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Long-Term Potentiation (LTP): A Simple yet Powerful Cellular Process in Learning and Memory

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Abstract

Learning and memory are natural responses of the body to assist us in living. Neurodegenerative diseases wreak havoc on the neuronal processes that control memory development and consolidation, causing mental, social, and financial hardship for millions of people around the world. In the mammalian brain, many neurotransmitters are involved in memory formation and consolidation. The cellular mechanisms and signaling pathway involved in this, however, are not fully understood. Donald Hebb suggested the synaptic reorganization hypothesis in support of memory development decades ago. Two types of synaptic plasticity, Long-Term Potentiation (LTP) and Depression (LTD), have been implicated in the formation and consolidation of memory in mammalian brains as a result of the advancement of modern electrophysiology and molecular biology techniques. The synapses are also thought to be the source of information storage, according to Hebbs' theory of neuronal connectivity and firing properties. As a consequence, information can be altered by altering synaptic intensity through LTP or LTD. The physiology of synaptic organization in the brain is altered in certain memory-related cognitive impairments. Although there is literature on the non-synaptic memory system in the mammalian brain, this review will concentrate on a few key findings from in vitro and in vivo synaptic plasticity studies to link the role of LTP and LTD-a signature model in memory formation and consolidation. This will help us better understand neurological disorders involving neural processes and get us closer to discovering a cure.

Keywords: Synaptic plasticity • Neural • Psychology

Introduction

The relationship between synaptic plasticity and memory has sparked discussion. Morris and colleagues put forward the Synaptic Plasticity and Memory (SPM) hypothesis, which states that "activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation and is both required and adequate for information storage underlying the type of memory mediated by the brain region in which plasticity is observed [1]. Countless studies have found a correlation between synaptic plasticity, such as Long-Term Potentiation (LTD) and Long-Term Depression (LTD), and memory development over the years. However, creating a clear link has proved difficult. Several intriguing in vitro and in vivo studies have identified molecular pathways responsible for synaptic strength changes [2-4]. There is a shortage of data demonstrating the role of synaptic plasticity during in-vivo learning. Indirect evidence for improvements in synaptic strength that coincide with learning and memory processes has been established by several seminal studies. We'll look at a few in vitro and in vivo studies that back up the theory that LTP is the same as memory formation. It will also look at a few primary in vitro and in vivo animal studies to see how synaptic plasticity plays a role in the learning and memory processes in mammals. This pioneering research on animal learning and memory development will be addressed after a summary of LTP and LTD, which will provide context for this study.

A Brief History of Memory Research

Over thousands of years of evolution, the human brain develops properties that allow us to adapt to our surroundings. Higher cognitive tasks such as learning and memory are handled by the brain's complex specialized structures.

Our current understanding of the role of synaptic plasticity and memory is based on research conducted by German psychologist Hermann Ebbinghaus in the late 18th and early 19th centuries (1850-1909). The memorization and testing of lists of nonsense syllables by Ebbinghas shown that memory retention is affected by length and repetition. Sergei Korsakoff (1887) invented the word "memory disease" to describe how people remember things. In his book Principles of Psychology, William James (1890) introduced the concepts of short-term (primary) and long-term (secondary) memory, as well as their distinguishing characteristics. When experimenting on animal models to study memory development, Edward Thorndike (1898) introduced the idea of operant conditioning. It's worth noting that, long before behavioral psychology was formulated to clarify memory's underlying mechanism, the great neuroanatomist Ramon y Cajal (1890) proposed that structural changes in synapses in the brain may be responsible for the creation of memory traces. Soon after, Charles Sherrington (1897) endorsed synapse-mediated improvements in brain function as a learning mechanism.

