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# Involvement of hippocampal synaptic plasticity in age-related memory decline

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**Abstract**

This article examines the functional significance of $Ca^{2+}$-dependent synaptic plasticity in relation to compromised memory function during aging. Research characterizing an age-related decline in memory for tasks that require proper hippocampal function is summarized. It is concluded that aged animals possess the mechanisms necessary for memory formation, and memory deficits, including rapid forgetting, result from more subtle changes in memory processes for memory storage or maintenance. A review of experimental studies concerning changes in hippocampal neural plasticity over the course of aging indicates that, during aging, there is a shift in mechanisms that regulate the thresholds for synaptic modification, including $Ca^{2+}$ channel function and subsequent $Ca^{2+}$-dependent processes. The results, combined with theoretical considerations concerning synaptic modification thresholds, provide the basis for a model of age-related changes in hippocampal synaptic function. The model is employed as a foundation for interpretation of studies examining therapeutic intervention in age-related memory decline. The possible role of altered synaptic plasticity thresholds in learning and memory deficits suggests that treatments that modify synaptic plasticity may prove fruitful for the development of early therapeutic interventions in age-related neurodegenerative diseases. 

*Keywords:* Learning; Memory; Neural plasticity; Calcium; Hippocampus; Rodent

## Contents



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## 1. Introduction

Impairments in cognitive function have been well-documented in elderly humans [92]. It has been more than three decades since the term ''benign senescent forgetfulness'' was first proposed to differentiate individuals with age-related decline in memory, from those with impaired memory attributable to neurological damage or disease [96]. More recently, a National Institute of Mental Health (NIMH) work group proposed the term ''age-associated memory impairment'' based on diagnostic evidence for memory loss in the absence of dementia [39]. It is clear that memory impairment with advanced age is a selective deficit rather than a generalized decline in all cognitive operations. Indeed, the ability to learn new skills or express memory in an implicit manner remains relatively intact in older humans. The term chosen by NIMH refers instead to older, but otherwise healthy, individuals who exhibit impaired memory on tasks involving the recall of recently acquired facts [32,44,77,79,87,141,151,188,197]. Memory capabilities that depend on proper hippocampal function appear to be of particular vulnerability to the aging process [79,123,133]. For example, memory for novel spatial information, which is compromised by hippocampal damage, is extremely sensitive to aging [92].

While qualitatively, age-related cognitive deficits point to hippocampal involvement, several important distinctions remain between consequential hippocampal damage and aging. In particular, the degree of impairment observed during aging is less severe than that observed for patients with disease-related damage to the hippocampus [132]. Enhanced forgetting becomes apparent in normal aged individuals as the retention interval is increased beyond 24 h [87,127,152]. Brain-damaged individuals or Alzheimer patients, in contrast, exhibit extremely rapid forgetting within minutes [82,126,132,150]. Because of these differences, it is likely that age-related memory deficits are the result of more limited and subtle changes in the hippocampus.

One primary difficulty in determining the mechanisms for cognitive decline in humans is related to the invasive nature of experiments that can determine cause and effect relationships. As a consequence, researchers have had to rely largely on correlational studies, or they have turned to animal models of brain aging [74]. The biological theories to emerge seem to polarize around models concerning the loss of neural components, which comprise the hippocampal system, and models related to divergence in physiological or biochemical aspects of hippocampal function [73]. These theories are not necessarily mutually exclusive; i.e., changes in physiology are likely to precede the elimination of synapses or neuronal death [101,180]. Furthermore, the loss of neural components will have profound influences on physiology [11,13,15,63,70].

## 2. Animal models of age-related memory impairments

Animal models have been developed to explore the connection between age-related memory deficits and changes in anatomy and physiology of the hippocampus. To establish an animal model for the investigation of the neurobiology of the aging hippocampus, one of the first steps has been to investigate whether aging is associated with a decline in performance on tasks which are sensitive to hippocampal damage. Some of the more commonly used tasks include delay-dependent matching/non-matching to sample operant tasks [58,59], trace eye blink conditioning [55,175], passive/inhibitory avoidance [120], and spatial mazes [76]. In the case of aging rats, it is clear that these animals can learn and retain information over short intervals. However, in comparison to younger rats, aged animals exhibit slower learning and rapid forgetting [10,37,58,59,63,78,116,119,142,146,175,194,199].

