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Learning and memory

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Abstract

Memory is broadly divided into declarative and nondeclarative forms of memory. The hippocampus is required for the formation of declarative memories, while a number of other brain regions including the striatum, amygdala and nucleus accumbens are involved in the formation of nondeclarative memories. The formation of all memories require morphological changes of synapses: new ones must be formed or old ones strengthened. These changes are thought to reflect the underlying cellular basis for persistent memories. Considerable advances have occurred over the last decade in our understanding of the molecular bases of how these memories are formed. A key regulator of synaptic plasticity is a signaling pathway that includes the mitogen activated protein (MAP) kinase. As this pathway is required for normal memory and learning, it is not surprising that mutations in members of this pathway lead to disruptions in learning. Neurofibromatosis, Coffin-Lowry syndrome and Rubinstein-Taybi syndrome are three examples of developmental disorders that have mutations in key components of the MAP kinase signaling pathway.

The ability to learn something new and then to store the information in long-term memories is part of normal development. As clinicians, we are often asked to evaluate whether a child is developing appropriately. Are particular skills emerging at the appropriate times or are they delayed? For example, important landmarks include the ability to read and interact appropriately with childhood peers. The mechanisms by which children learn to sit and crawl, walk and talk, and develop social skills have been the intensive focus of psychologists and psychiatrist over the years. Several theories that deal with these issues at a systems level have been put forward, including theories from psychoanalytic, cognitive, and learning perspectives.

It is only in the past few decades that investigators have begun to study these questions at the molecular level.[1] What has emerged is a fascinating story of how cells within the central nervous system communicate with each other during learning, and how neurons that are ultimately responsible for facilitating learning and memory accomplish this task.

It is equally interesting to learn how disruptions to these normal processes contribute to developmental disorders. Genes required for normal learning might be expected to lead to specific developmental disabilities when they are mutated. This brief review summarizes the major emerging concepts in the field of developmental disorders. First we discuss different forms of memory. Then we review some of the molecular events within neurons that are required for the formation of such memories. We use three examples to show how disrupting the normal sequence of molecular events leads to specific cognitive disorders. Finally, we discuss directions for future research. Space limitations require that this field be summarized broadly without complete citations on all subjects. Interested readers are encouraged to pursue the additional reading materials listed at the end.

Two central concepts have emerged from recent research in the area of learning and memory.[1] The first pertains to the question, discussed for many decades, of whether specific brain regions participate in specific forms of learning. An earlier view, postulating that the nervous system works en masse to achieve learning and memory, dictated that cortical lesions would produce cognitive deficits that would increase in severity with the size of the lesion. Today, however, it seems clear that specific kinds of tasks are learned within specific brain regions. This view emerged from the study of individuals with very discrete brain lesions accompanied by very distinct memory deficits, work that has been confirmed in experimental animals. Early studies concentrated on the role of the hippocampus for learning and memory. Hippocampal lesions prevent new memories of a particular sort, the type of memory we use to learn new facts or new events. Surprisingly, other types of memories remained intact.

This led researchers to postulate two broad forms of memory, declarative and nondeclarative. Declarative memories are those that we can talk about, such as last night's dinner, or the date of an historic event. Such memories involve conscious thought. We know that the hippocampus is required for the acquisition of these types of memories because lesions in this region prevent individuals from laying down new declarative memories. It is possible, however, to retrieve older declarative memories that were stored before the lesion occurred.

Nondeclarative memories are usually procedural or associative in nature and are often acquired unconsciously. For example, learning to ride a bicycle or playing a musical instrument is a procedural knowledge that depends on the learning of specific motor skills and typically require multiple repetitions. However, there are also aspects of declarative memories imbedded in these examples. You might remember the first bicycle you owned or the color of your music teacher's hair. Those types of declarative memories are processed through the hippocampus. On the other hand, how you learn the skill by which your fingers fly over the piano keys requires activation of the basal ganglia and associated circuitry. Thus, damage to these nuclei impairs procedural learning. Individuals with early stage Parkinson's disease or Huntington's chorea have specific deficits in their ability to learn procedural skills that are not explained by the loss of their motor coordination.

