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Molecular mechanisms of learning and memory

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Memory is the process by which organisms are able to record their experiences, and use this information to adapt their responses to the environment. As such, it is vital for survival. In recent years, the development of spatially and temporally selective techniques for the regulation of gene expression has allowed the molecular details of this process to emerge. Here we review the molecular mechanisms thought to underlie memory acquisition and storage, as well as discuss recent evidence regarding the mechanisms of subsequent memory consolidation.

At the cellular level, memories are thought to be formed subsequent to an increase in the strength of synaptic connections between simultaneously activated neurons (Ref. 1). The molecules responsible for this increase were initially characterised by studying the gill-withdrawal reflex of the marine snail *Aplysia*. The strength of this reflex can be modified by several forms of learning, with a corresponding increase in the strength of the synaptic pathways mediating this response, known as long-term facilitation (reviewed in Ref. 2). The later extension of these studies to organisms such as *Drosophila* and rodents revealed the molecular pathways underlying memory storage to be strongly evolutionarily conserved.

In mammals, an increase in synaptic strength known as long-term potentiation (LTP) is considered to be the cellular mechanism for encoding memories (Ref. 3), although questions remain about its precise role. Nonetheless, LTP possesses many properties expected of a memory storage system, such as a requirement for coincident presynaptic activity and postsynaptic depolarisation, and its presence in brain regions known to be involved in memory storage, such as the hippocampus (Ref. 4). Studies of the genes involved in learning and memory often examine the outcome of a genetic manipulation in terms of the effect on both mnemonic performance and LTP.

Methods of investigating gene function

Several methods have been employed to understand the involvement of genes in memory processes (Fig. 1). Initially, global knockouts were

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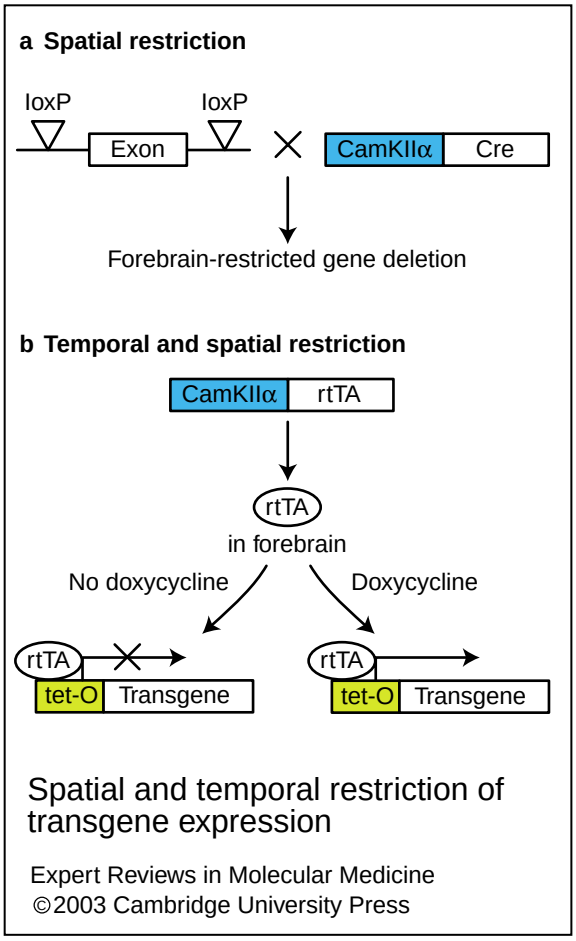

