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REVIEW

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GENES TO REMEMBER

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Summary

**It has been known for several decades that the formation of long-term memory requires gene expression. In recent years, the use of genetic and molecular approaches has led to the identification and characterization of genes and molecules that play a fundamental role in the biological mechanisms underlying learning and memory. From these studies, it appears that molecules and molecular mechanisms essential for the process of memory have been conserved throughout evolution. The cyclic AMP (cAMP)-dependent activation pathway and a cAMP-dependent cascade of gene expression have been shown to be essential**

**for memory formation in *Aplysia californica*, *Drosophila melanogaster* and rodents. Moreover, members of the transcription factor family cAMP response element binding proteins (CREBs) seem to represent key molecules for transforming incoming information into long-term memory. Here, we review the studies showing that conserved molecules and biological mechanisms are engaged in simple and complex forms of memory.**

Key words: memory, learning, gene, cAMP, transcription factor, CREB.

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Introduction

How does the brain form and recall memories? What are the biological changes that serve as the bases of memory? These questions are of great interest and have begun to be answered in the last decade.

Memory is the process by which incoming information is elaborated and stored. It can last for minutes (short-term memory), hours, days, months or even an entire lifetime (long-term memory). Our brain is able to store different kinds of information and form different kinds of memories that fall into two general categories: implicit and declarative. Implicit memories include such things as simple classical conditioning, non-associative learning and perceptual and motor skills. Riding a bicycle and playing the piano require the development of implicit memories. Declarative memory stores information about specific events and related temporal and personal associations. It is the memory we rely on every day to recognize people, faces and places and to remember facts from our past. This memory involves all our sensory perceptions, our feelings and motivation. When we remember an experience, we recall what we have seen, heard, smelled, tasted, touched and felt. How does the brain process and store all this information? And where is the information stored? The brain must undergo changes that are maintained as long as the memory is stored. What are these changes?

A few decades ago, the discovery that certain antibiotics inhibit memory formation when administered during learning showed that long-term memory formation requires biological

processes such as protein synthesis. This attracted wide attention among neurobiologists, and today it is clear from a large number of studies carried out in different species ranging from invertebrates to mammals that a fundamental and conserved prerequisite for long-term memory formation is the expression of genes during and immediately after learning (Agranoff, 1967; Barondes, 1975; Castellucci et al., 1989; Tully et al., 1994; Rose, 1995; Davis and Squire, 1984; Flexner et al., 1963). This critical period coincides with the consolidation phase of memory, the initial period necessary to transform incoming information into stable and storable modifications. If gene expression is blocked after this critical period is over, memory forms normally. In the last ten years, molecular neurobiologists have focused on the identification and characterization of the genes and molecular events required to form long-term memory. Studies begun in two invertebrate systems, *Aplysia californica* and *Drosophila melanogaster*, revealed much about the biological basis of learning and memory.

Invertebrate simple memory

*Aplysia californica*, a marine snail, was chosen more than 30 years ago as a model to study learning and memory. It offered the great advantage of having simple behavioral responses and a relatively small number of large and readily identifiable neurons. This made it possible to identify and

characterize the contributions of individual neurons to learned behavior. The form of learning that has been best characterized in *Aplysia californica* is sensitization of the gill and siphon withdrawal reflex, an enhancement of the animal's defensive reflex response to innocuous stimuli triggered by a previous encounter with an aversive stimulus. Both short- and long-term memory can be identified in the above form of learning and depend on the number of training trials applied (Frost et al., 1985). A groundbreaking finding that allowed biochemical and molecular investigations of this memory at the single cell level was provided by the work of Montarolo et al. (1986). These investigators showed that it is possible to reconstitute *in vitro* the main components of the neuronal circuit underlying sensitization and to reproduce the synaptic responses induced *in vivo* by learning. The parallel use of both the *in vitro* and *in vivo* models and the work of several groups in the last 15 years led to an understanding of the biological process underlying sensitization of the gill and siphon withdrawal reflex (Bailey et al., 1996; Byrne and Kandel, 1996; Carew, 1996). When a sensitizing stimulus is applied, it produces an increase in neurotransmitter release, called facilitation, at the synapses that connect the sensory neuron to the motor neuron. A short-term facilitation, lasting for few minutes, parallels short-term sensitization and a long-term facilitation, which can last for several days, underlies long-term sensitization. Both short- and long-term facilitation are mediated by the action of the neurotransmitter serotonin (5-HT), which is released *in vivo* by regulatory interneurons and acts on the serotonin receptors of the sensory neurons. Sensory neurons respond to 5-HT with an increase in cAMP level and the activation of cAMP-dependent protein kinase (PKA), both essential for short- and long-term facilitation. As in the case of behavioral memory, while short-term facilitation is mediated by PKA-dependent phosphorylation and other post-translational modifications of synaptic proteins, long-term facilitation is associated with the translocation to the nucleus of PKA catalytic subunits and requires the activation of gene expression during a brief, initial period (Castellucci et al., 1989; Ghirardi et al., 1995; Bacskey et al., 1993; Montarolo et al., 1986). Experimental gene cloning and manipulation carried out in Eric Kandel's laboratory using the *in vitro* model elegantly demonstrated that long-term facilitation requires the activity of transcription factors belonging to the cAMP response element binding protein (CREB) family (Alberini et al., 1994; Bartsch et al., 1995; Dash et al., 1990; Kaang et al., 1993). These proteins, recently cloned and characterized by Bartsch et al. (1995, 1998), include at least three isoforms, CREB1a, a transcription activator, CREB1b, a repressor, and CREB1c, a modulator, all derived by differential splicing from a single gene called CREB1. By a concerted action, CREBs appear to be the genetic switch that turns on the expression of genes necessary for long-term synaptic plasticity.

