



Involvement of Hippocampus in Learning and Memory Through Associated Synaptic Plasticity: the Role of Glutamate and GABA Receptors

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ABSTRACT

Synaptic plasticity is one of the most crucial physiological processes involved in learning and memory. Diseases such as Alzheimer's, depression, and epilepsy, which affect synaptic plasticity, lead to memory and learning impairments. The hippocampus is a key brain region in synaptic plasticity. Neural plasticity is a complex process dependent on neurochemical underpinnings. Next to the glutamatergic system which contributes to memory formation via long-term potentiation (LTP) and long-term depression (LTD), the main inhibitory neurotransmitter, GABA is crucially involved in neuroplastic processes. Therefore, understanding the mechanisms which are involved in the synaptic plasticity and memory processes can help us to overcome neurological disease which they affect memory function and synaptic plasticity.

Keywords: Hippocampus, Synaptic plasticity, Long-term potentiation, Long-term depression,

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INTRODUCTION

Synaptic plasticity is a vital physiological phenomenon that significantly contributes to the processing and storage of information ⁽¹⁾. Conditions that impact synaptic plasticity result in difficulties with memory and the acquisition of new knowledge ⁽²⁾. Synaptic plasticity, a crucial process for memory and learning, is impaired in disorders like Alzheimer's, depression, and epilepsy. Hence, it is crucial to comprehend the mechanisms underlying various types of synaptic plasticity, such as long-term potentiation (LTP),

long-term depression (LTD), and depotentiation. Several variables, such as glutamate receptors, GABA receptors, and molecules like calci-neurin, contribute to the development of long-term potentiation (LTP) and long-term depression (LTD), or post-tetanic potentiation ⁽³⁾. This review article will examine the significance of the hippocampus and several components involved in synaptic plasticity and memory.

The hippocampal formation

The hippocampal formation comprises many interconnected areas. These areas encompass the

dentate gyrus, hippocampus, presubiculum, subiculum, and parasubiculum. The hippocampus is a component of the cerebral cortex situated in the central region of the temporal lobe. It bends inward and lies adjacent to the amygdala nuclei. The hippocampal formation has numerous indirect connections with diverse parts of the brain cortex and essential elements of the limbic system. The primary sources of input to the hippocampus are the entorhinal cortex, the septal area, and the contralateral hippocampus. A substantial proportion of these inputs is provided by the entorhinal cortex, which enters the hippocampus through the perforant path. The entorhinal cortex gets inputs from the associative cortex, olfactory cortex, thalamic nuclei, and amygdala. The entorhinal cortex inputs project to both the dentate gyrus and the dendrites of neurons in the CA3 and CA1 areas. Moreover, the entorhinal cortex functions as the main hub for transmitting information from the hippocampus to other parts of the brain.

Studies conducted on the hippocampus have greatly enhanced our comprehension of the anatomical and electrical characteristics of temporal-lobe epilepsy. Temporal lobe epilepsy is distinguished by prominent structural irregularities, such as neuronal degeneration and an increased prevalence of astrocytes (referred to as hippocampal sclerosis). Most of these changes happen in the CA1 region of the hippocampus, along with a section of the subiculum. Hippocampal sclerosis involves the breakdown of glutamatergic mossy fibers, which leads to a decrease in their ability to excite inhibitory interneurons, such as basket cells. Consequently, natural stimuli provoke an exaggerated and abnormal surge in activity in these cells, which forms the basis for seizures ⁽⁴⁾.

The hippocampus is characterized by its heightened excitability, so that even minimal electrical stimulation has the potential to induce localized seizure activity in specific regions of the hippocampus. The hippocampus is vulnerable to seizure activity due to the existence of a one-way excitatory circuit and a scarcity of inhibitory neurons. The circuit starts with input going from the entorhinal cortex to the dentate gyrus. It then goes to the CA3 region, then to CA1, and finally back to the entorhinal cortex. This

communication loop is a potential mechanism that can contribute to the initiation or strengthening of seizures ^(4,5). Synaptic plasticity is a critical process that takes place in the hippocampus and has a basic impact on memory and learning ^(6, 7).

