



Memory in the hippocampus

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ABSTRACT

To date, there is no clear evidence for memory formation. In this article, we provide a framework to understand how memory is formed. The information collected by sensory organs is converted to a digital current that enters the presynaptic neuron through axonal conductance. Digital waves are converted to analog waves in the synapses.

The analog current of information flows into the postsynapse. The degree of Ca^{2+} influx in the postsynapse is proportional to the voltage of each wave of analog current. The activation (via dephosphorylation) of the phosphorylated phosphatase, Slingshot, is regulated by Ca^{2+} concentration in the spine. After dephosphorylation by Slingshot, activated cofilin binds the parallel actin bundle. The wide helical twist angle of an actin filament that has been decorated with cofilin confers high electric potential to the filament. Phosphorylation results in the deactivation of the actin filament bound to cofilin, which in turn results in the cleavage of cofilin and actin filament, followed by a decrease in the twist angle of the actin filament. Next, the electric potential energy is discharged by the actin filament as it returns to its non-cofilin bound state, resulting in the formation of additional analog waves in the postsynapse.

Introduction

The transcellular shift of Ca^{2+} to the presynapse as part of the digital current signal causes the release of glutamate from vesicles in the presynapses. Glutamate and Ca^{2+} flow into the gap between the pre- and post-synapse by exocytosis [1]. The released glutamate binds to the N-methyl-D-aspartate receptor on the postsynapse [2]. The digital wave current from the presynapse flows into the spine as a programmable analog wave, and the degree of Ca^{2+} influx into the spine is proportional to the voltage of the analog wave. Moreover, the number of proteins activated is proportional to Ca^{2+} concentration in the spine. Ca^{2+} signals activate calcineurin [3] via calmodulin, which results in the dephosphorylation of cofilin via Slingshot [4], thereby yielding free and active cofilin. Cofilin reacts with actin expressed in the spine, leading to the formation of protrusions on hippocampal neuron postsynapses [5].

Hypothesis. We hypothesize that memory can be generated in the hippocampus via parallel actin bundles, which play an essential role in the regulation of cell morphology and physiology [6–8]. Parallel actin filaments in the actin bundles share the same polarity and tightly bound in an axial alignment. Cofilin first reacts with globular actin (G-actin) via ADF at the pointed end of F-actin in the parallel actin bundle. This ADF-G-actin interaction occurs on both ends of the parallel actin bundle in a sterically unhindered manner. The actin filament is highly stably bound to cofilin

molecules such that the F-actin molecules cannot be severed [9]. The distribution of bound cofilin on the parallel actin bundle reflects the shape of the analog current wave. The internal energy of F-actin increases along with its helical twist angle upon cofilin binding [10–12]. Thus, the parallel actin bundle results in a high molecular electrostatic potential upon cofilin binding.

Discharge memory from the actin filament

The synaptic tag theory rejects the possibility that new information enters the same dendritic spine after the first set of information has entered [13]. Any additional information enters another dendrite in the neuron. Completion of the entry of information into the spine indicates that no further activation or enhancement of the cofilin will occur. On the contrary, p-21-activated p-21-activated kinase and Rho-associated kinase activate LIN kinase, resulting in the phosphorylation and subsequent dissociation of the cofilin bound to the actin filament in the parallel actin bundle. Phosphorylation of the cofilin bound to actin filaments occurs automatically under a regulatory mechanism similar to the reaction that results in the initial binding of cofilin to the actin filament. The helically twisted actin filament in the parallel actin bundle then reverts to its initial state as the phosphorylated cofilin dissociates from the actin filament. This event leads to the discharge of molecular electrostatic potential from the actin filament and indicates that the energy is released into the spine in the form of an analog

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current. Therefore, it may be impossible to synthesize proteins and perfectly consolidate the memory via weak, regenerated analog currents, whose memory would not be kept for extended periods.

Evaluation of the hypothesis

The mature dendritic spine is shaped like a mushroom; its cytoskeleton is held in a stable position by postsynaptic density, F-actin, branching actin, and F-actin-bundling protein (not for parallel bundles) activated by Ca^{2+} /calmodulin-dependent protein kinase. The existence of parallel actin bundles in the spine head has not been reported in the literature. However, drebrin, actinin, fastin, and espin are expressed in the dendritic spine as actin-binding proteins. These proteins can react with F-actin to form several kinds of parallel actin bundles in the dendritic spine.

Consequences of the hypothesis and discussion

Long-term memory formation requires a current powerful enough to generate proteins in the postsynapse. These synthesized proteins react with structural proteins in the brain at specific locations along the route of the current. The conformation of the structural proteins is altered by this reaction. Hydrogen bonds form between the structural proteins and newly synthesized proteins, and the bound proteins are maintained at sites in the neuron where the bonds are formed. However, although new proteins are not synthesized in response to weak currents of information, memory can still be established. In this paper, we propose a mechanism for the formation of memory that does not involve protein synthesis in the hippocampus. All synthesized parallel actin bundles in the spine have distinct characteristics, including their helical twist angles. Determination of the most suitable parallel actin bundles for the formation of memory in the hippocampus merits further research.

We have explained the mechanism of extinction of fear conditioning in a rat according to our theory. The formation of contextual fear conditioning requires the hippocampus [14,15]. Hippocampus is also involved to some extent in the extinction of fear conditioning, which is largely controlled by the prefrontal region and amygdala [16]. The limitation of this study was that information spreading radically in different directions could not influx into the same spine; hence, distinct information inputs must be stored in distinct dendrite spines [13]. Moreover, according to our theory, perception in the animal would be controlled by the influx of Ca^{2+} amount into the spine.

The external signal induced by a conditioned stimulus (C) is transmitted through a dendritic spine, and the signal induced by the unconditioned stimulus (U) is transmitted through another dendrite spine. Both these signals are consolidated through analog waves in the postsynaptic neuron. Learning occurs through the consolidation of (C) and (U), and this experience results in fear conditioning (CU). Further, the signal induced by an additional conditioned stimulus (C), which is similar to the first (C), is transmitted through the same spine after the same interval, and a second consolidation of information occurs. The combination of fear conditioning (CU) and the second consolidation

results in the next experience (Cx2.U), which has one more (C) factor than (CU). This process is repeated several times, such that (C) is repeatedly presented without (U). This increase in the frequency with which the animal experiences C, without an increase in the frequency of U, leads to the extinction of fear conditioning.

When signals from multiple conditioned stimuli are transmitted through the same dendritic spine, the concentration of Ca^{2+} in the postsynaptic region increases. This Ca^{2+} reacts with calmodulin, which then activates CaMKII kinase; the further increase in the Ca^{2+} concentration activates c-AMP-mediated PKA. These kinases phosphorylate CREB, resulting in the synthesis of several proteins [17], which contribute to long-term memory.

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Conflict of interest statement

None.

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