Figure 1. Spatial and temporal restriction of transgene expression. (a) Spatial restriction using Cre–loxP-mediated recombination. Disruption of a gene's function can be achieved by creating a transgenic mouse line containing loxP sites flanking an exon in the gene of interest. Crossing these mice with mice expressing Cre recombinase leads to the removal of the exon by site-specific recombination. Spatial control is attained by placing Cre recombinase under the control of the forebrain-specific CaMKIIα (Ca^{2+}/calmodulin-dependent protein kinase IIα) promoter. (b) Temporal and spatial restriction using the reverse tetracycline transactivator (tTA) system. In this system, use of a mutated tTA gene (rtTA) results in tet-O-controlled transcription only in the presence of the tetracycline analogue doxycycline, allowing temporal restriction of transgene expression. Combined spatial and temporal control is achieved by placing a CaMKIIα promoter 5' to the tTA gene **(fig001mda).**

used to infer the involvement of specific genes in memory processes (Ref. 5). However, the disruption of a gene in all cells of an organism often leads to developmental defects or later functional alterations capable of nonspecifically influencing the memory phenotype. For this reason, methods of restricting transgene expression both temporally and spatially have been devised.

Spatial restriction of transgene expression

Recently, a technique has been developed to restrict gene knockouts to the forebrain, an area implicated in several forms of memory storage. This is achieved by use of Cre–loxP-mediated recombination (Ref. 6), with Cre recombinase expression controlled by the forebrain-specific CaMKIIα (Ca^{2+}/calmodulin-dependent protein kinase IIα) promoter (Ref. 7) (Fig. 1a). Conversely, the CaMKIIα promoter alone can be used for forebrain-specific overexpression of the gene of interest.

Temporal restriction of transgene expression

The accurate performance of a memory-based task is attributable to a number of processes, including initial memory encoding, maintenance and retrieval. It is therefore important to restrict gene expression not only spatially, but also temporally, to delineate the distinct genetic requirements of different phases.

One way in which temporal restriction can be achieved is by use of the tetracycline-controlled transactivator (tTA) system. The tTA gene expresses a transcription activator that binds and activates transcription from the tet-O promoter. Transcription is blocked by the administration of the tetracycline analogue doxycycline, but resumes after its removal (Ref. 8). By placing the tTA gene under the control of a CaMKIIα promoter, and the transgene of interest under the control of the tet-O promoter, expression can be restricted in both the spatial and temporal domains (Ref. 9). However, as doxycycline itself has detrimental effects on learning and memory (Ref. 10), its constant application to suppress the transgene is not ideal. This limitation was overcome by mutation of the tTA gene to create a reverse tetracycline system, in which gene expression is switched on only in the presence of doxycycline (Ref. 11) (Fig. 1b).

Phases of memory storage

Memory acquisition – the NMDA receptor

At the majority of excitatory synapses in the central nervous system, neurotransmission is

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mediated by the binding of glutamate to receptors located in the postsynaptic membrane, and subsequent ionic conductance through receptor channels. Ionic glutamatergic receptors are designated as NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid) or kainate subtypes, on the basis of differing affinity for these ligands (Ref. 12). Of these subtypes, the NMDA receptor is of particular interest. Although highly permeable to calcium ions (Ca^{2+}) when activated, its ion channel is blocked by magnesium ions (Mg^{2+}) at the resting potential, and activation requires coincident membrane depolarisation and glutamate binding, properties consistent with those required for memory storage. While basal synaptic transmission is mediated by sodium ion (Na^{+}) and potassium ion (K^{+}) influx through AMPA receptors, repeated firing of the presynaptic neuron leads to the depolarisation of the postsynaptic membrane, removing the Mg^{2+} block and allowing Ca^{2+} influx through activated NMDA receptors (Ref. 13).

Pharmacological studies provided the initial evidence for the involvement of the NMDA receptor in memory storage (Ref. 14), but, more recently, targeted genetic manipulations of the receptor subunits have been able to address specific aspects of its function. The NMDA receptor is a heteromultimer consisting of the NR1 subunit, and one or more NR2 subunits (NR2A and B in the adult forebrain) (Ref. 15). While NR1 is essential for channel function, the NR2 subunits regulate channel gating and Mg^{2+} dependency (Ref. 16). Transgenic mice generated with a forebrain-restricted knockout of the NR1 subunit demonstrate deficits in several memory-based tasks – including spatial memory in the water maze (Ref. 17) and trace fear conditioning (Ref. 18) – and also exhibit impaired LTP. In contrast, forebrain-specific overexpression of the NR2B subunit was able to prolong the receptor channel open time, hence increasing the interval over which coincident activity could be detected. These mice demonstrated both enhanced LTP and superior memory on tests of both spatial and contextual memory (Ref. 19).

