcription 2 h after learning by recruiting KAT5 to the promoter region independently of CREB phosphorylation, enhancing H4K12 acetylation (Fig. 3). Given that increased H4K12 acetylation might be associated with memory enhancement (Guan et al., 2009; Peleg et al., 2010), nuclear translocation of CRTC1 and subsequent initiation of KAT5-dependent enhancement of H4K12 are critical for enduring synaptic plasticity and memory enhancement. More importantly, this study suggests that synaptic CRTC1 may be a “molecular sensor” that transmits data to the nucleus regarding the strength of synaptic input.

IMPLICATIONS OF CRTC1 FOR ALZHEIMER’S DISEASE

Alzheimer’s disease is a neurodegenerative disorder, characterized by progressive decline in memory, cognitive functions, and changes in behavior and personality (Mattson, 2004; Reddy and Beal, 2008). Alzheimer’s disease is also associated with the loss of synapses, synaptic function, and neuronal loss. Many molecules that are involved in the synaptically-localized proteins that influence activity-dependent regulation of gene transcription are implicated in Alzheimer’s disease. Among them, CRTC1 has been suggested to be associated with Alzheimer’s disease in both animal and human studies. Nuclear translocation of CRTC1 following learning was impaired in a mouse model of Alzheimer’s disease (Parra-Damas et al., 2017; Parra-Damas et al., 2014). It is interesting to note that CREB/CRTC1-mediated regulation of gene expression in the hippocampus of a mouse model of Alzheimer’s disease was changed not only in naïve conditions but also in response to learning (Parra-Damas et al., 2014). Moreover, disrupted memory and decreased induction of activity-dependent genes (*Nr4a1* and *Nr4a2*) following learning in mice lacking the Alzheimer’s disease-linked presenilin genes (presenilin conditional double knockout) were ameliorated by CRTC1 overexpression into the dorsal hippocampus (Parra-Damas et al., 2017), suggesting an impairment in activity-dependent gene regulation in Alzheimer’s disease. A study in humans found a reduction of both total and phosphorylated CRTC1 in human hippocampus at Braak IV and V–VI pathological stages of Alzheimer’s disease (Parra-Damas et al., 2014). Taken together, aberrant activity-dependent nucleocytoplasmic shuttling of CRTC1 and subsequent dysregulation of gene transcription are implicated in the pathophysiology of Alzheimer’s disease.

NUCLEOCYTOPLASMIC SHUTTLING OF HDAC4 REGULATES MEMORY

In addition to CRTC1, a recent study has shown that activity-dependent nuclear export of HDAC4 is important for gene transcription and memory formation (Fig. 2). HDAC4 is

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abundant in neurons, where it is predominantly localized to cytoplasm and dendritic spines (Darcy et al., 2010; Grozinger et al., 1999; Wang et al., 1999). Phosphorylation of HDAC4 by CaMKs promotes its localization to the cytoplasm. Phosphorylation of HDAC4 at Ser246, Ser467, and Ser632 through calcium signaling facilitates its nuclear export (Chawla et al., 2003; McKinsey et al., 2001; Schlumm et al., 2013) and derepression of transcription factor MEF2. Conversely, dephosphorylation of HDAC4 by calcineurin allows its nuclear translocation (Paroni et al., 2008). Nuclear HDAC4 binds to chromatin, as well as to MEF2A and CREB, leading to histone deacetylation and repression of neuronal gene expression (Bolger and Yao, 2005; Chen and Cepko, 2009; Li et al., 2012; Youn et al., 2000). In the dentate gyrus, the majority of HDAC4 is localized in the cytoplasm, but it is localized in the cell nuclei in a proportion of CA1 and CA3 areas (Darcy et al., 2010). Interestingly, a subset of puncta is associated with dendritic shafts and dendritic spines. Studies in primary cultures have shown that neuronal activity induces the nuclear export of HDAC4. The subcellular localization of HDAC4 is regulated by NMDA receptors, as application of the NMDA receptor antagonist AP5 induces nuclear accumulation of HDAC4 (Sando et al., 2012). Mutation of HDAC4 Ser246, Ser467, and Ser632 (HDAC4-3SA mutant) results in nuclear retention (Chawla et al., 2003; Sando et al., 2012; Schlumm et al., 2013). A recent report showed that HDAC4 regulates a transcription program that is essential for synaptic transmission and information processing in the brain (Sando et al., 2012). This pathway involves an activity-dependent association of HDAC4 with transcription factors and neuronal chromatin. In addition, transgenic mice expressing HDAC4-3SA mutant, a constitutive nuclear localization, showed reduced gene expression essential for synaptic function, including *Camk2a*, *Homer1*, and *Snap25* (Sando et al., 2012). Moreover, transgenic mice expressing a truncated form of HDAC4, which accumulates in the nucleus and thus acts as a gain-of-function transcriptional repressor, showed impaired acquisition and retention of memory in Barnes maze (Sando et al., 2012), indicating that nuclear HDAC4 is a negative regulator of memory formation. It should be noted that HDAC4-mediated repression of gene expression and reduced memory formation are independent of HDAC activity, as the truncated form of HDAC4 does not have the catalytic domain necessary for HDAC activity (Sando et al., 2012). This is likely mediated through repression of transcription factors such as MEF2 (Sando et al., 2012). However, it is still unclear whether nuclear import/export of HDAC4 occurs following learning. In addition, the nature of the interaction between HDAC4 and MEF2 or CREB during memory formation is largely unknown. Further examination will be necessary to uncover roles of nucleocytoplasmic shuttling of HDAC4 and its transcription machinery during memory formation.

