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REVIEW ARTICLE

The Genetics of Childhood Disease and Development: A Series of Review Articles

The following article is the second in this series. It reviews genes and metabolic pathways involved in learning and memory in lower animals and in humans. These new, exciting studies will contribute to greater understanding of the molecular abnormalities responsible for cognitive disorders in children.

Alvin Zipursky
Editor-in-Chief

Learning, Memory, and Transcription Factors

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ABSTRACT

Cognitive disorders in children have traditionally been described in terms of clinical phenotypes or syndromes, chromosomal lesions, metabolic disorders, or neuropathology. Relatively little is known about how these disorders affect the chemical reactions involved in learning and memory. Experiments in fruit flies, snails, and mice have revealed some highly conserved pathways that are involved in learning, memory, and synaptic plasticity, which is the primary substrate for memory storage. These can be divided into short-term memory storage through local changes in synapses, and long-term storage mediated by activation of transcription to translate new proteins that modify synaptic function. This review summarizes evidence that disruptions in these pathways are involved in human cognitive disorders, including neurofibromatosis type I, Coffin-Lowry syndrome, Rubinstein-Taybi syndrome, Rett syndrome, tuberous sclerosis-2, Down syndrome, X-linked α-thalassemia/mental retardation, cretinism, Huntington disease, and lead poisoning. **(*Pediatr Res* 53: 369–374, 2003)**

Abbreviations

AMPA, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid
BDNF, brain-derived neuronal growth factor
CaMKII, calcium/calmodulin-dependent protein kinase II
CaMKIV, calcium/calmodulin kinase IV
cAMP, cyclic AMP
CBP, CREB binding protein
CLS, Coffin-Lowry syndrome
CRE, cAMP response element DNA sequence
CREB, cAMP response element binding protein transcription factor
GAP, Ras GTPase-activating protein
GTP, guanosine triphosphate
LTD, long-term depression
LTP, long-term potentiation
MAPK, mitogen-activated protein kinase
NF1, neurofibromatosis type I
NMDA, *N*-methyl-D-aspartate type glutamate receptor
Ras, family of guanine trinucleotide binding protein (GTP) hydrolases
PKA, protein kinase A
PKC, protein kinase C
RSK2, ribosomal S6 kinase-2

More than a thousand types of mental retardation are listed currently in Online Mendelian Inheritance in Man (OMIM, 2002) and many milder learning disorders are seen in clinical practice. Many of these disorders are associated with syndromes, chromosomal disorders, or metabolic diseases, but it is unclear how most of them disrupt the brain's chemical machinery for learning and memory. Experimental work over several decades makes it clear that long-term memory storage, which is essential for cognition, involves activity-dependent synaptic plasticity and transcription of genes to synthesize synaptic proteins (1, 2). Recently, several genetic forms of mental retardation have been linked to mutations in intracellular pathways that mediate synaptic plasticity, learning, and memory in lower animals (3). These discoveries suggest that a

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framework is emerging for understanding the pathogenesis of cognitive disorders in children at a molecular level.

MEMORY IS STORED IN SYNAPSES

Learning is defined as the process of acquiring new information or skills, whereas *memory* refers to the persistence of learning that can be revealed at a later time (4). Memory is the usual consequence of learning and reflects the enduring changes in the nervous system that result from transient experiences (2). Synaptic plasticity refers to the changes in the strength of synaptic function, and this process is currently a major focus of research on the neurobiology of learning and memory (5–7). Synaptic plasticity includes both short-term changes in the strength or efficacy of neurotransmission as well as longer-term changes in the structure and number of synapses (1). Experimental models of changes in synaptic strength or effectiveness in response to repeated electrical stimulation are thought to mimic physiologic plasticity. These changes are referred to as LTP when synaptic strength increases or LTD when it decreases (5, 8). These modifications in synaptic strength, both positive and negative, distributed across thousands to millions of connections among neurons, are believed to form the physical and biochemical substrate for memory and learning (1, 4). A great deal has been learned about the details of these processes in lower animals, including snails, fruit flies and rodents, that is thought to be directly relevant to humans. In fact it has been suggested that it is the number and complexity of neuronal connections that distinguish the human brain from that of animals rather than the fundamental chemical processes (9). Molecular defects in synaptic function are probably responsible for many childhood cognitive disorders that are currently poorly understood.

