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Review

The relation of transcription to memory formation★

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A distinction between short-term memories lasting minutes to hours and long-term memories lasting for many days is that the formation of long-term memories requires new gene expression. In this review, the focus is on the current understanding of the relation of transcription to memory consolidation based on the data collected from behavioral studies performed primarily on genetically altered animals. Studies in *Drosophila* and *Aplysia* indicate that the transcription factor cAMP/Ca^{2+} response element binding protein (CREB) is critical in mediating the conversion from short- to long-term memory. More recent genetic studies in mice also demonstrated CREB and inducible transcription factor Zif268 involvement in information storage processes. Transcription seems to play essential role in memory formation but the mechanisms for activation of transcription and downstream processes during memory consolidation remain unclear.

Regardless, whether memory is examined in invertebrates or vertebrates, information is first stored in a transient short-term memory lasting minutes to hours which can be stabilized into long-term memory (LTM) lasting days to lifetime (Allweis, 1991; Baddeley, 1976; McGaugh & Hertz, 1972; Squire, 1987). A variety of inhibitors of protein and RNA synthesis have been shown to effectively block long-term memory without alteration of short-term memory (Andrew, 1980; Davis & Squire, 1984; Matthies, 1989; Montarolo *et al.,* 1986; Rosenzweig Bennett, 1984; Squire *et al.,* 1980). Thus, regulatory mechanisms directing transcription subsequent to the molecular changes in neurons during transient

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Abbreviations: CRE, cAMP responsive element; LTM, long-term memory.

memory formation play a pivotal role in the conversion of short- to long-term memory.

Genetic screens for learning mutants in *Drosophila* have led to the characterization of *amnesiac* (neuropeptide that binds to a G protein-coupled receptor that stimulates adenylyl cyclase), *rutabaga* (the enzyme adenylyl cyclase), *dunce* (the protein that regulate adenylyl cyclase, a cAMP phosphodiesterase) and *DCO* (catalytic subunit of cAMP-dependent protein kinase A) (reviewed by (Dubnau & Tully, 1998). Genetic disruption of any of these genes causes deficit in memory formation after classical (Pavlovian) conditioning of an odor-avoidance response in *Drosophila* but not in sensorimotor responses required for learning the task (Dubnau & Tully, 1998; Tully, 1996). The finding that four genes involved in cAMP signaling pathway arise from an unbiased phenotypic screen suggests that this signaling pathway must play a critical role in at least this form of olfactory learning. Further studies by Tully and others demonstrated that fruit flies that overexpress a CREB repressor transgene under the control of inducible heat shock promoter and tested for memory retention after Pavlovian olfactory learning showed drastically impaired long-term memory formation without affecting transient short-term memory (Yin *et al.,* 1994). Overexpression of a CREB activator decreased the number of training trials needed to establish long-term memory but did not affect short-term memory formation (Yin *et al.,* 1995). Thus, the level of active CREB is essential for determining the number of training trials required for long-term memory in *Drosophila* olfactory associative learning.

These observations in fruit flies are in agreement with reported studies on the gill-withdrawal reflex in *Aplysia* in which the cAMP signaling pathway appears also to play a central role (Byrne & Kandel, 1996; Castellucci *et al.,* 1980; Castellucci *et al.,* 1982). A single electric shock to the tail of the mollusk produces a transient enhancement of the gill withdrawal reflex. This short-term memory could be transformed into long-term memory by applying multiple stimuli. Reconstitution of the neurons that mediate the gill withdrawal reflex by co-culturing a single *Aplysia* sensory neuron with the motor neuron that mediates the reflex allows the study of the molecular and cellular mechanisms involved in this simple form of learning. In response to one pulse of serotonin this synapse undergoes short-term facilitation, while five repeated pulses of serotonin result in long-term facilitation. Serotonin activates adenylate cyclase in sensory neurons and injection of cAMP directly to the sensory neurons results in formation both short-term and long-term facilitation (Brunelli *et al.,* 1976; Schacher *et al.,* 1988). The physiological changes that accompany pre-synaptic facilitation were observed after intracellular injection of the catalytic subunit of cAMP-dependent protein kinase A (PKA) into *Aplysia* sensory neurons (Castellucci *et al.,* 1980) while inhibitors of PKA blocked both forms of facilitation (Ghirardi *et al.,* 1992). Additionally, injection of CRE (cAMP responsive element) oligonucleotides directly into the nucleus of the sensory neurons blocked selectively long-term facilitation (Dash *et al.,* 1990). Finally five repeated pulses of serotonin activated transcription of a CREB-reporter gene in *Aplysia* sensory neurons (Kaang *et al.,* 1993), while a single pulse of serotonin did not. Taken together, the conversion of short- to long-term memory requires removal of certain inhibitory constraints on the storage of long-term memory followed by an activation of CREB-controlled gene expression; both mechanisms are required for stabilization of transient memory (Abel *et al.,* 1998; Alberini *et al.,* 1994; Bartsch *et al.,* 1998; Bartsch *et al.,* 1995).