Proteomics analysis highlighted HDAC4 as a global regulator associated with the onset of memory deficits in both normal age-associated cognitive decline and Alzheimer's disease (Neuner et al., 2016). A recent paper showed that ApoE4, a major genetic risk factor for Alzheimer's disease, increased the nuclear import of HDAC4, which leads to histone deacetylation and epigenetic changes in *Bdnf* gene transcription (Sen et al., 2015).

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THE ROLE OF SYNAPSE-TO-NUCLEUS NF-κB SHUTTLING IN SYNAPTIC PLASTICITY AND MEMORY

NF-κB is a transcription factor that is ubiquitously expressed and responds to diverse stimuli including cytokines and growth factors (Hayden and Ghosh, 2012). In mammals, NF-κB consists of five subunits (RelA/p65, RelB, c-Rel, p105/50, and p100/52), possessing either transcriptional activator (Rel proteins) or repressor (p50, p52) activity. NF-κB signaling encompasses activation of mainly p65, c-Rel, and p50 containing heterodimers within the central nervous system (Engelmann and Haenold, 2016). NF-κB is normally found in the nucleus, but inactive NF-κB dimers are retained in the cytoplasm by binding IκB inhibitory protein. Upon stimulation, the IκB kinase complex becomes activated and phosphorylates IκB, leading to its degradation. This degradation, in turn, allows NF-κB to translocate to the nucleus and regulate gene expression of its target genes (Fig. 2). In mouse hippocampal cultures, synaptosomal NF-κB activity is enhanced by depolarization and exposure to the calcium ionophoreionomicin (Meffert et al., 2003). Some reports show synaptic localization of NF-κB in neurons (Kaltschmidt et al., 1993; Meberg et al., 1996; Meffert et al., 2003; Schmeisser et al., 2012), suggesting a function of NF-κB as a retrograde messenger. Indeed, p65-GFP fusion protein is travelling to the nucleus upon glutamate stimulation in neurons (Meffert et al., 2003; Wellmann et al., 2001). This nuclear accumulation of NF-κB is mediated by CaMKII, and followed by an increase in gene transcription (Meffert et al., 2003). Thus, NF-κB is activated at synapses following synaptic activity and is transported back to the nucleus to regulate transcription of its target genes such as those encoding BDNF, Fos, CaMKIIδ, IGF2, Zif268, C/EBP, PKA, NMDAR, and PKC (de la Fuente et al., 2015; Engelmann and Haenold, 2016; Kaltschmidt et al., 1999).