Because the function of CREB is to regulate the expression of genes, a great deal of interest was then – and currently is – focused on the identification of the target genes turned on or off by CREB and playing an essential role in long-term

memory. In *Aplysia californica*, a few genes induced during long-term facilitation have been identified and, although no definitive proof has been provided yet for a formal role of CREB in directly controlling their transcription, several lines of evidence support this possibility. Searching for CREB target genes, Mirella Ghirardi and I, working in Eric Kandel's laboratory, focused on transcripts regulated during the critical period of memory consolidation. We found that serotonin-evoked long-term facilitation requires a rapid expression of CCAAT enhancer binding protein (ApC/EBP), again a member of a transcription factor family. We observed that the level of ApC/EBP mRNA was very low in unstimulated conditions, but increased rapidly during the initial critical phase of long-term facilitation. Because its induction did not require new protein synthesis, it was clear that ApC/EBP is regulated as an immediate early gene. These results implied that ApC/EBP may be directly regulated by CREB and, in agreement with this hypothesis, we found that the promoter region of ApC/EBP, 19 base pairs upstream from the putative TATA box, contains a CRE consensus that can mediate long-term facilitation (Alberini et al., 1994). Moreover, another gene that is rapidly induced, possibly by the action of CREB, has been found to be required for long-term facilitation. This is a neuron-specific ubiquitin C-terminal hydrolase, an enzyme associated with proteasome-dependent proteolysis. This gene cooperates in the upregulation of the ubiquitin pathway and is hypothesized to participate in the degradation of specific proteins that inhibit long-term facilitation (Hegde et al., 1997).

In conclusion, studies carried out in *Aplysia californica* demonstrated that the activation of a genetic cascade is essential for long-term synaptic plasticity underlying memory consolidation. This cascade, initiated by the activation of the CREB unit as a result of the integration of incoming signals, requires the induction of transcriptional regulators such as ApC/EBP. The action of these transcription factors leads to the expression of downstream target genes, still to be identified, but among which are probably those encoding proteins that mediate memory storage (Bailey et al., 1996).

The importance of CREB in behavioral memory was demonstrated by Yin, Tully and collaborators using another invertebrate, the fruitfly *Drosophila melanogaster*. The use of this powerful genetic and behavioral system was crucial for the identification of a number of genes whose function is essential for memory formation. Behavioral studies began more than 25 years ago when Benzer and coworkers used Pavlovian olfactory learning to train flies to avoid an odor paired with an electrical shock and identified *dunce* and *rutabaga*, two different single-gene mutations that impair associative learning. Biochemical and molecular analysis later demonstrated that the two genes encoded for a cAMP-specific phosphodiesterase and adenylyl cyclase, respectively.

Tully and co-workers were able more recently to develop appropriate behavioral tests that distinguished between short- and long-term memory in *Drosophila melanogaster* and, using powerful molecular genetic techniques, identified and characterized genes required for memory (DeZazzo and Tully,

1995; Dubnau and Tully, 1998; Tully et al., 1994). Today several mutants, including *dunce*, *rutabaga*, *radish*, *DCO* and *amnesiac* are known, and their molecular characterization strikingly showed that they all share a common feature: they all affect, albeit in different ways, the cAMP cascade. Yin, Tully and collaborators cloned *Drosophila melanogaster* CREB (dCREB2) and used reverse genetic experiments with inducible transgenes encoding repressor (dCREB2-b) and activator (dCREB2-a) forms of CREB to analyze their functional role in memory. They found that the expression of a dominant negative CREB completely and specifically blocked long-term memory, while the expression of dCREB2-a enhanced long-term memory formation. On the basis of these observations, they proposed that differential regulation of CREB isoforms generates a molecular switch for long-term memory formation (Yin et al., 1995; Yin and Tully, 1996). Thus, cAMP activation leading to CREB-dependent gene expression turned out to be used by two very different invertebrates for memory formation.