Ivan Pavlov conducted research on classical conditioning in 1904, showing that a conditioned reflex (salivation) could be modified by learning. Behavioral psychologists John Watson, B.F. Skinner, and Clark Hull introduced learning theories to explain complex behavior in the 1930s and 1940s. Later, Tolman (1948) discovered that rats have cognitive maps that assist in learning and memory. Karl Lashley (1920) used rat models to investigate the impact of eliminating cortical tissue mass on

maze learning. He suggested that memories are distributed in the cortical region of the brain in a diffuse manner [5]. Wilder Penfield (1938) used electrical stimulation to evoke memories, visions, and hallucinations in his patients, including voices, pictures, and music. Furthermore, in his book The Structure of Actions, Canadian neuroscientist Donald Hebb (1949) proposed that memory storage in the brain is regulated by a neural network. Finally, Scoville and Milner (1968) researched the patient 'H.M' extensively and hypothesized the function of the hippocampus and associated medial temporal lobe regions in learning and memory. Brenda Milner (1968) later showed that procedural memory was unchanged in 'H.M.,' despite the fact that other memory types were abolished, meaning that different memory processes are preserved by different brain regions. Electrophysiology was later introduced, which offered more concrete evidence for the role of synaptic plasticity in learning and memory.

Synaptic plasticity in the mammalian brain: Long-Term Potentiation (LTP) and Long-Term Depression (LTD)

The bulk of our understanding of the role of LTP and LTD in synaptic plasticity comes from Aplysia experiments. These experiments showed that any improvement in synaptic strength promotes sensory information storage. There was no proof of such a process in the mammalian brain until the 1970s, when Bliss and Lomo discovered Long-Term Potentiation (LTP) of synaptic intensity after conducting a series of experiments in the rabbit hippocampal dentate gyrus, which was found to be close to Aplysia long-term sensitization [2,5]. When high-frequency electrical stimulation was applied to these synapses in the rabbit's hippocampus, they found a consistent increase in synaptic power, which was assumed to be responsible for the encoding of new knowledge. LTP tends to be the most significant occurrence in memory formation and consolidation, according to mounting evidence [1].

LTP has emerged as a leading contender for the brain's information storage system based on observations of its characteristics. One of the reasons for this assumption is that the period of LTP has been found to last for many hours, similar to how long-term memory can last for days or even years [6]. LTP has a variety of properties that make it a strong candidate for memory formation and storage. One of the most important characteristics of LTP is pathway specificity. In other words, only activated synapses are altered in LTP, not adjacent inactive synapses [7]. Via a complicated computational technique, this mechanism is needed to process information from individual synapses very precisely. Other properties of LTP have been developed, such as cooperatively and associativity.

Cooperatively refers to several presynaptic terminals firing at the same time to cause enough depolarization in the postsynaptic neuron to induce LTP [5]. Associativity, on the other hand, indicates that LTP may be elicited when a weak stimulus at one input is momentarily combined with a strong stimulus at another independent input [8]. Using the above properties, neurons can conduct new information processing and produce LTP [7,8]. Synaptic strength may also be stubbornly diminished, a condition known as long-term depression (LTD), which counteracts synaptic strength enhancement during LTP by interrupting synaptic strength saturation. Low-frequency stimulation of presynaptic neurons fails to depolarize the postsynaptic neuron, resulting in a decrease in synaptic strength between these neurons and the production of LTD. LTD is thought to play a significant role in information storage in the mammalian brain, according to studies [9].

We'll go through a few primary in vitro and in vivo studies, as well as their implications for learning and memory in mammals.

In vitro and In vivo experiments

If LTP is viewed as a process that promotes the creation of a spatial cognitive map of the external environment that can be retrieved later, disruption of LTP can interfere with the formation of spatial memory. More concrete evidence for a potential role of LTP in spatial memory formation came from experiments with two types of mutant mice. The NR1 subunit of

NMDA receptors was knocked out in the CA1 region of the hippocampus in the first type of mutant mouse, resulting in disruption of LTP and concurrent failure of spatial memory formation in the Morris water maze (MWM) test [10]. The persistently active form of Ca2+/calmodulin-dependent protein kinase can be turned on and off at will in a second mutant. The activation of this transgene affected LTP in the frequency range of 1–10 Hz, causing spatial memory instability.