Several lines of evidence have shown a key role of NF-κB in synaptic and structural plasticity, and memory formation. Genetic ablation of NF-κB in mice resulted in severe defects in the dentate gyrus (Imielski et al., 2012). These mice showed degenerating neurites, hampered axogenesis, synaptogenesis and memory impairment. These structural and behavioral deficits were reversed by the re-activation of NF-κB, suggesting that NF-κB is a crucial regulator of the homeostasis in the dentate gyrus. Another study indicated that NF-κB controls excitatory synapses and dendritic spine formation and morphology in mouse hippocampal neurons (Boersma et al., 2011). NF-κB is activated during LTP in the mouse hippocampus (Freudenthal et al., 2004). A growing body of evidence indicates the involvement of NF-κB in memory processes in rodents, in different learning tasks such as inhibitory avoidance (Freudenthal et al., 2005), radial arm maze (Meffert et al., 2003), contextual fear conditioning (Lubin and Sweatt, 2007) and novel object recognition (Federman et al., 2013).

Hippocampal NF-κB activity increases 45 min following training in inhibitory avoidance and returns to basal levels within 2 h after initial training (Freudenthal et al., 2005). Contextual fear conditioning also increases the activity of hippocampal NF-κB 45 min following training (de la Fuente et al., 2014). The intra-hippocampal injection of sulfasalazine, an NF-κB inhibitor, following contextual fear conditioning leads to deficits in long-term memory in mice (de la Fuente et al., 2014). Moreover, in the novel object

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recognition task, hippocampal NF-κB is active during memory consolidation, and the inhibition of hippocampal NF-κB signaling after training drastically impairs long-term memory in object recognition (Federman et al., 2013). These results suggest that NF-κB is involved in memory consolidation. Synaptic NF-κB is also activated by learning. Synaptosomal NF-κB activation occurs 5 min following inhibitory avoidance training during consolidation (Salles et al., 2015), suggesting a potential role of retrograde transport of NF-κB in memory consolidation.

In addition to the role of NF-κB in memory consolidation, several reports have shown the role of NF-κB in memory reconsolidation. Hippocampal NF-κB activity is increased after memory retrieval (Boccia et al., 2007; de la Fuente et al., 2011). Moreover, retrieval of contextual fear memory activates the NF-κB pathway to regulate histone H3 phosphorylation and acetylation at specific gene promoters in hippocampus (Lubin and Sweatt, 2007). Importantly, the inhibition of NF-κB DNA-binding complex activity leads to impairment in fear memory reconsolidation, and this deficit can be ameliorated by treatment with HDAC inhibitor, suggesting that histone acetylation is a mechanism by which NF-κB signaling exerts its effects in the process of memory reconsolidation (Lubin and Sweatt, 2007).

Taken together, NF-κB plays an important role in memory consolidation and reconsolidation and has dual function as a synaptic activity detector and as a transcription regulator. However, the role of synapse-to-nucleus shuttling of NF-κB remains unclear. Future studies should clarify direct contribution of synaptic NF-κB to regulation of gene transcription and subsequent memory formation.

CONCLUSION

Recent work has delineated some of the signaling pathways regulating activity-dependent gene transcription by transcriptional cofactors that are transported from synapses to the nucleus following neuronal activity. However, more research has to be done to fully understand the fascinating aspect of these unusual signaling pathways directly connecting synaptic activity with gene transcription, including but not limited to early development, ageing and gender differences. Considering the significant role these pathways play in organism’s responses to changes in the environment, unraveling the molecular interactions of these transcriptional cofactors are critical for understanding of their involvement in the regulation of both health and disease.

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Synaptically-localized transcriptional regulators, CRTC1, HDAC4 and NF-κB, can move to the nucleus upon neuronal stimulation

Their phosphorylation status regulates their synaptic or nuclear localization

These transcriptional regulators are unique, providing means of direct link between synaptic activity and gene transcription

