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Signaling from cAMP/PKA to MAPK and Synaptic Plasticity

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Abstract

The facilitation of hippocampus-based, long-lasting synaptic plasticity, which is frequently investigated in model systems such as long-term potentiation (LTP) and in learning paradigms such as the Morris water maze, is associated with several cellular key events: Ca^{2+} influx through the N-methyl-D-aspartate (NMDA) receptor, generation of cyclic AMP (cAMP) and activation of protein kinase A (PKA), phosphorylation of mitogen-associated protein kinase (MAPK) and cAMP-response element-binding protein (CREB), and subsequent transcription of plasticity-associated genes.

Recently, a signal-transduction cascade from cAMP/PKA to MAPK was discovered, which seems to be neuron-specific and comprises the critical events of hippocampus-based long-term plasticity described here into one single cascade. A major alternative to cAMP/PKA-MAPK signaling are the cascades from Ca^{2+} to MAPK via Ras. However, Ras is inhibited by PKA. This article reviews the studies that argue for the existence of two competing pathways, and discusses their implication for the molecular mechanisms underlying synaptic plasticity.

Index Entries: Long-term memory; hippocampus; synaptic plasticity; plasticity-associated genes; cAMP; PKA; Rap1; B-Raf; MAPK; CREB.

Introduction

The study of learning and memory is a central issue in the neurosciences. Cognitive psychology has generated several concepts and models of information storage in the human and animal brain, including short-term and long-term memory and declarative and nondeclarative memory. During the past few decades, the understanding of these mental processes has been greatly improved by advances in cellular and molecular biology. It became apparent that the storage and retrieval of information encoded in the nervous system are accompanied by cellular and morphological alterations in the participating neurons *(1)*. The more the information is engraved into the

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brain for long-term storage, the more this process appears to depend on the transcription and translation of a subset of genes, often referred to as plasticity-associated genes *(2).* Since the hippocampus seems to have a "bottleneck" position in the transformation of short-term information storage into long-lasting memory, this region of the brain has been intensely studied to reveal the molecular and cellular mechanisms underlying synaptic plasticity. A related or overlapping machinery may also be active in neocortical regions. When the information has been presented, there are several time windows during which transcriptional and translational activity are essential for the perceived event to be transformed into long-term memory. The first of these time windows is also the most extensively studied one; it consists of the first hours immediately after perception of the information. Within these first hours, a series of activity-regulated genes, which are referred to as *immediate early genes* because of their rapid upregulation, are transcriptionally upregulated in hippocampal neurons. Because of their suspected function, some of them are also believed to play a role in the modulation of synaptic plasticity. The signal-to-transcriptional activation of these plasticity-associated genes is transduced by several protein kinase cascades. This article focuses on a recently discovered part of these cascades.

Ca^{2+} Influx Through the NMDA Receptor, Activation of cAMP and PKA, and Phosphorylation of CREB and MAPK

The electrophysiological paradigm of hippocampal long-term potentiation (LTP) *(3,4)* and the water maze navigation task developed by Morris *(5)* are well-established experimental models of long-lasting plasticity in the hippocampus. Both paradigms are associated with long-lasting changes in synaptic strength. It is widely assumed that the mechanisms analyzed in these models contribute to long-term memory. One focus of the molecular approach was to identify cellular events that are essential components of the processes underlying these paradigms. The hallmark of LTP is the influx of extracellular calcium into the postsynaptic neuron, induced by glutamate-mediated activation of the N-methyl-D-aspartate (NMDA) receptor *(6).* Both LTP and the Morris water maze task are impaired when signaling through the NMDA receptor is antagonized *(7).* The late phase of LTP (L-LTP), which demands repetitive tetanic stimulation and persists for more than 24 h, can be initiated by cyclic adenosine monophosphate (cAMP), requires activation of protein kinase A (PKA) and depends on gene transcription *(8–10).* Similarly, PKA is required for spatial long-term memory in the Morris water maze *(8).* The transcription factor cAMP-responsive element-binding protein (CREB), which can be phosphorylated by PKA, appears to be essential for long-term plasticity in invertebrates *(11–14),* and was therefore proposed to act as a switch to plasticity-associated transcriptional activation. In mice that lacked the α and δ isoforms of CREB, LTP and spatial navigation skills were impaired *(15),* which was reproducible in some but not in all CREB mutants *(16).* These findings may suggest that additional transcription factors contribute to the induction of plasticity-associated genes in vertebrates. Recent studies have shown that phosphorylation of the 44-kDa and 42-kDa fractions of the mitogen-activated protein kinases (p44/42-MAPK, also known as extracellular regulated kinases 1/2, in the following called MAPK) is a critical event in the induction of LTP *(17,18),* in contextual fear-conditioning *(19),* and during water maze learning *(20–22).*