In addition, the mutant mice failed in spatial tasks. When the transgene was switched off, however, LTP was restored, and the animal's ability to form spatial memory was restored [11]. These two sets of early genetic experiments on mutant mice laid the groundwork for LTP as an effective spatial memory mechanism in the Schaffer collateral pathway. Whitlock recently discovered that animals (rats) that underwent Inhibitory Avoidance (IA) training (a memory trace formation test) showed an immediate NMDA receptor-dependent increase in phosphorylation at Ser 831 (but not Ser 845) of the GluR1 AMPAR subunits [12]. When opposed to naive or control subjects, IA training allows the GluR1/2 subunit of the AMPA receptor to traffic in the hippocampus of trained animals. Furthermore, it has been demonstrated using multielectrode recordings that IA training induces fEPSP enhancements, which obstruct subsequent LTP induction in the hippocampal CA1 area in vivo. These results back up the idea that learning induces LTP, which is a necessary corollary to the idea that LTP underpins learning.

Activity-dependent synaptic plasticity at glutamatergic synapses in hippocampal neurons, such as LTP and LTD, is thought to be a cellular mechanism for information encoding and memory consolidation. LTP and LTD mechanisms are subunit-specific NMDA receptor mechanisms, and pharmacological or genetic disruption of various subunits induces changes in LTP or LTD.

Pharmacologically blocking NMDA receptors prevents the development of associative memories needed to conduct the MWM [13].

However, the precise role of LTP and/or LTD in MWM test success is unclear, necessitating further research into selectively inhibiting either LTP or LTD in freely moving animals.

To this end, Ge et al. 2010 discovered that blocking LTP with an NR2A subunit-specific antagonist-NVP leaves spatial memory intact in freely moving rats, while preventing LTD with Ro25-698, which targets NR2B, impairs spatial memory output [14]. To validate their results, they administered bilateral intrahippocampal injections of Tat-GluA23Y, a membrane-permeable peptide that inhibits AMPA receptor endocytosis and thus prevents LTD expression. Injection of the Tat-GluA23Y peptide blocked the development of spatial memory in the same way as Ro25-698 did. As a result, the role of LTD in CA1 in the development of long-term spatial memory in an intact animal is confirmed by this research. Various learning paradigms, such as classical conditioning of eyeblink response include the hippocampus. Bilateral hippocampal lesions hinder the acquisition of trace eyeblink conditioning but does not impact delay conditioning [15-17]. Gruart used this knowledge to evaluate the hypothesis that "associative learning modifies the synaptic power of the hippocampal CA3–CA1 synapse [18]." They showed that the hippocampal CA3–CA1 synapses are involved in the acquisition, extinction, retrieval, and reconditioning of eyelid-conditioned responses using classical conditioning of eyelid responses (CRs). They also discovered that LTP induced by Schaffer collateral High Frequency Stimulation (HFS) interferes with the acquisition of CRs as well as the linear relationships between learning scores and extracellular recordings of Field Excitatory Postsynaptic Potential (fEPSP) slopes.

Saturating CA3–CA1 synapses with LTP-inducing stimulation prevented further synaptic plasticity changes, resulting in both anterograde and retrograde amnesia [19-20].

Gruart also demonstrated that an NMDA-receptor antagonist could inhibit both the formation of eyeblink CRs and functional changes in intensity

at the CA3–CA1 synapse, preventing LTP induction in vivo. "Functional transformations occurring at CA1 pyramidal cells appear to be needed for proper acquisition, extinction, recall, and reconditioning of eyelid CRs," they concluded. Inhibiting the molecular mechanisms responsible for plasticity is one way to assess the role of LTP in actions [21]. LTP is divided into two phases: induction and maintenance, which are close to learning and memory storage. Protein kinase Mzeta (PKMz), a brain-specific atypical PKC isoform, has been shown to be both necessary and appropriate for the maintenance of LTP21. PKMz is blocked by the application of a cell-permeable synthetic peptide (ZIP) [22]. On tetanized synaptic transmission, bath application of ZIP to hippocampal slices inhibits synaptic potentiation triggered by intracellular perfusion of PKMz and reverses developed late LTP, without reversing early LTP or affecting the baseline [23].

