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Different Processes involved in Learning and Memory: A Review.

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ABSTRACT

Learning is defined as the acquisition of information and skills or it is the process by which new information is acquired and subsequent retention of the information is called memory, which is the process by which acquired knowledge is retained. Learning and memory are the basic constituents of cognitive behavior and can be conceived as both a psychological process, as well as change in synaptic neural connectivity. Neuronal plasticity and more specifically synaptic plasticity are widely recognized as the processes by which information is stored in neuronal networks engaged during the acquisition of information. LTP and LTD has been on identifying the causal steps that occur at individual synapses mediating lasting changes in synaptic efficacy in terms of changes in presynaptic transmitter release, alterations in postsynaptic glutamatergic receptors, the action of neuromodulatory transmitters, the signal transduction pathways activated, gene activation and synthesis of new proteins. Memory consolidation is the process by which fragile short-term memory is converted into stable long-term memory. It is accepted today that synaptic plasticity is a cellular mechanism of learning and memory processes. Interestingly, similar molecular mechanisms subserve both memory and synaptic plasticity consolidation. In this review, we described how the different neurotransmitters and molecular mechanisms play an important role in different processes involved in Learning and Memory.

Keywords: Learning, Memory, Brain, Neurotransmitters, Long Term Potentiation, Long Term Depression, Synaptic Plasticity, Alzhiemer Disease.

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INTRODUCTION

Learning and memory is a property of all living organisms and the underlying cellular mechanism(s), or at least some primitive form(s) of it, must also have appeared very early during evolution. While learning and memory has been reported in unicellular organisms, it is only in more complex organisms that learning and memory has been extensively studied at the molecular and cellular levels. Indeed, some forms of learning and memory have been found in invertebrates as well as in early vertebrates [1]. It is generally assumed that learning and memory is due to the plasticity of the nervous system, and the search for the mechanisms of learning and memory at the molecular level has thus focused on those mechanisms that can account for activity-dependent modifications of synaptic strength. [2].

Memory is an organism's ability to store, retain and subsequently retrieve information. Memory is the ability of an individual to record sensory stimuli; events, information etc. retain them over short or long periods of time and recall the same at a later date when needed. In today's stressful and competitive world, problems like poor memory, lower retention and slow recall are very common. Age, stress, emotions are conditions that may lead to memory loss, amnesia, anxiety, high blood pressure, dementia or schizophrenia and Alzheimer's disease (AD)[3].

Learning is defined as the acquisition of information and skills or it is the process by which new information is acquired and subsequent retention of the information is called memory, which is the process by which acquired knowledge is retained. Learning and memory can be conceived as both a psychological process, as well as change in synaptic neural connectivity. Learning and memory are the basic constituents of cognitive behavior. [4]

Processes involved with memory: From the information processing point of view there are three main stages in the formation and retrieval of memory:

- Encoding or registration (processing and combining of received information)
- Storage (creation of a permanent record of the encoded information)
- Retrieval or recall (calling back the stored information in response to some cue for use in a process or activity)

We know that some memories last for only a few seconds, whereas others last for hours, days, months, or years. Simply memory can be classified into:

Short-term memory:	• Includes memories that last for seconds or at most minutes unless they are converted into longer-term memories. It may be due to *presynaptic facilitation or inhibition,*occurs at synapses that lie on terminal nerve fibrils immediately before these fibrils synapse with a subsequent neuron.
Intermediate long-term memories:	•It last for days to weeks but then fade away, intermediate long-term type can result from temporary chemical or physical changes, or both, in either the synapse presynaptic terminals or the synapse postsynaptic membrane.
Long-term memory	•Long-term memory once stored, can be recalled up to years or even a lifetime later and it is generally believed to result from actual *structural changes*, instead of only chemical changes, at the synapses, and these enhance or suppress signal conduction.

Mechanism for Facilitation: In the case of facilitation, at least part of the molecular mechanism is believed to be the following:

1. Stimulation of the facilitator presynaptic terminal at the same time that the sensory terminal is stimulated causes serotonin release at the facilitator synapse on the surface of the sensory terminal.
2. The serotonin acts on serotonin receptors in the sensory terminal membrane, and these receptors activate the enzyme adenyl cyclase inside the membrane. And, finally, the adenyl cyclase causes formation of cyclic adenosine monophosphate (cAMP) also inside the sensory presynaptic terminal.
3. The cyclic AMP activates a protein kinase that causes phosphorylation of a protein that itself is part of the potassium channels in the sensory synaptic terminal membrane; this in turn blocks the channels for potassium conductance. The blockage can last for minutes up to several weeks.
4. Lack of potassium conductance causes a greatly prolonged action potential in the synaptic terminal because flow of potassium ions out of the terminal is necessary for rapid recovery from the action potential.
5. The prolonged action potential causes prolonged activation of the calcium channels, allowing tremendous quantities of calcium ions to enter the sensory synaptic terminal. These calcium ions cause greatly increased transmitter release by the synapse, thereby markedly facilitating synaptic transmission to the subsequent neuron.

Structural changes occur in synapses during the development of long term memory: Development of true long-term memory depends on physically restructuring the synapses themselves in a way that changes their sensitivity for transmitting nervous signals. The most important of the physical structural changes that occur are the following:

1. Increase in vesicle release sites for secretion of transmitter substance.
2. Increase in number of transmitter vesicles released.
3. Increase in number of pre synaptic terminals.
4. Changes in structures of the dendritic spines that permit transmission of stronger signals.

Thus, in several different ways, the structural capability of synapses to transmit signals appears to increase during establishment of true long-term memory traces. Memories are frequently classified according to the type of information that is stored. One of these classifications divides memory into:

(A) ***Declarative memory*** basically means memory of the various details of an integrated thought, such as memory of an important experience that includes: (i) memory of the surroundings, (ii) memory of time relationships, (iii) memory of causes of the experience, (iv) memory of the meaning of the experience, and (v) memory of one's deductions that were left in the person's mind.