Ca^{2+} influx into the postsynaptic neuron leads to the activation of target proteins either directly, or indirectly via binding and activation of calmodulin (Ref. 20). Interestingly, the proteins targeted by Ca^{2+} include both positive and negative regulators of memory storage. Recent experiments suggest that the strength of memory storage is determined by the balance between positive and negative regulators of memory (Ref. 21).

Short- and long-term memory

Behavioural studies have demonstrated the existence of two distinct phases of memory storage. Short-term memory lasts several hours, and is resistant to inhibitors of protein synthesis, whereas long term memory can persist for longer than two hours and requires protein synthesis (Ref. 22). In parallel with these findings, it has been shown that LTP also possesses early and late phases (E-LTP and L-LTP), with a similar time course and requirement for protein synthesis (Ref. 23), and thus provides a useful framework for understanding the molecules involved in each process. Although distinct programmes of gene expression are associated with each stage of memory formation, the involvement of many molecules in both short- and long-term processes precludes a simple categorisation. In the interest of clarity, the multiple roles of these proteins are not detailed in this review.

It is thought that the length of time a memory persists is initially determined by the level of postsynaptic activation, and hence the duration of the Ca^{2+} influx, into the postsynaptic neuron (Ref. 24). A short-lasting Ca^{2+} influx will only activate those enzymes involved in short-term memory, whereas the enzymes activated by a more persistent Ca^{2+} influx are those able to initiate long-term memory storage (Ref. 25) (Fig. 2).

Genes involved in short-term memory

CaMKII

CaMKII is a serine/threonine protein kinase. It exists as a dodecameric holoenzyme, composed of both α and β subunits. Each subunit consists of four domains: a catalytic domain, an autoinhibitory domain, a variable segment, and a self-association domain (Ref. 26). The catalytic domain contains ATP- and substrate-binding sites, and sites for interaction with anchoring proteins. The autoinhibitory domain contains a pseudosubstrate region, which under resting conditions is bound to the catalytic domain, inhibiting catalytic activity. When Ca^{2+} enters the cell, it activates the Ca^{2+}-binding protein calmodulin, which binds a region overlapping the pseudosubstrate region, causing dissociation of

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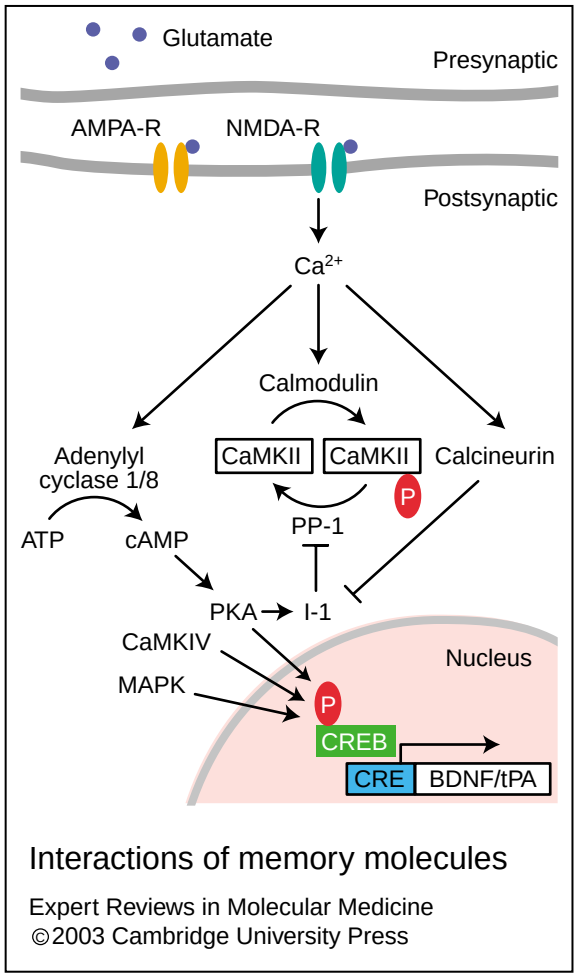