A DIALOGUE BETWEEN GENES AND SYNAPSES

Eric Kandel, who received the Nobel Prize in 2000, has described the process of memory storage as a "dialogue between genes and synapses" (1). Using the snail *Aplysia,* Kandel and his colleagues identified biochemical changes associated with short- and long-term changes in behavior that reflect simple forms of memory storage (Fig. 1). They identified a short-term form of sensitization, a process through which an animal responds in a heightened fashion to an innocuous stimulus after being exposed to a different, noxious one. This behavior in an animal resembles the startle from a door closing that a person might exhibit after experiencing a previous unrelated trauma. Kandel's group identified short-term biochemical changes after a single tail shock in a simple neuronal circuit that includes a serotonin-containing neuron synapsing upon a sensory neuron involved in the gill-withdrawal reflex. They found that the sensitizing stimulus enhanced the release of serotonin and caused elevations in the second messenger cAMP and PKA activity within the sensory neuron (Fig. 2). PKA then phosphorylated neurotransmitter channels, vesicles, and other proteins that strengthened the reflex by enhancing presynaptic neurotransmitter release. This form of short-term memory is linked to temporary changes in synaptic function

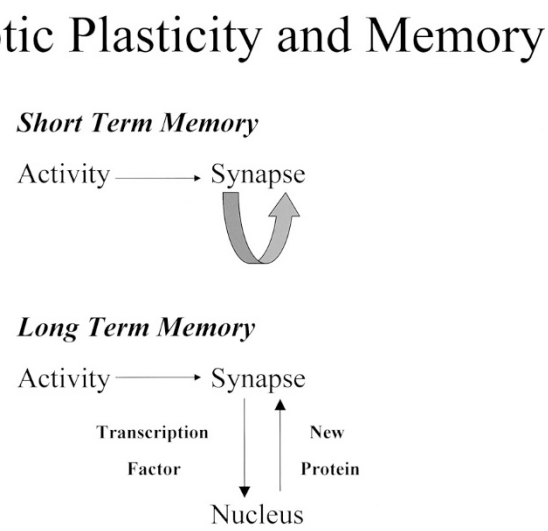

Figure 1. General model for short-term and long-term memory based on experimental models of synaptic plasticity. Short-term memory generally does not require protein synthesis but results from changes in synaptic strength within synapses. For example, activation of CaMKII in response to calcium/calmodulin is a model for this type of memory because this increases activity in AMPA glutamate receptors (19). In contrast, long-term memory storage generally requires transcription and translation of new protein that enhances the strength or number of active synapses.

that require enzyme activation and protein phosphorylation, but synthesis of new protein is not required (Fig. 1).

In contrast to short-term sensitization, repeated stimulation of the same circuit in *Aplysia* caused an enduring response that requires gene transcription and translation of new protein (Fig. 2). Persistent elevation of cAMP and activation of PKA associated with a repeated sensitizing stimulus leads to phosphorylation and activation of MAPK and the nuclear transcription factor CREB protein (1). CREB contains the basic leucine zipper motif , which allows two molecules to dimerize by juxtaposing basic amino acid residues to form a DNA binding domain that recognizes a specific nucleotide sequence (10). When activated by phosphorylation, CREB-1 binds to specific DNA sequences known as CRE, activating transcription of genes that enhance neurotransmitter release and expand synaptic connections (1). Activation of CREB-1 also removes the repressive action of a CREB-1 inhibitor, CREB-2. When oligonucleotides with CRE sequences are injected into cultured *Aplysia* neurons to sequester CREB-1, long-term but not short-term memory is blocked (1). These results indicate that long-term memory storage in this simple system requires communication from synapses to the nuclear transcriptional machinery back to the synapse (Fig. 2). Similar machinery for long-term memory storage has been identified in fruit flies and rodents, suggesting that it might also play a role in human cognition as well (11–13).