Learning and Memory

Learning refers to the processes by which we acquire new knowledge about the world, whereas memory refers to the processes by which we retain and store that knowledge. The year 1970 marked the inception of contemporary memory studies. In 1957, Scoville and Milner provided evidence that the surgical excision of both sides of the hippocampus in a patient named H.M. as a treatment for epilepsy resulted in a gradual decline in memory function. The discovery emphasized the significance of the hippocampus and its associated regions in the process of remembering ⁽⁸⁾. Although H.M. experienced significant memory loss, he nonetheless maintained the capacity to carry out motor tasks. The studies have established three crucial elements that will serve as a framework for future laboratory research: 1) Memory is a discrete cognitive function that is independent of other abilities. 2) The medial temporal lobe is essential for short-term memory since H.M. had the ability to retain numbers or images effectively, but only for a brief duration. H.M.'s impaired structures do not serve as the ultimate repository for memory, as he was able to recall memories from his infancy ⁽⁹⁾. Therefore, researchers deduced that memory comprises a complex system of various anatomical constituents ⁽¹⁰⁾.

Memory is usually classified into two distinct categories: 1) Declarative (explicit) memory refers to the conscious remembrance of knowledge about world facts (semantic memory) or specific events involving people, places, and objects (episodic memory). The function of this process depends on the presence of specific anatomical components inside the temporal lobe, including the hippocampus, subiculum, and entorhinal cortex. Declarative memory serves as a means to describe the external world and comprises the memory type popularly known as "memory." 2) Non-declarative (implicit) memory refers to the unconscious recollection of specific

tasks, such as motor abilities. This form of memory relies on the basal ganglia and cerebellum. Implicit memory encompasses various types of memory, including associative forms like classical conditioning and operant conditioning, as well as non-associative forms like habituation and priming ⁽¹¹⁾.

Spatial memory and hippocampus

Spatial memory is a cognitive function that allows an individual to recall various places and spatial connections between items ⁽¹²⁾. Table 1-1 shows that different parts of the brain are involved in forming different types of memories. However, the hippocampus is especially important for creating declarative memories, specifically episodic (related to events) and semantic (meaningful) memories. Research suggests that spatial memory in rats exhibits notable parallels with episodic memory in humans ^(12, 13). Recent non-invasive studies utilizing direct imaging techniques such as MRI and PET have revealed alterations in blood flow and oxygen use in the hippocampus area during learning and memory assessments ⁽¹⁴⁾.

An obstacle in the field of neuroscience involves identifying the processes that are responsible for memory formation. Because the hippocampus is involved in spatial memory and there are established methods for studying spatial memory (such as the Morris water maze and Y-maze), a significant amount of research has been dedicated to understanding how hippocampal pyramidal cells encode information related to location ⁽¹⁵⁾. Furthermore, research has shown that desert rats with damage to their hippocampus display subpar performance in spatial memory tasks. Thus, it seems that the hippocampus has a crucial function in the acquisition of knowledge and spatial memory through the creation of cognitive maps based on environmental signals. This process is facilitated by unique cellular mechanisms inside the entorhinal cortex ⁽¹⁶⁾.

Synaptic plasticity

Understanding the mechanisms that govern how the brain processes and stores information is a fascinating subject in neuroscience. Approximately a century ago, Sherrington's creation of specialized neuronal networks

connected by synapses gave rise to a hypothesis proposing that the brain retains knowledge through long-lasting modifications dependent on synaptic activity ⁽¹⁷⁾. Put simply, synaptic plasticity, which is the term used to describe changes in the strength of connections between neurons due to activity, has been suggested as the basis for storing knowledge in the brain ^(18, 19). In 1913, Cajal proposed a hypothesis that the storage of information in the brain is dependent on alterations in the potency of synaptic connections among activated neurons. Synaptic plasticity is a crucial factor in the creation of memories, taking place at specific synapses during the process of memory consolidation. Hebb later endorsed this concept in 1949, suggesting that simultaneous activation of two neurons (one before and one after the synapse) increases the strength of the connection between them. Lomo documented in 1966 that a short and solitary shock in the perforant route, followed by an initial phase of conditioned stimulus-induced shock, results in an intensified reaction in the dentate gyrus ⁽²⁰⁾. The three forms of synaptic plasticity—long-term potentiation (LTP), long-term depression (LTD), and depotentiation—exhibit essential features required for memory formation. The user's text is "(19)".