In rodents, spatial memory is particularly vulnerable to decline with advanced age. In recent years, researchers have focused on water-escape tasks to identify aged rats and mice with spatial memory deficits. However, care is required when using such tasks since, relative to young adults, aged animals are more sensitive to the parameters of the experimental paradigm which act on secondary processes, including stress and fatigue. As such, obvious age-related differences in acquisition can be observed under highly stressful conditions (e.g., colder water temperatures) [47,113,116]. When properly employed, the water-escape task provides a means of differentiating cognitive deterioration from sensory–motor deficits [74,111,118], and the ability of this task in identifying animals with memory deficits is a consistent finding [25,34,37,63,69, 70,72,111,112,116,142]. Under conditions designed to minimize stress, aged animals demonstrate a decrease in escape latency for the second of a pair of training trials when the intertrial interval is relatively short (e.g., 1 min)

[71,163], implying that aged rats can learn something about the task. However, performance deficits on the second trial are readily apparent as the intertrial interval is extended over hours [112,113,116]. Similarly, aged animals exhibit only a mild impairment in the acquisition of spatial discriminations (i.e., slower rate of acquisition) when short intertrial intervals are used, and training is massed into a single day [63,116,142]. However, marked performance differences emerge when training is conducted over several days [74]. Indeed, aged rats exhibit a characteristic ''saw-toothed'' pattern of behavior across days of training [51,71,163]. This pattern appears as an improved performance for training trials within a day, and a marked decrement in performance on the first trial of the next day. In contrast, young adult rats exhibit little or no evidence for a relapse in performance across days. Finally, with extended training, aged animals can acquire spatial discrimination behavior, which is stable across a longer (e.g., 24 h) time period [163]. The results indicate that aged animals can learn tasks that require an intact hippocampus; however, there maybe be deficits in the rate of learning. More pronounced age-related deficits involve impaired retention of previously acquired information. Delay-dependent effects in aged animals are a consistent finding across a number of different tasks [58,59,76,78, 119,146,175,194,199] and point to rapid forgetting as a behavioral characteristic of animal models of aging. The results indicate that aged animals possess the mechanisms necessary for memory formation, and memory deficits probably result from more subtle changes in memory processes such as storage or maintenance mechanisms.

## 3. Age-related changes in hippocampal synaptic function

Behavioral analyses alone may not be able to determine the processes which underlie memory and forgetting. Rather, one must determine whether the biological changes, which are thought to represent stored information, materialize and fade differentially over time in accord with behavioral measures [177]. While this view may be overly simplistic, it provides a starting place for examining neurobiological models of memory by describing relationships between neurological markers of aging and cognitive function. The fact, that tasks that depend on proper hippocampal function are primarily sensitive to aging, indicates that changes in memory involve the hippocampus, its afferents, or efferents. The general hypothesis that, age-related memory deficits will be associated with changes in the hippocampus, has been widely confirmed. A number of these studies have addressed neurological measures that are relevant to synaptic function. Indeed, altered hippocampal synaptic function provides one of the primary electrophysiological markers for memory deficits during aging (for reviews, see Refs. [11,66,76,98]).

### *3.1. Induction of long-term potentiation (LTP)*

Several forms of plasticity, either increasing or decreasing synaptic transmission, have now been described in the mammalian central nervous system. In nearly all cases, induction of synaptic plasticity involves a rise in intracellular $Ca^{2+}$ ($[Ca^{2+}]_i$). The best-characterized example is a long-lasting enhancement of excitatory synaptic transmission termed LTP. LTP can be observed at hippocampal synapses following patterned synaptic activation, usually involving high frequency (25–200 Hz) stimulation of afferent fibers. Several forms of LTP have been identified based on the necessity for $Ca^{2+}$ influx through postsynaptic *N*-methyl-D-aspartate receptor (NMDAR) activation. At hippocampal CA3–CA1 synapses, two forms of LTP have been described which differ in terms of their dependence on activation of NMDARs (NMDAR-LTP) or voltage-dependent $Ca^{2+}$ channels (VDCC-LTP) [28,81]. From the initial discovery [24], LTP has been proposed as a candidate neural model for memory storage. Evidence to support the LTP model of memory storage includes studies in which pharmacological or genetic manipulations that impair LTP induction also impair acquisition of hippocampal-dependent behavior [26,29,131]. Furthermore, increased hippocampal synaptic transmission is associated with differential experience, and the experience-dependent growth in synaptic transmission has been linked to LTP induction and expression mechanisms [64,65,159,193].