SIGNALING CASCADES AND GENE TRANSCRIPTION IN MAMMALIAN MEMORY

In contrast to sensitization, which is a simple form of nonassociative learning, more complicated forms of associative learning have been studied in mammals learning about the

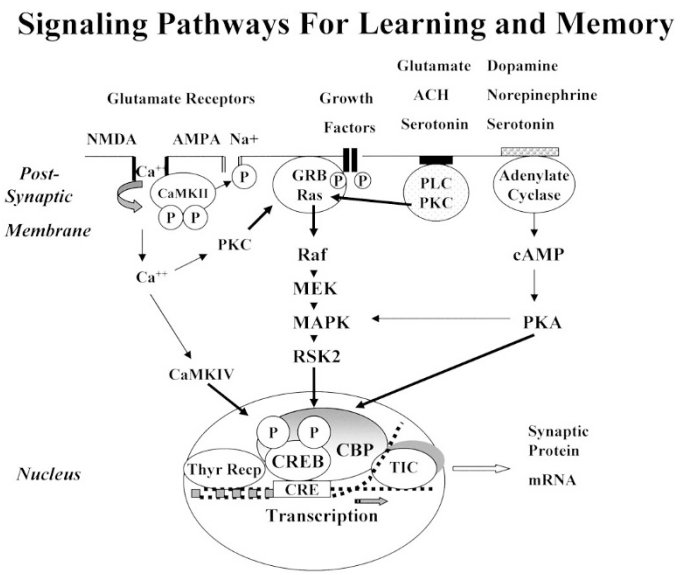

Figure 2. Signaling pathways for learning and long-term memory storage described in the text from work in animal models. Multiple synaptic signal transduction pathways contribute to reinforcement of a memory by multiple sensory stimuli, for example, sound, sight, and taste. Three types of neurotransmitter receptors are shown: ionotropic receptors that open ion channels (*e.g.* the NMDA- and AMPA-type glutamate receptors shown at *top left*), metabotropic receptors (*e.g.* for glutamate, acetylcholine, and serotonin at *upper right*) linked to synthesis of inositol phosphates and stimulation of PKC, and transmembrane receptors linked to generation of cAMP, shown at *upper far right*. Most long-term memories require gene transcription and translation of new protein, whereas short-term memories can result from local synaptic changes, for example, phosphorylation and/or addition of AMPA-type glutamate receptors shown at the *upper left*. Cross-talk among the pathways contributes to synergism among stimuli and also provides redundancy if one pathway is affected by genetic or acquired disorders. Genetic disorders of upstream pathways (*e.g.* NFI, which up-regulates Ras activity) tend to cause milder cognitive disabilities than disorders closer to the nucleus such as CLS caused by mutations in RSK2.

relationship between two stimuli (4). For example, synaptic activation of protein kinase signaling cascades, phosphorylation of transcription factors, and gene expression have been studied in rodents that learn to associate a foot shock paired with a novel odor, texture, or visual cue (2). This form of learning, called fear conditioning, has been linked to LTP in the hippocampus. Protein kinases required for LTP, including the MAPK extracellular signal regulated protein kinase, PKC, and α-CaMKII, are also activated in the hippocampus after fear conditioning (Fig. 2) (14). Downstream, activation of the MAPK cascade stimulates phosphorylation of the transcription factor CREB and may also enhance gene transcription by phosphorylating a transcription factor called CBP, which has intrinsic histone acetyltransferase activity (15). Acetylation of histones neutralizes their positive charges, weakening their interaction with DNA, resulting in an open chromatin conformation that promotes transcription (16). Unlike CREB, which binds directly to a specific DNA sequence, transcriptional co-activators like CBP interact with proteins such as *trans*-acting transcriptional factors and proteins in the basal transcriptional complex (Fig. 2) (10). Pharmacologic inhibition of the activator of MAPK, MAPK kinase, blocks fear conditioning (2). This suggests that the MAPK signaling cascade is an important final common pathway for this form of learning.