These studies in invertebrates inspired and guided the investigation of a possible evolutionarily conserved role for the cAMP-CREB-dependent pathway in mammalian learning and memory.

#### More complex memory: conserved molecules

In mammals, CREB is a large family of transcription factors that includes several isoforms generated by alternative splicing. A mutation targeted to exon 2 was used to generate mice with a disruption of the CREB gene. These CREB<sup>-</sup> mice lacked the two main CREB isoforms  $\alpha$  and  $\delta$  (Hummler et al., 1994). Bourtchuladze, Silva and co-workers investigated the memory of CREB<sup>-</sup> mice using tests that analyzed different kinds of memories. When the animals were trained using a Pavlovian conditioning test (cued conditioning) to associate a tone with an electric shock, the CREB<sup>-</sup> mice had impaired long-term memory, tested 24 h after training, but normal short-term memory, tested 30 or 60 min following training. A different conditioning test, measuring the ability of the animals to remember an environment in which they originally received a shock (contextual fear-conditioning), showed that CREB<sup>-</sup> mice are impaired 24 h after training, while their short-term memory tested at 30 min is intact. CREB<sup>-</sup> mice were again found to be selectively impaired in a third test of long-term memory that evaluated hippocampal-dependent spatial memory (the Morris water maze). In this task, the animal is required to recall the location of a submerged platform in a water tank. Consistent with these findings, the CREB<sup>-</sup> mice also showed impaired hippocampal long-term potentiation (LTP), a synaptic response thought to underlie the process of memory (Bourtchuladze et al., 1994). Moreover, the stimulus paradigm that generates late (L-)LTP increases CREB phosphorylation and CRE-mediated gene transcription (Impey et al., 1996).

These studies showed that the action of CREB is required to form long-term memory in mammals and raised the following

questions. Where in the brain and when is CREB activated during memory formation? Which signals induce the CREB response? Which signal transduction cascade regulates CREB in mammalian memory? Which are the CREB-regulated target genes necessary for memory? Very recently, these issues have been explored and, to some degree, clarified.

Recent work by Bernabeu, Izquierdo, Medina and collaborators, using pharmacological and biochemical approaches, has shown that cAMP concentration and PKA expression and activity are increased in the hippocampus of the rat following step-down inhibitory avoidance training (a contextual fear-conditioning learning). These observations suggest that CREB responsiveness is modulated by the cAMP/PKA signaling pathway during memory consolidation in mammals as in invertebrates (Bernabeu et al., 1997; Izquierdo and Medina, 1997).

This emphasis on the cAMP-PKA dependent pathway, however, does not exclude a possible contribution of other signaling pathways to the modulation of CREB in memory formation, perhaps by cross talk with cAMP/PKA activation. Calcium-calmodulin kinases II and IV (CaMKII and CaMKIV) and mitogen-activated protein kinase (MAPK) can mediate CREB phosphorylation and, together with protein kinase C (PKC), have been found to be activated in the hippocampus after fear conditioning (Atkins et al., 1998; Bito et al., 1996; Deisseroth et al., 1996; Impey et al., 1998a; Nogues et al., 1996; Wolfman et al., 1994). However, further studies are needed to ascertain whether and at which stage of the memory process all these kinases, perhaps activated by different incoming signals, modulate CREB phosphorylation and activity.

Recently, we and others have begun to document those regions of the brain where CREB is activated during memory formation. For these studies, inhibitory avoidance, a hippocampus-dependent form of learning, has been used. The advantage offered by this paradigm for molecular studies of memory consolidation is that it produces a long-term memory after a single learning trial. In the inhibitory avoidance task, animals are asked to associate a location with an aversive stimulus. The subjects demonstrate memory by avoiding the negatively reinforced location. Impey et al. (1998b) found, in mice, that Ser133 phosphorylation of the endogenous CREB, a step required for transcriptional activity of CREB, is increased after training compared with naive controls. Moreover, they generated CRE-Xgal transgenic mice and tested their response to inhibitory avoidance learning. They found that CRE-dependent gene expression is activated in CA1 and the dentate gyrus (DG) of the hippocampus 8 h following training (Impey et al., 1998b). Using the same learning paradigm in rats, we observed that CREB phosphorylation in Ser133 is strongly increased in the same hippocampal subregions immediately after training and that this increase is sustained for at least 6–9 h (Taubenfeld et al., 1999). Therefore, a CREB-mediated response is activated in the mammalian hippocampus, a structure known for over 40 years to be essential for forming new memories.