(B) ***Skill memory*** is frequently associated with motor activities of the person's body, such as all the skills developed for hitting a tennis ball, including automatic memories to (i) sight the ball, (ii) calculate the relationship and speed of the ball to the racquet, and (iii) reduce rapidly the motions of the body, the arms, and the racquet required to hit the ball as desired all of these activated instantly based on previous learning of the game of tennis then moving on to the next stroke of the game while forgetting the details of the previous stroke.

Consolidation of memory: For short-term memory to be converted into long-term memory that can be recalled weeks or years later, it must become "consolidated." i.e. the short-term memory if activated repeatedly will initiate chemical, physical, and anatomical changes in the synapses that are responsible for the long-term type of memory, this process requires 5 to 10 minutes for minimal consolidation and 1 hour or more for strong consolidation. Rehearsal enhances the transference of short-term memory into long-term memory, rehearsal of the same information again and again in the mind accelerates and potentiates the degree of transfer of short-term memory into long term memory and therefore accelerates and enhances consolidation. The brain has a natural tendency to rehearse newfound information, especially newfound information that catches the mind's attention. Therefore, over a period of time, the important features of sensory experiences become progressively more and more fixed in the memory stores. This explains why a person can remember small amounts of information studied in depth far better than large amounts of information studied only

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superficially. It also explains why a person who is wide awake can consolidate memories far better than a person who is in a state of mental fatigue.[5]

Role of specific parts of the brain in the memory process: The cerebrum and hippocampus are considered important for declarative memory, and the cerebellum for procedural memory. The most popular candidate site for memory storage is the synapse, where nerve cells (neurons) communicate. In other words, a change in the transmission efficacy at the synapse (synaptic plasticity) has been considered to be the cause of memory. A particular pattern of synaptic usage or stimulation, called the conditioning stimulation, is believed to induce synaptic plasticity. The LTD in the cerebellum has been considered to be the cellular basis of motor learning.[6]

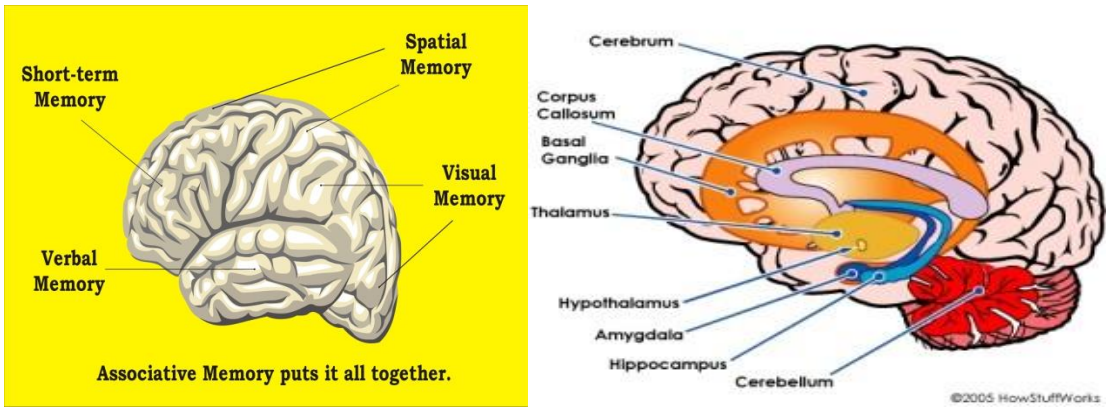

Fig 1 Parts of brain in the memory process

Hippocampus: The hippocampus is located deep inside the temporal lobe, and it receives inputs from virtually all association areas in the neocortex, including those in the parietal, temporal and frontal lobes, via the adjacent parahippocampal gyrus and entorhinal cortex. Therefore, the hippocampus has available highly elaborated multimodal information, which has already been processed extensively along different, and partially interconnected sensory pathways. Additional inputs come from the amygdale and via a separate pathway, from the cholinergic and other regulatory systems. Its extensively divergent system of output projections enables to feedback into most of the areas from which it receives inputs. Lesion studies indicate that the hippocampus is important in the encoding of various types of memory such as declarative, episodic or working memory. Neurophysiological evidence also directly indicates that many of the synapses within the hippocampus can become modified as a result of experience. [7]

The hippocampal forms part of three related but different circuits: one at the time of acquisition, another at the time of memory formation and another at the time of retrieval. During acquisition it must receive information from the working memory manager regions of the prefrontal cortex, which is related by the entorhinal cortex and the dentate gyrus. At the time of retrieval, in the first few amygdala integrate a network with the entorhinal and parietalcortex, which are needed for retrieval.

The sequence of biochemical events in hippocampus: The sequence involves the activation of NMDA, AMPA and metabotropic glutamate receptors followed by changes in second messengers and biochemical cascade led by enhanced activity of protein kinase A, C and G and Calcium-calmodulin protein kinase II, followed by changes in glutamate receptor subunits and binding properties and increased expression of constitute and inducible transcription factors. 20-120% increased in the activity of enzymes such as NO syntase, heme oxygenase, PKG, PKA,PKC or C a Mk II, several- fold increased in cGMP and cAMP, 20-80% increased in AMPA binding or in the amount of measurable GluR1 or NMDA1 were seen after inhibitory avoidance learning.

Some of the biochemical changes are no doubt, structure-specific (they are not seen in other brain regions) and all appear to be learning- specific (they are not seen in animals exposed to the footshock alone or to the apparatus without the footshock). Some consequences of the biochemical changes may be synapse-specific, if they preferentially affect the synapses that are being activated at the time. [8]

Dorsal striatum: The dorsal striatum plays a vital role not only in learning new response strategies but also in the inhibition of pre-existing strategies when a shift in strategy is required. A dorsal striatum-dependent

system may be necessary for the formation of reinforced S-R associations. In addition, a hippocampus–mediated system appears to be centre for acquiring multiple relationships among stimuli, this system is called as a declarative or relational memory system appears to be essential for processing information about and flexible utilization of the relationship between multiple external cues and events. it is necessary for the mediation of stimulus response learning. [9]

