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The molecular and cellular biology of enhanced cognition

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Abstract

Most molecular and cellular studies of cognitive function have focused on either normal or pathological states, but recent research with transgenic mice has started to address the mechanisms of enhanced cognition. These results point to key synaptic and nuclear signalling events that can be manipulated to facilitate the induction or increase the stability of synaptic plasticity, and therefore enhance the acquisition or retention of information. Here, we review these surprising findings and explore their implications to both mechanisms of learning and memory and to ongoing efforts to develop treatments for cognitive disorders. These findings represent the beginning of a fundamental new approach in the study of enhanced cognition.

A number of psychiatric and neurological disorders, such as Alzheimer's disease¹, schizophrenia², depression³, Parkinson's disease⁴, learning disabilities⁵, age-related cognitive decline⁶ and mental retardation⁷ are associated with learning and memory (L&M) impairments. The dominant paradigm for the development of treatments for these disorders is based on the idea that insights into the specific mechanisms that underlie each of these conditions will lead to the development of targeted interventions. The problem with this approach is that there are a large number of different causes for cognitive deficits. Genetic analyses of schizophrenia and depression, two disorders that are associated with significant cognitive impairments, have shown that they are caused by numerous mutations and many developmental and environmental factors. Similar genetic heterogeneity has been demonstrated in every other major cause for cognitive deficits, including Alzheimer's disease, learning disabilities, mental retardation and age-related cognitive decline. Thus, developing targeted therapies for each of the multiple causes of these conditions will be a formidable task. Even if targeted therapies for one or more of these specific genetic conditions are forthcoming, it is unlikely that they will have a significant impact on the cognitive impairments thought to afflict more than one in 20 people worldwide. Therefore, in addition to the prevalent targeted therapy approach, there is a need to develop alternative strategies that could have a more general impact on cognition. One possibility would be to develop strategies to ameliorate cognitive deficits irrespective of their specific genetic or environmental cause.

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DATABASES

OMIM: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>

Alzheimer's disease | Parkinson's disease

UniProtKB: <http://ca.expasy.org/sprot>

α CaMKII | ATF4 | Cbl-b | Cdk5 | HDC | intercellular adhesion molecule 5 | KIF17 | MAOA | ORL1 | pleiotrophin | p25 | RAGE | S100Bb

FURTHER INFORMATION

Genes to Cognition programme: <http://www.genes2cognition.org>

Alcino J. Silva's homepage: <http://silvalab.org>

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Although there is considerable evidence for animals and people with dramatic cognitive enhancements^{8,9}, mechanistic studies of exceptional cognition are relatively rare. Remarkably, transgenic and KO studies in mice have revealed a surprisingly large number of mutations that seem to enhance cognitive function (TABLE 1). These mutations target a number of different signalling pathways and affect a plethora of behaviours. Surprisingly, nearly all of them seem to enhance a form of synaptic plasticity referred to as long-term potentiation (LTP).

This Review focuses on a subset of representative mutant mice with enhanced performance in well-characterized L&M behavioural tasks such as the Morris water maze and fear conditioning (BOX 1). We classify these ‘smart’ mutant mice into several groups according to the signal transduction pathways affected, and briefly summarize how each of the mutations is thought to affect synaptic plasticity and L&M. We will also highlight commonalities and propose mechanisms that could be targeted for the development of drugs for L&M disorders.

NMDA receptors and enhanced cognitive function

The critical role of *N*-methyl-D-aspartate receptors (NMDARs) in synaptic plasticity and memory has been extensively researched with both genetic and pharmacological manipulations^{10–18}. NMDARs are composed of an obligatory subunit NR1 and other modulatory subunits including NR2 (with A, B, C and D subtypes) and NR3 (with A and B subtypes). The receptor subunit compositions change during development^{19,20}.

Upregulation of NR2B

There have been previous reports of mice with enhanced L&M²¹, but the *doogie* mouse, which overexpressed the NR2B subunit in the adult forebrain, was the first widely-publicized ‘smart’ mouse⁹. Normally, the expression of NR2B is decreased during post-natal development¹⁹. The prolonged NMDAR currents resulting from overexpression of NR2B led to the enhancement of hippocampal CA1 LTP, a finding that is consistent with more robust levels of LTP during the developmental stages expressing higher levels of this receptor subunit²². *Doogie* mice were shown to have enhanced performance in several different hippocampal L&M tasks (BOX 1), including novel-object recognition⁹ and spatial memory tested with the Morris water maze²³. In addition, both contextual and tone (cued) fear memory and fear extinction were enhanced in *doogie* mice. Fear extinction is thought to reflect learning that the tone no longer is associated with shock, and is known to be NMDAR-dependent²⁴. A recent follow-up study showed that even aged *doogie* mice out-perform age-matched controls, indicating that the NR2B-dependent L&M enhancement lasts into old age²⁵.

Box 1. Behavioural tests for learning and memory

Morris water maze

This is one of the most used spatial learning and memory (L&M) tasks known to depend on the hippocampus. Animals swim in a murky pool of water to find the location of a submerged platform just beneath the surface of the water. To escape the water, mice use a variety of cues and strategies, including spatial cues around the pool in the room. Animals are trained for several days and the time/path length they take to find the platform is usually measured as a learning index. A more sensitive measure of spatial learning is performance in probe trials in which the platform is removed from the pool and the mice are allowed to search for it for a short period of time (for example, 60 seconds). A common learning index for this test is the percentage of time that the mice spend looking for the platform in the quadrant where the platform was during training.

Novel-object recognition task

This is a non-aversive, non-spatial test that requires hippocampal function. In this test, animals are allowed to freely explore two objects in an open field during training sessions. In the test sessions, one of the objects is replaced by a novel object. Short (for example, 1 hour) or long-term memory (for example, 24 hours) is measured as a ratio of time spent exploring the novel object versus the familiar object. Variants of this task use other stimuli, such as smells and even conspecifics (social recognition).

Radial arm maze

This is a spatial learning task with various versions. The apparatus has several arms (most commonly eight) that can be baited with food pellets at the end. Food-deprived animals are allowed to enter the arms and search for the hidden food. In a common version of this task, which is sensitive to both hippocampus and prefrontal cortex lesions, food-deprived animals are first (phase A) allowed to retrieve food pellets from 4 accessible arms of an 8-arm maze (the remaining 4 arms are blocked). After a retention interval of (for example, 2 minutes) animals are brought back to the maze (phase B) and are given access to all 8 arms, but only the 4 previously blocked arms are now baited. Within-phase errors are committed when mice enter an arm previously visited in the same trial; across-phase errors are committed when mice enter an arm in phase B that they had already visited in phase A.

Fear conditioning

This is a Pavlovian aversive learning task in which animals associate a non-aversive conditioned stimuli (CS), such as a tone or context, with an aversive unconditioned stimulus (US; for example, footshock). Conditioned responses, usually freezing (cessation of all but respiratory movement) are used as measures of memory. There are two common versions of this test: in tone conditioning the CS is a tone that precedes and co-terminates with the US; in context conditioning the CS is the context in which the animals are conditioned (that is, a chamber). Fear memories can last a lifetime but they can also be extinguished by repeated exposures to the CS without the US.

Conditioned taste aversion

This is an aversive learning task in which animals associate a food source (for example, saccharine flavoured water; CS) with malaise usually induced by LiCl injection (US). Avoidance of the food previously associated with malaise is used as a memory index.

Inhibitory avoidance

In this task the training apparatus has metal grids on the floor which can deliver a footshock. One part of the grid is covered to provide a safe platform for animals. During training, animals are placed on the safe platform and once they voluntarily step down to the grids they automatically receive a shock. Memory is assessed by measuring the time the animals spend on the platform before stepping down.

Passive avoidance

Here the animal learns to inhibit a natural tendency, namely to step into an apparently safer, dark compartment that has previously been associated with footshock.

Latent inhibition

In this group of tasks, extended pre-exposure to a stimulus prevents its association with an US, such as footshock. For example, extensive exposure to a conditioning chamber before conditioning weakens or even prevents association between the chamber and the footshock.

Mutant mouse in which the $\beta 3$ subunit of the voltage-dependent Ca^{2+} channels ($\text{Ca}_v\beta 3$) was knocked out also showed enhanced LTP and memory due to increased NMDAR function. The

NMDA-mediated current and NMDAR-dependent LTP were increased in the hippocampus of $Ca_v\beta 3$ -knockout mice. Although the underlying molecular mechanism is unclear, NR2B expression was slightly, but significantly increased in the knockout mice. These mice performed better than controls in a series of hippocampus-dependent L&M tasks, including contextual fear conditioning, novel-object recognition and social transmission of food preferences²⁶. These studies suggest that NR2B or related downstream signalling molecules could be promising targets for the development of cognitive enhancement strategies for aged subjects.