Considering the prominence of LTP as a model of memory storage, it is not surprising that a number of studies have examined changes in LTP induction and expression during aging. In general, no age-related differences are observed in the magnitude of LTP [10,47,50,52,102,130,143,171]. However, an increased threshold for LTP induction has been reported such that stronger (e.g., higher frequency) stimulation is required to induce LTP. In addition, more induction sessions are required to saturate LTP mechanisms in aged animals. The results indicate that, although the fundamental mechanisms for LTP are present in aged animals, there are differences in LTP threshold, which adjusts the relationship between the strength of LTP-inducing stimulation and the magnitude of synaptic growth, resulting in altered susceptibility to LTP induction.

### *3.2. Maintenance of LTP*

One defining characteristic of LTP, which makes it a good model of memory, is its extended duration. Depending on the experimental preparation and induction protocol, LTP can last from hours to weeks [13,14,162,165]. The variability in the duration of LTP may represent differential recruitment of mechanisms for the consolida-

tion of increased synaptic strength [3,85], or a shift in the form of LTP expressed, with each form having a different decay constant [162,171]. Interestingly, enhanced synaptic transmission due to experience or induction of LTP decays more rapidly in aged animals [10,14,47,48,100,102, 130,171]. It is particularly intriguing that LTP decay rates are correlated with the rate of forgetting of spatial information [14]. Taken together, the results suggest that the processes that define the decay of LTP may provide a model of forgetting.

There are several possible explanations for the increased LTP decay rate observed in aged animals. One possibility is that the form or type of LTP in the hippocampus changes with aging. Recent evidence indicates that, in region CA1, there is a shift in the mechanisms for induction of LTP such that VDCC-LTP contributes more to the expression synaptic enhancement of aged rats following stimulation to saturate LTP mechanisms [171]. Furthermore, NMDAR-LTP was found to decay more rapidly in aged animals. Therefore, in cases where a rapid LTP decay is observed, it is possible that LTP expression is mainly of the NMDAR-dependent form. However, it is still unclear why LTP should decay more rapidly with aging.

### *3.3. Induction of long-term synaptic depression (LTD)*

The rapid decay of LTP in aged animals may relate to a reduced threshold for activity-dependent LTD. In contrast to LTP, LTD is characterized by a reduction in synaptic efficacy induced by low-frequency stimulation (for reviews, see Refs. [19,66,110]). LTD, like LTP, depends on $Ca^{2+}$ influx, and induction is blocked or impaired by treatments that block NMDARs or VDCCs [33,56, 138,143,144]. In contrast to LTP, LTD induction is thought to require only a modest rise in $[Ca^{2+}]_i$ [114]. The key evidence linking LTD to limitations in LTP maintenance is the finding that stimulation parameters for LTD induction act to decrease or reverse LTP, a process referred to as LTP reversal or depotentiation [107,143]. In this regard, it may be significant that stimulation-induced LTD and LTP reversal are among the few forms of neural plasticity that increase with aging [66,143]. The adjustment in synaptic modifiability for aged animals results from a reduction in the threshold for LTD, such that robust LTD is observed for lower frequency stimulation patterns (i.e., 1 Hz). Similarly, more extensive LTP reversal is observed for brief bursts of stimulation (e.g., 30 pulses), suggesting a reduction in the threshold for depotentiation. These results suggest that the threshold for synaptic depression, LTD and depotentiation, is reduced during aging such that less neural activity is required to initiate processes which reduce synaptic strength. Together, the increased threshold for LTP induction and decreased threshold for induction of synaptic depression could underlie the reduction in synaptic strength which is characteristic of CA3–CA1 synapses of older animals.

## 4. Mechanism for age-related changes in synaptic plasticity

### *4.1. Altered thresholds for synaptic modification*

A popular model for the regulation of synaptic modification thresholds proposes that the direction of altered synaptic efficacy is determined by the level of the postsynaptic $[Ca^{2+}]_i$ during neural activity [6,23,66,67,170]. The thresholds for induction of synaptic modification, as defined by afferent activity, are thought to reflect activity-dependent changes in the level of $[Ca^{2+}]_i$, which, in turn, activate $Ca^{2+}$-dependent enzymes localized to the synapse [114]. These enzymes control the phosphorylation state and function of other proteins, including glutamate receptors [17,21,109,191,192]. The plasticity threshold can be defined according to the frequency–response function for induction of synaptic modification (e.g., see Refs. [56,66,121]). Fig. 1 provides an example of a theoretical frequency–response function for CA1 hippocampal synapses of region CA1 in young adults. The function illustrates two synaptic plasticity thresholds. As neural activity increases, the threshold for LTD is observed first. A further increase in neural activity leads to a smooth transition from net LTD to induction of LTP. The cross-over point, representing the second threshold, is the LTP threshold [6,23].