Parahippocampal region (PHR): The PHR receives inputs from widespread secondary or 'association' cortical regions and provides the major conduct for hippocampal outputs to the same cortical association areas. The anatomical evidence indicates that the PHR occupies a pivotal position for mediating memory functions of the hippocampal region. Neurophysiological findings indicate that the PHR plays a critical role in recognition memory, independent of its role as an intermediary for cortical-hippocampal interactions. This evidence comes mainly from experiments examining the effects of damage to the hippocampal region on performance in a simple recognition memory test known as delayed nonmatching to sample (DNMS). PHR contains the necessary coding elements for identifying individual stimuli, for maintaining individual stimuli representations across long delays and for mediating specific match-nonmatch comparisons. [10]

Basal forebrain: The cholinergic basal forebrain comprises cholinergic cell bodies in the medial septal nucleus, the diagonal band of Broca, and the nucleus basalis magnocellularis. Apparently regardless of training protocol Morris Water Maze (MWM) deficits were reported in rats with nucleus basalis lesions. Most severe hidden-platform acquisition and probe trial deficits were seen in rats with combined basal forebrain lesions of the medial septum/ diagonal bands and the nucleus basalis. [11]

Cerebellum: It has been shown that mice with cerebellar damage do display impaired MWM learning. The cerebellum receives input from brain areas involved in many aspects of MWM learning including visual cortex, superior colliculus and hippocampus, and, apart from motor control and acquisition/ retention of conditioned reflexes, its specific functions may include a variety of cognitive processes as well. Petrosini et al. suggested that the role of the cerebellum in spatial learning is primarily that of controlling the procedural aspects of the task.

Various Ions, Neurotransmitters and Messengers associated with Memory: Memories are thought to be due to lasting synaptic modifications in the brain. Synaptic modifications within memory traces have been linked to a number of mechanisms that involve multiple and interacting afferent pathways, neurotransmitters, messenger molecules and gene products.

Calcium (Ca^{+2})	**Potassium (K^{+})**
- It plays an essential role in a variety of intracellular signaling cascade which underlie mechanisms for the dynamic control of cell functions. - Ca^{+2} participates in control of not only the formation and development of neural structures that cognition depends on, but also signal processing and synaptic plasticity that define learning and memory. - Temporal and spatial control of Ca^{+2} signaling through the neutral networks involved in learning and memory are fundamental for cognitive capacities. - The Ca^{+2} signals can not only spread through neurons as global Ca^{+2} waves, but can also be highly localized within micro-domains of sub-cellular components such as at close oppositions of mitochondria and the endoplasmic reticulum (ER), dendritic spines or	- Potassium-selective channels are constituents of plasma membranes. In neurons, both synaptic transmission and the onset and duration of excitations are governed to a large extent by K^{+} channel kinetics. - These properties of K^{+} channel facilitate higher-order membrane phenomena such as signal integration, spike patterning and synaptic plasticity. Modulations of the sAHP and A-type K^{+} channel modification in hippocampal pyramidal neurons are thought to contribute to learning and memory. - The sAHP amplitude in hippocampal pyramidal neurons can be reduced by signaling pathways triggered by a variety of neurotransmitters, like Acetylcholine which have been implicated in learning and memory. [12]

presynaptic terminals. Losing effective control of cytosolic free Ca^{+2} concentrates (Ca^{+2}) according to fundamental demands undoubtedly contributes to neurobiological and memory disorders and ageing. - Blocking L- and N- type voltage- operated Ca^{+2} channel (VOC C) or N-methyl- D-aspartate (NMDA) receptors has also been reported to cause degeneration of neurons. - Action potentials reliably evoke Ca^{+2} transients in axons and boutions through VOCCs. The VOCCs are involved in providing the Ca^{+2} for neural signals underlying learning and memory in neurals networks. Blocking the L-type VOCCs with ninodipine, has been reported to impair learning and memory. [12]	

Principle Neurotransmitters:

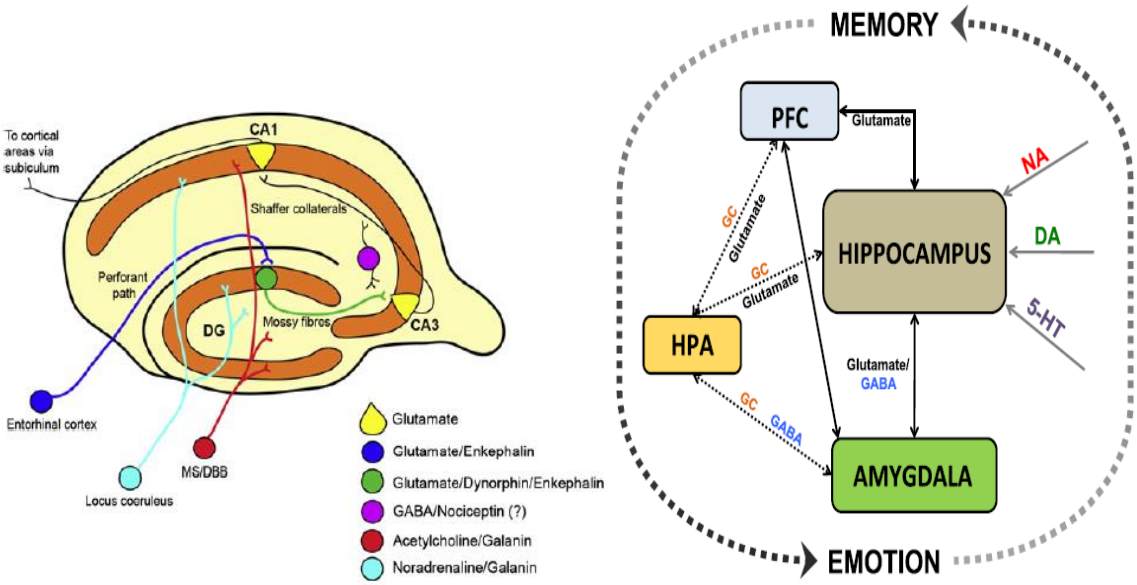

Fig 1.2 Role of neurotransmitters in the memory processes

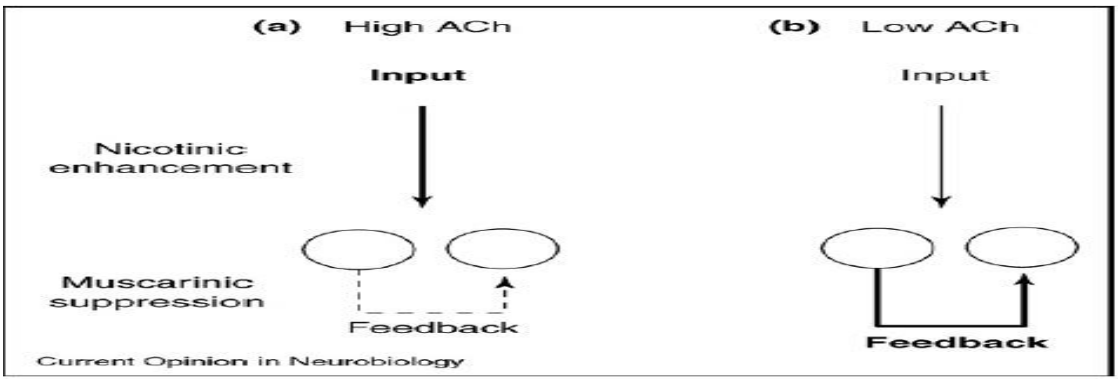

Fig: 1.3 Effect of acetylcholine on cortical dynamics

Acetylcholine: Pharmacological data clearly indicate that muscarinic and nicotinic acetylcholine receptors have a role in the encoding of new memories. Localized lesions and antagonists infusions demonstrate the anatomical locus of these cholinergic effects, and computational modeling links the function of cholinergic modulation to specific cellular effects within these regions. Computational models demonstrate that the cellular mechanisms of these effects could enhance the encoding of memories. These cellular mechanisms include: i) enhancement of the influence of afferent input to excitatory feedback; ii) regulation of inhibition and theta rhythm oscillations; iii) enhancement of persistence spiking for active maintenance and iv) enhancement of synaptic modification. As shown in figure 1, acetylcholine might enhance the encoding of memory by enhancing the influence of feed forward afferent input to the cortex, making cortical circuits responds to features of sensory stimuli, while decreasing excitatory feedback activity mediating retrieval. This change in dynamics results from effects including nicotinic enhancement of excitatory afferent input and muscarinic presynaptic inhibition of excitatory feedback.

Ach might also enhance encoding via muscarinic presynaptic inhibition of excitatory feedback system within cortical circuits. High cholinergic levels during waking support feedback, providing dominant feedback effects appropriate for encoding, and reducing the influence of hippocampus on entorhinal cortex. it might also enhance encoding through its role in increasing theta rhythm oscillations within the hippocampal formation. Learning is enhanced when stimuli are presented during periods of theta rhythmicity. During the encoding phase, strong entorhinal input ensures accurate storage of new memories, whereas the reduction of CA3 input prevents retrieval of previously stored associations from causing interference. During the opposite phase, strong CA3 input ensures accurate retrieval of old memories. Acetylcholine has been demonstrated to enhance persistent spiking of individual cortical neurons. In standard control conditions, entorhinal neurons will respond to an intracellular depolarizing current injection by generating spiking activity during the current injection, but will terminate spiking after the end of current injection. By contrast, during perfusion with the cholinergic agonist carbachol, neurons respond to the same magnitude and duration of depolarizing current injection with an increased number of spikes, and when the current injection ends, they persist in spiking for an extended period of many seconds or even minutes. [13]

Glutamate receptor: Glutamate is the major excitatory neurotransmitter in the brain. It mediates its functions through two types of receptors, ionotropic gluatamate (iGlu) receptors, such as the NMDA, AMPA and kainite receptors and metabotropic gluatamate (mGlu) receptors. mGlu1 receptors have also been suggested to play a role in the modulation of cognitive processes, based on results obtained with mouse mutants, or using either non-selective mGlu1/mGlu5 antagonists and/or compounds that were locally administered into the hippocampal area. [14]. Hippocampal long-term potentiation (LTP) was impaired in knockout mice lacking the mGlu1 receptor and more recently it was demonstrated that pharmacological mGlu1 receptor blockade also impairs hippocampal LTP. All this suggests a prominent role of the mGlu1 receptor in learning and memory processes.AMPA (α-amino- 3- hydroxyl-5-methyl-4-isoxazolepropionic acid)-type glutamate receptors mediate fast excitatory transmission throughout the central nervous system. Positive modulation of these receptors can potentially enhance cognition by, firstly, offsetting losses of glutamatergic synapses; secondly promoting synapting plasticity; and thirdly increasing the production of tropic factors.

Induction of LTP, a presumed substrate of memory, requires intense depolarization of spine heads by AMPA receptors; increasing currents through the receptors is a plausible route for promoting the formation of LTP. Ampakines (AMPA receptor modulators) enhance the encoding of memory in a variety of animal models.[15].

GABAergic receptor: The central inhibitory neurotransmitter γ-aminobutyric acid (GABA) is found in all areas of the brain. It is well established that the GABA system is a target for a variety of central pharmacological agents including sedatives, analgesics and anticonvulsants. The interaction between the cholinergic and GABAergic systems in learning and memory has been shown by several studies. The amygdala and hippocampus are some of the neuronal systems taking part in memory formation and are rich in cholinergic synapses that are under the inhibitory control of the GABAergic system. The findings suggest that GABAergic drugs might impair memory formation through effects on cholinergic systems. However, other investigators have shown that the GABA receptor agonist's muscimol and baclofen enhance memory.[16].

Serotonin: There are two robust effects of 5-HT in the hippocampus. First, 5-HT exerts a hyperpolarizing influence on principal cells; directly, via 5-HT_{1A} receptors, and indirectly, via facilitation of GABA release from

local interneurons through 5-HT_3 receptors. Activation of 5-HT_{2A} and 5-HT_{2C} receptors has been suggested to induce depolarization in principal cells, but these effects appears to be dominated by the depolarizing effects of 5-HT, as both application of 5- HT will hyperpolarize principal cells in slice preparations of the dentate gyrus. In addition, through 5-HT_{2C}, 5-HT_4 and 5-HT_7 receptors, after hyperpolarizing (AHP) currents are down regulated, leading to reduced adaptation in principal cells. The increased firing rate observed in slices after prolonged application of 5-HT has been linked to this mechanism. Serotonin receptor subtypes that have been demonstrated to occur in brain regions capable of playing a role in learning and memory include the 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, and 5-HT_7 class of receptors. [17]. Serotonin receptor agonist Buspirone impaired the memory in rats in conditioned avoidance response by acting on 5-HT_{1A}, Quipazine in rats shows enhanced effect by acting on 5-HT_{2A}.