Figure 2. Interactions of memory molecules. The binding of glutamate and postsynaptic depolarisation allows the entry of Ca^{2+} through the NMDA receptor channel. The Ca^{2+}-binding protein calmodulin then activates substrates that are involved in memory formation. Low-level Ca^{2+} influx leads to short-term memory, involving the covalent modification of proteins such as the serine/threonine protein kinase CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II); this phosphorylates the AMPA receptor, increasing conductivity and creating the short-term increase in synaptic efficacy referred to as E-LTP (early phase of long-term potentiation; not shown). This phosphorylation decays after an hour as calcineurin inactivates the inhibitor (I-1) of protein phosphatase 1 (PP-1), which dephosphorylates CaMKII. Long-term memory storage is thought to be initiated by increased Ca^{2+} influx. This leads to the activation of protein kinase A (PKA), which activates the inhibitor of PP-1, thereby preventing CaMKII dephosphorylation. PKA translocates to the nucleus, and along with several other kinases, including CaMKIV and mitogen-activated protein kinase (MAPK), phosphorylates cAMP-response-element-binding protein (CREB), a transcription factor that activates both effectors and regulators of long-term memory storage, such as brain-derived neurotrophic factor (BDNF) and tissue plasminogen activator (tPA). Abbreviations: AMPA-R, receptor for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cAMP, cyclic AMP; NMDA-R, receptor for *N*-methyl-D-aspartate **(fig002mda).**

this region from the catalytic domain, and exposing Thr286 in the autoinhibitory domain for phosphorylation by the catalytic domain of a neighbouring subunit (Ref. 27).

Once phosphorylated, CaMKII remains active, even in the absence of Ca^{2+} (Ref. 28), and is able to phosphorylate target proteins, such as the GluR1 subunit of the AMPA receptor. Phosphorylation of the GluR1 subunit increases its ionic conductance (Ref. 29), and also facilitates the insertion of further AMPA receptors into the postsynaptic membrane (Ref. 30). This creates a mechanism by which synaptic efficacy can be increased, and is responsible in part for the formation of E-LTP.

Both deletion of the CaMKIIα gene (Ref. 31) and mutation of Thr286 to a nonphosphorylatable Ala (Ref. 32) have been shown to lead to impaired spatial memory, indicating a critical role for this kinase.

Receptor-clustering effectors

Synaptic efficacy requires the localisation of relevant receptors within synaptic regions, in close contact with intracellular signalling cascades. This is illustrated by the insertion of AMPA receptors into the postsynaptic membrane in response to Ca^{2+} influx, as discussed above. The postsynaptic density is a macromolecular cluster of receptors and signalling proteins, linkage of which is achieved by a variety of postsynaptic tethering proteins (reviewed in Ref. 33). One such molecule, PSD-95, which contains multiple protein–protein interaction domains, has been implicated in memory formation, as mice lacking PSD-95 exhibit impaired memory acquisition (Ref. 34). A similar phenomenon has been demonstrated for spinophilin knockout mice (Ref. 35), although the relative importance of many other scaffolding proteins remains to be determined.

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Calcineurin and PP-1

E-LTP decays after about an hour, the length of time that CaMKII can remain active in the absence of Ca^{2+} (Ref. 36). The dephosphorylation of CaMKII (and GluRI) is mediated by PP-1, a protein phosphatase active only when its inhibitor, I-1, is suppressed by the phosphatase calcineurin (Ref. 37).

Calcineurin possesses a high affinity for Ca^{2+}, and is thus activated by the low levels of Ca^{2+} influx generated by low-frequency stimulation (Ref. 38). It exists as a heterodimer, comprising a catalytic subunit (CNAα or β) and a regulatory subunit (CNB1) (Ref. 39). Once activated, calcineurin dephosphorylates I-1 and hence inactivates it. It is also able to dephosphorylate both NMDA (Ref. 40) and AMPA (Ref. 41) receptors.