Signal-Transduction Cascades and the Induction of Plasticity Genes

If one views these findings as key events of the molecular machinery required for long-term plasticity in the postsynaptic neuron, two

questions may arise: first, are these events connected to each other, and if they are, in which way? Second, what are the downstream effects when this machinery is activated? In parallel with the discovery of cellular key events of synaptic plasticity, much was learned about the signal-transduction cascades that are induced in the postsynaptic neuron after the induction of neuronal plasticity. The cellular key events described here are part of these pathways. Fig. 1 provides an overview of some of these cascades. Interestingly, these signaling pathways show some overlap with proto-oncogene cascades *(23).* This could reflect an evolutionary development in which the cellular machinery mediating cell-cycle progression and the growth of neuroectodermal cells, which itself is genetically of partial retroviral origin, is used by post-mitotic neurons for synaptic plasticity and misused by neuroectodermal tumors for proliferation and invasion. The transcription factor c-fos was one of the first discovered, and thus well-characterized, plasticity-associated genes. However, c-fos expression is usually more closely associated with cellular survival than synaptic plasticity. The transcription factor zif268 (also known as krox-24, egr-1, or NGFI-A) and the "effector" genes arg3.1/arc (also known as arc or arg3.1) and homer1a are important plasticity-associated genes that are also immediate early genes. The induction of these plasticity-associated genes depends on the same cellular key events that modulate long-lasting synaptic plasticity (Table 1). Moreover, a targeted deletion of some of these genes has been shown to alter LTP and water maze skills. Therefore, the induction of plasticity-associated genes seems to be a major target for the signaling cascades that are dependent on NMDA-receptor activation.

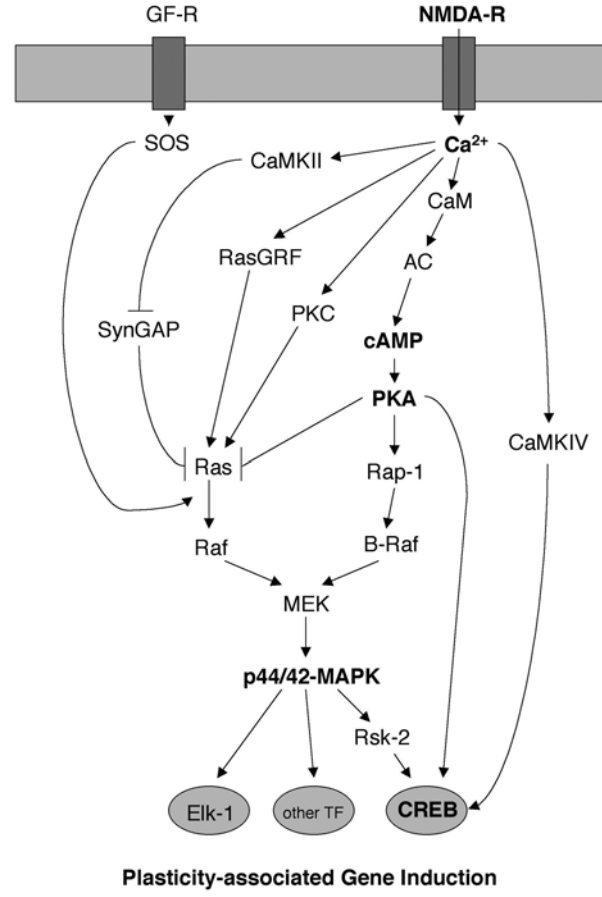

Fig. 1. Signaling pathways activated by calcium influx through the NMDA receptor (NMDA-R) to the transcriptional activation of plasticity-associated genes. Detailed description of the cascades is provided in the text. Molecular key events during facilitation of synaptic plasticity are highlighted. Note that Ras is also phosphorylated by the growth factor receptor (GF-R) pathway via SOS. Unidentified transcription factors (other TF) in addition to Elk-1 and CREB are believed to contribute to MAPK-regulated transcription of plasticity-associated genes.