Dopamine: Thierry and colleagues described in 1973 that dopamine in the brain was not restricted in its occurrence to the rigrostriatal system and the tubero-infundibular systems, but also occurred in the cerebral cortex. A few years later evidence was obtained that dopamine has a great impact on cognitive processes. Comparable findings in rats were obtained by Simon and Colleagues. Lesions of dopaminergic cells in the ventral segmented area impaired retention of previously learned delayed alteration responses. In the field of memory and learning studies the mesolimbic dopaminergic and especially the mesolimbic system clearly have received most of the scientific attention. These areas are known to play a crucial role in various cognitive processes. In studies of dopamine function in working memory have focused on the D_1 and D_2 receptors, with most evidence suggesting a dominant role for the D_1 receptor. Since the dopamine D_4 receptor is highly expressed in PFC, it may also contribute to working memory.

The data strongly suggest that both dopamine D_2 and D_3 receptors mediate the effects of dopamine on the integrative function of learning and memory. Dopamine D_1 receptors in the prefrontal cortex selective modulate working memory processes responsible for the accurate recall of the location of food reward. In contrast, dopamine D_1 receptors in the nucleus accumbens modulate memory-based search behavior, without prior knowledge of the location of food. [18].

Histamine: It was found that histamine produced a concentration-dependent increase in glutamate release in the hippocampus via H_1 and H_2 receptors. Therefore, the glutamate released from the hippocampus by histamine may be responsible for the spatial memory deficits. It has also been reported that postsynaptic H_1 -receptors and presynaptic H_3 -receptors are important for learning and memory in both active avoidance responses and radial maze performance in rats.[19].

Neuromodulators:

Cannabinoid receptor: Cannabinoids presynaptically alter release of GABA and glutamate from hippocampal neurons, points to a potentially critical role for the cannabinoid receptor within this critical substrate for memory processing. Recent observations have in fact shown that successful DNMS behavioral performance can be attributed to the intensity of encoding of trial-relevant information by hippocampal CA3 and CA1 neurons, and that cannabinoids disrupt this encoding phase. Thus, short-term memory likely represents a process involving not only the hippocampal cells, but also reciprocal projections between entorhinal cortex and hippocampus. [20].

Opioid receptor: Endomorphins 1 and 2 have been shown to impair passive avoidance learning in mice. β-Funaltrexamine, a μ-opioid receptor antagonist, antagonizes the endomorphins-induced impairment of learning and memory. Furthermore, there is a possibility that endomorphins 1 and 2 markedly decrease acetylcholine release in the brain through the mediation of μ-opioid receptors, because opioid substances have been shown to decrease the output of acetylcholine in the brain area connected to learning and memory. It was reported that κ-opiod receptor agonists, dynorphin A-(1-13) and U-50,488H, improved the scopolamine-induced impairment of spontaneous alteration performance in mice, carbon monoxide (CO) - induced delayed amnesia in mice and also the β-amyloid peptide and carbacol-induced impairment of learning and memory in mice and rats respectively. (-)-Pentazocine shows analgesic effects by acting on κ-receptors in mice and human, and (+)-Pentazocine improves learning and memory impairments in mice, acting on σ receptors. When cholinergic neuronal transmission is impaired, κ-opioid and σ receptor agonists enhance this neuronal transmission, and as a result, the learning and memory impairment is improved. [21].

Corticosteroids: Studies from two laboratories have demonstrated that chronic treatments with either corticosterone or restraint stress induce a remodeling of apical dendrites of layer II/III pyramidal neurons in the mPFC , such that there is greater proximal branching, whereas spine density is reduced. Although alterations of the corticosteroid milieu have also been reported to result in impaired spatial working memory, as measured in the T-maze.[22].

Neuropeptides: Endogenous neuropeptides such as vasopressin (AVP), adrenocorticotropin and opioids have significant effects on learning and memory. Researchers have demonstrated that either peripheral or central administration of AVP during the training process or after training significantly delays the extinction of the active avoidance response in intact rats. It appears that AVP and the C -terminal fragments may affect learning and memory processes through vasopressinergic receptors. One study indicates that vasopressin modulates the noradrenergic system in some nuclei, such as the septum, hippocampus, and lateral nuclei of the thalamus which are related to memory formation. Peptides such as AVP, DGAVP (desglycinamide arginine vasopressine) and PLG (L-prolyl-leucyl-glycinamide) have been found to increase or modulate the means and percentage of θ rhythms in the hippocampal EEG. One can assume that vasopressin can modulate hippocampal θ rhythm or hippocampal electrical activities to facilitate memory processes.

Subsequent to Murphy and Miller's demonstration in the 1950s that ACTH delayed the extinction of shuttle box avoidance behaviour in intact rats. Not only shock-motivated responses were influenced by ACTH and MSH, but also appetitively motivated tasks such as T-mazes with food or sex as the reward. They found that ACTH and MSH can enhance reversal learning in a two-choice visual discrimination paradigm in which rats were trained to avoid a shock by running to a white door. The effects of endorphin and encephalin on learning and memory have been analyzed by observing the increasing of passive avoidance responses after injection (i.p.) of β-endorphin before learning. Both seem to have an effect on memory consolidation. Different endorphins or encephalins have different effects on memory retention.

The experimental results show that the major influences of endorphin and encephalin are memory consolidation and retention. β-endorphin, α-endorphin, and Met-encephalin facilitate memory consolidation; β-endorphin promotes memory retention as well. Retrograde-amnesia and impairment of memory consolidation are caused by γ-endorphin and Leu-encephalin. Endorphin or encephalin could modulate other peptides related to learning and memory and thus influence the learned behavior.[23].