The low-frequency stimulation that leads to the activation of calcineurin is also associated with the generation of a long-lasting decrease in synaptic plasticity referred to as long-term depression (LTD). Calcineurin contributes to the development of LTD by dephosphorylation of the endocytotic machinery, facilitating the removal of AMPA receptors from the synapse (Ref. 42).

The role of LTD in memory processes remains unclear, with studies proposing on the one hand a deleterious effect on memory storage (Ref. 43) and on the other hand a role in certain forms of memory (Ref. 44). The bidirectional plasticity conferred by the ability to generate either LTD or LTP may therefore increase the potential range of information storage at a synapse. In support of the latter hypothesis, a forebrain-specific knockout of CNB1 was observed to selectively impair both LTD and the performance of specific memory tasks (Ref. 45).

Genetic manipulations of calcineurin have provided additional insight into how this phosphatase places an inhibitory control on memory formation. Selective spatial and temporal overexpression of a constitutively active, truncated form of calcineurin (lacking the autoinhibitory and calmodulin-binding domains of CNAα) was shown to impair both L-LTP and long-term spatial memory. Interestingly, spatial memory could be rescued by increasing the number of training trials per day, suggesting that calcineurin's inhibitory constraint on memory storage can be overcome, perhaps by increased expression of positive modulators of memory storage subsequent to training (Ref. 46).

Overexpression of the CNAα autoinhibitory domain under the reverse tetracycline system (Ref. 11) led to the facilitation of L-LTP. In parallel with this facilitation, mice demonstrated enhanced learning, and strengthened short- and long-term memory in both object recognition and spatial navigation tasks (Ref. 47). Similarly, overexpression of a constitutively active form of I-1 improved the mnemonic ability of mice on a variety of tasks. Mice demonstrated enhanced learning of a spatial memory task, and improved spatial memory retention. In addition, the increase in levels of phosphorylated CamKII and GluRI observed after spatial training was higher in mutant mice relative to controls, suggesting that inhibition of PP-1 had removed a constraint on the activation of these proteins (Ref. 48).

Genes involved in long-term memory

PKA

An increased influx of Ca^{2+} into the postsynaptic neuron leads to the activation of further enzymes, some of which are capable of removing the inhibitory constraints on memory storage. In particular, adenylyl cyclases isoforms 1 and 8 are activated (Ref. 49), and subsequently catalyse the conversion of ATP to cAMP. cAMP then binds to and activates protein kinase A (PKA).

PKA is composed of two regulatory subunits and two catalytic subunits, and is thought to represent a molecular switch, converting memories from short- to long-term storage (Ref. 50). Initial activation of PKA leads to the phosphorylation of I-1, and hence the inhibition of PP-1, preventing PP-1 from dephosphorylating its substrates CamKII and GluRI (Ref. 51). PKA's action on I-1 directly opposes that of calcineurin, and, as calcineurin is also able to inactivate adenylyl cyclase (Ref. 52), these two proteins are considered to be positive and negative regulators of a gate for LTP formation and hence memory storage. As support for this hypothesis, a double knockout of adenylyl cyclase isoforms 1 and 8 has been shown to lead to impaired L-LTP and a long-term memory deficit (Ref. 53). Additionally, mice expressing a forebrain-restricted dominant-negative form of the PKA regulatory subunit, with mutations in both cAMP-binding sites, exhibit normal E-LTP, but deficient L-LTP and long-term memory (Ref. 50). After PKA has been activated, the catalytic subunits translocate to the nucleus, where PKA is one of several kinases capable of phosphorylating the transcription

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factor cAMP-response-element-binding protein (CREB) (Ref. 54), initiating the protein synthesis required for long-term memory.