Transport of NMDA receptors

The trafficking of glutamate receptors from the cytoplasm to synaptic sites is known to have an important role in synaptic plasticity and in L&M^{27,28}. Transgenic mice overexpressing KIF17, a protein that transports NR2B along microtubules, outperform controls in spatial learning and working memory tasks²⁹. Interestingly, both NR2B mRNA and protein levels were higher in the KIF17 transgenic mice, but it is unknown whether the levels of NR2B are increased specifically in synaptic sites. Functional inhibition of KIF17 in cultured neurons, driven by the overexpression of a dominant negative form of KIF17, decreased the number of synaptic NR2B clusters. It is therefore conceivable that enhanced transport of NR2B and thus, higher levels of this subunit in synaptic NMDARs could explain better learning in mice overexpressing KIF17³⁰. The transcription factor cyclic-AMP response-element-binding protein (CREB) in these mice showed higher levels of phosphorylation at serine 133 (S133), which is associated with higher levels of CREB-dependent transcription³¹. As discussed below, this transcription factor is required for the stability of LTP and memory^{32,33} and it is activated downstream of NMDAR stimulation³⁴. Therefore, it is possible that overexpression of KIF17 results in a train of events leading to higher levels of NR2B at synaptic sites, larger NMDAR currents, stronger CREB activation, higher and more stable LTP, faster learning and better memory.

Degradation of NMDA receptors

The Ca^{2+} -dependent protease calpain regulates the degradation of NMDA receptors^{35,36}. Calpain is activated by Ca^{2+} entry through NMDARs and rapidly cleaves NMDAR subunits resulting in a decrease in the number of functional NMDA receptors in the postsynaptic density^{36,37}. There is evidence that cyclin-dependent kinase 5 (Cdk5) may regulate calpain-dependent proteolysis of NR2B; deletion of Cdk5 in adult mouse forebrain reduced NR2B degradation and consequently augmented NMDA-mediated current, resulting in stronger LTP and enhanced contextual fear conditioning, faster fear extinction and more flexible learning in the reversal water maze task³⁸. This indicates that Cdk5 plays a part in modulating the proteolysis of NR2B and that this is important for synaptic plasticity and learning.

The involvement of Cdk5 in L&M is complex, perhaps because this molecule has a variety of substrates and binds many different cofactors^{39,40}. Chronic activation of p25, a strong activator of Cdk5, caused neuronal loss in the cortex and hippocampus, and severely impaired synaptic plasticity and learning⁴¹. Surprisingly, transient expression of p25 in mice forebrain enhanced synaptic plasticity and hippocampus-dependent memory, including contextual fear conditioning and the Morris water maze⁴¹. NR2A phosphorylation and NMDAR-mediated currents were both increased after transient overexpression of p25 (REF. 41). It would be interesting to investigate whether calpain-mediated NR2B cleavage and/or the NR2B-mediated current is changed in this mouse model.

Activation of CaMKII

One of the first genetic manipulations reported to enhance learning and synaptic plasticity in mice involved the nociceptin receptor (ORL1)²¹. Mice lacking ORL1 showed normal pain

sensitivity but enhanced L&M in the Morris water maze and passive avoidance tasks (BOX1). Moreover, LTP was significantly enhanced in this mutant. Follow-up studies indicated that the ORL1 mutation resulted in enhanced NMDA receptor function and more rapid activation of its key downstream effector, a calcium calmodulin kinase II (α CaMKII)⁴². Interestingly, application of the nociceptin peptide should increase the function of the nociceptin receptor and, not surprisingly, this had opposite molecular, electrophysiological and behavioural effects to nociceptin receptor knockout⁴³. These results suggest that nociceptin-mediated signalling regulates NMDA receptor-dependent activation of α CaMKII and functions as a key constraint of plasticity and L&M.

Besides genetic manipulations, pharmacological drugs targeting glutamatergic systems have been developed. For example, ampakines, which are known to enhance attention span and L&M, positively modulate α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-type glutamate receptors (AMPA receptors) and subsequently facilitate NMDAR-dependent LTP induction⁴⁴. Interestingly, the appetite hormone leptin is reported to enhance synaptic plasticity and L&M by upregulating NMDAR function and α CaMKII activity^{45,46}. These findings demonstrate that upregulation of NMDAR function can result in enhancements of L&M (FIG. 1). One of the consequences of upregulating NMDAR function is an increase in synaptic Ca^{2+} . Next, we describe how manipulating other regulators of intracellular calcium can also result in enhanced plasticity and L&M.

Tipping Ca^{2+} homeostasis

Postsynaptic rises in Ca^{2+} and subsequent activation of downstream signalling molecules are crucial for long-term forms of synaptic plasticity, including LTP and long-term depression (LTD)^{47,48}. In addition to influx through membrane channels, Ca^{2+} can be released from internal stores through inositol trisphosphate (IP_3) or ryanodine-sensitive receptors (RyRs). RyR3-deficient mice showed better L&M in the spatial version of the Morris water maze. Unlike controls, in which the induction of NMDA-independent LTP can only be triggered after very strong stimulation protocols (four stimulus trains, 200 Hz, 500 ms), which are thought to recruit internal Ca^{2+} sources⁴⁹, in these mutants NMDA-independent LTP could be induced with a relatively weak stimulation protocol (four stimulus trains, 100 Hz, 100 ms), suggesting that this mutation altered the dynamic interaction between extracellular and intracellular calcium release involved in LTP. By contrast, another mutation of this receptor failed to enhance LTP or improve learning in mutant mice⁵⁰. Differences in the genetic background of the mouse strains⁵¹ could explain the difference between the results of these two studies. A great deal of caution is required when interpreting memory-enhancing phenotypes in mutants: does the mutation enhance memory by upregulating memory mechanisms or by merely compensating for unknown mutations in the genetic background of a specific inbred mouse line? Using hybrid strains, in which most of recessive alleles are likely to be suppressed, would help to defray this concern. In this Review we emphasize memory-enhancing mechanisms, such as enhanced NMDAR signalling, with convergent evidence from different mutants, different strains and from different learning tasks. This convergence is crucial for demonstrating the specificity and reliability of the findings.

Clearance of intracellular Ca^{2+} is another important mechanism for regulating intracellular Ca^{2+} concentrations. The $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) is known to have a role in Ca^{2+} homeostasis by extruding Ca^{2+} from neurons at high turnover rates in the brain⁵². Mutant mice lacking NCX2, the predominant isoform in adult brain, exhibited enhanced performance in a number of hippocampal tasks, including the Morris water maze, contextual conditioning and object recognition⁵³. Previous studies indicated that the magnitude and temporal pattern of internal Ca^{2+} triggers different downstream signalling pathways and determines whether LTP or LTD are induced^{54,55}. Remarkably, not only did the NCX2 mutants show enhanced LTP,

physiological protocols that normally induce LTD, triggered LTP instead. This result indicates that it is possible to enhance L&M even when the fundamental rules of potentiation and depression are seemingly altered.

These studies demonstrate that it is possible to enhance plasticity and L&M by manipulating mechanisms that regulate intracellular calcium concentrations. However the relation between these processes and L&M is poorly understood.

Balance between kinases and phosphatases

There is growing evidence that opposing kinases and phosphatases that are downstream of NMDARs determine whether incoming signals enhance or suppress synaptic plasticity and therefore facilitate or dampen L&M processes^{55,56}. CaMKII, as discussed above, protein kinase A (PKA), mitogen-activated protein kinase (MAPK) and protein kinase M ζ (PKM ζ) are well-known positive regulators^{57–61}, whereas the phosphatase calcineurin (also known as PP2B) and protein phosphatase 1 (PP1) serve as negative regulators of both synaptic plasticity and L&M^{62–65}.

Calcineurin

Calcineurin can affect synaptic plasticity in many different ways, including modulation of NMDAR-mediated currents, PP1 and the GTPase activity of dynamin I^{66–68}. In addition, the existence of calcineurin-activated adenylyl cyclase (AC) in hippocampal neurons was also reported⁶⁹.