Brain-derived neutrophic factor (BDNF): During vertebrate development, neuronal survival depends on the supply of target-derived trophic factors such as nerve growth factor (NGF). Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, including NGF, neurotrophin-3 (NT-3) and NT-4/5, which play important roles in the survival, maintenance, and growth of neurons in the central and peripheral nervous systems. It has been demonstrated, using a nuclease protection assay and in situ hybridization that the level of BDNF mRNA is elevated in the rat hippocampus but not in the cerebellum, striatum, frontal, and mid- or caudal neocortex in learning groups compared with control groups after 3 and 6 days of training in a water maze. In situ hybridization revealed a rapid and selective induction of BDNF expression in the CA1 subfield of the hippocampus during hippocampus-dependent contextual learning in rats. It has also been reported, using a RT-PCR method, that BDNF mRNA levels in the dentate gyrus of the hippocampus are significantly increased in rats showing good retention, compared with the poor retention of passive avoidance learning. Mitogen-associated protein kinase (MAPK), phospholipase C -γ (PLC -γ) and phosphatidylinositol-3 kinase (PI3-K) are the three major signaling molecules known to mediate neurotrophin signaling. [24].

Eph receptors: In molecular biology, ephrins and Eph receptors are components of cell signaling pathways involved in animal development, and implicated in some cancers. The infusion of EphA5-Fc into hippocampus resulted in impaired performance in behavioral paradigms, whereas infusion of ephrinA5-Fc enhanced performance and improved anesthesia-induced memory loss.

Then in 2001, two articles simultaneously reported changes in synaptic plasticity in EphB2 knockout mice. These mice show deficits in NMDA-dependent, hippocampal synaptic plasticity and minor defects in spatial memory. [25].

Second messenger and enzymes:

Adenylyl cyclase: Different types of learning have been associated with changes in the activity of particular adenylyl cyclase (AC) subtypes in a mammalian brain. Current data support the idea that calcium- insensitive AC isoforms may subserve different forms of memory. For instance, decreased calcium-insensitive AC activity was observed in the hippocampus after spatial learning in a water-maze task, whereas, in contrast, an increase in this enzyme activity was found after acquisition in a procedural version of the task or in a barpressing task. [26]

Phospholipase: The tight regulation of PLA2 activity is necessary for maintaining basal leve ls of arachidonic acid, lysophospholipid, and PAF for performing normal brain function. C ollective evidence from many recent studies suggests that increased PLA2 activity and PLA2-generated mediators play a central role not only in acute inflammatory responses in brain but also in oxidative stress associated with neurological disorders such as ischemia, Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). Rat brain synaptosomes or differentiated PC 12 cells release sPLA2 upon stimulation via acetylcholine and glutamate receptors or via voltage-dependent calcium channels through depolarization. Thus, sPLA2 may play an important role in neuronal metabolism. [27]

Potein kinase: PKC plays an important role in many types of learning and memory. Evidence has been provided that PKC activation and translocation are induced in associative learning tasks. PKC inhibition, on the other hand, impairs learning and memory, consistent with the observations that transgenic animal models with a particular PKC isoform deficit exhibit impaired capacity in cognition. The dramatic impact of PKC pharmacology on learning and memory is further emphasized by a regulatory role of PKC isozymes in amyloid production and accumulation. The study reveals that PKC activation greatly reduces neurotoxic amyloid production and accumulation. [28]

General cellular mechanisms, enzymatic cascades including the cAMP-dependent protein kinase (protein kinaseA, PKA) signaling pathway in CA1 region of the hippocampus have been demonstrated to be crucial to memory processing. The importance of the PKA pathway to memory formation is indicated by its unique profile of activation following learning experiences: PKA has two peaks of activity during long term memory consolidation period, the first within the first few minutes after training, and the second in a protracted way, beginning 2-3 h after the experience, after most enzymatic cascades have ceased their contribution. Casein kinase II (CK2) is a multifunctional serine/threonine protein kinase that is associated with the development of neuritogenesis and synaptic plasticity. The phosphoinositide 3-kinase (PI-3K)/Akt pathway is implicated in long-term memory formation. In addition, serum- and glucocorticoid-inducible kinase 1 (SGK1) is another downstream target of PI-3K signaling that was shown to play an important role in spatial memory formation. C K2 impairs spatial memory formation through differential cross talk with PI-3 kinase signaling by activation of Akt and inactivation of SGK1 through protein phosphatase 2A. [29]

Protein kinase C (PKC) is a serine/threonine kinase that has been widely reported to be involved in plasticity processes. It has been reported that this kinase is necessary for the establishment of memories and undergoes changes in its activity level after behavioral training or LTP induction. This kinase can lead to CREB activation inducing gene expression, which is an essential step in the formation of long-term memories. In the case of taste learning, it has been reported that PKC is necessary in the IC (Insular cortex), amygdale and parabrachial nucleus to form a taste aversive memory. In this regard, it is known that the injection of PKC inhibitors into the IC, amygdala or parabrachial nucleus (PBN) impairs CTA memory formation. [30].

A-kianse anchoring proteins (AKAPs) form large macromolecular signaling complexes that specifically target cAMP-dependent protein kinase (PKA). Since strengthening or weakening of synaptic transmission is widely considered to be the cellular mechanism that underlies learning and memory, a role of AKAP/79150 in learning and memory can be expected. AKAP150 is widely distributed throughout the mouse brain. The highest AKAP150 expression levels were observed in striatum, cerebral cortex and several other forebrain regions. AKAP150 is strongly expressed in mouse brain regions involved in learning and memory. [26]

Long Term Potentiation (LTP): Long term potentiation (LTP), a persistent strengthening of synapses based on recent patterns of activity. These are patterns of synaptic activity that produce a long-lasting increase in signal transmission between two neurons [31]

