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Molecular Learning and Memory of Brain Aging

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This chapter discusses the molecular basis of learning and memory, specifically the Hebbian theory, which suggests that coincident activation of pre- and postsynaptic neurons leads to modifications in synaptic efficacy, creating associative links between the neurons. Memories are stored as alterations of these synaptic changes. The chapter will also discuss three basic assumptions regarding the neurochemical basis of learning and memory, including the requirement for protein synthesis for long-term memory formation, and the storage of memory in synaptic connections. The passage also discusses long-term potentiation (LTP) as the most frequently studied cellular basis of learning and memory in vertebrates, including its properties such as state-dependence, input specificity, and associativity. LTP is considered an analog of memory since it is a long-lasting alteration in neuronal function that results from a brief period of stimulus.

Keywords: Brain Aging, Age related cognitive, Impairment, synaptic communication, dementia, neuronal function.

As humans age, their cognitive function declines, leading to difficulties in learning and memory retention. With the growing elderly population, understanding the molecular mechanisms underlying cognitive aging has become increasingly important. This chapter explores the role of various molecular factors in memory formation and how changes in these factors with age can affect learning and memory retention. Moreover, it offers a comprehensive overview of the latest research in this field and highlights the potential for therapeutic interventions to improve cognitive function in aging individuals. We will discuss different aspects of molecular memory and learning in aging and explore the latest research in this area.

Learning and Memory

An individual's daily life was impacted by central nerves system (CNS) dysfunction that leads to learning and memory deficits. The term "learning" is defined as the acquisition of an altered behavioral response due to an environmental stimulus, and "memory" is defined as the process by which the learned item is stored and retrieved [1–3]. Two types of memory are defined depending on how long it persists: short term (minutes to hours) and long term (days to years). It is generally accepted that memory results from changes in

the particular synaptic structure and/or function. Long-term memory has the general attribute that it undergoes a period of consolidation that involves the formation or elimination of specific synapses in the brain and the synthesis of new mRNAs and proteins. Since short-term memory is too rapid to be attributed to such alterations, it was suggested that changes in the release and function of neurotransmitters at particular synapses are the basis of short-term memory [4–7].

Molecular Learning and Memory

The current molecular basis of learning and memory was based on the Hebbian theory. Hebb hypotheized that the simultaneous activation of pre- and postsynaptic neurons lead to modifications of synaptic efficacy between the two neurons, thereby creating associative linkages between them. Memories are then stored as alterations of these synaptic alterations [8–10]. The current hypothesis regarding the neurochemical basis of learning and memory is based on three basic assumptions [2,3,11,12]. The first assumption is that the basic behavioral paradigms in learning and memory studies are conditioned responses. For example, in Pavlov's characterization of condition experiment, when a food stimulus is presented to a dog, a strong salivatory response is elicited. This salivation is referred as an unconditioned response and the food stimulus is referred to as an unconditioned stimulus [2,13–15]. The dog could then be trained to associate the food stimulus with the ringing of a bell where, over time, the bell ring alone would cause a salivatory response similar to the food does. This bell-elicited salivation was termed conditioned response, and the bell ring was termed the conditioned stimulus (CS) [2,13–15]. In order for learning to occur, the conditioned stimulus must precede the unconditioned stimulus. The second assumption is that protein synthesis occurs only in long-term memory, and not in short-term memory. The formation of long-term and short-term memory can be distinguished by their susceptibility to protein synthesis inhibitors [12,16–20]. Since learning and short-term memory occur within milliseconds and last for minutes to hours, they are proposed to be mediated by post-translational modifications at the synapse. However, since long-term memory require longer acquisition time and last life time. It is predicted to be mediated by processes that (1) require protein synthesis, (2) is neuronal genome dependent; and (3) require intraneuronal communication, such as axonal transport [12,16–20]. The last assumption is that memory is stored in synaptic connections. The development and environment stimulation increase the synaptic complexity, and such synaptic alterations are dependent on the genome regulation phenotypic expression generated in the nucleus to response to the environment [12,16–20].