NEUROTRANSMITTERS AND GROWTH FACTORS INVOLVED IN LEARNING

A number of neurotransmitter receptors and growth factors appear to influence synaptic plasticity and memory through these molecular pathways (Fig. 2) (17). The NMDA-type glutamate receptor has been shown to be important in hippocampal LTP because of its role as a coincidence detector that opens its channel when pre- and postsynaptic neurons fire together (18). The large amount of calcium entering through its channel activates CaMKII *via* phosphorylation, which in turn phosphorylates AMPA receptors and increases their number in the postsynaptic membrane (Fig. 2) (19). A change in the number and activity of AMPA receptors in synapses is thought to be an important mechanism for up- or down-regulating synaptic function in LTP or LTD (19, 20). CaMKII is required for LTP in the hippocampus and it has been suggested that this kinase could serve as a molecular switch for local storage of memory in individual synapses (19). NMDA receptor activation can also activate the MAPK cascade by stimulating both the PKC and PKA pathways and can phosphorylate CREB directly through CaMKIV (17). Several other neurotransmitter receptors, including metabotropic glutamate, muscarinic cholinergic, serotonin, dopamine, and β-adrenergic receptors are coupled to MAPK activation through PKA or PKC (Fig. 2) (17). Linkages between these receptor pathways and the MAPK cascade and transcriptional activation may be responsible for effects of commonly prescribed drugs on cognition. For example, anticholinergic or glutamate blocking drugs can impair memory, whereas stimulants or antidepressants that enhance effects of serotonin, dopamine, or norepinephrine can enhance cognition (21). Growth factors such as BDNF and nerve growth factor, acting through receptor tyrosine kinase receptors, also stimulate synaptic plasticity through several mechanisms, including activation of the MAPK cascade (22, 23). Recently, Kovalchuk *et al.* (24) showed that BDNF facilitates LTP in the dentate gyrus of the hippocampus by activating sodium channels on dendrites, enhancing dendritic depolarization and the amount of calcium fluxed through NMDA channels. BDNF has also been shown to stimulate local synaptic synthesis of mRNA and protein for CaMKII (19, 25).

GENETICALLY ALTERED MEMORY PATHWAYS IN ANIMALS

Early attempts by the behavioral biologist Seymour Benzer to identify genetic mutations in memory pathways in fruit flies (drosophila) are described in the book *Time, Love, Memory* (26). Benzer and his students established a learning paradigm is which fruit flies learned to avoid an odor paired with an electrical shock delivered by a wire mesh in a closed glass tube. From more than 500 mutants they identified one that was normal except for its inability to learn in this paradigm. This particular strain, named *dunce,* is caused by a mutation at the end of the X chromosome and codes for a defective form of cAMP phosphodiesterase, altering the same pathway studied in

the snail experiments. A number of other fruit fly mutants, including those with names like *amnesiac, turnip,* and *rutabaga,* have been studied. Some, like *rutabaga*, learn normally but forget easily. Yin and Tully (27) showed that transgenic fruit flies expressing a repressor isoform of CREB have defective long-term memory whereas those with enhanced expression of an activator isoform exhibit the fly equivalent of a "photographic memory." Similar approaches have been used in mice. Inactivation of PKA activity or enhanced activity of the endogenous calcium-sensitive phosphatase calcineurin impairs memory and LTP in transgenic mice (1). Mice with targeted mutations in CREB or infused with antisense oligonucleotides that sequester CREB have diminished long-term but not short-term memory (28, 29). Memory is also impaired in mutants in which CaMKII or CaMKIV is abnormal (30, 31). Impaired learning and LTP have also been found in mice lacking NMDA receptor subunits or metabotropic glutamate receptor type 5 (32, 33). In contrast, overexpression of the NMDA receptor subunit 2B in transgenic mice enhances learning and memory (34). These examples suggest that similar biochemical pathways link synaptic receptors with activation of gene transcription during storage of long-term memory in flies, snails, and mice.

