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Synaptic Plasticity Mechanisms Underlying Memory Formation in the Hippocampus

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Abstract. Synaptic plasticity is the biological basis of cognition used in building memories. Synaptic plasticity is a mechanism by which synapses vary in their strength with the degree of neural activity and it seems to be relevant to learning. Numerous studies have revealed that long term potentiation (LTP) is an important cellular process in forming memories in the brains of human beings. These kinds of mechanisms need to be understood in order to fill the apparent gap between behavioral memory and events occurring at the molecular level. The purpose of this project is to explore how NMDA/AMPA receptors modulate synaptic transmission through means of plasticity of the hippocampus, and to propose some hypothetical experiments, in which, once the synapses are canonically stimulated, the strength of the synapse can be measured. The results may help to support the general notion that memories are encoded in the brain's biological system through synaptic plasticity. This study could also furnish information pertaining to neurological disorders associated with memory dysfunctions, and possibly result in a greater insight into cognitive functions in various aspects.

Keywords: LTP, NMDA Receptor, AMPA Receptor, Hippocampus

1. Introduction

Synaptic plasticity plays a major role in the formation of memory and thus on the way information is coded and retrieved in the brain. Synapses are the points at which two different neurons meet and are involved in the communication of two neurons [1]. The alterations in the functioning of synapses through the variation of the level of synaptic activity are the mechanisms underlying the storage of memories. The hippocampus is a particular region of focus with regard to these mechanisms. Synaptic mechanisms can be the basis for research on how neural activity can relate to the formation of new memory.

Memory can take many forms and the best studied form of memory is known as declarative memory. The declarative memory is all the factual information that is contained in the long-term memory that can be consciously recalled and all the events included in it. Non-declarative memory, on the other hand, refers to learned skills and/or habits that are expressed via the performance of those skills/habits [2]. Declarative memories are all formed or created in the hippocampus. If the hippocampus is damaged, ability to develop additional declarative memories will be lost [3]. Now, it is known that there are different types of memories and they are stored in different neural

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structures. Further, the knowledge of the function of various kinds of memory is essential to grasp the impact of neurological diseases.

Synaptic plasticity is the change in strength of a synapse as a result of changing in one or more of the following factors. LTP is the long-term increase in strength of a particular synapse as a result of repeated high frequency stimulation and there is no definite biological end point [4, 5]. Studies have shown a strong correlation between LTP and learning and memory.

In order for LTP to occur, NMDA receptor activation is requisite. The necessity for activation takes place when magnesium ion blocks the NMDA receptor channels at resting potential. During strong depolarization of the postsynaptic neuron, the magnesium ion dissociates from the NMDA receptor and calcium ion is able to enter the cytosol of the neuron. This increase in calcium into the cell will trigger an increase in calcium/multi-functional protein kinase and consequently make more AMPA receptors appear on the postsynaptic membrane and thus increase the postsynaptic neuron's response to glutamate released from the presynaptic terminal [6].

The hippocampus is used to study synaptic plasticity related to memory due to its high level of LTP in live animals, as well as in brain slices.

Failure in synaptic plasticity has been associated with many neurological disorders such as Alzheimer's disease. The alteration of LTP at the hippocampus may be another mechanism of cognitive impairment in Alzheimer's, where the synapse is damaged. Besides, there is also synaptic dysfunction in patients with schizophrenia [7]. Therefore, the identification and understanding of how enhancing activity increases the link between neurons in the brain (synapse) may provide opportunities in basic science and clinical practice.

Several publications have discussed the role of NMDA and AMPA receptors in the process of hippocampal LTP and this is reviewed here. Through these mechanisms, the understanding of the involvement of synaptic mechanisms in memory and cognitive functions can be better understood. This review additionally aids in understanding neurological problems that are related to recollections. Brain plasticity is essential for memory formation, and it is also the basis for the brain to code and retrieve information. Synapses are the specialized connections between neurons which facilitate the communication between the neurons [1]. Memory is a result of alternates in synaptic activity. These processes are particularly dependent on the hippocampus. Understanding the mechanisms of synapses can thus offer some clues to explain how neural activity might underlie memory formation.

2. Role of the hippocampus in memory

2.1. Structure and function

The hippocampus has shown evidence that it is a critical part of forming declarative memory. Subregions of the hippocampus seem to perform distinct computational operations (e.g., the dentate gyrus appears to be responsible for pattern separation, CA3 is thought to support pattern completion, CA1 appears to integrate convergent information, and the subiculum is involved in the retrieval of memories) [5]. The example of patient H.M. having a profound anterograde amnesia due to his bilateral hippocampal removal suggests that the hippocampus is critical to forming declarative memories, however, he still retained all other types of non-declarative memory [3]. Another example that suggests that the Morris water maze produces converging data also indicates that an animal with a hippocampal lesion would be unable to locate a submerged platform using spatial cues [7]. Collectively these pieces of evidence indicate that a hippocampus-dependent task has become an established methodology for studying the in vivo mechanisms of synaptic plasticity. The

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hippocampus is critical for memory. The present data indicate that there is clear evidence that the hippocampus is involved in declarative memory. Thus, these data may help clarify how the hippocampus contributes to supporting declarative memory by way of separate contributions from different hippocampal subregions.