A basic assumption of these models is that the second threshold, the cross-over point for synaptic modification, can ''slide'', or is modifiable. A shift in the frequency–response function to the left would favor LTP induction and a shift to the right would promote synaptic depression by expanding the range of frequencies that induce LTD. Thus,

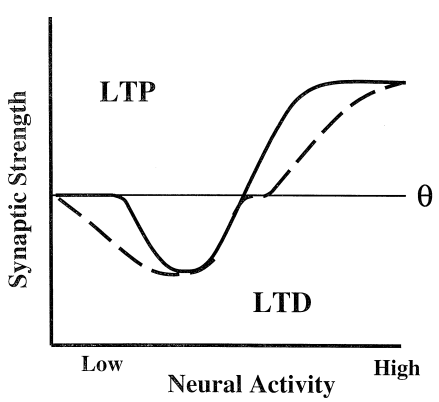


Fig. 1. Hypothetical frequency–response functions for young adult (solid line) and aged (dashed line) animals. The cross-over point from a net LTD to net LTP is indicated by the line θ. The function for adults is based on models of synaptic modifiability, which suggest a smooth transition from LTD to LTP as neural activity increases. The function for aged rats is based on experimental evidence that indicates a lower threshold for LTD in aged animals, resulting in an expanded range over which LTD can be induced. In addition, older animals exhibit a higher threshold for LTP induction and require more intense stimulation or more induction sessions in order to achieve saturation of LTP mechanisms.

plotting changes in synaptic strength as a result of different conditioning stimulation frequencies can identify changes in the thresholds for synaptic modifiability. Previous work indicates that, for young animals, the cross-over threshold from LTD to LTP is observed within a range of intermediate stimulation frequencies (5–10 Hz) [38,57,66,121]. As discussed above, aged animals appear to exhibit an increased threshold for LTP induction. However, the change in LTP threshold is not due to a rightward shift in the entire frequency–response function. Rather than a single cross-over point, representing a smooth transition between net LTD and LTP, the frequency–response function for older animals appears to include a pronounced plateau region in which no change in synaptic strength occurs for intermediate stimulation frequencies (Fig. 1). In addition, the fact, that more intense stimulation is required to achieve the same level of LTP, indicates that the rate of rise for the function is reduced for older animals.

Compared to young adult rats, the frequency–response function in aged animals exhibits an expanded range over which LTD can be induced. Again, the change in synaptic modifiability for aged animals is not due to a rightward shift in the cross-over point or an expansion of the upper threshold for LTD induction. Rather, the increased susceptibility to LTD induction results from a leftward shift in the lower threshold for LTD such that robust LTD is observed for lower frequency stimulation patterns (i.e., 1 Hz) [66,143]. Thus, changes in synaptic plasticity during aging can be characterized by a shift in the thresholds for synaptic modifiability with a reduced threshold for induction of LTD and an increased threshold for LTP induction.

### *4.2. $Ca^{2+}$ homeostatic changes shift synaptic plasticity thresholds*

As noted above, the threshold for synaptic modification appears to depend on the level of the postsynaptic $[Ca^{2+}]_i$ during neural activity. Thus, $Ca^{2+}$ regulation would be expected to play a significant role in determining synaptic function. The role of $Ca^{2+}$ regulation has long been a focus of research on age-related neurodegenerative mechanisms and development of potential treatments for dementia in humans [93,180]. Altered homeostasis of $[Ca^{2+}]_i$ is believed to underlie changes in hippocampal pyramidal cells function during aging [54,66,67,94,99,139,180,189]. The regulation of $[Ca^{2+}]_i$ could be modified by changes in a number of mechanisms for handling $Ca^{2+}$, including intracellular buffering, extrusion, and/or influx of $Ca^{2+}$.