Pastalkova answered two related questions based on this research Is it possible to reverse the late phase of LTP in vivo by inhibiting PKMz with ZIP? If so, does ZIP result in retrograde spatial memory loss? Injecting ZIP into the rat hippocampus reversed both LTP maintenance and the loss of 1-day-old spatial information in vivo [24]. The persistence of synaptic potentiation and spatial memory can share a common molecular mechanism, according to this research. As a consequence, it adds to the proof that the processes that preserve LTP often maintain spatial memory. Although establishing a causal relation between hippocampal LTP and memory development was challenging, two groups presented evidence by specifically demonstrating the frequency of LTP in animals during behavioral training [25,26]. LTP in the amygdala in response to fear conditioning training (either ex vivo or in vivo recording techniques). Both groups ultimately came to the same conclusion: fear conditioning triggers synaptic potentiation in the amygdala. This form of LTP is analogous to hippocampal synaptic plasticity, according to further research. These were the first studies to show that LTP could be activated by naturally occurring neuronal firing patterns caused by environmental signals. Although it has been difficult to specifically demonstrate LTP in connection with spatial learning physiologically, biochemical markers of LTP induction, such as ERK activation, CaMKII activation, PKA/PKC activation, and altered gene expression, have been shown to occur with spatial learning.

The large range of molecular changes observed during LTP occurrence in vitro and spatial learning in vivo strongly indicates that LTP and hippocampus-dependent memory formation are related [27,28]. Attempts to understand the endogenous conditions for information storage in the hippocampus during memory output have been made in a number of studies. As previously mentioned, LTP is commonly regarded as the mechanism responsible for this data storage. Individual synapses undergo both functional and structural reorganization as a result of synaptic plasticity in the form of LTP, which progresses over time. LTP induction (post-tetanic potentiation), short-term potentiation, LTP expression (early LTP), and maintenance (late LTP) are all stages of hippocampal LTP [26,29,30].

Although the network conditions under which LTP initiated are uncertain, it is assumed that theta frequency (5–12 Hz) filed possible oscillations are crucial for the acquisition of new information. Intracellular recordings from the somata and dendrites of CA1 pyramidal cells [31], principal and basket cells in anesthetized rats have extensively studied theta frequency field oscillation, which represents synchronized synaptic potentials that entrain the discharge of neuronal populations within the approximately 100–200 ms range [32]. Theta frequency (4–8 Hz) oscillations, according to Vertas and Kocsis are the source of a prominent EEG signal [33]. The functionally related patterns of network operation, which may occur due to intrinsic oscillatory properties of principal cells and interneurons powered by intra and extra hippocampal connections, are the mechanism that attribute to the generation of theta rhythm [32,34]. Theta rhythm has been related to neurotransmitters such as GABA and NMDAR-dependent neuron transmission. Transmissions of cholinergic and serotonergic neurons have also been related to the production of theta rhythms [35,36].

Theta oscillations are mainly correlated with voluntary activities such as running, novel environment exploration, spatial navigation, warning states and the rapid eye movement sleep period [36-40]. The production of theta rhythmic behavior has also been related to the learning of conditioned responses [41,42]. There is a clear correlation between theta waves, hippocampal development, and related behaviors, according to the data. Theta rhythm is thought to play an important role in memory and learning [33,42,43]. Theta rhythm is shown to play an important role in coding the velocity and position of the animal in spatial learning and memory output [38]. This enables neocorticohippocampal transmission of new spatial information when secondary and motor information is acquired and/or encoded [35,44].