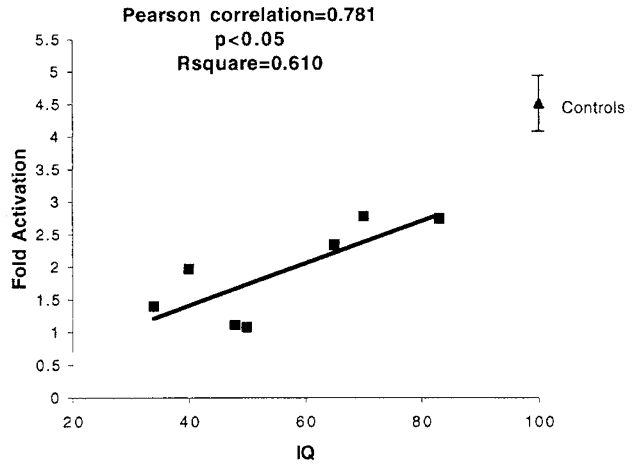

Figure 3. Intelligence is correlated with maximal activation of RSK2 to phosphorylate CREB in lymphoblast cultures from seven patients with CLS. RSK2 was immunoprecipitated from lymphoblasts after stimulation with the PKC agonist phorbol ester. Phosphorylation of CREBtide, a nine-amino acid synthetic peptide containing the amino acid 133 target phosphorylation site, was measured using a radiometric assay. Ordinate shows maximal stimulation of CREBtide phosphorylation over baseline in each patient compared with normal controls at the *upper right*. (Reprinted with permission from Ref. 38).

DEFECTIVE CREB PHORPHORYLATION IN CLS

CLS is an X-linked neurodevelopmental disorder characterized by variable mental retardation and facial, soft tissue, and bony abnormalities (35). The somatic abnormalities include frontal bossing, hypertelorism, down-slanting palpebral fissures, thickened lips, and broad nasal septum. Patients with CLS have mutations at Xp22.2, the short arm of chromosome 22.2, in the gene coding for RSK2 (ribosomal S6 kinase-2), a protein kinase that activates CREB through phosphorylation at serine 133 (36). RSK2 itself is activated through phosphorylation by several membrane receptor-coupled signaling cascades, including the adenylate cyclase, Ras-MAPK, PKC, and CaMKII pathways (Fig. 2) (23). De Cesare *et al.* (37) reported that CREB phosphorylation was markedly reduced when fibroblasts from a CLS patient with nonfunctional RSK2 activity were stimulated with the epidermal growth factor, which activates the Ras-MAPK pathway *via* its receptor tyrosine kinase receptor. We confirmed this result and found that CREB phosphorylation by the PKC agonist phorbol ester was also defective in CLS whereas CREB phosphorylation *via* adenylate cyclase and PKA was preserved. In lymphoblasts from seven patients with CLS, five boys and two girls, phosphorylation of the CREB-like peptide CREBtide was variably impaired in response to phorbol ester stimulation (Fig. 3) (38). Interestingly, there was a linear correlation between the capacity for phorbol ester to stimulate CREBtide phosphorylation over baseline and intelligence in these patients. This correlation provides additional evidence in humans that RSK2-mediated CREB phosphorylation stimulated by the Ras-MAPK cascade is involved in cognitive development as it is in lower organisms. It is noteworthy that another X-linked mental retardation syndrome has also been reported to result from mutations in RSK4, a homolog of RSK2 (39).

SEVERE COGNITIVE IMPAIRMENT CAUSED BY MUTATIONS IN TRANSCRIPTION FACTORS

Several severe cognitive disorders are associated with mutations in genes coding for transcription factors (Table 1). Although mutations have not been reported in CREB itself, point mutations in the gene for the related transcriptional co-activator CBP on chromosome 16 cause the Rubinstein-Taybi syndrome, characterized by mental retardation, broad thumbs and toes, dysmorphic facial features, and growth retardation (40). It is interesting that nuclear depletion of CBP resulting from sequestration with polyglutamine-containing aggregates of the Huntington disease protein has been implicated in the neurodegenerative features of the disease (41). In a fruit fly model of Huntington disease, neurodegeneration can be arrested by histone deacetylase inhibitors, presumably by counteracting the loss of histone acetylase activity present in CBP (42). When occupied by its hormone, nuclear thyroid receptor binds to steroid receptor co-activators and CBP to promote transcription (43). When not occupied by hormone, the thyroid receptor is a transcriptional co-repressor, probably