Another form of nondeclarative memory is particularly relevant to clinicians. If you are walking in the woods and hear a rattling sound, you may freeze or take defensive actions against what you think is a snake. This type of learning is particularly important for survival, as it involves the fight or flight response. This type of learning, which is sometimes called emotional or associative learning, requires an intact amygdala. Current theories regarding the amygdala and learned fears suggest that this brain region is involved in several psychiatric disorders, including panic attacks, phobias, anxiety disorders, and post-traumatic stress disorder.

The amygdala is often spoken of in the context of learning fearful or other negative emotional responses, but it also participates in processing memories related to positive emotions. For example, the amygdala is activated when children learn to respond to their mother's face and when learning social skills. Amygdala disruption and the consequences for this type of learning have recently been implicated in the development of autism, and may help explain the severe disruption of social relatedness observed in these children.

The second central concept to emerge from research on learning and memory is that the formation of long-term memories requires structural and other functional modifications to neurons. A series of critical findings has shown that learning requires morphological changes at specialized points of neuronal contact termed synapses. Synapses change as learning proceeds—new synapses are formed and old ones are strengthened. This phenomenon, termed synaptic plasticity, is seen in all parts of the brain.

Electrical signals called action potentials travel down the neuron's axonal process to reach the synapse. When it arrives at the end of the axon, called the presynaptic terminal, microscopic packages, called vesicles, break open and release one or another of the various neurotransmitters used within the CNS into the synaptic cleft, the space between two neuronal processes. The transmitters diffuse across the narrow synaptic cleft and bind to specific receptors on the opposite side, the postsynaptic site. Neurons communicate within each other in this way, and how this signal is next processed may result in long-lasting synaptic changes, resulting in experience-induced synaptic plasticity.

A series of intracellular events are necessary for the structural modifications to the synapse required for learning.[2] An overview of what happens is useful before we turn to some of the details of the molecular events initiated by the incoming signal. When signals arrive at the postsynaptic site, the release of neurotransmitter, or sometimes growth factor, activates intracellular signaling pathways in the postsynaptic cell that ultimately result in the production of new proteins used for synaptic modifications. A tremendous amount of research has been devoted to understanding this process over the last decade. We now know some of the critical proteins in the pathway from the surface of the postsynaptic neuron where the signal arrives to the nucleus of the postsynaptic cell, where genes are activated to produce the proteins needed for synaptic modification.

A key player in these events is a signal transduction pathway known as the MAP kinase pathway.[3-4] Mitogen-activated protein kinases (MAPK) are important signaling proteins activated by neurotransmitters and various growth factors. One member of this family is the extracellular-signal regulated kinase (ERK). The ERK cascade is used in all brain regions where synaptic plasticity occurs, and its activation is required for the formation of new memories.[5] If you block the activity of the ERKs by injecting an inhibitor into a brain region, such as the amygdala, you block the

formation of all forms of learning associated with that structure. Similarly, if you block ERK activity within the hippocampus, you prevent the formation of of hippocampal forms of declarative memories.

ERKs are members of a family of enzymes called kinases. Kinases add a phosphate group to a substrate protein. The addition of a bulky negatively charged phosphate group often leads to a change in the shape of the target protein, called a conformation change, which is a prerequisite to the activation of many proteins. When an appropriate signal arrives at the synapse, a series of proteins are sequentially phosphorylated as a means of amplifying the signal. This cascade of protein activation leads to the regulation of transcription factors, a family of master control genes.[6] Transcription factors bind to regulatory sites of genes and initiate their transcription. In this way, the signal originating at the surface of the postsynaptic neuron is transferred to the nucleus, and a group of proteins is produced that leads to structural changes within that neuron. The neuron becomes more sensitive to future synaptic input of the same kind. For example, a signal that previously was unable to activate the neuron is now able to do so.