Long term potentiation induction

Long-term potentiation (LTP) refers to the enhancement of synaptic effectiveness between two neurons over an extended period of time. Bliss and Lomo provided the initial thorough explanation of long-term potentiation (LTP) in 1973. They showed that a series of stimuli sent to the perforant route in the hippocampus of rabbits improve the long-term effectiveness of synapses in the granule cells of the dentate gyrus area. Researchers have suggested multiple pathways for causing long-term potentiation (LTP). The primary process in the CA1 hippocampus area includes the stimulation of NMDA glutamate receptors and voltage-dependent calcium channels (VDCC). Long-term potentiation (LTP) induction in the CA1 area is dependent on glutamate release activation of NMDA receptors. This leads to glutamate binding to both NMDA and AMPA receptors, causing simultaneous depolarization of the postsynaptic membrane

through AMPA receptor activation. Additionally, the removal of the magnesium block from NMDA receptors allows for calcium influx through these receptors. Elevated intracellular calcium levels trigger a range of metabolic pathways that result in the initiation and manifestation of long-term potentiation (LTP). Protein kinases like calcium/calmodulin-dependent protein kinase II (CaMK-II), protein kinase C, and protein kinase A are activated, which begins important steps in this process ⁽¹⁷⁻²¹⁾. CaMK-II enhances the sensitivity and quantity of AMPA receptors in the postsynaptic membrane by phosphorylating them and activating silent receptors ⁽²²⁾. Studies indicate that the liberation of presynaptic neurotransmitter vesicles relies on the activation of NMDA receptors. This framework suggests a specific form of backward-moving messenger called nitric oxide. The postsynaptic cell produces nitric oxide, which, by influencing kinases at the presynaptic terminal, triggers an enhanced release of neurotransmitter vesicles crucial for long-term potentiation (LTP).

LTP is divided into two types based on whether it requires pre- and postsynaptic neuron activity for induction: 1) Associative (Hebbian LTP) and 2) Non-Associative (Non-Hebbian). Non-Associative LTP does not require simultaneous depolarization of pre- and postsynaptic neurons. The mossy fiber pathway actually consists of axons from granule cells in the dentate gyrus region that release glutamate from their terminals. However, in the synapses of this pathway with pyramidal cells in the CA3 region, NMDA receptors play a minor role in the synaptic plasticity of LTP.

Long-term potentiation (LTP) in this pathway depends on calcium entering the presynaptic terminal after tetanic activation. Calcium influx appears to activate calcium/calmodulin-dependent adenylate cyclase, resulting in elevated cAMP levels in the presynaptic neuron and subsequent activation of protein kinase A. In order to induce associative long-term potentiation (LTP), it is necessary for both the pre- and postsynaptic neurons to be depolarized simultaneously. The lateral perforant route establishes a connection between the CA3 pyramidal cells and the CA1 pyramidal cells within the hippocampus. The lateral perforant

route, like mossy fiber synapses, also releases glutamate from its presynaptic terminals. There are two main differences between long-term potentiation (LTP) in the lateral perforant path and LTP in the mossy fiber pathway. NMDA receptors play a role in both of these differences. Cooperativity is the first characteristic of LTP, which implies that the induction of LTP in the lateral perforant channel necessitates the simultaneous activation of many afferents. Cooperativity occurs when NMDA receptors permit calcium entry only when two conditions are fulfilled: 1) Glutamate must attach to these receptors in the postsynaptic membrane, and 2) the postsynaptic membrane must be adequately depolarized to eliminate the magnesium block from the NMDA receptor channel, thereby enabling calcium influx. This mechanism requires the simultaneous activation of many afferents. Associativity is the second property, which means that inducing long-term potentiation (LTP) in the lateral perforant path requires the simultaneous depolarization of both the pre- and postsynaptic neurons ⁽²³⁾.

Stimulation at a frequency of 100 Hz through NMDA receptors and stimulation at frequencies of 200 Hz and above through the NMDA-independent pathway by activating voltage-dependent calcium channels (VDCC) result in long-term potentiation (LTP) ⁽²⁴⁾. NMDA-dependent long-term potentiation (LTP) can be hindered by the particular antagonist AP5, but VDCC-dependent LTP can be suppressed by nifedipine, a type L inhibitor of voltage-dependent calcium channels (VDCCs) ⁽²⁵⁾.

Multiple studies suggest that various elements within the postsynaptic neuron contribute to the initiation and sustenance of long-term potentiation (LTP). The development of long-term potentiation (LTP) relies on the activation of NMDA glutamate receptors, the entry of calcium into the cell, and the activity of CaMK-II. On the other hand, the stability of LTP depends on variables such as MAPK, CaMK-IV, and the phosphorylation of CREB, which ultimately lead to gene expression ⁽²⁶⁾.