Table 1. *Cognitive disorders with defects in signaling pathways or transcription factors*

Coffin-Lowry syndrome
Rubinstein-Taybi syndrome
Neurofibromatosis I
Tuberous sclerosis 2
X-linked α-thalassemia
Other X-linked mental retardation syndromes
Faciogenital dysplasia
Rett syndrome
Huntington disease
Lead poisoning
Cretinism

explaining the severe retardation seen in cretinism. Mutations in the thyroid receptor have been associated with mild mental retardation, learning disability, and hyperactivity (44). In contrast, enhanced transcription at a critical period in postnatal development is probably responsible for the severe X-linked disorder Rett syndrome caused by mutations in the transcriptional repressor methyl-CpG binding protein 2 (45). Girls with Rett syndrome present with behavioral regression and acquired microcephaly in infancy as well as seizures, a characteristic hand-wringing movement disorder, and autonomic disturbances. Since the identification of the gene, mutations in methyl-CpG binding protein 2 have been found in a broader range of phenotypes, especially in boys, where it can present as mental retardation (46). X-linked mental retardation associated with α-thalassemia (ATR-X syndrome) is caused by mutations in the XH2 protein, which has helicase activity to allow DNA to unwind to permit transcription (10, 47). Mutations are clustered in a zinc-finger-like motif and patients usually have genital abnormalities, dysmorphic features, short stature, and skeletal abnormalities as well as mental retardation. Mutations in transcription factors are associated with severe neurodevelopmental and somatic disabilities, probably because the defect in transcriptional activation is difficult to circumvent. Dysregulation of transcription factors may also play a role in some cognitive disorders. Bahn *et al.* (48) reported that genes regulated by the neuron-restrictive silencer factor were repressed in neuronal precursor cells derived from the cortex of a fetus with Down's syndrome.

COGNITIVE DISORDERS CAUSED BY DEFECTS IN UPSTREAM SIGNALING PATHWAYS

Several human cognitive disorders are associated with mutations in upstream intracellular signaling pathways that link the synapse with the nuclear transcription machinery (Fig. 2). NF1, caused by mutations in the neurofibromin protein, is one of the most common genetic disorders that causes learning deficits (49). Neurofibromin has several functions, serving as a GAP protein as well as modulating adenylate cyclase and microtubule binding activity (50). GAP proteins normally act to convert Ras from the active GTP-bound form to the inactive guanosine diphosphate–bound form, so that mutations would be expected to increase the activity of Ras and the downstream MAPK signaling pathway. This is consistent with the report that learning deficits can be rescued in a mouse model of NF1 by genetic and pharmacologic manipulations that decrease Ras function (50). In this model, enhanced Ras activity is associated with enhanced γ-aminobutyric acid-mediated inhibition and deficits in LTP. Similar deficits may be responsible for learning deficits in tuberous sclerosis 2, resulting from mutations in tuberin, another GAP protein (51), and for X-linked mental retardation with seizures and ataxia resulting from mutations in oligophrenin-1, a rho GAP protein (52). The Aarskog or faciogenital dysplasia syndrome and nonsyndromic mental retardation resulting from mutations in p21-activated kinase 3 (PAK3) are also due to disorders in pathways related to Ras activation (53). A similar mechanism may contribute to cognitive impairment in children exposed to environmental lead, inasmuch as this toxin can activate PKC, which in turn can enhance Ras activity (54, 55). It seems probable that additional cognitive disorders in children will be linked to defects in these pathways.

CONCLUSION

Long-term memory storage requires signaling from synapses to the nucleus, where transcription factors such as CREB bind to DNA and activate expression of proteins that contribute to synaptic plasticity. These molecular mechanisms for learning and memory appear to be conserved in snails, flies, and mice, making it reasonable to search for defects in the same pathways in children with mental retardation and learning disabilities. Recent reports described in this review suggest that this will be a fruitful area of research.

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