Mice expressing a truncated, constitutively active form of calcineurin exhibited deficits in hippocampal LTP and memory^{62,70}, supporting the idea that this phosphatase inhibits LTP and learning⁷¹. When calcineurin was inhibited in adult mice forebrain in a spatially and temporally regulated fashion, namely by expressing the reverse tetracycline-responsive transcription factor (rtTA) under the control of a forebrain-specific α CaMKII promoter (see BOX 2 for details)⁷², the inducible expression of a calcineurin inhibitor significantly suppressed calcineurin activity in the hippocampus and cortex of mutant mice, leading to enhancements in LTP and improvements in both short- and long-term object recognition memory. Enhanced L&M was also observed in the spatial version of the Morris water maze, conditioned taste aversion and cued fear conditioning^{72,73}. These and other studies have indicated that enhancing calcineurin function disrupts LTP and learning, whereas decreasing its function facilitates these two processes⁷⁴.

Box 2. Evolution of transgenic technology

The first generation of mutant mice used in molecular and cellular cognition studies included germ-line targeted disruption or overexpression of genes of interest. Following studies with α calcium calmodulin kinase II (α CaMKII) homozygous-null mutants, showing that disruption of this gene led to impairments in long-term potentiation (LTP) and learning and memory (L&M)^{59,60}, similar findings were reported upon deletion of the tyrosine kinase Fyn¹⁷². These early studies demonstrated the power of mammalian transgenic and knockout approaches in integrative studies of physiological mechanisms of behaviour, and they pointed to LTP as a key synaptic mechanism involved in L&M.

The second generation of mouse transgenic technologies introduced spatial and temporal control^{17,33,173–175}. For example, transgenic mice with the P1 bacteriophage Cre recombinase under the regulation of the α CaMKII promoter¹⁷⁵ allowed the deletion of loxP-flanked genes in principal neurons of the postnatal forebrain. Temporal control of transgenic expression in the brain was first achieved by employing the tetracycline

system¹⁷⁶. Doxycycline binds to the tetracycline-responsive transcription factor tTA (or rtTA) and is used in this system to temporally turn on or off transgene expression^{17,173,176}. This transcription factor can be expressed under the control of cell-type and region-specific promoters, such as the α CaMKII promoter, to add spatial control to this inducible system. Introducing heterologous genes from another organism can be combined with this technique. For example, overexpression of an *Aplysia* octopamine receptor (Ap oa₁), a G_s-protein-coupled receptor, which selectively stimulates PKA signalling, provided an ideal system to study the role of acute manipulation of cAMP signalling in synaptic plasticity and L&M^{82,177}. Despite its power, the doxycycline system is limited by the requirement for the derivation and crossbreeding of several mouse mutant lines.

Another powerful inducible and region restricted transgenic system takes advantage of gene fusions with the mutant version of the ligand-binding domain of the oestrogen receptor (LBD) under the regulation of tissue- and cell-specific promoters such as the α CaMKII promoter³³. Binding of tamoxifen to the LBD changes its conformation, excluding large heat-shock proteins that prevent the fusion protein of interest to bind, therefore modulating the function of its partners³³. The significant advantage of this system is that it requires only a single transgene and manipulations can be turned on and off much faster than the tetracycline system (hours versus days)³³. The limitation is that not all proteins can be regulated with LBD fusions.

Recently, chemical-regulation of engineered proteins, such as kinases, has been used to quickly activate and inactivate them in plasticity and L&M studies¹⁷⁸. Genetic manipulations with even higher spatial and temporal resolution, targeting specific neurons in networks of interest, are currently under development and will undoubtedly have a key role in the next generation of molecular and cellular cognition studies¹⁷⁹. Even though mutant mouse studies of L&M have certain limitations¹⁸⁰, it is obvious that they have had an enormous impact on our understanding of the molecular mechanisms of cognitive function, including those that can be recruited to enhance L&M.

A genetic approach to inhibit calcineurin, by deletion of its regulatory subunit CNB1 in excitatory forebrain neurons of adult mice, led to suppression of hippocampal LTD and only to slight enhancements of LTP⁷⁵. This mutant did not show enhanced performance in hippocampus-dependent memory tasks including the Morris water maze and contextual fear conditioning^{72,75}. Furthermore, hippocampus-dependent working memory tasks, such as the delayed matching-to-place task and radial arm maze were impaired. Another study in rats showed that blocking calcineurin expression by infusing antisense oligonucleotides into brain ventricles enhanced hippocampal LTP induction and contextual fear conditioning, but not spatial learning in the Morris water maze^{76,77}.

These studies show that the memory enhancements seem to be sensitive to the conditions in which the experiments were carried out. Considering the complexity of calcineurin signalling in neurons, it is not surprising that two different manipulations with different degrees of calcineurin inhibition resulted in inconsistent cellular and behavioural phenotypes.

Serine/threonine phosphatase PP1

Calcineurin regulates the activity of another serine/threonine phosphatase, PP1, by dephosphorylating inhibitor-1 (I-1)⁶⁸ (FIG. 1). PP1 has a key role in inducing LTD and, like calcineurin, this phosphatase is also thought to be a negative regulator of memory⁷⁸. To suppress PP1, a constitutively active form of I-1 (I-1*) was inducibly and reversibly expressed in adult brain with the rtTA system⁶⁴ (BOX 2). The induction of I-1* suppressed PP1 activity by ~70% in the hippocampus. Mice expressing I-1* showed improved object recognition memory when they were trained with 5-minute intervals (massed training), whereas there was

no difference between genotypes when they were trained with 10-minute intervals (spaced training), as if these longer intervals occluded the advantage conferred by the expression of the I-1* transgene. Interestingly, endogenous PP1 activity was found to be significantly larger in control mice trained with the shorter intervals (massed training), suggesting that one of the physiological consequences of using longer intervals between trainings is the repression of PP1 activity. The mutants also showed enhanced L&M in the spatial version of the Morris water maze. Strikingly, inhibition of PP1 after training strengthened memory, suggesting that PP1 expression normally weakens memory. Whether this is due to active erasure mechanisms or to failure of memory retrieval remains to be resolved. CaMKII, the AMPA receptor subunit GluR1 and CREB-dependent gene expression are modulated by PP1 and changes in any of one of these components could modulate the stability of memory.

Adenylyl cyclases

ACs have a role in synaptic plasticity and memory by coupling NMDAR Ca²⁺ signalling to downstream cAMP-dependent pathways⁷⁹, including the PKA-dependent phosphorylation of I-1 and therefore, the inactivation of PP1. Of all the ACs identified, AC1 and AC8 are neuron-specific⁷⁹. AC1 overexpression in the forebrain facilitated LTP in a PKA-dependent manner, enhanced memory in an object recognition task⁸⁰ and remote memory for contextual conditioning⁸¹. To achieve both temporal and spatial specificity of cAMP-PKA activation, a novel transgenic system using an *Aplysia* octopamine receptor (Ap oa₁) in mouse forebrain was introduced⁸² (BOX 2). Activation of Ap oa₁ in the forebrain of mice enhanced LTP and memory in contextual fear conditioning and object recognition tasks⁸². PKA signalling can also be pharmacologically enhanced by inhibiting phosphodiesterases (PDEs) and degradation of cAMP. PDE4 inhibitors were shown to enhance synaptic plasticity and L&M in wild-type mice and in a mouse model of Rubinstein-Taybe syndrome^{83–85}. These mice have a heterozygous mutation in CREB-binding protein (CBP), a transcriptional co-activator that binds active (phosphorylated) CREB. Just as with the I-1*, AC1 and Ap oa₁ transgenics, PDE treatments resulted in enhanced CREB activity, a result that we will explore in the next section.

Together, these studies demonstrate that the balance between kinases and phosphatases is crucial for plasticity and learning, and that shifting this balance towards kinases could be used to enhance L&M (FIG. 1).

Relieving transcriptional repression

CREB and C/EBPs

In addition to gating plasticity and memory, cAMP-PKA/phosphatase regulated signalling is crucial for the activation of transcription factors, including CREB^{17,32,86–89} (FIG. 2). Genetic manipulations that result in decreased CREB transcription in mice lead to deficits in both LTP and long-term memory in a wide range of tasks^{32,33}, whereas overexpression of CREB in flies, mice and rats results in memory enhancements^{17,90–92}. CREB is thought to regulate the transcription of proteins needed to stabilize the synaptic changes that are triggered during learning. Increasing the levels of CREB transcription is thought to boost the levels of rate-limiting proteins required for the stability of plasticity and memory¹⁰³. Increased CREB activity, due to overexpression of CaMKIV in mouse forebrain, also enhanced contextual fear and social recognition memory, as well as LTP, in both hippocampus and anterior cingulate cortex^{93,94}.