Evidence indicates that synaptic processes associated with some types of memory and learning may bear similarities to long-term potentiation (LTP) ⁽²⁷⁾. One piece of evidence that

supports this claim is that long-term potentiation (LTP) mostly takes place in the hippocampus, which is a critical area for memory and learning. B) The rhythmic bursts of activity that trigger long-term potentiation (LTP) mimic the rhythmic theta waves observed during exploratory actions. Blocking long-term potentiation (LTP) in the hippocampus impairs the process of acquiring new knowledge and remembering information. Several physiological changes that occur during memory and learning processes are similar to the events that happen after LTP induction^(28, 29).

Depotentialiation

If synaptic plasticity relies exclusively on the strengthening caused by activity, synaptic efficacy would eventually reach saturation, resulting in the inability of a brain network to learn. While some of the synapses that were initially strengthened may eventually return to their original levels, a process that decreases long-term potentiation (LTP) or causes depotentialiation increases the adaptability of the network. As a result, the concept of a compensating occurrence for long-term potentiation (LTP) arose and has been proven by experimentation⁽¹⁻³²⁾. Depotentialiation is the term used to describe the process of reversing the enhanced synaptic transmission back to its original levels before long-term potentiation (LTP) occurred. Depotentialiation can function as a technique to avoid synaptic saturation and increase the capacity for storing information in a neural network⁽²¹⁻³³⁾.

Postulated mechanism involved in depotentialiation

The study of the biochemical and pharmacological mechanisms involved in depotentialiation, particularly in connection to long-term potentiation (LTP) and long-term depression (LTD), has been very limited. Multiple forms of depotentialiation have been identified, each triggered by different experimental procedures. Depotentialiation often occurs with the use of low-frequency stimulation (LFS). Given that AP5 efficiently inhibits this kind of depotentialiation, it suggests that the activation of NMDA receptors is a crucial role in the process of depotentialiation^(30, 31, 34). Calcium ions are conducted via NMDA

receptors, and the entry of calcium through these channels during LFS may generate the required calcium signal to induce depotentialiation. Following the influx of calcium through these channels, there may be biochemical alterations that could potentially impact the functioning of protein phosphatases. Activation of protein phosphatases is essential for the process of depotentialiation triggered by LFS^(35, 36). Protein phosphatase 1 (PP1) is one of the primary protein phosphatases involved in this process. The synaptic strength may be determined by the equilibrium between CaMK activity and PP1. As PP1 is not directly affected by intracellular calcium, various calcium-dependent intermediaries are required to convert the calcium signal and increase protein phosphatase activity. Calcineurin and adenosine are two primary possibilities for this pathway^(37, 38).

Researchers have found that calcineurin has a big effect on how synapses change shape, and there is evidence that its A- α isoform is involved in changing the shape of neurons in the hippocampus⁽³⁻³⁹⁾. Calcineurin is a protein phosphatase that relies on calcium and calmodulin for its function. It can indirectly control the activity of PP1 by dephosphorylating regulatory proteins or inhibiting the PP1 inhibitor-1 (I-1) protein. I-1 that has undergone phosphorylation functions as a potent inhibitor of PP1. According to this concept, calcium first enters the postsynaptic cell by activating the NMDA receptor during the depotentialiation induction process. When calcium binds to calmodulin, it triggers the activation of calcineurin (PP2B). Calcineurin subsequently removes phosphate groups from PP1, leading to its deactivation and preventing protein 1 from inhibiting PP1. PP1, on the other hand, removes phosphate groups from proteins and renders them inactive. These proteins are responsible for maintaining synaptic potentiation⁽²³⁻³⁸⁾. Previous research has demonstrated a link between heightened neuronal excitability and heightened calcineurin activity. Additionally, epilepsy triggers an increase in calcineurin activity, but this rise in activity does not necessarily coincide with alterations in gene expression⁽⁴⁰⁻⁴²⁾.