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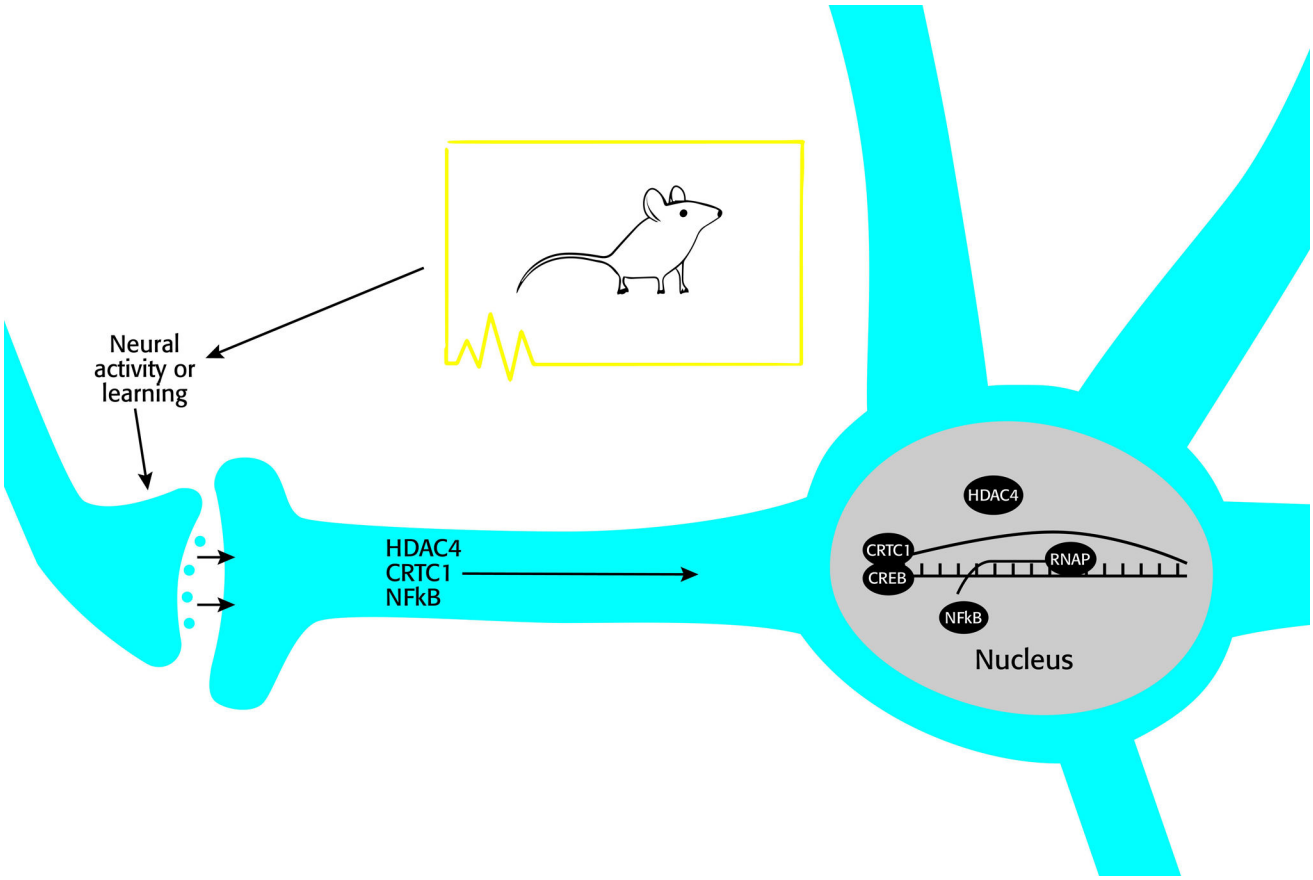

Figure 1. Schematic presentation of synapse-to-nucleus transport of transcription modulators HDAC4, CRTC1 and NF-κB to regulate gene transcription