A key point in the present discussion is that a series of specific proteins are required for the activation of the ERK pathway, and that activation of this pathway leads to protein synthesis. The signal arriving at the cell surface activates a kinase that sequentially activates other kinases and eventually phosphorylates transcription factors — the final step in the events that lead to the synthesis of new proteins. It follows that disrupting any of the components of this pathway may impair the formation of structural changes within the synapse required for memory. Mutations have recently been discovered in several genes that encode proteins involved in this pathway. Individuals with these mutations develop the developmental disorders that are discussed next.

Neurofibromatosis is an autosomal dominant disease with several clinical features, including neural-derived tumors that appear throughout the body. Approximately half of the affected individuals are also mentally retarded. Interestingly, the mental retardation is not a result of brain tumors, and occurs only with certain types of mutations in the neurofibromatosis gene.

The gene that causes neurofibromatosis (*NF1*) was recently characterized and several different mutations were identified in affected patients.[7] Variability in the types of mutations (point mutations, insertions, or deletions) reflects the high level of phenotypic heterogeneity in this disorder. The portion of the gene that is mutated determines whether or not the child develops cognitive deficits, in addition to the characteristic benign tumors. In other words, the normal protein associated with this gene has several amino acid domains with specific cellular functions. The site and type of mutation affect one or another of these functions

The protein encoded by the *NF1* gene is neurofibromin. One of the amino acid domains of neurofibromin regulates the MAP kinase pathway. Mutations present in this domain result in cognitive deficits. Neurofibromin normally inactivates one of the initial proteins activated by neurotransmitters and growth factors at the cell surface. Mutations within this domain of the protein interfere with its ability to regulate the ERK pathway. The result is that the MAP kinase pathway cannot be turned off. The resulting constitutive activation of the MAP kinases disrupts the ability of this pathway to respond appropriately to incoming neuronal signals. The end result is that normal learning does not occur and individuals with this type of mutation are mentally retarded.

A mutation in a second protein in the pathway leads to Coffin-Lowry mental retardation syndrome.[8] One of the targets of MAP kinase is a downstream kinase called ribosomal S6 kinase (rsk2). Rsk2 is a protein kinase that rapidly enters the nucleus upon activation. Within the nucleus, it phosphorylates CREB, a key transcription factor. CREB activation is required to bind to target genes and induce their transcription. Mutations in the *rsk2* gene once again disrupt the normal cascade from the neuronal surface to the nucleus. As a consequence of mutations to the *rsk2* gene, normal gene transcription does not occur and proteins that are required for synaptic modifications are not produced. Normal learning is therefore impaired.

A third disorder associated with mutations in this pathway is Rubinstein-Taybi syndrome (RTS).[9] RTS individuals have a number of characteristic clinical signs including facial abnormalities, broad digits, and mental retardation. Recently, a mutation to the CREB binding protein gene (CBP) was discovered in patients with the RTS phenotype. The CBP protein is required for the normal activation of the CREB transcription factor. As a result of the mutation, CREB does not function properly and the normal complement of proteins is not produced. Once again, synaptic plasticity is disrupted and normal learning cannot occur.

In upcoming years, many laboratories will focus on discovering other mutations in the genes that encode members of the MAP kinase pathway. These are sure to exist and to contribute to the development of mental retardation disorders that today are of unknown origin. Researchers will also determine whether some of proteins that are involved in the MAP kinase pathway are expressed only within specific brain regions. Mutations in these genes might then lead to a variety of psychiatric disorders. For example, many genes are only expressed within specific brain regions and during precise developmental periods. The tissue and time-specific expression of these genes are under the control of various transcription factors. It is plausible that mutations could disrupt the timing or the amount of the proteins that regulate the MAP kinase pathway within neurons of the amygdala, for example, and that these mutations could disrupt the amygdala's ability to mediate the fear response.

The putative mutations in the MAPK pathway could also lead to the pathway being overactive. Affected individuals might then learn too easily or quickly, and associate fear with something that is not a realistic danger. This type of mutation might make some individuals vulnerable to developing panic attacks, specific phobias, or anxiety disorders. This field is changing rapidly, largely because of the use of molecular techniques, which have proven to be powerful additions to our armamentarium as we attempt to understand some of the underlying molecular causes of developmental disorders.

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