Hippocampal pyramidal cells and GABAergic interneurons in the stratum oriens-alveus and stratus lacunosum-molecularae, according to studies, have resonance at 3–10 Hz [45-47]. They often show a preference for inputs in the 2–7 Hz range while shooting. Furthermore, frequent membrane potential oscillations have been observed in CA3 pyramidal neurons as early as postnatal day 10, and their frequency increases with age [48]. In light of these results, it has been suggested that different types of neurons in the hippocampal network transmit input signals with different frequency components, with pyramidal cells and some interneurons responding preferentially to theta frequencies, while fast spiking interneurons respond to inputs at beta or gamma frequencies (30–50 Hz) [47].

Theta rhythm has been related to place cell firing, which is seen when an animal is doing exploratory navigation, and this bursting pattern is within the same range as the EEG theta [49]. In vivo studies have found a close correlation between LTP formation in CA1 neurons and theta oscillations in CA3 pyramidal neurons, indicating a potential link between LTP formation, theta rhythm, and learning [37,50-52]. Evidence indicates that the firing patterns of pyramidal neurons and network-driven (field) oscillations (5 Hz) are identical. As a consequence, frequencies in this range may be especially important for inducing synaptic plasticity in the context of spatial memory formation [53]. In animal models, the rate of learning was significantly associated with hippocampal EEG theta control, indicating a role for theta rhythm in promoting learning [41,42,54]. Short-term memory functions, on the other hand, have been connected to a frequency of about 4 Hz [55,56].

In animal models, lesions in the medial septum and the resulting decrease in hippocampal theta rhythm have been related to impaired spatial memory tasks [43]. The role of hippocampal theta activity in memory formation rather than consolidation has been confirmed in more studies [57]. In addition, studies were conducted to better understand the role of cross structural and cross frequency-coupling mechanisms in human spatial working memory. In a recent study, Alekseichuk found that theta and high gamma synchronization in the prefrontal cortex are mainly responsible for spatial working memory in humans. Several studies have looked into the impact of different novel molecules or neurotransmitters on LTP and related brain waves. Several proteases involved in the formation of LTP have recently attracted the attention of researchers. Calpains are a group of calcium-dependent proteases that play an important role in the central nervous system's physiological and pathological conditions [58].

Calpains occur in two isoforms in the mammalian brain: calpain-1 (also known as -calpain) and calpain-2 [59,60]. Calpain-1 appears to be important for the development of LTP in the CA1 regions of the hippocampus elicited by theta burst stimulation. Calpain-2 activation during the one-hour consolidation cycle after theta burst stimulation, on the other hand, is thought to restrict the degree of synaptic potentiation, but its inhibition results in increased LTP [61]. A recent research indicates that calpain-1 and calpain-2 play opposing roles in learning and memory, and that this disparity in behavior is due to their opposing roles in LTP [62]. Sulpiride, a D2 receptor blocker, was shown by Monte-Silva, 2011 to abolish the motor cortical LTP/LTD effects of theta burst Transcranial Magnetic Stimulation (TBS) in humans [63].

Gong on the other hand, found that genetic deletion of GABA transporter-1 (GAT1) decreased hippocampal theta oscillations, which was expressed in mice as impaired hippocampus-dependent learning and memory behaviors. It's worth noting, however, that genetic deletion of the GABA transporter-1 transporter had no effect on LTP induced by

high frequency stimulation or LTD induced by low frequency stimulation [64]. Dale explored the effects of the novel antidepressant 'vortioxetine' on hippocampal plasticity and the generation of theta waves. In whole animal electroencephalographic recordings, vortioxetine improved fronto-cortical theta capacity during active wake and enhanced LTP in the CA1 region of the hippocampus [65].

The prevention of 5-HT-induced increases in inhibitory post synaptic potentials from CA1 pyramidal cells, which is thought to be due to 5-HT receptor antagonism, is said to be the cause of these results. Increased pyramidal cell production resulted in improved synaptic plasticity in the hippocampus and improved cognitive performance as a consequence of the latter impact.