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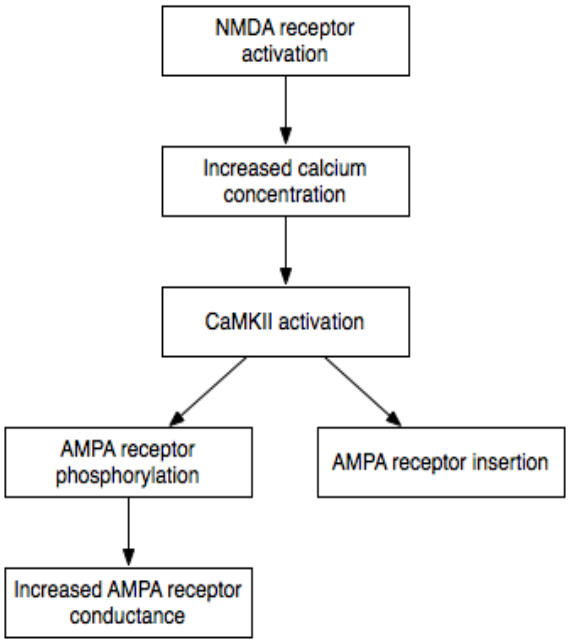
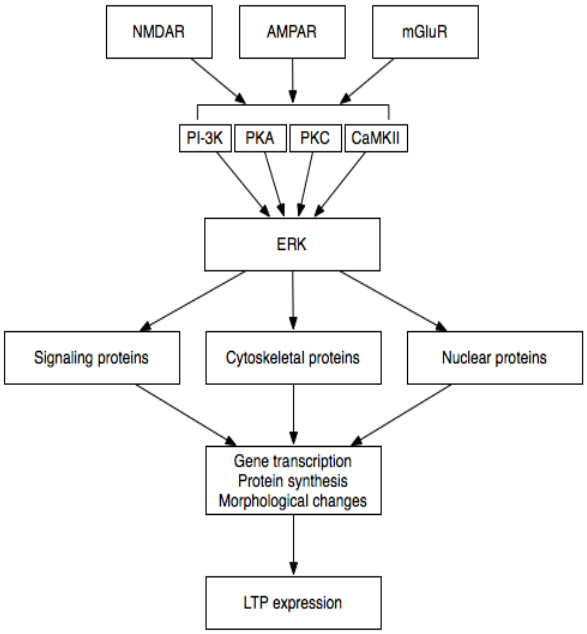
The opposite of LTP is long-term depression which produce long lasting decrease in synaptic strength. It is one of several phenomena underlying synaptic plasticity, the ability of chemical synapses to change their strength. As memories are thought to be encoded by modification of synaptic strength, [32]. LTP is widely considered one of the major cellular mechanisms that underlies learning and memory. Since its original discovery in the rabbit hippocampus, LTP has been observed in a variety of other neural structures, including the cerebral cortex, cerebellum, amygdala, [33] and many others. Robert Malenka, a prominent LTP researcher, has suggested that LTP may even occur at all excitatory synapses in the mammalian brain. Different areas of the brain exhibit different forms of LTP. The signalling pathways used by a particular cell also contribute to the specific type of LTP present. For example, some types of hippocampal LTP depend on the NMDA receptor, others may depend upon the metabotropic glutamate receptor (mGluR), while still others depend upon another molecule altogether. [34]. The variety of signaling pathways that contribute to LTP and the wide distribution of these various pathways in the brain are reasons that the type of LTP exhibited between neurons depends in part upon the anatomic location in which LTP is observed. For example, LTP in the Schaffer collateral pathway of the hippocampus is NMDA receptor-dependent, whereas LTP in the mossy fiber pathway is NMDA receptor-independent. [35]. LTP is characterized by three basic properties: Input specificity, Associativity, and Cooperativity.

There are two phases of LTP (1) Early phase: The transient activation of CaMKII and PKC, maintenance of E-LTP (early-form LTP) which carry out the two major mechanisms underlying the expression of E-LTP. [36]. First, and most importantly, they phosphorylate existing AMPA receptors to increase their activity. Second, they mediate or modulate the insertion of additional AMPA receptors into the postsynaptic membrane. [34] (2) Late LTP (L-LTP) is the natural extension of E-LTP. Unlike E-LTP, which is independent of protein synthesis, L-LTP requires gene transcription [37] and protein synthesis [38] in the postsynaptic cell. Two phases of L-LTP exist: the first depends upon protein synthesis, while the second depends upon both gene transcription and protein synthesis.[39]. Late LTP is induced by changes in gene expression and protein synthesis brought about by the persistent activation of protein kinases activated during E-LTP, such as MAPK. [39][36][40]. Recent research has shown that the induction of L-LTP can depend on coincident molecular events, namely PKA activation and calcium influx, that converge on CRTC1 (TORC1), a potent transcriptional coactivator for cAMP response element binding protein (CREB). [41]



The early phase of LTP



The late phase of LTP

Modulation: A mediator of LTP is a molecule, such as the NMDA receptor or calcium, whose presence and activity is necessary for generating LTP under nearly all conditions. By contrast, a modulator is a molecule that can alter LTP but is not essential for its generation or expression

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Modulator	Target
β-Adrenergic receptor	cAMP, MAPK amplification
Nitric oxide synthase	Guanylyl cyclase, PKG, NMDAR
Dopamine receptor	cAMP, MAPK amplification
Metabotropic glutamate receptor	PKC, MAPK amplification

Proposed Modulator of LTP (Sweatt *et al.*, 1999)

Clinical significance: The role of LTP in disease is less clear than its role in basic mechanisms of synaptic plasticity. However, alterations in LTP may contribute to a number of neurological diseases, including depression, Parkinson's disease, epilepsy, and neuropathic pain. [31] Impaired LTP may also have a role in Alzheimer's disease and one study demonstrated that the enzyme Protien Kinase Mzeta (PKMζ), an atypical protein kinase C (PKC) isoform, plays a key role in the maintenance of long-term potentiation (LTP), accumulates in neurofibrillary tangles, which are a pathologic marker of AD. [42].