Another family of transcription factors that has been implicated in memory is the CCAAT/enhancer-binding protein (C/EBP) family. The expression of these transcription factors is upregulated in *Aplysia* and in rodents in response to CREB activation^{109–111}. In *Aplysia*, C/EBP was identified as an immediate early gene that is rapidly induced after repeated treatment

with serotonin. This treatment induces long-term synaptic facilitation (LTF), the cellular mechanism of behavioural sensitization, in sensory to motor synapses in *Aplysia*. Importantly, inhibition of C/EBP in presynaptic sensory neurons blocked LTF^{95,96}. In mice, the inhibition of C/EBP β in the hippocampus blocked the consolidation of inhibitory avoidance memory⁹⁷. Surprisingly, the deletion of C/EBP δ enhanced contextual fear memory⁹⁸. Although it is a transcriptional activator, C/EBP δ might be less efficient than other activators with similar target sequences and therefore, work in opposition to these other transcription factors. Alternatively, C/EBP δ could mediate the activation of target genes whose products inhibit memory formation⁹⁸.

Expression of a broad dominant negative inhibitor of the C/EBP family of transcription factors (EGFP-AZIP) in mouse forebrain⁹⁹ suppresses the repressor isoform of C/EBP β and decreases the expression of the activating transcription factor 4 (ATF4). ATF4, is a mammalian homologue of *Aplysia* CREB2 that interacts with the C/EBP family of transcription factors and is a negative regulator of CREB in vertebrates¹⁰⁰. Thus, EGFP-AZIP, by suppressing two different transcriptional repressors, shifts the balance towards CREB and C/EBP transcriptional activator isoforms. Importantly, this lowered the threshold for LTP and memory formation: a tetanus that induces only early stages of LTP (E-LTP) in controls can induce transcription-dependent later forms of LTP (L-LTP) in EGFP-AZIP mice. Interestingly, LTD induction was reduced in hippocampal slices from mutant mice. Additionally, mutant mice showed enhanced learning when trained with a weak protocol in the Morris water maze⁹⁹. These and other results^{101,102} show that relief of transcriptional repression can be used to enhance L&M across a wide range of species. It is important to note that C/EBP is thought to control the activation of several transcriptional cascades, therefore it is difficult to pin-point the exact molecular mechanisms underlying the memory enhancements that are observed in the EGFP-AZIP transgenics⁹⁹. To identify genetic changes that might be associated with memory enhancement, gene expression profile studies were carried out with the EGFP-AZIP transgenics. Microarray analyses revealed eight genes that were differentially expressed⁹⁹. Functional studies of these downstream molecules could shed light on the mechanisms responsible for the plasticity and memory enhancements of EGFP-AZIP transgenics.

eIF2/ATF4

Recently, other genetic manipulations thought to suppress ATF4 have also been reported to enhance L&M^{103,104}. Phosphorylation of the α subunit of elongation factor 2 (eIF2 α) can stimulate translation of ATF4, while inhibiting general translation^{105,106}. Mice that are heterozygous for a point mutation which prevented phosphorylation of the eIF2 α at serine 51 (eIF2 $\alpha^{+/S51A}$) showed decreased levels of ATF4 (REF. 104). Stimulation protocols that induced E-LTP in controls were able to induce L-LTP in the eIF2 $\alpha^{+/S51A}$ mutants, therefore lowering the threshold for L-LTP induction. Importantly, these mice showed improved L&M in various behavioural tasks including contextual and cued-fear conditioning, conditioned taste aversion and latent inhibition (BOX 1).

Deletion of GCN2, a conserved eIF2 α kinase, reduced phosphorylation of eIF2 α , suppressed the translation of ATF4 mRNA¹⁰³ and enhanced L&M. These studies support the hypothesis that the transcriptional repressor ATF4 is an important negative regulator of synaptic plasticity and memory and thus, a potential target for drugs designed to enhance these phenomena.

Epigenetic mechanisms

Neuronal gene expression can be regulated by epigenetic mechanisms such as histone modification and chromatin remodeling¹⁰⁷. Recent evidence suggests that the repression of gene transcription by epigenetic mechanisms such as histone deacetylation in mice and rats regulates synaptic plasticity and L&M^{85,108–111}. Moreover, enhancing histone acetylation

with histone deacetylase (HDAC) inhibitors has been shown to enhance L&M through CREB and CBP-dependent transcriptional activation^{85,109,110,112}. These results suggest that synaptic plasticity and memory can be enhanced by chromatin changes that favour transcriptional activation.

Extracellular factors

Growth factors

Molecules that orchestrate or mediate synaptic structural changes often play a role in synaptic plasticity and memory. For example, tissue-type plasminogen activator (tPA), an extracellular serine protease that converts plasminogen into plasmin, is an activity-induced gene in the hippocampus¹¹³ that modulates plasticity and memory. Genetic deletion of tPA in mice resulted in deficits in L-LTP as well as impairments in several forms of memory^{114–116}. Importantly, transgenic neuronal overexpression of tPA enhanced both LTP and hippocampus-dependent spatial memory¹¹⁷. Recent findings indicated that plasmin converts brain-derived neurotrophic factor precursor (proBDNF) to mature BDNF (mBDNF) and that this conversion is critical for L-LTP in mouse hippocampus¹¹⁸. Various studies indicate that BDNF has a key role in synaptic plasticity and learning^{119,120}. Interestingly, some ampakines, are also reported to increase BDNF expression¹²¹. Therefore, it is possible that the increased conversion of proBDNF to mBDNF in the tPA mutants contributes to enhanced LTP and memory.

Cell adhesion molecules

Studies in *Aplysia* and *Drosophila melanogaster* suggest that synaptic growth and plasticity involves the downregulation of cell adhesion molecules (CAMs)^{122–124}. For example, the *Aplysia* cell adhesion molecule (apCAM) is internalized in response to LTF-induction in sensory neurons and blocking this internalization impairs LTF and synaptic growth^{124,125}. This internalization is thought to relieve the CAM-dependent structural constraints during synaptic remodeling that are required for long-term plasticity and memory.

Ablation of the CAM telencephalin (TLCN, also known as intercellular adhesion molecule 5) enhanced LTP and performance in some learning tasks, especially when a positive reward was involved, such as radial maze and water-finding tasks¹²⁶, but not others such as the Morris water maze or fear conditioning tasks, suggesting that the effect of this mutation is task-specific. Pre-pulse inhibition, a measure of sensorimotor gating which involves many brain regions including prefrontal cortex, hippocampus, amygdala and nucleus accumbens, was found to be enhanced in TLCN-knockout mice¹²⁶. Determining how this mutation affects different brain systems might provide clues for the specific modulation of appetitive learning. The relation between CAMs and learning is complex as other CAM deletion studies resulted in behavioural abnormalities^{127,128}.

Extracellular matrix

Heparin-binding growth-associated molecule (HB-GAM, also known as pleiotrophin) is an extracellular matrix-associated protein that is implicated in the regulation of neurite outgrowth, axon guidance and synaptogenesis^{129,130}. Transgenic overexpression of HB-GAM in the brain improved spatial learning in the Morris water maze. Although initially these mice were thought to have deficits in LTP¹³¹, a more thorough analysis¹³² showed that this deficit was due to enhanced γ -aminobutyric acid A (GABA_A) inhibition and that when this is accounted for, LTP mechanisms show a slight, but not statistically significant enhancement. These results are an example of the power and limitations of studying LTP in tissue slices versus the far more complex *in vivo* recordings. Although slice preparations facilitate the study of synaptic plasticity, results are occasionally misleading because they do not always reflect *in vivo*

conditions. It is possible that the enhanced L&M in HB-GAM transgenic mice is caused by their higher LTP which is not masked by enhanced inhibition *in vivo* during learning. Interestingly, HB-GAM is also a proto-oncogene. Next we will describe other studies that involve this class of molecules in memory enhancement.