Signaling from cAMP/PKA to MAPK

Assuming that calcium influx in response to NMDA-receptor activation results in MAPK or CREB phosphorylation, the following major pathways are possible, on the basis of current knowledge of these cascades: i) Ca^{2+}-cAMP/PKA-CREB, ii) Ca^{2+}-CaMKIV-CREB, iii) Ca^{2+}-Ras-MAPK (-CREB), and iv) Ca^{2+}-cAMP/PKA-MAPK (-CREB). Only the latter pathway comprises all key events as defined here because it connects the activation of cAMP/PKA with the phosphorylation of MAPK. Thus, it is likely that this pathway is of

Table 1
Selected Characteristics of Plasticity-Associated Genes

	C-FOS	ZIF268	ARG3.1/ARC	HOMER1A
Transcriptionally activated with hippocampal LTP induction	weakly *(49,50)*	yes *(51)*	yes *(50,52,53)*	yes *(54)*
Transcriptionally activated with generalized convulsions	yes *(55)*	yes *(56)*	yes *(52,53)*	yes *(57)*
Transcriptional activation dependent on PKA	partially *(50,58)*	yes *(58)*	yes *(50)*	
Transcriptional activation dependent on MAPK	partially *(50)*	yes *(59)*	yes *(50)*	yes *(60)*
Altered LTP in mice with targeted deletion		L-LTP reduced *(61)*	LTP severely aberrant *(62)*	
Impaired water maze skills in mice with targeted deletion		yes *(61)*		

great importance for signal transmission during the induction of synaptic plasticity. A signaling pathway from cAMP/PKA to MAPK was described by Stork and colleagues in PC12 phaeochromocytoma cells *(24).* Cyclic AMP stimulates guanosine 5′ triphosphate (GTP) loading of the small G-protein Rap1. PKA, which is ubiquitously phosphorylated by cAMP, induces the association of Rap1 and the Raf homolog, B-Raf. Rap1 activates B-Raf, which in turn phosphorylates MAPK/ERK kinase (MEK). MEK phosphorylates MAPK. MAPK activates both transcription factors Elk-1 *(24)* and CREB *(25).* This pathway is functionally active in PC12 cells, but not in COS-7 immortalized kidney cells, which lack appropriate levels of B-Raf. COS-7 cells that were transfected with B-Raf acquired a functional cAMP/PKA-MAPK pathway *(24).* This pathway is also active in cultured hippocampal neurons *(26).*

Roles for Rap1 and B-Raf in Synaptic Plasticity

Although the cAMP/PKA-MAPK connection was shown for PC12 cells and hippocampal neurons in vitro, it has not been proven active in the brain in vivo. Provided that the link from cAMP/PKA to MAPK can be activated—especially in regions such as the cortex or hippocampus—both Rap1 and B-Raf should be important mediators of the signaling process that promotes long-term plasticity.

Both Rap1 and B-Raf were first described in the context of oncogenic signal transduction. They are members of the superfamilies of Ras- and Raf-related proteins. Rap1 is expressed in many tissues, including all major parts of the nervous system *(27).* It has been localized to the Golgi apparatus *(28),* unlike Ras, which is associated with the cell membrane. B-Raf is abundantly expressed in the brain. In brain sections, the highest immunoreactivity of B-Raf is seen in the hippocampus *(29,30).* Moreover, B-Raf expression is specifically upregulated during LTP *(31).*

For both Rap1 and B-Raf, mutation studies in mice focused on the characterization of the synaptic plasticity phenotype are in progress. A transgenic mouse that expresses a dominant-negative form of Rap1 in the forebrain is currently being studied by Kandel and colleagues *(32,33).* In these mice, B-Raf activity was decreased, whereas Raf activity is increased. In hippocampal slices, MAPK phosphorylation in response to cAMP was reduced. The mice exhibited normal LTP when multiple 100-Hz trains were delivered, but displayed a reduc-

tion of LTP when theta frequency (5 Hz) or forskolin were used. Moreover, Rap1-mutant mice showed impaired spatial learning in the water maze and deficits in social recognition.