CREB

CREB is a transcription factor identified as both necessary and sufficient for long-term memory formation in organisms including *Aplysia* (Ref. 55), *Drosophila* (Ref. 56) and mammals (Ref. 57). Once a serine residue located at position 133 is phosphorylated, CREB dimers can initiate transcription by binding to the CRE located in the promoter region of target genes (Ref. 58).

This residue can be phosphorylated by a number of kinases in addition to PKA, making this a convergence point for several molecular pathways. There are now thought to be several temporal phases of CREB phosphorylation, with CaMKIV linked to a rapidly induced, early phosphorylation event, and MAPK [mitogen-activated protein kinase; also known as ERK (extracellular-signal-regulated kinase)] mediating the later, long-lasting phase (Ref. 59). Phosphorylation of serine residues adjacent to Ser133 also appears to be important for both positive and negative regulation of CREB-mediated transcription (Ref. 60).

Overexpression of a dominant-negative CaMKIV in the forebrain of mice impaired L-LTP, while sparing basic synaptic function and E-LTP. These animals were able to acquire learning normally, but were impaired in processes of consolidation and retention (Ref. 61), demonstrating the temporal specificity of CaMKIV's involvement in memory. The involvement of MAPK in memory storage has yet to be investigated with targeted genetic manipulations. However, MAPK has been shown to be activated after learning, and memory storage is impaired by pharmacological MAPK inhibition (Ref. 62).

CREB knockout mice (Ref. 57) and mice with reversible inactivation of CREB in the forebrain (Ref. 63) display impaired long-term memory. In contrast, overexpression of CREB in *Drosophila* (Ref. 56) and rats (Ref. 64) has led to improved long-term memory storage. Interestingly, a key feature of CREB-overexpressing organisms is their ability to demonstrate maximal memory after massed training sessions, whereas normal animals require spaced training to achieve the same effect. It has been suggested that CREB activators and inhibitors are induced equally after training, and that the presence of rest intervals allows for the faster decay of inhibitors. However, CREB transgenic animals already have elevated levels of CREB activator relative to inhibitors, and would thus circumvent this requirement (Ref. 56).

CRE-mediated transcription

Memory storage has been shown to require not only CREB, but also the activation of CRE-containing genes (Ref. 65). Over 100 genes have now been identified as potential targets of CREB, controlling functions as diverse as neurotransmission, cell structure, signal transduction, transcription and metabolism (Ref. 66). It is thought that many of these proteins contribute to the consolidation of long-term memory by generating long-term structural changes in neuronal pathways.

Synaptic tagging

A key problem in understanding the molecular mechanisms of memory is the means by which changes in synaptic efficacy are restricted to only one synapse of a neuron, particularly as CREB controls long-term memory formation via the induction of transcription in the nucleus. The 'synaptic tagging' hypothesis has been introduced as a potential explanation. In this model, initial weak synaptic stimulation results in the formation of E-LTP, and the deposition of a protein tag at this synapse. Further stimulation at the same synapse will initiate L-LTP, which requires protein synthesis in the nucleus. Although the newly synthesised proteins are transported to all synapses of the neuron, L-LTP is restricted to the stimulated synapse as a result of the presence of the protein tag. Furthermore, the presence of newly synthesised proteins at all synapses of a neuron after L-LTP induction allows for L-LTP to be generated by a weak stimulus at another synapse that would usually only produce E-LTP (Ref. 67).

It now appears that synapses might be tagged by the protein products of CRE-driven genes. Expression of a constitutively active form of CREB (VP16-CREB) in the mouse forebrain lowers the threshold for L-LTP in all synaptic inputs to a neuron (Ref. 68). It is not yet clear what effect the expression of constitutively active CREB would have on learning and memory. In the VP16-CREB mouse, potentiated synapses are unable to depotentiate, which could block the formation of further memories, although it has been speculated

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that temporally regulated expression of VP16-CREB could lead to improved learning.

Memory consolidation

Although it is not known which CRE-containing genes are responsible for synaptic tagging, several have been shown to play a role in memory consolidation. New memory is initially labile, and sensitive to disruption by interfering events or agents such as protein synthesis inhibitors (Ref. 69).