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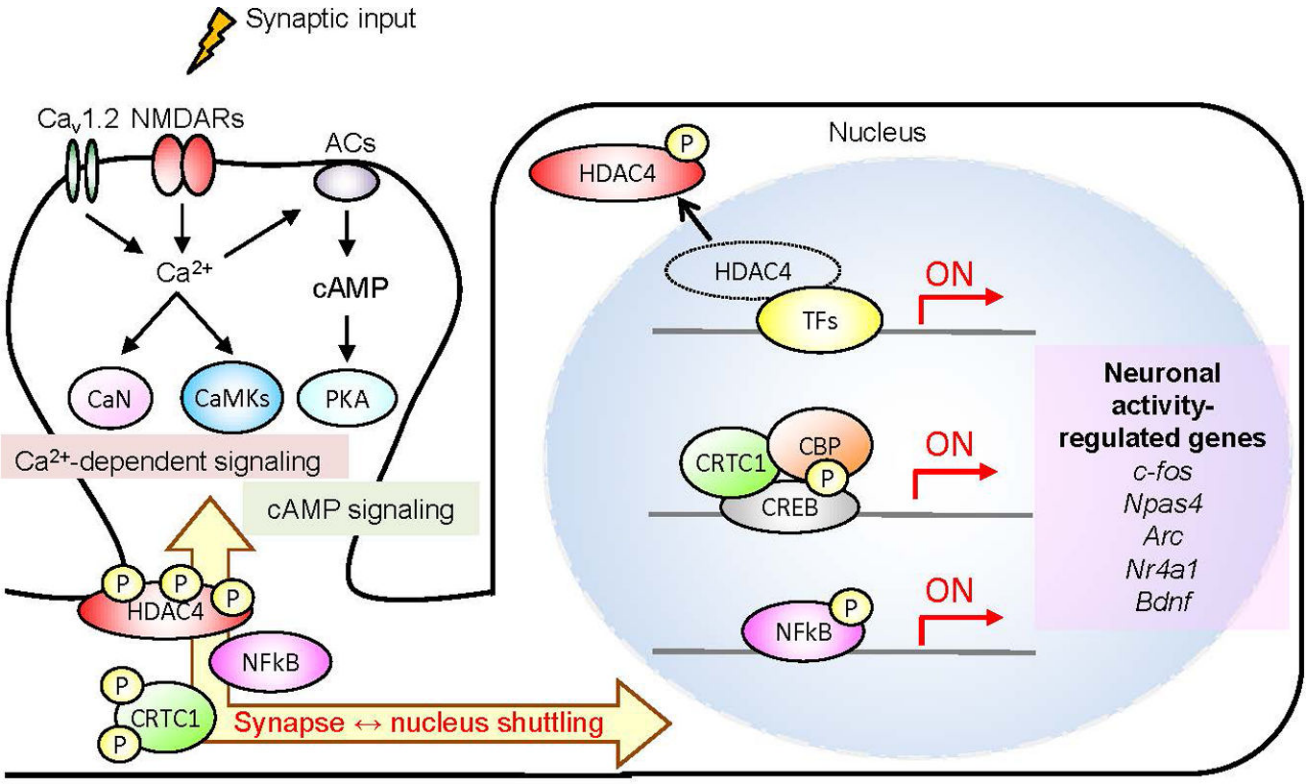

Figure 2. Neuronal activity-dependent gene expression program required for memory formation

Activation of NMDA receptors (NMDARs) and L-type voltage-sensitive calcium channel ($Ca_v1.2$) triggers calcium influx and induces calcium-dependent signaling molecules such as calcineurin (CaN) and Ca^{2+}/calmodulin-dependent protein kinases (CaMKs). Calcium influx also activates members of the cAMP signaling pathway, such as protein kinase (PKA) via Ca^{2+}-sensitive adenylate cyclase (ACs). These signaling molecules modulate the synapse-to-nucleus shuttling of transcription modulators (HDAC4, CRTC1 and NF-κB) via phosphorylation and dephosphorylation. Then, these transcriptional modulators contribute to the control of activity-dependent gene transcription which is required for synaptic plasticity and memory formation. P: phosphorylation; the red arrow marked with “ON” represents gene transcription.