Long-Term Potentiation (LTP)

LTP is the most frequently studied as the cellular basis of learning and memory in vertebrates. LTP is defined as a long-lasting (hours to weeks) increase of excitatory postsynaptic potentials amplitude in synaptic efficacy as a result of high-frequency stimulation of afferent pathways [19–21]. It is measured both as the amplitude of excitatory postsynaptic potentials and as the magnitude of the postsynaptic cell population spike [19] . LTP was first discovered by application of high frequency electrical stimulation to enhance synaptic transmission in the rabbit [22,23]. The brief period of stimulation can increase the strength of synaptic connections of neurons and the likelihood of the cells firing action potentials in response to a constant synaptic input for hours [22,23]. These phenomena were termed LTP [22,23] . LTP is considered as an analog of memory since LTP is a long-lasting alteration in neuronal function which is resulted from a brief period of stimulus [2,13,24,25]. Several other properties of LTP make it a good analog of mechanisms from learning and memory. There properties are state-dependent, input specificity, and associativity [26–28]. LTP is state-dependent since LTP only occurs when the postsynaptic cell reaches a certain degree of depolarization with a specific period of time [2,13,24,25]. For example, the increased firing action potential is only possible if the postsynaptic depolarization occurs within about 100 ms of presynaptic transmitter release. Since a requirement for coincident activation of presynaptic and postsynaptic elements is necessary for the formation of memory according to Hebbian theory [8–10], LTP forms a theoretical framework of the synaptic changes underlying learning and memory. LTP is also exhibits input specific. When LTP is induced by the stimulation of one particular synapse, other synapses of the same neurons remain inactive. Therefore, LTP is restricted to activated synapses rather than to all of the synapses on a given neuron This properties of LTP is consistent

with the memory formation in which only the activated synapses are potentiated, leading to selectively enhancement particular sets of inputs, as is required for learning and memory [26–28]. Another important property of LTP is associativity, which is analog of the linkage of one set of information with another in neuronal network. Since weak stimulation of a synapse cannot trigger LTP by itself, a simultaneous input from a weak stimulation and a strong stimulation of a neighboring synapse of the same neuron can trigger both synaptic pathways to undergo LTP [26–28] . This conjoint enhancement of synaptic inputs is often considered as a neuronal analog of associative conditioning observed in Pavlov's conditioning experiment [2,13]. It should be noted that LTP does not equal to memory. Rather, it is an important component of memory formation. Moreover, LTP is a mechanism of activity-dependent synaptic plasticity that is capable of detecting multiple conincidence events. Such properties suggest that LTP contributes to memory consolidation, formation of complicated association, sequentially serving as a short-term memory buffer for assicative conditioning [2,13]

Synaptic Remodeling

As mentioned in the previous section, environmental stimulation leads to the shaping and tuning of neuronal connectivity during development, and this process, termed synaptic remodeling, continues throughout the life-span of the organisms. Since neuronal connectivity is a dynamic process, the remodeling of synaptic connectivity occurs in response to general environmental manipulations, sensory stimulation or learning a specific new task and may even be associated with cyclic changes in the physiological status of the organism [12,16–18]. The mechanisms that are known to be involved in the initiation and maintenance of synaptic plasticity are base on Hebbian theory [24,29–31]. It is generally believed that the calcium influx into postsynaptic neurons through excitatory amino-acid receptors, specifically NMDA (N-methyl-D-aspartate) receptors, and possibly L-type voltage-gated calcium channels (VGCCs), is the initial event of synaptic plasticity [13,23,25,31,32]. Receptor mediated calcium influx is usually blocked by magnesium at resting membrane potentials. However, when glutamate is released presynaptically, it binds and activates NMDA receptors, thereby relieving the magnesium and allowing calcium enters the neuron at the synapse. Since activation of NMDA receptors by glutamate will only occur when the postsynaptic cell membrane is depolarized, the NMDA receptor act as a coincidence detector that only allows calcium influx when presynaptic activity and postsynaptic activity coincide [24,31,33,34]. Calcium also influx into postsynaptic membrane during depolarization through VGCCs [13,23,25,31,32]. VGCCs are opened by back-propagating action potential, an action potential that initiate at the cell body and back -propagating into the dendrites plasticity. The opening of VGCCs amplifies the excitatory postsynaptic potentials at the synapse that were recently activated by glutamate receptors [24,31,33,34], thereby shaping the integration of synaptic activity and influencing the induction of synaptic. The net result of calcium influx is the activation of signaling pathways. For example, calcium influx causes phosphorylation of calcium/calmodulin-dependent protein kinases (CaMKs) and protein kinase C [7,32,35–37], which results in an increase in synaptic efficacy, and subsequently activation of gene transcription and protein synthesis that can also lead to structural changes in synapses [38–40]. Moreover, elevation of calcium leads to rearrangement of the cytoskeleton at the synapse by actin polymerization and cytoskeletal rearrangements. These processes result in new synaptic structures [7,41–43]. Since these structural alterations occur too quickly to be accounted for by nuclear or even dendritic protein synthesis, they are not considered to be the result of protein synthesis. Therefore, such changes might participate in both short-term and long-term memory [24,29–31]. The rapid changes in the concentrations of calcium and other signaling molecules take place in dendritic spines. Spines are specialized compartments on dendrites that contain receptors, channels and signaling molecules that couple synaptic activity with postsynaptic biochemistry [7,44–46]. Since the induction of synaptic plasticity (LTP induction or memory formation) leads to changes in the number or shape of spines [47–49], modulation of the number of dendritic spines and their morphology were proposed to associated with the excitatory synaptic transmission alterations during learning [50–53]. Alteration of spine number and morphology depends on the specialized structure of cytoskeletal actin filament [41–43,54]. Actin is present ubiquitously