One version of the $Ca^{2+}$ hypothesis of aging states that a postsynaptic increase in $Ca^{2+}$ influx through VDCCs and reduced $Ca^{2+}$ influx through NMDARs modifies the threshold for induction of $Ca^{2+}$-dependent synaptic plasticity, favoring induction of LTD [66,67,144]. In support of this idea, an antagonist to the L-type VDCC, nifedipine, blocks induction of synaptic depression, and lowers the threshold for induction of LTP in aged animals [144]. The results suggest a pivotal role of L-channels in regulating synaptic modifiability during aging. While inhibition of LTD via blockade of $Ca^{2+}$ entry may not be too surprising, the fact, that $Ca^{2+}$ channel blockade facilitates LTP induction, is paradoxical, in that LTP induction depends on a substantial rise in $[Ca^{2+}]_i$. The link between synaptic potentiation and VDCCs may be mediated by an age-dependent increase in $Ca^{2+}$-dependent, $K^+$-mediated hyperpolarization including the afterhyperpolarization (AHP) [99,134,144]. Because the duration of the hyperpolarization, which follows cell discharge activity, can encompass several hundred milliseconds, it can have profound effects on voltage-dependent events that occur within this temporal window. For example, the AHP amplitude can influence the frequency and pattern of cell discharge activity [135]. A large AHP could reduce the frequency of afferent activity, altering synaptic plasticity and information processing, particularly for processes that require high frequency neural activity (e.g., LTP induction).

In addition to altering the pattern of cell discharge activity, large amplitude AHPs can shunt subsequent depolarizing synaptic events, impairing NMDAR-mediated processes, including LTP induction [166]. In this way, preceding stimuli influence later synaptic events. The extent of this influence depends on the location of the shunt within neuronal processes, the interval between the initial afferent activation or cell discharge, and subsequent afferent activity (i.e., the frequency of patterned stimulation). Importantly, the amplitude and duration of the AHP are consistently increased in aged hippocampal pyramidal cells, with a peak $\sim$200 ms after the action potential [27,134, 158,179]. The time course of the AHP would be expected to influence cell discharge activity and the integration of synaptic events as the rate of afferent stimulation increases towards the threshold for induction of synaptic modification (e.g., beyond 1–2 Hz). Evidence that an increase in $K^+$ channel activation during aging regulates the threshold for NMDAR-dependant LTP induction comes from a study in which apamin was used to directly block the $Ca^{2+}$-activated $K^+$ channel [144]. Under these conditions, the threshold for NMDAR-LTP was reduced in aged rats without blocking the induction of LTD. The authors suggest that the enhanced AHP of older animals, which is mediated by increased $Ca^{2+}$ influx through VDCCs, acts to limit the activation of NMDARs. Thus, a short-circuiting of the synaptic potential response by dendritic $K^+$ channels or a large AHP may explain the reduced effectiveness of brief stimulation bursts on LTP induction in aged animals. The results point to changes in $Ca^{2+}$ regulation and the subsequent AHP in mediating the shift in synaptic plasticity thresholds during aging.

Together, the combination of theoretical approaches concerning activity-dependent changes in the level $[Ca^{2+}]_i$ for synaptic modification with experimental studies provides the basis for a model describing changes in the threshold for synaptic plasticity during aging. Fig. 2 sum-