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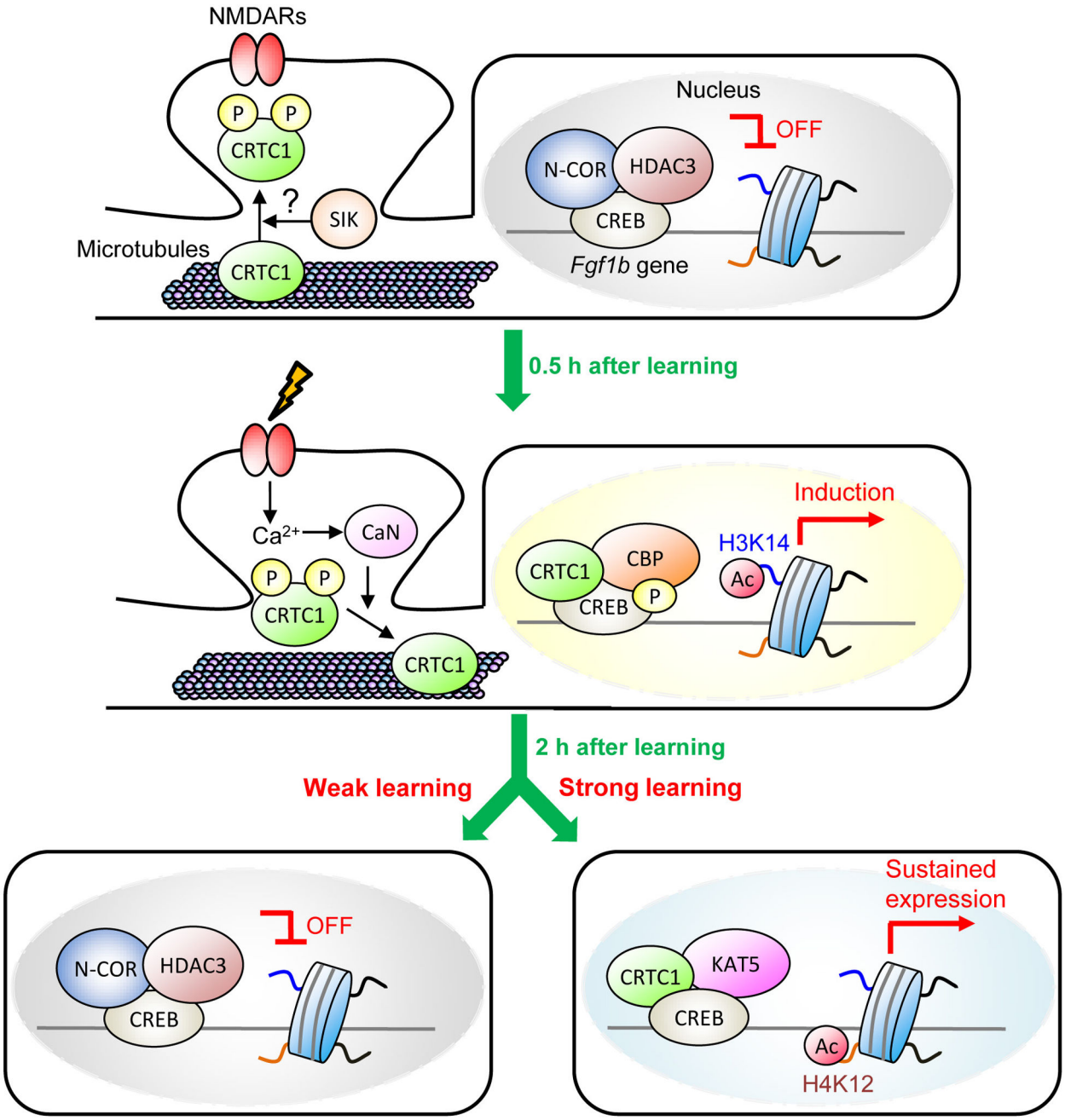

Figure 3. Proposed model how CRTC1 controls *Fgf1b* transcription and enhances memory

Under basal conditions, CRTC1 is phosphorylated and anchored to the synapses and dendrites. In the nucleus, HDAC3–N-CoR complex represses *Fgf1b* transcription. Upon learning (both weak and strong learning), Ca2+ signal potentiate CRTC1 dephosphorylation via activation of calcineurin (CaN). Dephosphorylated CRTC1 translocates to the nucleus, where it binds to phosphorylated CREB (pCREB) and histone acetyltransferases (CBP) and enhances *Fgf1b* gene transcriptional activity by increasing the acetylation of H3K14 on its promoter. These molecular events are terminated at 2h following weak training (*e.g.*, one foot-shock contextual fear conditioning). Conversely, strong training (*e.g.*, three foot-shock

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contextual fear conditioning) maintains nuclear localization of CRTC1 and upregulates *Fgf1b* transcription independently of pCREB even 2 h after learning by enhancing H4K12 acetylation via KAT5 recruitment to its promoter region. Learning-induced KAT5 recruitment acetylates H4K12 on the *Fgf1b* promoter, thereby enhancing synaptic plasticity and memory formation. P: phosphorylation; Ac: acetylation.