CRE-binding factors such as CREB seems to be conserved from mollusks to mammals and their activity is regulated by both cAMP and calcium influx (reviewed in Brindle & Montminy, 1992). These CREB/ATF or CREM families of activators and repressors belong to the

bZip transcription factor class. A proposed mechanism, in which CREB activates its target promoters, is based on the observation that PKA phosphorylates CREB at Ser-133 in response to elevated levels of cAMP. CREB mediates transcriptional induction upon its phosphorylation by PKA (Gonzalez & Montminy, 1989) or a calcium-dependent nuclear kinase (Deisseroth *et al.,* 1996) followed by direct interaction with coactivator of transcription CBP, CREB binding protein (Chrivia *et al.,* 1993) which facilitates the assembly of the basic transcriptional machinery. CREB has a bipartite transactivation domain consisting of constitutive domain, Q2 and inducible domain, KID. It has been shown that Q2 domain can potentially interact with TFIID *via* hTAF135 bridging protein. On the other hand, phosphorylation of the KID domain (Ser-133) induces interaction with KIX domain (CREB interaction domain in CBP). Although it is unclear how the transactivation occurs it is believed that CBP/CREB-P complex formation enables direct association with the RNA polymerase II complex. CBP was demonstrated to posses an intrinsic histone acetyltransferase activity (Ogryzko *et al.,* 1996) which is required for CREB-mediated gene expression (Korzus *et al.,* 1998). The intrinsic protein acetyltransferase activity in CBP might directly destabilize promoter bound nucleosomes facilitating activation of transcription.

CBP has been directly linked with synaptic activity-induced transcription (Chawla *et al.,* 1998; Hardingham *et al.,* 1999; Hu *et al.,* 1999). It has been previously postulated that nuclear and cytoplasmic calcium signals have distinct function in CREB-dependent transcription. Although both nuclear and cytoplasmic calcium signals are required for the induction of CREB-dependent transcription, only cytoplasmic calcium signals promotes CREB phosphorylation on Ser-133. Selective inhibition of nuclear calcium transients blocked efficiently CREB-dependent transcription but not CREB phosphorylation at Ser-133 (Hardingham *et al.,* 1997). Conversely, calcium influx *via* NMDA receptors or voltage-sensitive calcium channels induces CBP-dependent transactivation (Hardingham *et al.,* 1999; Hu *et al.,* 1999). Moreover, a signal-regulated transactivation domain found in CBP is controlled by nuclear calcium and cAMP levels (Chawla *et al.,* 1998). Further studies led to the conclusion that CBP is an important target for calcium signaling pathway and may act as a regulatory switch for glutamate-induced transcription in hippocampal and cortical neurons (Hardingham *et al.,* 1999; Hu *et al.,* 1999).

The discovery that PKA together with its nuclear target CREB are required and also are sufficient for long-term memory formation in *Drosophila* as well in *Aplysia* prompted the study of the function of the CREB gene in the mammalian brain. The importance of CRE-mediated transcription in long-term neuronal plasticity in mammals was recently emphasized by Storm and colleagues in the series of experiments performed in transgenic mice harboring CRE-linked to a LacZ reporter gene. The association of the induction of CRE-dependent gene expression with the generation of late phase of LTP in the Schaffer collateral pathway in mouse hippocampus has been demonstrated (Impey *et al.,* 1996; Impey *et al.,* 1998a). Moreover, the transgenic mice tested after behavioral training on the contextual conditioning task showed hippocampus-specific induction of the CRE-LacZ reporter gene (Impey *et al.,* 1998b). This provided direct evidence that experience that leads to memory formation also induces CRE-dependent transcription.

Analysis of CREB phosphorylation occurring during hippocampal synaptic plasticity revealed at least two opposite calcium/calmodulin-regulated mechanisms in hippocampal neurons which determine expression of CRE-regulated genes: a CaM kinase cascade involving nuclear CaMKIV and a calcineurin-dependent regulation of nuclear protein phosphatase 1 activity (Bito *et al.,* 1996).