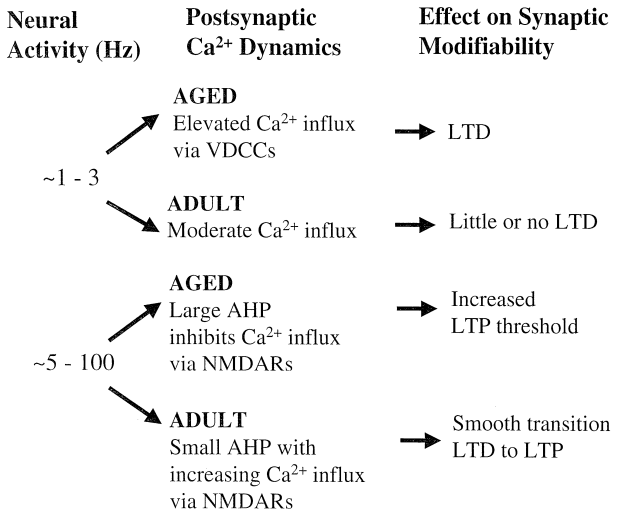


Fig. 2. Theoretical model relating age-associated changes in $Ca^{2+}$ homeostasis and subsequent $Ca^{2+}$-dependent processes to altered thresholds for $Ca^{2+}$-dependent synaptic modifications. During low-frequency activity ( ~ 1–3 Hz), the influx of $Ca^{2+}$ through VDCCs is increased in the aged, relative to adult animals, resulting in a moderate rise in $[Ca^{2+}]_i$. The enhanced $Ca^{2+}$ influx acts to lower the threshold for induction of LTD, thus increasing the susceptibility to LTD induction. As neural activity increases ( ~ 5–25 Hz), synaptic activation begins to overlap the large AHP of aged animals, generated by the preceding stimuli. The larger amplitude and extended duration of the AHP limit the voltage-dependent activation of NMDARs, restricting $Ca^{2+}$ influx from this source. The interaction of synaptic activity with the AHP results in a flattening of the curve near the LTD–LTP cross-over point (see Fig. 1). The limitations imposed on $Ca^{2+}$ influx by the larger AHP increases the threshold for LTP induction. During high-frequency activity (100 Hz), the increased rate of activation overcomes the limits imposed by the AHP, and $[Ca^{2+}]_i$ is raised to levels needed for LTP induction.

marizes the points of the model which indicate that an age-related shift in the state of L-channel activation can lower the threshold for LTD induction by increasing $Ca^{2+}$ influx during low-frequency neural activity. Normally, an increase influx of $Ca^{2+}$ would be expected to facilitate induction of LTP as the neural activity increases. However, the increased $Ca^{2+}$ through VDCCs acts to augment the amplitude and duration of the AHP, which, in turn, raises the threshold for LTP induction. The net result would be a propensity for induction of synaptic depression, through activation of $Ca^{2+}$-dependent enzymes. In this way, two primary electrophysiological correlates of aging, the decrease in synaptic strength and an increase in the AHP, may be causally linked.

### *4.3. $Ca^{2+}$-dependent enzymes regulating synaptic plasticity thresholds*

Evidence collected from several laboratories supports the involvement of $Ca^{2+}$-activated protein phosphatase and kinase cascades in LTD and LTP [60,84,115,117,136–138,145,181,190,196]. According to a model proposed by Lisman [114], a modest rise in $[Ca^{2+}]_i$ interacts with calmodulin to activate the protein phosphatase calcineurin to regulate the activity of protein phosphatase 1 (PP1). PP1 is abundant at the synapse, and can inhibit the activity of enzymes (e.g., $Ca^{2+}$ calmodulin kinase II; CaM-KII) thought to influence synaptic strength [114,121]. As $[Ca^{2+}]_i$ increases to higher levels, $Ca^{2+}$-dependent kinases, such as CaM-KII, are activated to enhance synaptic transmission, possibly through phosphorylation of glutamate receptors which, in turn, may increase receptor affinity or conductance [17,21,65]. If the age-related decrease in synaptic strength is due to alterations in the threshold for synaptic modification as proposed by the model illustrated in Fig. 2, then the balance of serine/threonine protein kinase and phosphatase activities should also be shifted to favor protein phosphatase activity. Direct evidence for an age-related decline in synaptic transmission attributable to a shift in the balance of enzyme activity came from a study in which the application of protein phosphatase inhibitors selectively increased the synaptic response for aged animals [145]. In addition, these researchers demonstrated that inhibition of protein kinases selectively decreased synaptic transmission in young adults [145]. This initial discovery, that a naturally occurring decrease in synaptic strength with aging is mediated through the same enzyme pathways that mediate LTP and LTD, establishes the plausibility of $Ca^{2+}$-dependent protein phosphorylation as a mechanism for regulating endogenous changes in synaptic strength. Furthermore, the results suggest that a shift in the threshold for synaptic modification has relevance for neuronal function.

A shift in the balance of protein phosphatase/kinase activity as a result of processes proposed in the model could explain a number of physiological changes which are characteristic of aged neurons. For example, the characteristic decrease in synaptic strength for aged animals [15,47,104,145] could result from a decrease in the phosphorylation state of glutamate receptors [17,21,109,145, 191,192] which, in turn, reduces the postsynaptic responsiveness to transmitter [15]. In addition, the function of VDCCs is thought to be regulated by phosphorylation state [83] and an increase in VDCC activity and subsequent rise in $[Ca^{2+}]_i$ may occur as a result of increased phosphatase activity [174] or a reduction in kinase activity [61]. Moreover, the other major electrophysiological marker of aging, an increase in the AHP, could also result from increased phosphatase activity [155,164] or a decrease in kinase activity [1].