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Table 1

Brief summary of activity-dependent nucleocytoplasmic shuttling of CRTC1 and its role in synaptic plasticity and memory.

References	System	Findings
(Zhou et al., 2006)	Cultured hippocampal neurons Hippocampal slices	Neuronal stimulation induces nuclear translocation of CRTC1.
		CRTC1 regulates neuronal stimulation-induced gene expression of *Bdnf*.
		TORC1 nuclear translocation correlates with late-phase LTP induction.
		Requirement of TORC1 for late-phase LTP.
(Kovacs et al., 2007)	Cultured hippocampal or cortical neurons Hippocampal slice cultures	CRTC1 imports to the nucleus upon activation of calcium and cAMP pathways.
		CRTC1 mediates the synergistic activation of CREB-mediated transcription by calcium and cAMP in neurons.
		CRTC1 is involved in L-LTP maintenance in the Schaffer collateral–CA1 pathway.
(Li et al., 2009)	Cultured cortical neurons	Increased nuclear translocation of CRTC1 in response to neuronal stimulation.
		CRTC1 is required for activity-induced dendrite arborization.
	Mouse	CRTC1 is required for dendrite growth in the cortex.
(Espana et al., 2010)	Cultured hippocampal neurons	Amyloid β oligomers impair CRTC1-dependent signaling. impair
		Amyloid β impairs CRTC1/CREB-dependent transcription by CRTC1/CREB affecting CRTC1 dephosphorylation.
	Mouse	Gene transcription mediated by CRTC1 is impaired in the hippocampus from an animal model of Alzheimer's disease.
(Ch'ng et al., 2012)	Cultured hippocampal neurons	Activity-dependent synapse-to-nucleus translocation of CRTC1 in excitatory neurons.
		Nuclear translocation of CRTC1 requires activation of calcineurin. cAMP regulates the persistence of CRTC1 in the nucleus.
		CRTC1 is required for activity-dependent induction of specific CREB target genes (*c-fos*, *Arc*, *Zif268*).
	Hippocampal slice cultures	Chemical LTP induces synapse-to-nucleus translocation of CRTC1.
(Sekeres et al., 2012)	Mouse	Herpes simplex virus-mediated local and acute increase of CRTC1 levels in the dentate gyrus of hippocampus during training enhances consolidation of contextual fear memory.
		Increasing CRTC1 levels in the dentate gyrus of hippocampus enhances reconsolidation of an established contextual fear memory.
(Parra-Damas et al., 2014)	Mouse	Learning (Morris water maze)-induces nuclear accumulation of CRTC1 in the CA1 and CA3 subregion of hippocampus.
	Human	Altered CRTC1 levels and transcriptional changes (*ARC*, *NR4A2*) in human brain at intermediate Alzheimer's disease pathological stages.
(Nonaka et al., 2014)	Cultured hippocampal or cortical neurons	Dephosphorylation of CRTC1 at Ser151 and Ser245 is critical for its activity-dependent nuclear import and CRE-dependent transcriptional activity.
		CRTC1 mutant lacking calcineurin-binding motifs disrupts nuclear translocation of CRTC1 following neuronal stimulation.
	Mouse	Overexpression of the constitutive active form of CRTC1 (Ser151Ala/Ser245/Ala) in the CA suregion of hippocampus enhances activity-dependent gene expression (*Arc*, *c-fos*, *Bdnf*) and long-term fear memory formation.
		Learning (contextual fear conditioning) induces nuclear accumulation of CRTC1 in the basolateral amygdala.