Inhibition of several genes downstream of CREB, including the transcription factor CCAAT-enhancer-binding protein (C/EBPβ) (Ref. 70), and Krox 24 (Ref. 71), has been shown to lead to an impairment of both L-LTP and long-term memory storage. Conversely, and of particular interest, the overexpression of the serine protease tissue plasminogen activator (tPA) leads to improved spatial memory (Ref. 72). However, the means by which these genes contribute to memory consolidation is currently unclear.

Several molecules involved in memory consolidation also have roles at earlier stages of memory formation. One such example is the NMDA receptor. Mice were generated expressing an NR1 subunit in the CA1 region of the hippocampus that could be inactivated at different time points after learning. Switching off NR1 in the CA1 region during the first week after a spatial or contextual task led to an impairment when memory of the task was tested two weeks after training. However, this deficit was not observed when NR1 was switched off for the second week after training, suggesting that NMDA receptor activation is required only for the early stages of consolidation, and not for later consolidation or retrieval (Ref. 73).

It is thought that the role of the NMDA receptor in the early phase of consolidation might be to mediate a series of synaptic modifications, reinforcing the changes induced during initial learning. This phenomenon is referred to as the synaptic re-entry reinforcement (SRR) hypothesis (Ref. 73). It is thought that NMDA receptor reactivation could be triggered by processes such as conscious recall, or sleep, both of which are thought to impact on the strength of memory consolidation. Later phases of consolidation involve the transfer of memories to the cortex, a process that might also be explained by the SRR hypothesis, as the reactivation of the NMDA receptor might act as a coincidence regenerator for activating neurons in the cortex. This would allow cortical neurons previously responding to different sensory modalities to act together, leading to the strengthening of their connections. Once the cortical connections have been established, the hippocampus is no longer required for memory storage (Ref. 73).

Downstream of the NMDA receptor, CaMKII is also involved in the consolidation of cortical memories. Mice heterozygous for CaMKII display normal contextual fear conditioning up to 3 days after training, but are impaired at longer delays (10–50 days). CaMKII is more abundant in the hippocampus than the cortex, so this decrease in expression might affect cortical memory storage more severely. Additionally, these mice exhibit impaired cortical but not hippocampal LTP, suggesting the involvement of this synaptic strengthening mechanism at multiple stages of memory storage (Ref. 74).

Clinical implications

An understanding of the molecular processes of memory formation has important implications for the treatment of memory dysfunction. Several forms of mental retardation have already been linked to specific deficits in signalling pathways (e.g. see Refs 75, 76), suggesting potential therapeutic targets. In addition, memory disorders influenced by a combination of genetic and environmental factors, such as mild cognitive impairment, might also benefit from such intervention.

Memory may also be enhanced in the absence of any prior impairment, as evidenced by a number of studies cited in this review. Although the ethical implications of such treatments remain the subject of debate, the widespread expression of many memory-related genes and their involvement in multiple cellular processes suggest that in practice this might be difficult to achieve.

Conclusions and future developments

The advent of targeted genetic manipulations has allowed the molecular mechanisms governing memory formation and storage to be carefully delineated. These studies have revealed memory to be a tightly regulated process, requiring a balance between activating and inhibitory proteins at several points of the pathway. Despite the progress in understanding memory at the molecular level, much remains to be discovered.

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To date, little is known about the specific contributions of genes activated downstream of CREB in maintaining memory storage, or the process by which memories are transferred to permanent storage in the cortex. The continued application of such specific genetic techniques will allow for the further elucidation of the molecular pathways underlying mnemonic processes.

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Further reading, resources and contacts

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Website

A good summary of the field of molecular cognition, including a list of significant papers, can be found at the SilvaLab (University of California, Los Angeles, USA) website:

http://www.silvalab.org.

Features associated with this article

Figures

Figure 1. Spatial and temporal restriction of transgene expression (fig001mda).
Figure 2. Interactions of memory molecules (fig002mda).

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