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Review

Multiple cellular cascades participate in long-term potentiation and in hippocampus-dependent learning

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ABSTRACT

Since its discovery by Bliss and Lomo, the phenomenon of long-term potentiation (LTP) has been extensively studied, as it was viewed as a potential cellular mechanism of learning and memory. Over the years, many signaling cascades have been implicated in its induction, consolidation and maintenance, raising questions regarding its real significance. Here, we review several of the most commonly studie signaling cascades and discuss how they converge on a common set of mechanisms likely to be involved in the maintenance of LTP. We further argue that the existence of cross-talks between these different signaling cascades can not only account for several discrepancies in the literature, but also account for the existence of different forms of LTP, which can be engaged by different types of stimulus parameters under different experimental conditions. Finally, we discuss how the understanding of the diversity of LTP mechanisms can help us understand the diversity of the types of learning and memory.

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Contents

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1. Introduction

The discovery of the phenomenon of long-term potentiation by Bliss and Lomo in 1973 (Bliss and Lomo, 1973) launched an avalanche of studies directed at relating changes in synaptic efficacy resulting from various patterns of electrical activity in various neuronal networks to various forms of learning and memory. Fundamental to this search were the assumptions that (i) learning episodes trigger certain patterns of neuronal activity in various locations within the brain, resulting in long-lasting modifications of synaptic contacts, and (ii) the distribution of the modified synapses forms an internal representation of the memory of the events responsible for the initial neuronal activity. Recall of the memory would then consist in the reactivation of these modified synapses and networks. As usual in science, this search has led to numerous findings, opened numerous paths – some of them turning out to be dead-ends, generated countless debates, resulted in one Nobel prize, but has yet to provide a comprehensive theory of learning and memory. As has been repeatedly mentioned, a major difficulty to integrate all the findings is due in part to the use of different experimental protocols by the majority of research laboratories working on this topic, and the apparent lack of reproducibility of experimental data resulting from these differences.

In the original report from Bliss and Lomo, a brief train of high frequency stimulation (100 Hz, 1 s) to the perforant path resulted in a long-lasting increase in synaptic responses elicited in the dentate gyrus granule cells (Bliss and Lomo, 1973). This finding was rapidly extended to other monosynaptic glutamatergic synapses throughout the hippocampus, and it became apparent that this phenomenon could represent a cellular mechanism for some forms of learning and memory (Lynch and Granger, 1992; Barnes, 1995; Maren and Baudry, 1995; Stevens, 1998; Lynch, 2004; Sacktor, 2008). This idea was further strengthened by the discovery that theta-burst stimulation (TBS) (trains of brief bursts of stimulation delivered at theta frequency, 5–7 Hz) also produced LTP (Larson and Lynch, 1986, also see Larson, this Issue), since the electroencephalogram theta rhythm is associated with exploration of new environment and is used to synchronize activity of networks in different brain regions (Winson, 1978). Since then, HFS and TBS have been widely used by numerous laboratories to elicit LTP and to study the cellular pathways underlying LTP at the synaptic level.

Numerous molecular/cellular pathways have been shown to be involved in this process, leading some scientists to even question the biological reality of the phenomenon (Sanes and Lichtman, 1999; Lisman et al., 2003). Thus, it has been extremely difficult to reach a consensus on the details of the events critically involved in linking activation of NMDA receptors, a widely accepted mechanism required to induce LTP, to the increase in AMPA receptors and changes in dendritic spine structure, two of the most widely accepted mechanisms involved in the long lasting maintenance of LTP (Morris et al., 1986; Matsuzaki et al., 2004). Because activation of NMDA receptors leads to a brief influx of calcium in postsynaptic structures, and is critical for LTP induction by both HFS and TBS, the search for intracellular cascades has focused on calcium-dependent enzymes, which could trigger changes in structure and function of dendritic spines. Calmodulin-dependent Protein Kinase II (CamKII) was thus found to be activated and to play a critical role in LTP induced by either HFS or TBS, and it is generally thought that it serves to both transiently phosphorylate and enhance the function of AMPA receptors and to create new slots to insert AMPA receptors in postsynaptic densities (see Lisman and Raghavachari, this Issue). Two other major pathways involving different protein kinases, cAMP-dependent protein kinase (PKA) and extracellular regulated kinase (ERK), have also been proposed to link NMDA receptor activation and extracellular signals, including the neurotrophic factor, BDNF, to long-lasting changes in synaptic function.

More than 30 years ago, we proposed that another calcium-dependent process participated in LTP, consisting in the activation of the calcium-dependent protease calpain (Lynch and Baudry, 1984). At that time, very limited information was available regarding the properties of calpains and the nature of their substrates, which could be involved in LTP, with the exception of the cytoskeletal spectrin (Siman et al., 1984). Finally, the role of protein synthesis has been debated since the beginning of the discovery of the LTP phenomenon and there is still no general consensus regarding its role in LTP induction, consolidation and maintenance (Gold, 2008). Lynch et al. (this Issue) discuss recent findings from their laboratory, which provide a potential explanation for the wide range of experimental results obtained with protein synthesis inhibitors in LTP. We recently summarized the roles of several of the pathways mentioned above in a review dedicated to the 80th birthday of Richard Thompson (Baudry et al., 2011) (Sadly, Richard Thompson passed away during the preparation of this Special Issue of Brain Research for which he still provided a review the weeks before his death). Quite remarkably, the years since then have seen an explosion of findings regarding both the mechanisms underlying LTP and the links between the properties of LTP and those of some forms of learning and memory. What has emerged over the years is the idea that multiple intracellular cascades are activated by various patterns of electrical activity, resulting in long-lasting enhancement of synaptic transmission at glutamatergic synapses, and that different parameters of the stimulus used to induce LTP (frequency, intensity, pattern) result in the activation of different intracellular cascades. Accordingly, there are probably several forms of LTP, some of them co-existing in the same synapses and some of them occurring in different synapses and possibly brain regions. As we will discuss, the debate has now shifted into identifying the relationships between the parameters of tetanic stimulation and different forms of LTP as well as between different forms of LTP and various types of learning and memory. We will start by reviewing new findings regarding the roles of the two major calpain isoforms, calpain-1 and calpain-2, in LTP induction and consolidation, which we referred to as the calpain cascades. We will then follow by a brief review of the CaMKII cascade, as this theme is discussed extensively by John Lisman (Lisman and Raghavachari, this Issue). We will then review the role of the PKA cascade in LTP. We will then briefly discuss how all these cascades converge onto a common set of mechanisms, which thus become central