Long Term Depression (LTD): LTD is an activity dependent reduction in the efficacy of neuronal synapses lasting hours or longer following a long patterned stimulus. LTD occurs in many areas of the CNS with varying mechanisms depending upon brain region and developmental progress. LTD in the hippocampus and cerebellum have been the best characterized, but there are other brain areas in which mechanisms of LTD are understood. LTD has also been found to occur in different types of neurons that release various neurotransmitters, however, the most common neurotransmitter involved in LTD is Lglutamate. L-glutamate acts on the N-methyl-D- asparate receptors (NMDARs), α-amino-3-hydroxy-5- methylisoxazole-4-propionicacid receptors (AMPARs), kainate receptors (KARs) and metabotropic glutamate receptors (mGluRs) during LTD. Long-term potentiation (LTP) is the opposing process to LTD; it is the long-lasting increase of synaptic strength. In conjunction, LTD and LTP are factors affecting neuronal synaptic plasticity. [43]

LTD is one of several processes that serve to selectively weaken specific synapses in order to make constructive use of synaptic strengthening caused by LTP. This is necessary because, if allowed to continue increasing in strength, synapses would ultimately reach a ceiling level of efficiency, which would inhibit the encoding of new information. [44] Long-term depression can be described as either homosynaptic or heterosynaptic. Homosynaptic LTD is restricted to the individual synapse that is activated by a low frequency stimulus. Heterosynaptic LTD, in contrast, occurs at synapses that are not potentiated or are inactive. The weakening of a synapse is independent of the activity of the presynaptic or postsynaptic neurons as a result of the firing of a distinct modulatory interneuron. Thus, this form of LTD impacts synapses nearby those receiving action potentials.[45].

Synaptic plasticity: Synaptic plasticity is the ability of synapses to strengthen or weaken over time, in response to increases or decreases in their activity [46].Plastic change also results from the alteration of the number of neurotransmitter receptors located on a synapse [47]. There are several underlying mechanisms that cooperate to achieve synaptic plasticity, including changes in the quantity of neurotransmitters released into a synapse and changes in how effectively cells respond to those neurotransmitters. [48] . Synaptic plasticity in both excitatory and inhibitory synapses has been found to be dependent upon postsynaptic calcium release. [47]. Since memories are postulated to be represented by vastly interconnected networks of synapses in the brain, synaptic plasticity is one of the important neurochemical foundations of learning and memory.

Two molecular mechanisms for synaptic plasticity involve the NMDA and AMPA glutamate receptors. Opening of NMDA channels (which relates to the level of cellular depolarization) leads to a rise in post-synaptic Ca^{2+} concentration and this has been linked to long-term potentiation, LTP (as well as to protein kinase activation); strong depolarization of the post-synaptic cell completely displaces the magnesium ions that block NMDA ion channels and allows calcium ions to enter a cell probably causing LTP, while weaker depolarization only partially displaces the Mg^{2+} ions, resulting in less Ca^{2+} entering the post-synaptic neuron and lower intracellular Ca^{2+} concentrations (which activate protein phosphatases and induce long-term depression, LTD).[49]. The second mechanism depends on a second messenger cascade regulating gene transcription and changes in the levels of key proteins at synapses such as CaMKII and PKAII. Activation of the second messenger pathway leads to increased levels of CaMKII and PKAII within the dendritic spine. These protein kinases have

been linked to growth in dendritic spine volume and LTP processes such as the addition of AMPA receptors to the plasma membrane and phosphorylation of ion channels for enhanced permeability. [50]

Short term synaptic plasticity acts on a timescale of tens of milliseconds to a few minutes unlike long-term plasticity, which lasts from minutes to hours. It can either strengthen or weaken a synapse, which resulted from an increased probability of synaptic terminals releasing transmitters in response to pre-synaptic action potentials. Synapses will strengthen for a short time because of either an increase in size of the readily releasable pool of packaged transmitter or an increase in the amount of packaged transmitter released in response to each action potential.

Long-term synaptic plasticity has two forms *Long-term depression (LTD)* and *Long-term potentiation (LTP)* which lasts for minutes or more, that occur at excitatory synapses. [45]. NMDA-dependent LTD and LTP have been extensively researched, and are found to require the binding of glutamate, and glycine or D-serine for activation of NMDA receptors.The modification of synaptic strength is referred to as functional plasticity. Changes in synaptic strength involve distinct mechanisms of particular types of glial cells, the most researched type being astrocytes. .[51]

Conclusion: The brain is the organ that is responsible for what we call the mind. It is the basis for thinking, feeling, wanting, perceiving, learning and memory, curiosity, and behavior. Memory is a fundamental mental process, and without memory we are capable of nothing but simple reflexes and stereotyped behaviors. Thus, learning and memory is one of the most intensively studied subjects in the field of neuroscience. Various approaches have been used to understand the mechanisms underlying this process. The most popular candidate site for memory storage is the synapse, where nerve cells (neurons) communicate. In other words, a change in the transmission efficacy at the synapse (synaptic plasticity) has been considered to be the cause of memory. A particular pattern of synaptic usage or stimulation, called the conditioning stimulation, is believed to induce synaptic plasticity. [6]

In our quest for understanding 'mechanisms' in neuroscience, a focus in research on activity-dependent synaptic plasticity such as long term potentiation (LTP), long-term depression (LTD) and synaptic plasticity has been on identifying the causal steps that occur at individual synapses mediating lasting changes in synaptic efficacy in terms of changes in presynaptic transmitter release, alterations in postsynaptic glutamatergic receptors, the action of neuromodulatory transmitters, the signal transduction pathways activated, gene activation and synthesis of new proteins. A contemporary focus is on the endo- and exocytosis of specific sub-types of glutamate receptors, and alterations in the scaffolding molecules that make up the pre and postsynaptic elements of neuronal connectivity. [52]

We are left with some fascinating unsolved problems in the neurobiology of learning. We must understand in much greater detail several steps in the learning and memory of temporal information. First, we must understand the plastic changes that underlie the rapid and encoding and storage of time (or any aspect of an event). This process must be occurring continuously. Next we must understand how patterns of events are detected and the encoding that underlies the retrieval of this information in an episodic chunk. And, finally we must understand the mechanisms of computation that allow the extraction of information that guides the decision underlying what to do at any particular time. These are all difficult challenges but ones that must be met if we are to understand the neurobiology of learning and memory.

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