The role of NMDA receptors in LTP and spatial memory

There is ample evidence that strongly supports the crucial involvement of NMDA receptors in the process of acquiring spatial memory. Morris and colleagues conducted a study in 1986 and found that blocking NMDA receptors with AP5 negatively affects spatial learning. Surprisingly, this result fits with earlier findings that AP5 also blocks long-term potentiation (LTP), which means that the systems involved in LTP and those in consolidating spatial memory are becoming more similar ⁽³⁴⁾. Tsien and his colleagues developed a mouse model in which they genetically removed NMDA receptors from the hippocampus. The findings indicated that the mice experienced a disruption in their ability to remember spatial information, whereas their ability to remember non-spatial information was unaffected ⁽⁴³⁾. In addition, the absence of the NR2A subunit of NMDA receptors in mice resulted in poor spatial memory and LTP ⁽⁴⁴⁾. Long-term potentiation (LTP) and certain types of memory are linked genetically. This shows that the mechanisms involved are similar and highlights how memory processes and synaptic plasticity work together ⁽³⁴⁾.

The role of GABA receptors in LTP and spatial memory

Studying the control of activity-dependent plasticity in inhibitory synapses is complex because of the diversity of GABAergic cell types and the difficulties in differentiating specific inhibitory inputs. However, it is well accepted that GABAergic synapses, similar to excitatory synapses, demonstrate plasticity. This means that long-term alterations in their strength, including both enhancement and reduction, have been found in different areas of the brain. Various forms of inhibitory synaptic plasticity have been observed, depending on the specific inhibitory interneurons and brain region involved (Table 1-2). These forms of plasticity can involve modifications in the release of the GABA neurotransmitter from the cells sending the signal or changes in the number, sensitivity, and responsiveness of the GABA receptors in the cells receiving the signal ^(45, 46).

Considering the crucial function of inhibitory synapses in controlling the activity of neurons and their influence on excitatory synapses, alterations in the effectiveness of GABAergic synapses can result in important functional outcomes. Inhibitory synaptic plasticity is crucial in modifying the equilibrium between excitation and inhibition, and it has a significant impact on the formation and refinement of neuronal circuits during different types of experience-dependent learning in the fully developed hippocampus ⁽⁴⁷⁾.

Studies suggest that the process responsible for long-term potentiation (LTP) at inhibitory synapses in the CA1 area of the hippocampus takes place after the synapse. The process entails the stimulation of metabotropic glutamate receptors type I (mGluR-I) and GABA-B receptors, which then triggers G-protein activity and leads to elevated levels of intracellular calcium in pyramidal cells. Ultimately, this results in the long-term strengthening of inhibitory postsynaptic potentials (IPSPs) or postsynaptic potentials. The elevation in calcium levels initiates the release of a retrograde signal, most likely glutamate. This signal, through the activation of metabotropic glutamate receptors, amplifies the release of the GABA neurotransmitter from interneurons. As a result, there is a long-lasting increase in the strength of the connections between neurons, specifically in the electrical currents that occur in the receiving neuron after the transmission of signals from the sending neuron ^(46, 48).

GABAergic interneurons in the hippocampus have many mechanisms that enable them to regulate synaptic plasticity and learning that is influenced by experience. While these systems are typically examined independently, it is crucial to acknowledge that they all interact within the hippocampal neuronal network. GABAergic interneurons in spatial control have two functions:

1. **Filtering:** In the beginning, when the mouse hippocampus is engaged in exploratory behavior, there is an increase in paired-pulse inhibition associated with inhibitory postsynaptic potentials (IPSPs) in the dentate gyrus. During the process of learning a new environment, there is an increase in the activity of the inhibitory system. This is likely due to an increase in dendritic

inhibition, which allows only strong excitatory signals to reach the synaptic layer.

2. Compartmentalization: Hippocampal interneurons have a wide range of characteristics that allow them to perform specific functions in preparing memory processing in individual main cells. For example, distinct categories of interneurons selectively focus on various parts of the main cell membrane. Therefore, depending on different behavioral settings, different types of interneurons become active, resulting in alterations in the spatial arrangement of inhibitory modulation. Interneurons that specifically target dendrites may play a role in regulating synaptic plasticity. When an animal investigates a particular habitat, the firing of pyramidal cells triggers action potentials, which in turn suppresses dendritic inhibition. This leads to the long-term strengthening of synaptic connections in the postsynaptic currents. Hence, the function of GABAergic interneurons is vital in controlling synaptic plasticity during memory-related activities and learning (49).

CONCLUSION

The coordinated regulation of excitatory and inhibitory plasticity indicates that GABAergic and glutamatergic synapses act as two partners working together to achieve the excitatory/inhibitory balance necessary for the brain functions like learning and memory. Therefore, understanding the mechanisms which the glutamatergic and GABAergic neurons are involved in the synaptic plasticity and memory can help us to overcome neurological disease which they affect synaptic plasticity and memory function.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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