Proto-oncogenes and the regulation of memory

H-ras

Although the memory enhancement studies reviewed so far were focused on postsynaptic signalling mechanisms, there is emerging evidence for a role of presynaptic signalling^{133, 134} in mammalian plasticity and learning. Studies of mice expressing a constitutively active form of the proto-oncogene H-ras (H-ras^{G12V}) in axons of pyramidal neurons of the postnatal hippocampus, revealed a role for presynaptic Ras/MAPK signalling in LTP and L&M¹³⁵. Confocal and electron microscopy analysis demonstrated predominant expression of H-ras in presynaptic axon terminals, suggesting that the Ras family of signalling molecules might have a role in presynaptic function. Although a postsynaptic role had also been reported previously, it remains to be demonstrated whether this has functional implications for L&M¹³⁶. H-ras^{G12V} presynaptic expression resulted in increases in the activation of MAPK and in the phosphorylation of its substrate, synapsin I. In agreement with a role for synapsin I phosphorylation in vesicle docking and neurotransmitter release, LTP in the hippocampal CA1 region was enhanced in these mutants, and behavioural studies demonstrated dramatic hippocampal-dependent learning enhancements. Importantly, a synapsin I mutation, which alone had no measurable effect in LTP and learning, reversed the physiological and behavioural enhancements of the H-ras^{G12V} mice, indicating that H-ras^{G12V}-dependent phosphorylation of synapsin I has a key role in the learning enhancements of these mutants. These results provided strong evidence that the learning enhancements described were caused by presynaptic mechanisms involving Ras/MAPK upregulation and subsequent phosphorylation of synapsin I at its MAPK site. Extensive studies in *Aplysia*^{137,138} have provided compelling evidence for a role for presynaptic signalling mechanisms in synaptic plasticity and learning, and the H-ras^{G12V} studies indicated that presynaptic signalling also has a crucial role in plasticity and learning in mammals.

Cbl

Cbl belongs to another family of proto-oncogenes that are ubiquitin ligases and function as negative regulators of activated tyrosine-kinase-coupled receptors in the immune system¹³⁹. Cbl-b is highly expressed in the brain including hippocampus¹⁴⁰ and mice lacking cbl-b¹⁴⁰ showed specific enhancements in remote memory: spatial learning and 1-day memory were normal, but memory tested at 45 days was considerably more robust in the mutants. Although little is known about the role of cbl-b in the brain, it is possible that this proto-oncogene controls plasticity processes in the neocortex that are required for remote memory^{141,142}.

Glial regulation of memory enhancements

Studies of L&M have largely focused on neuronal cells. However, there is increasing physiological and behavioural evidence that glial cells have an active role in information processing^{143,144} and might also have a role in L&M¹⁴⁵. Overexpression of S100b, a Ca²⁺ binding protein secreted from astrocytes¹⁴⁶, impaired LTP and spatial learning in mice¹⁴⁷. Targeted disruption of S100b enhanced LTP and exogenous S100b treatment reversed this enhancement¹⁴⁸; Behavioural analysis with the Morris water maze and contextual fear conditioning revealed enhanced L&M in the S100b mutants. Future studies will reveal the underlying mechanism, as altered neuronal signalling through the neuronal S100b receptor

RAGE (receptor for advanced glycation end products) might be responsible for the LTP and L&M enhancement in this mutant.

Simultaneous binding of glutamate and glycine is known to be required for efficient activation of NMDARs¹⁴⁹. D-serine, which is mainly produced in glial cells, is a potent agonist of the glycine binding site in NMDARs¹⁵⁰. The concentration of D-serine in the forebrain of mice lacking D-amino-acid oxidase (DAAO) was found to be higher than in control mice. Consequently, the mutant mice showed larger NMDA currents¹⁵¹, enhanced LTP and improved performance in the Morris water maze¹⁵¹. These results highlight the involvement of glial processes in L&M and suggest that manipulations of these processes could be used to enhance L&M.

Modulatory neurotransmission and memory

Although many of the studies mentioned above focused on NMDAR function, manipulations of other neuro-transmitter systems also result in plasticity and learning enhancements. For example, donepezil (an acetylcho-esterase inhibitor)¹⁵² and modafinil, two US Food and Drug Administration approved drugs to treat cognitive deficits, are thought to affect catecholamines, serotonin, glutamate, GABA and histamine systems¹⁵³. However, the exact mechanisms of action for many cognitive drugs remain unclear. Genetic manipulations can be a powerful approach to dissect the role of each neurotransmitter system in plasticity and L&M. For example, mice overexpressing the ionotropic 5-HT₃ receptor displayed enhanced contextual fear conditioning, whereas cued conditioning and fear extinction were not affected¹⁵⁴. In accordance, deletion of monoamine oxidase A (MAOA), an enzyme which metabolizes serotonin, also resulted in enhancement of classical fear conditioning¹⁵⁵. These studies show that modulation of serotonin-mediated signalling can modulate certain forms of memory.

Similarly, manipulations of the histamine system¹⁵⁶ have also been shown to enhance some forms of learning. Mice lacking histidine decarboxylase (HDC), an enzyme that synthesizes histidine^{157,158}, showed enhanced L&M in the fear conditioning and the Morris water maze tasks. Unexpectedly, this mutation impaired object discrimination¹⁵⁷. The histamine deficiency in these mutants altered dopamine metabolism in the striatum, a structure with a key role in reward and reinforcement¹⁵⁷. Thus, it is possible that changes in motivation might have played a central role in the behavioural phenotype of these mutants. Tissue- or cell type-specific genetic lesions, may help to further elucidate the role of HDC in motivation and memory.

Integrating different signalling pathways

The studies reviewed here suggest that there might be a core of molecular mechanisms associated with enhanced cognition (FIG. 3). We noted that many of the 33 mutant mice reviewed (TABLE 1) included enhancements in NMDAR signalling. Accordingly, D-cycloserine, a partial agonist at the strychnine-insensitive glycine-binding site on the NMDAR, potentiates NMDA currents and enhances learning in rodents and humans^{159–161}, suggesting that pharmacological upregulation of NMDAR signalling might be a general strategy for enhancing memory. Nevertheless, it is important to note that the studies reviewed here show that manipulations which do not have an obvious connection with NMDAR signalling can also enhance L&M. In general, genes associated with enhanced L&M might regulate rate-limiting steps or bottle necks in the molecular and cellular events underlying L&M. Powerful molecular tools, such as microarray analysis, could be used to unravel molecular mechanisms that are common among mutants with L&M enhancements. The relevance of these molecular genetic mechanisms to L&M could then be studied by both disrupting and overexpressing the relevant

genes in mice, and then studying the resulting molecular, cellular, systems and behavioural changes.

Conclusions

Molecular and cellular cognition studies in mice have examined more than 200 mutant genes. Although the majority of those mutations resulted in behavioural deficits (see Further Information), our review of the literature revealed that at least 33 of the mutant mice generated showed L&M enhancements (TABLE 1). Remarkably, in 26 out of 29 studied mouse lines LTP was found to be enhanced (TABLE 1). Nevertheless, it is noteworthy that not all enhancements in LTP result in L&M enhancements, probably because of disruptions in other mechanisms involved in learning (BOX 3).

The results summarized here demonstrate that it is possible to engineer mice with cognitive enhancements by manipulating either the acquisition or consolidation of memory. For example, NR2B, calcineurin and H-ras are thought to be involved in the acquisition of memory, whereas ORL1, CaMKIV, eIF2 α and cbl-b seem to modulate memory consolidation. Calcineurin and Zif268 are involved in the establishment, but not in the extinction, of memory⁷³. These are examples of how genetic manipulations can be used to analyse the role of specific genes in different phases of memory.

The remarkable consistency of the reviewed findings provides considerable evidence for a role of LTP mechanisms in L&M. There is compelling evidence that during learning synaptic transmission is strengthened in a manner consistent with LTP, and the vast majority of the pharmacological and genetic manipulations that disrupt LTP also impair L&M. Together with the extensive theoretical work that outlines how LTP-like mechanisms in the brain could be used in information processing and storage, this body of data provide conclusive evidence that stable changes in synaptic plasticity have a role in L&M (but see REF. ¹⁶²). These data however, have not elucidated how LTP-like mechanisms are involved in processing, storing or retrieving information. It will be crucial to identify other physiological mechanisms that modulate and interact with LTP during the acquisition, consolidation and retrieval of information. Indeed, changes in inhibition (GABA_A α 5-knockout)¹⁶³, excitability (Kv β 1.1-knockout)¹⁶⁴ and short-term plasticity (H-ras^{G12V}-transgenic)¹³⁵ can facilitate LTP and result in L&M enhancements.

Studying enhanced cognition represents an exciting opportunity as there are a number of fascinating questions that can be addressed with mutant mice that could have an impact well beyond the molecular and cellular mechanisms explored so far. For example, how do mutations that enhance L&M affect circuit properties such as place representations in the hippocampus or emotional information processing in the amygdala? Do these representations form faster, are they more refined, flexible or specific than in normal mice? Do these mutations affect the interaction between brain regions during L&M? For example, does the cortical expression of memory-enhancing mutations accelerate the rate of cortical information transfer that is originally processed in the hippocampus?^{141,142} Does expressing these mutations in the hippocampus affect either the interaction between the hippocampus and striatum during spatial learning¹⁶⁵ or the interaction between the hippocampus and the amygdala during contextual conditioning?¹⁶⁶

There are a number of caveats that hamper the interpretation of the findings reviewed. Most of the studies described here carried out a limited behavioural analysis and did not explore in detail the behavioural nature of the L&M enhancements reported. For example, although enhancements in the Morris water maze were common among the mutants reviewed, it is not clear whether spatial components that cannot be measured in the version of the task used, would

also be enhanced, such as pattern completion, pattern separation or some other specific aspect of spatial learning^{11,13}.