2.2. Synaptic plasticity in the hippocampus

The consistent findings from LTP in the hippocampus suggest that a generally acceptable general system for studying the cell basis of memory may produce measurable plasticity in acute brain slices and in whole animals [5]. In addition, the central hypothesis would suggest that high-frequency stimulation of the Schaffer collateral, which is the axonal projection that synapses on CA1 pyramidal cells, is a reliable method to elicit LTP. This potentiation may also show quantifiability when measured by field potentials. Furthermore, this preparation appears to have been the foundation of the field, as it has been consistently reproduced and has shown to be an important experimental model system [8]. From these results, it is likely that theta burst stimulation, which approximately simulates the innate theta wave activity, provides a physiologically relevant means of inducing LTP in both the hippocampus and neocortex. The results could further support that sustained high-frequency tetanisation as the protocol used in the original LTP studies is a reasonable standard alternative method for inducing LTP [9]. These results support the utility of LTP as a model in the hippocampus.

3. Experimental evidence from published studies

3.1. NMDA receptor blockade experiments

Multiple investigations proposed that the necessity of NMDA receptor activation for LTP could demonstrate significant experimental support across published findings. Moreover, the significant evidence might indicate that in the defining 1983 experiment, Collingridge and colleagues applied D-AP5 to hippocampal slices and could demonstrate complete abolition of LTP induction with no disruption to baseline synaptic transmission [10]. Furthermore, the findings may suggest that this result appears to have been extended to behaving animals by Morris and colleagues. These researchers infused D-AP5 directly into the rat hippocampus and could demonstrate concurrent blockade of dentate gyrus LTP alongside impairment of spatial learning in the water maze. Notwithstanding initial scepticism, the key evidence might indicate that D-AP5-treated rats appear unable to acquire the platform location in the Morris water maze, suggesting that NMDA receptor activation could demonstrate indispensability for spatial memory encoding [11]. Blockade shows NMDA receptor necessity.

Subsequent temporal analyses recommend that NMDA receptor activation is confined to the induction phase of LTP. Application of D-AP5 immediately following high-frequency stimulation failed to prevent potentiation, establishing that NMDA receptors are not required for LTP maintenance [8].

3.2. AMPA receptor trafficking experiments

Complementary investigations could indicate that AMPA receptor changes accompany LTP. Malinow and colleagues expressed trafficking-deficient mutant AMPA receptors in hippocampal neurons and demonstrated that preventing receptor insertion at the synapse was sufficient to abolish

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LTP expression [12]. Furthermore, the significant findings from Hayashi and colleagues shows that the GluA1 subunit is indispensable. Mice lacking GluA1 displayed neither hippocampal LTP nor normal spatial memory performance, directly linking AMPA receptor trafficking to learning behavior [13]. In light of these results, biochemical quantification of surface AMPA receptor levels before and after LTP induction could indicate that high-frequency stimulation elevated surface receptor levels by 50–100% within 10 minutes. This increase persisted for at least 60 minutes post-stimulation [8]. Evidence supports that LTP involves AMPA trafficking.

3.3. Hippocampal LTP and behavioral studies

Convergent evidence from behavioral studies which could propose a causal link between hippocampal LTP and memory formation appears established. Moreover, the key findings from Morris and colleagues' 1986 landmark study demonstrate that pharmacological NMDA receptor blockade simultaneously impaired LTP induction and spatial learning, with a single agent producing both deficits [12]. Additionally, the significant results from Nakazawa and colleagues could indicate that mice with a selective deletion of NMDA receptors in CA3 pyramidal cells exhibited preserved LTP at CA1 synapses but impaired LTP at CA3 synapses and deficits in pattern completion. This finding reveals functionally distinct contributions of hippocampal subregions [12]. Given that the evidence demonstrates a correspondence between LTP longevity and memory duration, the findings from Pastalkova and colleagues might indicate that robust learning was associated with LTP persisting for days, whereas weaker learning produced LTP lasting only hours. The two timescales closely paralleled memory retention [13]. Studies show that LTP links to memory duration.

4. Summary of key findings

4.1. Increase in synaptic strength

Published studies may suggest that high-frequency stimulation reliably induces LTP. The significant results from Bliss and Lømo demonstrate that a 150–200% increase in synaptic response lasting several hours in anaesthetized rabbits appears subsequently replicated in slice preparations and awake animals. Furthermore, the key findings could indicate that potentiation is restricted to activated synapses. Andersen and colleagues confirmed that neighboring, unstimulated synapses show no change, an input-specificity that appears to confer the selectivity necessary for the encoding of discrete memory traces [14]. Therefore, the evidence might indicate that this input-specificity could demonstrate the selectivity that underlies the encoding of discrete memory representations. Input-specificity shows that synapses encode memory selectively.