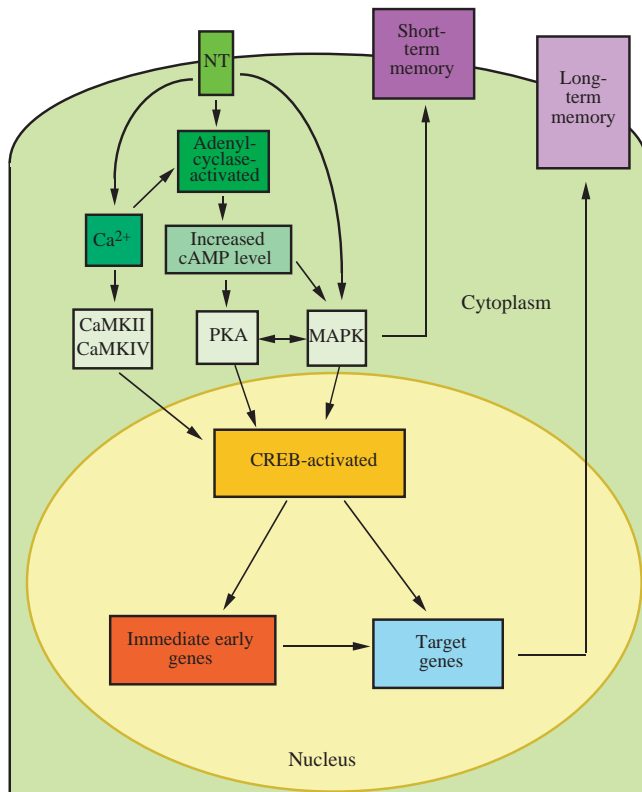


Fig. 1. Schematic representation summarizing the molecular events leading to short and long-term memory. CaMKII, CaMKIV, calcium-calmodulin-dependent kinases II and IV; CREB, cAMP response element binding protein; MAPK, mitogen activated protein kinase; PKA, cAMP-dependent protein kinase; NT, neurotransmitter.

Bilateral lesions of the hippocampal system in humans is associated with a profound anterograde amnesia, an inability to store new information into an accessible long-term memory. Recall of previously stored information, however, is relatively intact. We reasoned that, if lesions of the hippocampus prevent memory consolidation, they may do so by preventing the CREB-mediated response. Major pathways afferent to the hippocampus are organized in the fimbria-fornix and cingulate bundles, which provide the hippocampus with cholinergic, noradrenergic and serotonergic inputs. Lesions of the fornix induce memory impairments similar to those caused by hippocampal damage, suggesting that the fornix modulates the hippocampal activity required for memory formation. To test this hypothesis, we generated rats in which the fornix was lesioned bilaterally and determined their behavioral and CREB-dependent responses. Animals with fornix lesions learned inhibitory avoidance and retained the memory at control levels for up to 6 h; however, by 24 h, the memory was significantly impaired. The amnesic animals also failed to exhibit any increase in hippocampal CREB phosphorylation after training (Taubenfeld et al., 1999). These results suggested that hippocampal inputs passing through the fornix regulate consolidation of this form of memory *via* CREB-mediated gene expression in hippocampal neurons.

Although several important questions remain, the approaches described above show that mammalian systems are now ready to provide appropriate experimental models for investigating the biochemical modulators engaged by the fornix input, the signal transduction pathway(s) activated by this modulation and affecting CREB and, finally, the target genes regulated by CREB and perhaps the site of memory storage. The discovery of the target genes is a major objective because it would provide information about the basis of memory storage and would indicate what mechanisms are used by neurons to store long-term information. Does storage reside in the synapses? If so, how are these synapses different from others? Suggestions for candidate genes may be found in the *Aplysia californica* model, since if CREB-dependent gene expression is evolutionarily conserved, homologues of target genes discovered in *Aplysia californica* may play a conserved role in mammalian memory. Recent work by Sterneck et al. (1998) demonstrated a selective enhancement of contextual fear-conditioning in mice with a targeted deletion of the C/EBP $\delta$  gene, implying that C/EBP isoforms may play a role in mammalian memory formation.

More studies are needed to uncover fully the molecular mechanisms and molecules that allow neurons to remember, and knowledge available today suggests that it should be possible to identify the critical chemical signals, their transduction pathways and the genes regulated by CREB. This information may suggest treatments for amnesia associated with damage to the temporal lobe memory system. A schematic representation summarizing the molecular events leading to short- and long-term memory is shown in Fig. 1.

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