Long-Term Potentiation (LTP) of synaptic transmission at CA3-CA1 Schaffer collateral synapses is impaired when highly sulfated Heparan Sulfate (HS) is removed with heparinase 1.

In a fear conditioning model, this digestion of HS results in impaired background discrimination and oscillatory network activity in the low theta band after fear conditioning, suggesting a role for heparan sulfate (HS) proteoglycans in controlling hippocampal LTP and theta band activity [66]. In freely moving rats, the effect of memantine, an uncompetitive N-methyl-D-aspartate receptor antagonist, on electrographic activity and hippocampal LTP was examined [67].

The injection of scopolamine (5 mg/kg ip) before the administration of memantine had no effect on the enhancement of LTP in the hippocampus. During walking and awake immobility, memantine (5 or 10 mg/kg ip) significantly strengthened the auditory startle response and enhanced gamma oscillations in hippocampal local field potentials of 40–100 Hz [67]. Other novel methods for manipulating hippocampal LTP and related brain waves have been examined in both human and animal models. One of these is the peripheral vestibular system and its connection to the hippocampus. According to studies, vestibular stimulation is not needed for the generation of theta rhythm, as it occurs prior to the start of movement [68,69]. However, studies show that peripheral vestibular system activation can modulate hippocampus function.

In rats, Bilateral Vestibular Loss (BVL) induced major dysfunction of hippocampal place cells as well as theta rhythm [70-74]. Although it is clear that vestibular loss impairs learning and memory, especially spatial learning and memory [75,76], it is unclear how vestibular knowledge contributes to hippocampal theta.

Another tool for addressing plasticity in the context of LTP is repetitive TMS (rTMS).It is a safe tool for diagnosing and treating a wide range of severe pathological disorders, such as stroke, depression, Parkinson's disease, epilepsy, pain, and migraines. Although long-term TMS has an impact on neurotransmitters and synaptic plasticity through LTP and LTD, the pathophysiological mechanisms that underpin these effects are unknown [77]. Our knowledge of the structural and functional signatures of learning and memory (possibly LTP/LTD and theta waves, respectively) has assisted the scientific community in designing and evaluating novel therapeutic strategies for conditions in which cognitive decline is a significant clinical manifestation. A growing body of evidence indicates that a variety of environmental factors/agents, including man-made agents including electromagnetic radiation, influence these signatures or associated behaviors in animal models [78-82].

Understanding these learning and memory signatures will help us learn more about how these agents affect synaptic plasticity in vivo. Synaptic dysfunction is also a symptom to a variety of neurological disorders, including Alzheimer's disease [83-85]. Understanding synaptic transmission, the formation of LTP and LTD in the hippocampal formation will aid in the production of multiple therapeutic agents through targeted pharmaceutical intervention to combat not only this crippling disease but also other degenerative diseases that impair learning and memory signatures [86].

Conclusion

Although further research is required to pinpoint the exact mechanism linking LTP to memory, our current understanding strongly indicates that LTP and or LTD are causally related to memory formation and consolidation. The large amount of data produced by LTP and LTD has allowed researchers to investigate the role of genetic and epigenetic mechanisms in neuromodulator-induced learning and memory. Norepinephrine-induced LTP, for example, induces epigenetic modifications to histone and DNA molecules, resulting in the synthesis of new plasticity-related protein. In neurodegenerative disorders, the normal physiology of neuronal synapses is impaired, resulting in cognitive impairment. Alzheimer's disease, PTSD, ADHD, and depression have all been related to changes in synaptic neurotransmission. As a result of this study, prospective researchers will be able to pursue new areas of neuroscience for the treatment of memory-related cognitive dysfunctions. An increasing body of research has found evidence of epigenetic processes being impaired in cognitive impairments. Neuroscience research has advanced well beyond our realistic standards in the past. Future study using multimodal approaches may be able to establish the direct role of LTP/LTD in learning and memory, as well as conditions associated with these functions.

Ethical Clearance

Not applicable

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Conflict of Interest

Nil

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