in the spine to interact with the receptors, channels and signaling molecules, and the reorganization and/or polymerization of actin alter spine stability and contribute to structural plasticity of spines after LTP induction and learning [24,29–31]. The orientation, kinetics of assembly and stability of actin filaments are regulated by extracellular stimulation, such as NMDA receptor activation [41–43,54 41–43,54], indicating that NMDA-dependent actin polymerization is important for the consolidation of memory. Another glutamate receptor, AMPA (áamino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor, is found to stabilize spine morphology [34]. Therefore, NMDA receptors is important in the initial phase of spine motility, followed by a stabilization phase that is mediated by AMPA receptors. Since AMPA receptor is activated spontaneously with NMDA receptor during glutamate release in synapses, the alteration and stabilization of dendritic spine also occurs simultaneously [24,29–31]. Moreover, AMPA receptor levels increase after LTP induction or learning experiences, indicating that an increase in AMPA receptors in spines could contribute to spine stability and thereby memory formation [25,31,52]. Cytoskeleton-mediated alteration of spine and dendritic morphology is regulated by Rho GTPases and their downstream effectors (Luo et al, 2002). Another role of Rho GTPases played in synaptic plasticity is to mediate the activity of adhesion molecules and to regulate cellular interactions [24,29–31]. Adhesion molecules, such as integrins, cadherins, neurexin and the immunoglobulin superfamily, are membrane-bound molecules that interacts with proteins in the extracellular matrix and synaptic membranes to adhere the membranes between the pre- and postsynaptic components [24,29–31]. This adhesion is a dynamic process that involves morphological alterations and modulation of connection between the pre and postsynaptic neurons, and result in new contacts [31]. Adhesion molecules can also mediate signaling pathways to regulate the extracellular connectivity with intracellular events that control spine morphology [24,29–31]. Therefore, adhesion molecules play a critical role in neuronal connectivity and spin morphology, as well as stabilization of synaptic connectivity that leads to consolidation of memory [24,29–31]. The formation of memory involves learning and consolidation. During learning, stimulation on specific synapses initiate molecular changes, and cellular alterations are progressively stabilized during consolidation. The initiate molecular alterations caused by learning are complex and require coordination within and between signaling pathways that involved Rho ATPases [55–57], and the modulation and stabilization of neurons after LTP induction or learning is controlled in part by actin dynamics, a process that is initiated by NMDA receptor activation and stabilized by AMPA receptor activation. The process of actin dynamic in neuron causes morphological changes in dendritic spins and leads to the formation and stabilization of new synaptic contact of the pre and postsynaptic elements [24,29–31]. The formation of new neuronal connections is regulated by adhesion molecules that are also affected by both the cytoskeleton and glutamate receptors. The remodeling of the synapses results in modified neuronal circuit which represent the memory stored in the brain, and synaptic plasticity are mediated by molecular activity at the synapse during specific time windows after learning [24,29–31].

Learning and Memory in Aging

Learning and memory decline is a part of the aging process [58–60]. The most noticeable cognitive decline in age human is the hippocampus-dependent forms of memory deficits, which is manifested by the difficulty of learning and remembering of new names, recent events and even spatial information [2,13]. These types of cognitive impairment can be recapitulated in aging rodent by assessing their cognitive function by learning and retention paradigms. Therefore, the age-related cognitive impairment in behavioral and cellular manifestations of learning and memory is well 52 established in humans and other mammals [2,13]. Moreover, LTP is diminished in aged animals [58–60]. However, the mechanisms underlie the cognitive impairment in aged animals and human are still not clear. Although the bases of such decline remain unknown, oxidative stress is proposed to play a significant role in age-related memory and synaptic plasticity dysfunction [13,19,25]. Moreover, the decline of cognitive function in aging subjects can be more server due to numerous reasons, such as stroke, vascular problems, psychiatric disorders, Parkinson's Disease and Alzheimer's Disease. These conditions can cause cognitive impairment to be more pronounced in normal aging [2,13].

CONCLUSION

Understanding the molecular mechanisms underlying cognitive aging has become increasingly important. This chapter explores the role of various molecular factors in memory formation and how changes in these factors with age can affect learning and memory retention. It offers a comprehensive overview of the latest research in this field and highlights the potential for therapeutic interventions to improve cognitive function in aging individuals.

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