Silva and colleagues reported preliminary findings in B-Raf knockout mice *(34,35).* Homozygous B-Raf deletion was embryonically lethal. Heterozygous knockouts showed impaired performance in the Morris water maze, contextual conditioning, and social recognition. Like Rap1 knockouts, the B-Raf mutation presented with normal LTP at 100-Hz tetanic stimulation; however, theta bursts revealed a LTP impairment. The basal MAPK phosphorylation was reduced in the hippocampi of knockout animals.

These data indicate that both Rap1 and B-Raf play a critical role in hippocampus-based long-term plasticity.

Alternative Signaling: Ras-MAPK and cAMP/PKA-CREB

If cAMP/PKA is not the mediator of signal tranduction from Ca^{2+} to MAPK, Ras seems to be the major alternative pathway. Ras activates the MEK/MAPK cascade via Raf, and, via several parallel pathways, Ca^{2+} influx through the NMDA receptor results in Ras phosphorylation. RasGRF is one such signal transducer from Ca^{2+} influx to Ras activation. Mice that carry a homozygous knockout deletion of RasGRF showed no difference to wild-type mice in the Morris water maze and in hippocampal LTP. However, amygdala-based fear conditioning and theta-burst LTP in the amygdala revealed a significant impairment in the affected mice *(36).* Other signal mediators from Ca^{2+} influx to Ras have been implicated in learning and memory: PKC *(37–40)* and CaMKII, which inhibits SynGAP, a negative regulator of Ras *(40–43).* The significance of Ras in synaptic plasticity is further supported by studies of knockout mice that mimic the neurofibromatosis (NF1) mutation, an inactivation of the RasGAP (Ras GTPase-activating protein) gene *neurofibromin,* which is a negative regulator of Ras because of GAP function. Human NF1 is an inherited disorder associated with mental retardation. NF1-knockout mice show impaired performance in the Morris water maze. This phenotype is dependent on the RasGAP function of *neurofibromin (44,45).* If the pathway from Ca^{2+} influx to MAPK phosphorylation essentially depends on Ras signaling, what is the function of cAMP/PKA activation by Ca^{2+}? Several years ago, activation of the transcription factor CREB, which is believed to play a major role in the transcription of plasticity-associated genes, was linked to the direct phosphorylation by PKA. However, more recent studies found that CREB phosphorylation in the hippocampus is mainly caused by either MAPK or CaMKIV *(46–48).*

What is the Biological Significance of Two Competing Pathways: Ras-MAPK and Rap1-MAPK?

Current evidence suggests that signaling from Ca^{2+} to MAPK is mediated by two major pathways: one via Ras with no involvement of cAMP/PKA, and the other via Rap1 with participation of cAMP/PKA. Since cAMP/PKA effectively inhibits the Ras-MAPK pathway, it does not seem likely that both cascades are physiologically activated at the same time and at the same place.

The present concepts on cAMP/PKA-MAPK and Ras-MAPK signaling are largely based on cell–culture experiments that allow little insight regarding a hypothetic spatiotemporal dissociation. Although such studies are difficult to develop in vivo, they are ultimately essential for an understanding of the signaling cascades that determine plasticity-associated gene expression. Several experimental findings—for example, the phosphorylation of MAPK during Morris water maze training that occurred specifically in the dorsal CA1/CA2 subregion of the hippocampus *(21)*—suggest a spatial distribution of these pathways that has not yet been investigated systematically.

Study of the effect of both pathways—either by overregulation or by inhibition—on kinetics and anatomical expression patterns of plasticity-associated genes should therefore provide important insight into the molecular mechanisms of learning and memory.

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