Another possibility worth considering is that the enhancements of L&M described might trigger unintended physiological changes that complicate the behavioural analyses. For example, NMDAR modulates pain perception¹⁶⁷ and it is unclear how this affected the fear conditioning studies reported. Similarly, AC1 transgenic mice showed better recognition memory, but lost memory flexibility⁸⁰. Is one the result of the other? Could some of the L&M enhancements documented reflect changes in other behavioural mechanisms, such as anxiety, motivation or attention? Could some of these L&M enhancements have unknown behavioural costs that escaped the incomplete behavioural characterization of the mutants? Could more extensive tests reveal that all of these mutant mice have undetected but significant behavioural deficits? The mice studied were kept in traditional impoverished housing conditions; would the same enhancements be observed in environmentally enriched housing conditions? The answers to these questions are unknown, but the extent and consistency of the findings reviewed suggest that the key conclusions, namely that LTP-like mechanisms have a role in L&M and that there are a core of rate-limiting mechanisms that can be used to enhance L&M, may well stand the test of time.

Box 3. LTP enhancements without learning and memory improvements

Long-term potentiation (LTP) enhancements do not always result in better learning and memory (L&M), either because the tests used might not be sensitive enough or because the enhancements in LTP are accompanied by significant physiological disruptions that interfere with learning. Here are some examples:

- Deletion of *Psds95*¹⁸¹ enhances LTP in the CA1 region of the hippocampus, but disrupts the postsynaptic density and dramatically changes the synaptic properties in the mutant mice. Not surprisingly, these mice show profound L&M deficits.
- Deletion of *inositol 1,4,5-triphosphate 3-kinase A* also enhances LTP in the CA1 region of the hippocampus, but does not affect spatial L&M assessed by the Morris water maze¹⁸².
- Deletion of *Limk1* resulted in synaptic structural abnormalities¹⁸³. CA1 LTP with high-frequency stimulation (50–100 Hz) was enhanced, but low frequency (10Hz)-induced LTP was impaired. Although cued fear conditioning was enhanced in these mutants, both contextual fear conditioning and initial learning in the Morris water maze were unaffected; reversal learning in the Morris water maze was impaired¹⁸³.
- Deletion of *Fmr2* increases mortality, results in abnormalities in sensory perception, impaired contextual fear conditioning, and enhanced LTP in the CA1 region of the hippocampus¹⁸⁴.
- Deletion of *Ptpδ* increases mortality rates, causes growth retardation and learning impairments in the Morris water maze and radial arm maze. These animals also show enhanced LTP in the CA1 and CA3 region of the hippocampus¹⁸⁵.
- Dystrophin-deficient mice have altered γ -aminobutyric acid (GABA) inhibition¹⁸⁶ and altered metabolism¹⁸⁷. These mice show enhanced LTP but impaired L&M in object recognition tasks and in the Morris water maze¹⁸⁸.

It is important to note that despite enhanced LTP, each of these mutations resulted in other abnormalities that could account for the L&M impairments. Many of the mutants described above were generated to model human diseases associated with cognitive deficits such as

Williams syndrome (LIMK1), fragile X syndrome (FMR2) and Duchenne muscular dystrophy (dystrophin), and thus, it is not surprising to find deficits in L&M in these mutant mice.

The severity of cognitive disorders and the number of people affected by them (>5% of the population) adds urgency to the effort to develop treatments^{168,169}. Targeting the synaptic and nuclear mechanisms associated with L&M enhancements might lead to the development of general therapies for cognitive disorders that circumvent the need to develop targeted therapies for the myriad of genetic and environmental insults underlying these disorders. Manipulations of signalling pathways that can enhance L&M in mice regardless of genetic background might be able to overcome individual genetic heterogeneity in patients and enhance cognitive function. Nevertheless, a word of caution is in order: could the manipulation of some of the systems associated with enhanced cognition lead to an increase or exacerbation of neurological and psychiatric symptoms? For example, as D-serine is suspected to be involved in brain pathologies such as schizophrenia¹⁵⁰, DAAO-mediated signalling may not be an appropriate target for memory enhancing drugs. It is also important to stress that memory enhancing manipulations raise a number of ethical issues that are outside of the scope of this Review, but that merit careful consideration and discussion^{170,171}.

The findings reviewed here represent the beginning of a fundamental new approach in the study of cognition, one that focuses on the molecular and cellular mechanisms that gate and limit cognitive function. We are only beginning this journey, but the results obtained so far demonstrate the tremendous potential of this approach for basic science and for clinical applications.

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Glossary

Rubinstein-Taybe syndrome

Rubinstein-Taybe syndrome is a genetic disorder that occurs in 1/125,000 births and is characterized by mental retardation, broad thumbs and toes, and facial abnormalities. It can be caused by heterozygous mutations in CREB binding protein (CBP).

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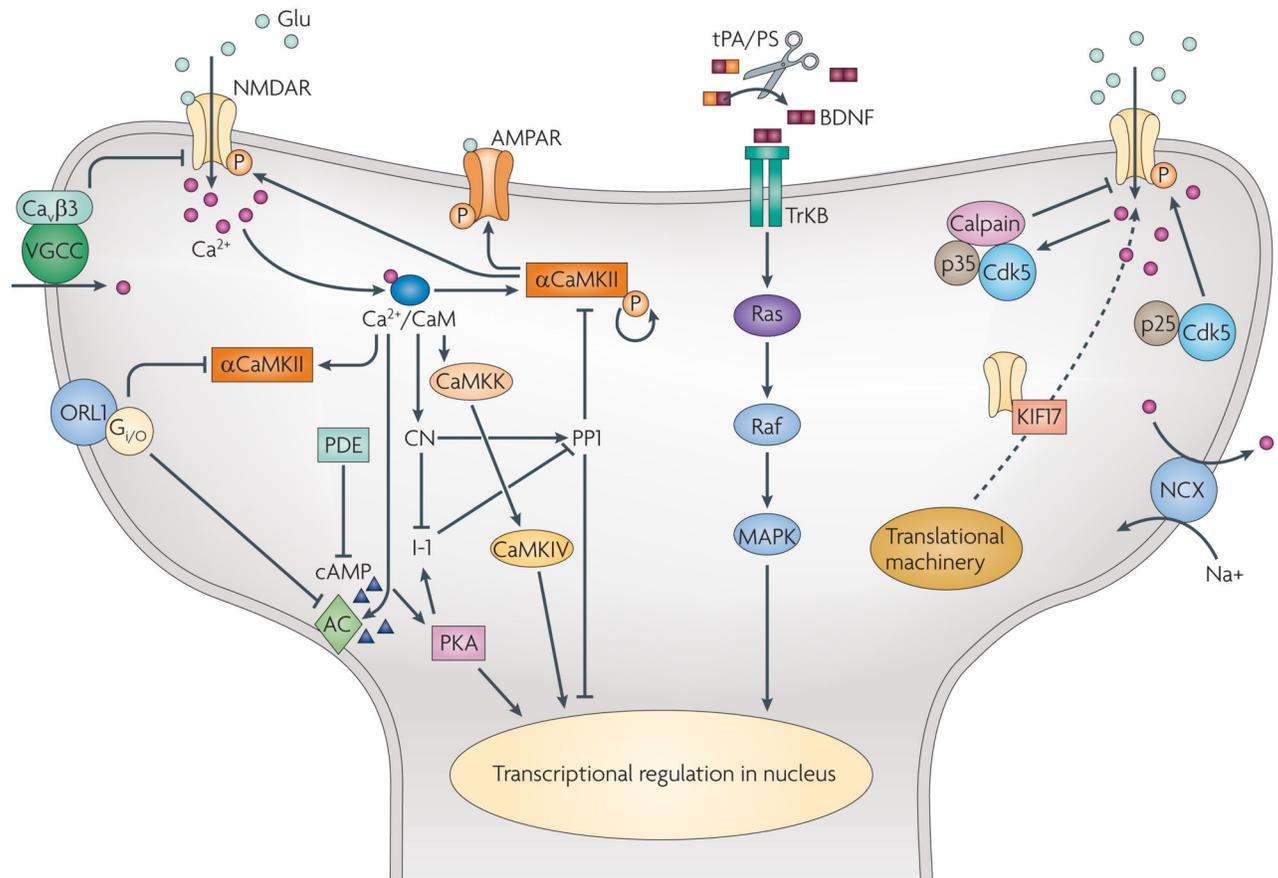