4.2. Role of NMDA receptors

The activation for NMDA receptor is extremely necessary for LTP induction. Collingridge and colleagues showed this in hippocampal slices through using D-AP5. Morris and colleagues then confirmed it in intact, behaving animals [12]. This receptor requirement also explains how LTP shows associativity. NMDA receptors open when and only when two things happen at once: presynaptic glutamate release and postsynaptic depolarization, so the receptor acts as a coincidence detector for LTP induction.

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4.3. Changes in AMPA receptors

AMPA receptor trafficking plays a key role in studying how LTP is expressed. Malinow and Malenka reviewed this evidence. Hayashi and colleagues showed that the GluA1 subunit is critical. After LTP induction, more and more AMPA receptors appear on the surface area. How many more receptors appear matches how much the synapse strengthens. This link shows that moving receptors directly boosts transmission. Thus, AMPA receptor trafficking is critical for LTP expression.

4.4. Interpretation

The published evidence supports these claims. LTP is a long-lasting increase in synaptic strength. NMDA receptor activation is necessary to induce LTP. AMPA receptor trafficking is necessary to express LTP. LTP in the hippocampus correlates with spatial memory. Together, these findings show how synaptic plasticity provides a biological foundation for memory. This foundation holds across many experimental setups. So, plasticity underlies how memories are formed.

5. Conclusion

One of the fundamental brain functions is memory formation. It relies on the modifications of synapses. Synaptic plasticity is a trait that allows individual synapses to either get stronger or weaker throughout a certain amount of time. Some other form of this plasticity is also known as LTP. Numerous scientists believe that LTP is one of the most important cells in both learning and memory. The paper has discussed the different, though complementary roles played by NMDA and AMPA receptors in synaptic plasticity located within the hippocampus.

LTP is a chronic, long-term, progressive augmentation of synapses. It is generally a follow-up of the high-frequency stimulation. There are some important properties of this type of plasticity. Firstly, it is input-specific meaning that only active synapses were able to strengthen. The opposite ones that are at the end of us do not make any difference, even in little bit. Secondly, associative; a weak stimulus can be potentiated when it is combined with a strong stimulus. Thirdly it is chronic. Effects are lasting in days or weeks in living animals. This makes LTP selective and long-lasting as it is required to encode discrete memory traces due to the consistency of these properties.

The NMDA receptor is a receptor which functions as a molecular coincidence detector. It requires two occurrences to take place approximately simultaneously. The glutamate is released by the presynaptic neuron. The postsynaptic neuron also depolarizes to an extent that it removes a magnesium block in the channel pore. When the block is lost, the calcium ions get into the cell via the NMDA receptor. This influx of calcium causes a number of intracellular signaling pathways. These are in turn transported to the postsynaptic membrane to bring more AMPA receptors. The more AMPA receptors that are added to the neuron, the more sensitive the neuron becomes to glutamate. This enhances the synapse.

Hippocampus plays an important role in the formation of declarative memories. This idea is well supported by the fact that patients who have suffered bilateral damage to the hippocampus have problems with numerical memory. Robust LTP is found in the hippocampus in the major subregions of the hippocampus which include the dentate gyrus, CA3 and CA1. LTP properties of each sub region are slightly different. The differences are probably adaptive to different tasks such as a dentate gyrus pattern separation and pattern completion in CA3. In behavioral studies, the hippocampal LTP is always correlated with learning in space. Not only the induction of LTP but also spatial memory tasks is inhibited in NMDA receptor inhibition.

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Impairment of synaptic plasticity has been implicated in various disorders of the brain. For instance, Alzheimer's disease causes a loss of synapses and reduces LTP in the hippocampus. Other disorders, like schizophrenia, also are related to abnormal synaptic function. Therefore, understanding the mechanisms of synaptic strength modification may be useful to better understand memory impairments. The knowledge could also help to develop new treatments for memory disorders. It is therefore important to study synaptic plasticity as it is crucial for developing therapies.

The similar main conclusion the published evidences support: is that the biological basis of memory formation is synaptic plasticity. NMDA receptor-dependent LTP is one of these. Now the basic molecular pathways are known. NMDA receptors are coincidence detectors, and it's AMPA receptors that are responsible for the actual strengthening of synapses. These mechanisms are used by the hippocampus in the service of declarative memory. Future studies should also investigate other brain areas besides the hippocampus, including the amygdala and cortex. Other types of plasticity, also involved in memory, may occur in these areas.

To conclude, plasticity in the hippocampus seems to play a critical role in cellular mechanisms involved in memory formation. Now the literature explains the mechanisms of action of NMDA and AMPA receptors in these pathways. Furthermore, such knowledge provides insights into the brain's function with regard to cognitive tasks such as learning and memory. It also offers a scientific understanding to help create new treatments for memory disorders. In the future, both female and male subjects should be used as different groups may use different plasticity mechanisms. Strategies such as optogenetics should also be applied to study the brain. These more recent techniques allow one to make a more direct connection to cause and effect.

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