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Cellular and Molecular Life Sciences

Memory: Cellular and molecular networks

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Abstract. Our understanding of the cellular and molecular mechanisms underlying learning and memory formation derives from studies of species as diverse as worms, mollusks, insects, birds and mammals. Despite the quite different brain structures and neuronal networks, the studies support the current notion that neuronal activity leads to changes in synaptic connections as the neural substrate of behavioral plasticity. The analysis of the mechanisms underlying learning and memory formation reveals a surprisingly high conservation between invertebrates and mammals, both at the behavioral as well as the molecular level. This special issue provides an overview of the current knowledge on cellular and molecular processes underlying memory formation. The contributing reviews summarize the findings in different organisms, such as *Aplysia*, *Drosophila*, honeybees and mammals, and discuss new approaches, developments and hypotheses all aimed at understanding how the nervous system acquires, stores and retrieves information.

Keywords. Learning, memory, brain, signaling cascades.

One of the most remarkable aspects of nature is the ability of animals to modify their behavior by learning. In both invertebrates and vertebrates memory formation after initial learning is a very complex and highly dynamic process that can be divided into at least two different phases: short-term memory (STM) and long-term memory (LTM). The initially labile STM, which exists in the range of minutes, is transformed into stable LTM, which can last for a lifetime. This transformation into LTM is called consolidation and requires messenger RNA (mRNA) and protein synthesis [1]. Studies of various systems, including mollusks, insects and mammals, support the notion that the neural substrate of both STM and LTM resides in the synaptic connections between neurons, as already proposed by Cajal [2]. A major breakthrough was the finding that in *Aplysia*, *Drosophila*, rodents and many other species induction of long-lasting neuronal changes or LTM require cyclic AMP-dependent processes [3]. Meanwhile, it is clear, that many other signaling cascades have equally important functions in different aspects of learning and memory formation. Again, the basic functions are highly conserved throughout the animal kingdom.

This multi-author review represents an overview of our current knowledge of memory formation, with a focus on molecular and cellular aspects. The first two articles summarize contributions from *Aplysia* and *Drosophila*, both pioneer systems used to uncover cellular and molecular principles of neuronal plasticity and memory formation. In their article on recent investigations of *Aplysia*, Reissner, Shobe and Carew focus on the identification of molecules which act as central ‘molecular nodes’ in synaptic plasticity and learning. Due to the increasing number of molecular processes implicated in learning, this issue is becoming more and more important. The demonstrated application of nodal analysis to a well-investigated signaling pathway implicated in learning and memory elegantly demonstrates the potential to unravel complex molecular networks and to extract the essentials. The contributions derived from studies in *Aplysia* perfectly complement that from *Drosophila*, where genetic approaches have been successfully used to dissect the processes underlying learning and memory formation [4]. The review by Skoulakis and Grammenoudi provides a thorough overview on the impact *Drosophila* has made on our understanding of learning and memory. A very recent development, the use of *Drosophila's* sophisticated repertoire of molecular techniques to explore the molecular basis of human cognitive disorders, is also addressed in this article.

Processes of memory formation are highly dynamic, and the action of the underlying molecular pathways cover time windows in the range of seconds to even a lifetime of the organism. Especially the identification of fast actions of signaling cascades and the characterization of their function in memory formation has proved technically to be a challenging problem. The review by Schwärzel and Müller focuses explicitly on temporal aspects of memory formation and summarizes results from honeybee and *Drosophila*, two organisms ideally suited for studying transient molecular events underlying dynamic memory processing *in vivo*.

In contrast to these fast and transient modulations in the nervous system, the review by Alberini, Milekic and Tronel addresses a phenomenon that occurs at the other end of the time scale, namely the stabilization and destabilization of LTMs [5]. The recent observation that stable LTM becomes labile after recall and requires another stabilization process, called reconsolidation, for its maintenance has triggered many discussions in the field. The review provides an overview of this phenomenon, observed in invertebrates and vertebrates, and discusses its implications for stability and loss of LTM in general.

Even though the properties of observed LTM are quite well described, the question of which molecular substrates are responsible for the maintenance of long-lasting neuronal changes in neurons that may endure for a lifetime is still unsolved. Inspired by initial evidence that evolutionarily conserved processes regulating gene expression by changing chromatin structure are implicated in neuronal plasticity, Levenson and Sweatt summarize the recent findings supporting this intriguing new idea. The authors discuss the idea that epigenetic mechanisms, which act as cellular memory in development and cell determination, are used again for storing memory by modifying the DNA-chromatin structure itself.

Although far from complete, this series of reviews provides an overview on the cellular and molecular features of memory formation. Highlighting contributions of different model systems, it becomes apparent that the basic molecular requirements of distinct aspects of memory formation are highly conserved among different species. In addition to key discoveries, recent approaches, ideas and hypotheses are addressed that reflect some current developments in the search for the basic principles of learning and memory formation.

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