Figure 1. NMDAR-dependent signalling and downstream kinases and phosphatases implicated in learning and memory enhancement

N-methyl-D-aspartate receptor (NMDAR) function can be positively regulated by α calcium calmodulin kinase (α CaMKII) phosphorylation and by the transient activation of cyclin-dependent kinase 5 (Cdk5) through the positive regulator p25. Transport of the NR2B subunit to synaptic sites can be increased by overexpressing the motor protein KIF17. Calpain, possibly modulated by Cdk5, downregulates NR2B by proteolysis. The β 3 subunit of voltage-gated calcium channel (VGCC) and the nociceptin receptor ORL1 also negatively regulate NMDAR expression or function by unknown mechanisms. Calcium influx through NMDARs activates α CaMKII, which in turn positively regulates NMDAR and α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) function, contributing to the induction and expression of long-term potentiation (LTP), respectively. In addition, neuronal calcium concentration can be regulated by Na⁺/Ca²⁺ exchangers (NCXs), which extrude Ca²⁺ from neurons. Calcium/calmodulin (CaM) activates downstream kinases and phosphatases: it activates adenylyl cyclase (AC) to produce cAMP, which activates protein kinase A (PKA) and eventually regulates cyclic-AMP response-element-binding protein (CREB) activity in the nucleus. By phosphorylating inhibitor-1 (I-1), PKA can antagonize the action of protein phosphatase 1 (PP1), which is activated by the calcium/CaM-activated phosphatase calcineurin (CN). CaM also activates calcium CaM kinase kinase (CaMKK), which in turn activates calcium/CaM kinase IV (CaMKIV), another positive regulator of transcription. Activation of TrkB by brain-derived neurotrophic factor (BDNF) triggers the mitogen-activated protein kinase (MAPK) signalling pathway and ultimately regulates transcription. Sharp and blunted arrows represent positive and negative regulation, respectively. tPA/PS, tissue-type plasminogen activator/plasmin; PDE, phosphodiesterase.

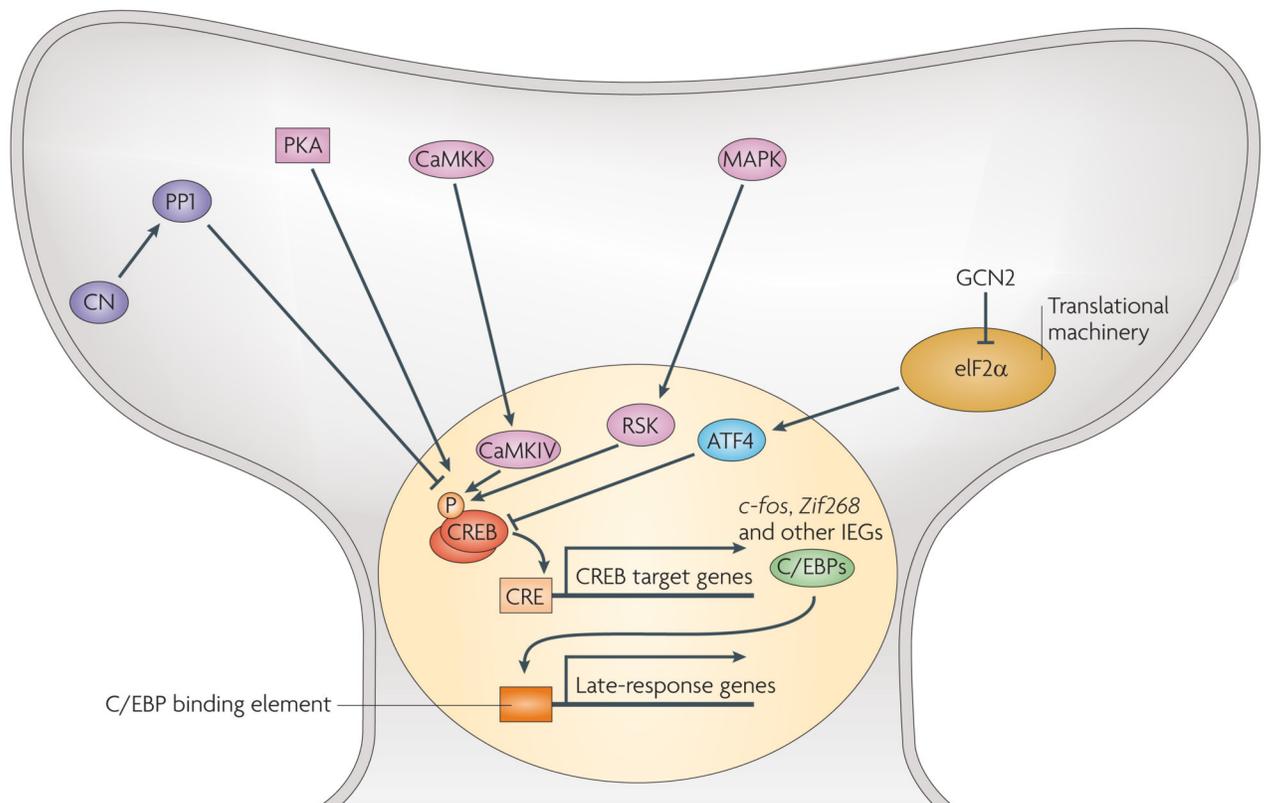


Figure 2. Regulation of CREB-dependent gene expression involved in memory formation

The activity of cyclic-AMP response-element-binding protein (CREB) is regulated by phosphorylation or by molecular interactions. Protein kinase A (PKA), calcium calmodulin kinase IV (CaMKIV) and ribosomal S6 kinase (RSK) (activated by mitogen-activated protein (MAPK)) phosphorylate CREB at serine 133, whereas protein phosphatase-1 (PP1) dephosphorylates CREB. Another phosphatase, calcineurin (CN, also called PP2B) indirectly inhibits CREB function. Phosphorylated CREB recruits the CREB-binding protein (CBP) and activates the transcription of immediate early genes (IEGs) such as *c-fos*, *Zif268* and *C/EBPs* (CCAAT/enhancer-binding protein). *C/EBPs* themselves function as transcription factors activating or inhibiting the expression of another group of genes (late-response genes). Transcriptional activity of CREB can be repressed by activating transcription factor 4 (ATF4), which is translationally regulated by the α subunit of elongation factor 2 (eIF2 α). Inhibition of eIF2 α phosphorylation by GCN2 (general control non-depressible 2) reduces the translation of ATF4 mRNA and subsequently enhances CREB-dependent gene expression and learning and memory. ATF4 is thought to compete with CREB to bind to CRE and other transcriptional components including CBP. Sharp and blunted arrows represent positive and negative regulation, respectively. CaMKK, CaMK kinase.