Moreover, studies with fear conditioning and Morris water maze performed in mice with a hypomorphic CREB allele (Hummler *et al.,* 1994) showed that CREB mutant mice have normal short-term memory but deficient long-term memory and impaired LTP measured in hippocampal slices (Bourtchuladze *et al.,* 1994). In these mice, the two major physiological isoforms of CREB, α and Δ, are disrupted, but a third form β and several activator and repressor form of CREM are up-regulated (Blendy *et al.,* 1996; Hummler *et al.,* 1994). However CRE$B\alpha\Delta$ mutant mice phenotype strongly depends on genetic background as well as on a CREB gene dosage effect (Gass *et al.,* 1998). In contrast to the previously obtained data using CRE$B\alpha\Delta$ with different genetic background deficits in social transmission of food preference (Kogan *et al.,* 1997) and in hippocampal LTP (Bourtchuladze *et al.,* 1994) have not been observed this time (Gass *et al.,* 1998). The homozygous CREB null mice in which all three forms of CREB are inactivated, are not available for behavioral learning tests because this mutation is lethal due to developmental abnormalities (Rudolph *et al.,* 1998).

The presence of multiple CREB forms in mammals complicates the genetic study to establish the role of CREB-dependent transcription in the transition from short- to long-term memory. Recent advances in mouse neurogenetics (Mayford, 2002) helped significantly in understanding the role of *creb* gene in long-term memory formation. Kandel and collaborators showed that inhibition of CREB/ATF transcription factors in dorsal hippocampus disrupts spatial memory in mice but not fear memories (Pittenger *et al.,* 2002). On the other hand, more broad expression of CREB inhibitor into excitatory forebrain neurons including hippocampus, amygdala and cortex resulted in disruption of fear memories (Kida *et al.,* 2002). Different types of memory were disrupted due to a different pattern of CREB inhibitor expression in these two transgenic mice. It provides additional evidence for neuroanatomical distinction between spatial memory and fear memory. In both cases the expression of CREB inhibitor disrupted only long-term memory processes. The short-term memory was spared in both CREB mutant mice.

CREB has been the most intensely studied transcriptional factor in relation to memory formation across species but it is not the only transcription factor considered to play a role in the information storage. Many studies showed that both LTP and learning induce expression of immediate-early genes including transcription factors: Fos, Jun, Zif268 in specific area of the mammalian brain (reviewed in Bozon *et al.,* 2002; Cole *et al.,* 1989; Tischmeyer & Grimm, 1999; Worley *et al.,* 1990). Even though these studies have not yet offered any convincing molecular mechanism explaining how would immediate-early genes contribute to memory formation, it is striking, how the expression pattern of immediate-early genes induction correlates with the model of memory formation at the systems level. This model postulates that declarative memories such as memory of facts, faces or context require integrity of hippocampus whereas amygdala is essential for non-declarative memories such as procedural memory or memory of fear (Phillips & LeDoux, 1992; Squire & Zola, 1996). Interestingly, an elevated expression of Zif268 was recorded within hippocampus, during the retrieval of contextual, but not cued, fear associations. In contrast, Zif268 expression was increased within amygdala (lateral, basal, and central nuclei) when both contextual and cued fear memories were retrieved (Hall *et al.,* 2001). Perhaps the strongest evidence for an involvement of immediate-early genes in long-term memory formation came from behavioral analysis performed on Zif268 (–/–) mutant mice (Jones *et al.,* 2001). It has been demonstrated that the Zif268 mutant mice has strong deficiency in long-term memory formation tested on variety behavioral tasks including social transmission of food preference,

novel object recognition and conditioned taste aversion but normal short-term retention (Jones *et al.,* 2001). The fact that these mutant animals can learn a task and show intact short-term memory provides very good control eliminating possibility that the mutation has an effect on the performance or is causing some developmental defects resulting in a cognitive dysfunction.

It is understandable that many genes will be required to maintain the basic cellular function and subsequently their long-lasting deficiency due to introduced gene mutation might result in many kinds of secondary effects causing deficiency in performance or cognitive dysfunction. Therefore it is often difficult to prove beyond a reasonable doubt a direct involvement of a gene in the molecular mechanism underlying memory consolidation based only on genetic studies, even though, genetics provides the most convincing data in the field. Moreover, elucidation of the molecular mechanism controlling memory formation would not necessary mean that we will understand how information is stored. The most difficult challenge in modern neuroscience is to discover how memories are encoded as a pattern of synaptic connections. However understanding of the molecular and cellular mechanisms of memory formation is imperative in order to pin point targets for drug development that could be used for treatment of memory disorders such as Alzheimer's disease, aging-related memory weakening, some forms of mental retardations, and even for pharmacologically enhancing memory in absence of pathological signs. At this point it is unclear how the long-term memory is induced, and even less is known about downstream processes leading to memory consolidation. Many neuroscientists agree that there is a cellular mechanism that underlies memory formation involving a generation of a pattern of synaptic strengths. It is very likely that those changes induced in neurons would involve transcription-dependent mechanisms directing the process that sets a pattern of synaptic strengths encoding new information. Combined approach using molecular neurogenetics together with recent advancements in genomics, proteomics and subcellular imaging should help to understand cellular and molecular mechanisms underlying memory consolidation.

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