The implication, illustrated in Fig. 3, is that altered $Ca^{2+}$ homeostasis during aging may involve a substitution of sources for $[Ca^{2+}]_i$. Enhanced phosphatase activity results in enhanced L-channel function, leading to a further influx of $Ca^{2+}$ through these channels. In addition, the influx of $Ca^{2+}$ through NMDARs is decreased due to dephosphorylation of NMDARs [109,191,192] and mechanisms that limit postsynaptic depolarization needed for NMDAR activation, including augmentation of the AHP and reduced cell excitability. In turn, changes in $Ca^{2+}$

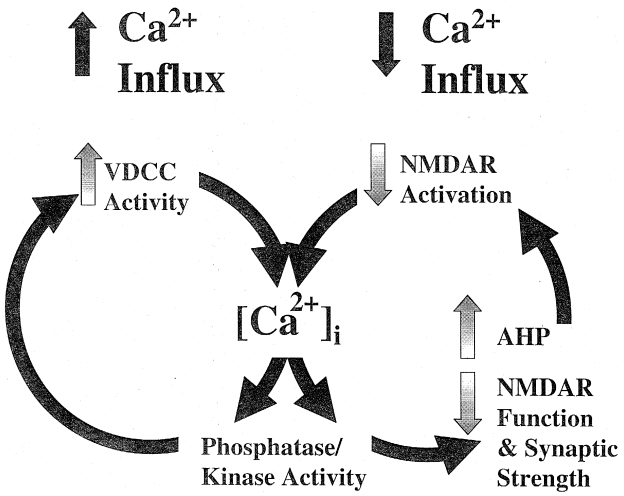


Fig. 3. A shift in the source of $Ca^{2+}$ may underlie age-related changes in $Ca^{2+}$ homeostasis. The increase in phosphatase activity in aged animals results in enhanced L-channel function, leading to increased influx of $Ca^{2+}$ through these channels and an increase in the amplitude of the AHP. In addition, phosphatase activity acts to dephosphorylate glutamate receptors including NMDARs. The decrease in glutamate receptor function and increase in the AHP restrict $Ca^{2+}$ influx through NMDAR activation.

influx act to maintain the enhanced phosphatase activity. Under this scenario, the electrophysiological markers of aging, decreased synaptic strength and an increase in the AHP, are expressions of postsynaptic $Ca^{2+}$ dysregulation. In addition, the electrophysiological changes contribute to the maintenance of dysregulation. Interestingly, recent work suggests that reducing $[Ca^{2+}]_i$ can differentially increase synaptic strength in aged animals [143,144,149].

Alternatively, age-related neurodegeneration is thought to involve excess $[Ca^{2+}]_i$ due to overstimulation of NMDARs [122]. Thus, physiological changes that limit depolarization of CA1 cells, including a decrease in synaptic strength and an increase in the AHP, may reflect neuroprotective mechanisms that limit the rise in $[Ca^{2+}]_i$ by restricting NMDAR activation. In this regard, changes in biological markers of aging may represent compensatory mechanisms that attempt to limit the extent of $Ca^{2+}$ dysregulation associated with the aging processes [11,63].

## 5. Role of altered $Ca^{2+}$-dependent synaptic plasticity in age-related cognitive decline

### *5.1. Correlational studies*

Provided that studies of synaptic plasticity promote insight into memory mechanisms, the model concerning age-related changes in the threshold for hippocampal synaptic modification may explain, in part, certain aspects of cognitive decline observed for hippocampal-dependent tasks. For example, it can be concluded that because aged animals can acquire hippocampal-dependent tasks, the fundamental mechanisms that underlie information storage may not differ greatly across age groups. Rather, the slower rate of learning and increased rate of forgetting indicate a more subtle change in memory processes such as storage or maintenance mechanisms. Correlational analysis has been employed as an initial method for exploring the biological mechanisms for age-related changes in cognitive function. A number of these studies address neurological measures that are relevant to the proposed models of synaptic plasticity in memory. For example, age-related memory deficits are correlated with impaired induction of synaptic potentiation [48,98], impaired duration of LTP [9,10], impaired PKC translocation [37,62,154], and reduced synaptic strength [16]. The model in Fig. 2 describes mechanisms for increasing the threshold for induction of synaptic enhancement through an enhancement of the AHP. In fact, the magnitude of the AHP is inversely related to learning during aging [55]. In this regard, it is also important to note that learning is associated with neurological changes that are opposite that observed in aged memory-impaired animals such that learning is associated with an increase in synaptic strength [64,65,80,159] and a reduction in the AHP [53,185]. Thus, if the mechanisms that regulate experience-dependent neural plasticity are compromised, then behavioral training may actually enhance the correlation between age-related changes in neurological measures and memory function (e.g., see Ref. [75]).