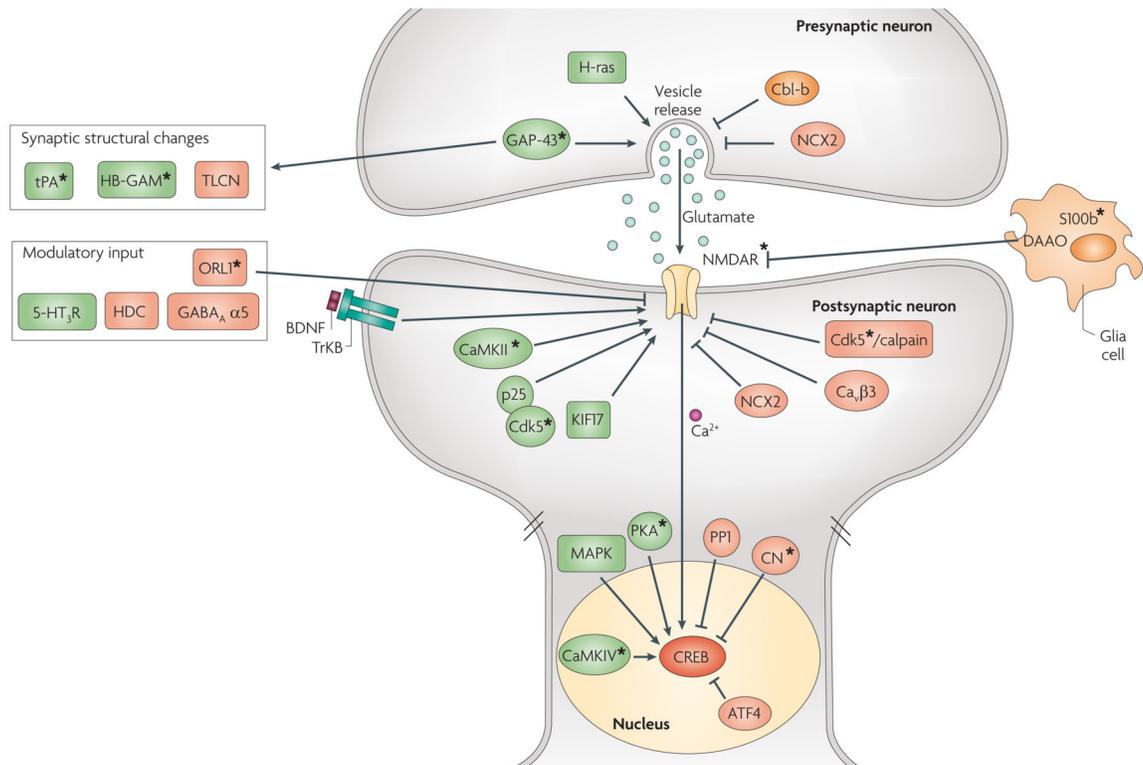


Figure 3. Integrating pathways for learning and memory enhancement

Memory enhancements have been achieved by manipulating signalling largely in four different domains of the synapse. First, in the presynaptic axonal terminal; molecular manipulations that increased glutamate release have been shown to enhance learning and memory (L&M). Second, at the postsynaptic site; manipulations that upregulate the levels or enhance the function of *N*-methyl-D-aspartate receptors (NMDAR) either directly (through KIF17 for example, or by phosphorylation through calcium calmodulin kinase II (CaMKII) or p25/Cdk5) or indirectly (for example through deletion of $Ca_v\beta 3$ or D-amino-acid oxidase (DAAO)) have been shown to enhance L&M. Third, in the nucleus through the postsynaptic transcription factor cyclic-AMP response-element-binding protein (CREB); actions of several kinases/phosphatases, that are regulated by calcium influx mainly through NMDAR, converge on CREB. *De novo* gene expression contributes to the stabilization and consolidation of synaptic plasticity and memory. Fourth, by structural changes at the synapse; molecules that participate in key structural changes involved in memory, such as the formation of new synapses, can be manipulated to enhance memory. Manipulations of structural molecules such as heparin-binding growth-associated molecule (HB-GAM) and telencephalin (TLCN) result in L&M enhancement. The molecules marked with an asterisk (*) are examples of genes for which bidirectional manipulations lead to deficits and enhancements in L&M. For example, inhibition of calcineurin (CN) enhances memory whereas overexpression of CN impaired L&M (see text for details). In addition to NMDAR, manipulations of other modulatory neurotransmitter systems such as serotonin, γ -aminobutyric acid (GABA) and histamine can enhance memory. Glial proteins (S100 calcium-binding protein5(S100b) and DAAO) also play active roles in L&M. Sharp and blunted arrows represent positive and negative regulation, respectively. Either the overexpression or activation of molecules in green, or the deletion or inhibition of molecules in red enhance L&M. HDC, histidine decarboxylase; NCX2, Na^+/Ca^{2+} exchanger type 2; ORL1, nociceptin receptor; PKA, protein kinase A; PP1, protein phosphatase 1; tPA, tissue-type plasminogen activator; 5-HT₃R, 5-HT₃ receptor.

Table 1
 Mouse models showing enhancement of learning and memory

Gene	Tg/KO	Strain	Behavioural phenotypes				Plasticity phenotypes		Comments	Refs
			wm	ext	cue	ext	obj	LTP		
NMDA receptor-related signalling										
NR2B	Tg	B6/CBF1	↑	↑	↑	↑	↑	↑	NA	9
Cdk5	C-KO	NA	↑	↑	—	↑	↑	ND	Only reverse water maze enhanced	38
p25	C-Tg	C57Bl/6J	↑	↑	—	ND	↑	ND	Only transient expression enhances memory	41
KIF17	Tg	BDF	↑	ND	ND	ND	ND	ND	Working memory is also enhanced	29
Ca _v β3	KO	B6/129	ND	↑	—	ND	↑	↑	NA	26
Calcium homeostasis-related signalling										
RyR3	KO	C57Bl/6J	↑	ND	ND	ND	↑	↑	But also see 50	189
Ncx2	KO	B6/129	↑	↑	—	ND	↑	↑	NA	53
Kinase and phosphatase										
Calcineurin	C-I	C57Bl/6J	↑	ND	↑	↓	↑	↑	But also see 75	72, 73
PP1	C-I	C57Bl/6J	↑	ND	ND	ND	↑	↑	NA	64, 190
AC1	Tg	C57Bl/6	ND	—	—	↓	↑	ND	NA	80
Ap oa ₁	Tg	C57Bl/6J	ND	↑	ND	ND	↑	↑	NA	82
CaMKIV	Tg	C57Bl/6N	ND	↑	ND	ND	↑	↑	Also see 93	94
RNA and protein synthesis										
eIF2α	Tg	C57Bl/6J	↑	↑	↑	ND	↑	↑	NA	104
GCN2	KO	129SvEv	↑	↓	—	ND	↑	↑	Learning and LTP are impaired with strong training	103
ATF4, C/EBP	C-I	C57Bl/6	↑	ND	ND	ND	↑	↑	Learning is enhanced after only weak training	99
Proto-oncogenes										
H-ras	Tg	B6/129	↑	↑	ND	ND	↑	↑	NA	135
Cbl-b	KO	C57Bl/6	↑	ND	ND	ND	—	—	Only remote memory is enhanced	140
Structural genes										
tPA	Tg	NA	↑	ND	ND	ND	↑	↑	NA	117

Gene	Tg/KO	Strain	Behavioural phenotypes				Plasticity phenotypes			Comments	Refs	
			wm	ext	cue	ext	obj	LTP	LTD			
HB-GAM	Tg	FVB/NHsd	↑	—	↓	ND	ND	ND	↑, —	ND	Gene controls inhibition and this complicates the LTP studies	131, 132
TLCN	KO	C57 × CBA	—	—	ND	ND	ND	ND	↑	ND	Learning and memory for non-aversive tasks are enhanced	126
GAP43	Tg	C57BI/6	↑	ND	ND	ND	ND	ND	↑	ND	But also see 192	191
<i>GABA-related signalling</i>												
GABA _A α5	KO	B6/129	↑	ND	ND	ND	ND	ND	—	ND	NA	163
GRPR	KO	C57BI/6J	—	↑	↑	ND	ND	ND	↑	ND	LTP in amygdala is enhanced	193
<i>Glial signalling</i>												
S100b	KO	C57BI/6J	↑	↑	ND	ND	ND	ND	↑	ND	NA	148
DAAO	KO	NA	↑	ND	ND	ND	ND	ND	↑	ND	NA	151
<i>Miscellaneous</i>												
ORL1	KO	B6/129	↑	↑	—	ND	ND	ND	↑	ND	Enhanced fear memory only 7 days after training	21, 42
5-HT ₃ R	Tg	B6SJL/F2	ND	↑	—	—	—	ND	ND	ND	NA	154
MAOA	KO	C3H/HeJ	ND	↑	↑	ND	ND	ND	ND	ND	NA	155
HDC	KO	C57BI/6 (129Sv)	↑	↑	↑	ND	ND	↓	↑	—	Water maze phenotype was found in 129Sv background	157, 158
HCN1	KO	B6/129	↑	—	—	ND	ND	ND	↑	ND	LTP at perforant path is enhanced. Also see 195	194
DEF45	KO	B6/129	↑	ND	ND	ND	ND	↑	ND	ND	Better recognition memory, only up to 3 hours after training	196, 197
Kvβ1.1	KO	C57BI/6	↑	ND	ND	ND	ND	ND	↑	ND	18 month-olds mice were used. Also 198	164
EC-SOD	Tg	C57BI/6 × C3H	↑	↓	—	ND	ND	ND	↑	ND	20 month-olds mice were used. Also see 200	199

GABA, γ -aminobutyric acid; C-I, conditional inhibition; C-KO, conditional knockout; C-Tg, conditional transgenic; cue, cued fear conditioning; ext, context fear conditioning; ext, fear extinction; KO, knockout; LTD, long-term depression; LTP, long-term potentiation; NA, not applicable; ND, not determined; NMDA, N-methyl-D-aspartate; obj, object recognition task; Tg, transgenic; wm, water maze; —, no change.