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References	System	Findings
		Knockdown of CRTC1 in the basolateral amygdala reduces long-term fear memory.
		Overexpression of the constitutive active form of CRTC1 induces a significant enlargement of spine heads.
(Uchida et al., 2017)	Primary hippocampal neurons	Neuronal stimulation induces nuclear translocation of CRTC1.
		Two phosphorylation sites of CRTC1 at Ser151 and Ser167 are important for its nuclear retention rather than nuclear import following neuronal stimulation.
	Mouse	Learning (contextual fear conditioning and object location task) induces synapse-to nucleus translocation of CRTC1 in the CA subregion of hippocampus and these are dependent on the strength of learning.
		Learning-induced nuclear translocation of CRTC1 is dependent on microtubule stability.
		Loss-of-function CRTC1 in the CA subregion of hippocampus disrupts LTP and long-term memory.
		Gain-of-function CRTC1 in the CA subregion of hippocampus leads to memory enhancement.
		Calcineurin-mediated CRTC1 nuclear translocation is required for memory enhancement.
		CRTC1/CREB/KAT5-mediated epigenetic regulation of *Fgf1b* expression is required for memory enhancement.
(Parra-Damas et al., 2017)	Mouse	Contextual fear learning induces CRTC1 dephosphorylation in the hippocampus.
		Contextual fear learning induces CRTC1 nuclear translocation in the CA3 subregion of hippocampus.

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Table 2

Brief summary of activity-dependent transcriptional regulators implicated in neuropsychiatric disorders.

Disease or model		Targets	Findings	References
Alzheimer's disease	Human study	CREB, CBP/p300	Reduced CREB, pCREB (Ser133), and CBP/p300 levels in prefrontal cortex in Alzheimer's disease.	(Bartolotti et al., 2016)
		MEF2	Association of SNP rs190982 with Alzheimer's disease.	(Lambert et al., 2013) (Ruiz et al., 2014)
	Animal model	HDAC4, MeCP2	HDAC4 and MeCP2 are identified as top canonical pathways by proteomics analyses.	(Neuner et al., 2016)
		HDAC4	Increased nuclear HDAC4 levels in the hippocampus.	(Sen et al., 2015)
		CRTC1	Impaired learning-induced nuclear translocation of CRTC1.	(Parra-Damas et al., 2017; Parra-Damas et al., 2014)
			The changes in CRTC1/CREB target genes.	
			Reduced memory in model mice was restored by hippocampal overexpression of CRTC1.	
Autism/Rett syndrome	Human study	MECP2	Mutations in the *MECP2* gene in approximately 90% of patients with Rett syndrome.	(Amir et al., 1999)
		MEF2	MEF2C haploinsufficiency in autism. Small deletion encompassing the MEF2C gene in autism.	(Novara et al., 2010) (Le Meur et al., 2010)
		HDAC4	HDAC4 haploinsufficiency in autism.	(Pinto et al., 2014)
	Animal model	MeCP2	Cognitive and social abnormalities.	(Ebert et al., 2013; Li et al., 2008; Moretti et al., 2006)
			Deficit in motor behavior.	
		MEF2	Altered spine number and impaired memory.	(Barbosa et al., 2008)
Depression	Human study	CREB, HDAC4	Decreased levels of CREB and increased levels of HDAC4 in patients with depression.	(Hobara et al., 2010; Ren et al., 2011)
	Animal model	CREB, CRTC1, MEF2, MeCP2, HDAC4,	CREB overexpression in the dentate gyrus induces antidepressant-like behavior.	(Chen et al., 2001; Higuchi et al., 2016; Hutchinson et al., 2012; Lepack et al., 2016; Meylan et al., 2016a; Meylan et al., 2016b; Sailaja et al., 2012; Sarkar et al., 2014; Uchida et al., 2011)
			CRTC1 knockout mice showed increased depression-like behavior.	
			Decreased *Mef2* mRNA in depressed mice.	
			Increased MeCP2-HDAC2 binding in depressed mice.	
			MeCP2 mutant mice showed increased depression-like behavior.	
			Hippocampal overexpression of HDAC4 induced depression-like behaviors.	

Disease or model	Targets	Findings	References
		Increased HDAC4 in the hippocampus or medial prefrontal cortex of depressive mice.	

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