The shift in mechanisms regulating synaptic modifiability with aging could limit experience-dependent neuronal plasticity necessitating additional training sessions for aged animals to acquire hippocampal-dependent tasks. Furthermore, a reduced threshold for induction of LTD and LTP reversal could act to reverse or erase experience-dependent changes. Indeed, experience-dependent growth in the synaptic response decays more rapidly in aged animals [172]; rapid forgetting in aged animals is associated with a rapid decay of LTP [14] and increased susceptibility to LTD induction (unpublished observations). Furthermore, an increase in L-channel function, which is thought to underlie the shift in the threshold for LTD [66,67,144], is correlated with and age-related impairment on the Morris water maze [179]. Together, the results suggest that memory function and neurological correlates of age-related memory impairment may be manifestations of the same neural plasticity processes activated by experience, and age-related memory deficits may be due to an inability to initiate or maintain these neural plasticity processes.

### *5.2. Impaired LTP induction is associated with learning deficits*

The mechanisms hypothesized to regulate the threshold for synaptic plasticity can be altered by pharmacological treatments. A more convincing argument for the model of age-related changes in synaptic plasticity threshold as a mechanism underlying memory deficits requires experi-

mental tests of specific predictions set out in the model. A major prediction of the model is that treatments that facilitate LTP induction or lower the threshold for LTP induction will improve learning in aged animals. As noted above, pharmacological or genetic manipulations that impair LTP induction impair acquisition of hippocampal-dependent behavior. The impairment is thought to result from blockade of the mechanisms that underlie experience-dependent synaptic plasticity [26,64,131]. A major point for regulation of synaptic plasticity is $Ca^{2+}$ entry through the NMDAR. Pharmacological manipulations of the glycine site of the NMDAR act to modulate channel function and influence the susceptibility to LTP induction [147]. Furthermore, agonists of this site have been successfully employed to improve learning in young and aged animals [7,18,88,183,184]. Together, these studies support the prediction that altered susceptibility to LTP induction will shift learning ability.

One of the central elements of the plasticity threshold model is that the age-related increase in the magnitude and duration of the $Ca^{2+}$-dependent, $K^+$-mediated AHP is responsible for impaired LTP. The hypothesis is that the large hyperpolarizing response will limit the ability to activate NMDARs, particularly for stimulation patterns that are near the threshold for LTP induction. Confirmation of a link between the amplitude of these $K^+$ currents and age-related changes in susceptibility to LTP comes from studies using $K^+$ channel blockers. Apamin, a toxin from bee venom, directly blocks the $Ca^{2+}$-activated, $K^+$ channel, reduces the AHP in hippocampal neurons from aged rats, and lowers the threshold for induction of LTP [144]. In accord with predictions from the model, that facilitation of LTP will facilitate learning, apamin treatment increases the rate of acquisition in adults [45,46] and improves memory [20]. Currently, it is unknown whether apamin can improve performance in aged animals.

### *5.3. Increased susceptibility to LTD induction is associated with memory deficits*

A second prediction of the plasticity threshold model is that increased susceptibility to LTD leads to impaired retention, such that treatments that block the rapid decay of LTP or block LTP reversal will facilitate retention. NMDAR blockers can inhibit induction of LTD and LTP reversal [143], and antagonism of the NMDAR, after induction of LTP, inhibits the decay of LTP [12]. The fact, that NMDA antagonists block activity-dependent LTP reversal and the decay of LTP, suggests that the decay of LTP may be due to an active mechanism. Interestingly, several studies have observed that, following training, treatment with NMDAR antagonists can slow forgetting [129,142,160]. Using the water-escape task, young adult and aged rats can be trained in 1 day to discriminate the spatial location of a hidden platform. However, in contrast to young adults, aged animals exhibit rapid forgetting of the spatial location over a 24-h period [63,116,142]. However, in aged rats, injection of the non-competitive NMDAR antagonist, MK-801 (0.05 mg/kg), immediately following training for spatial discrimination, improved retention tested 24 h later [142]. Normally, NMDAR blockade is associated with blockade of LTP and impaired learning. Therefore, it is possible that the MK-801 blocked retroactive interference of memory, due to subsequent learning over the 24-h period. However, improved retention was not observed following a posttraining injection of scopolamine, another compound known to inhibit learning. The results suggest that improved retention was specific to NMDAR function and not due to blockade of retroactive interference of memory. The authors hypothesized that amelioration of rapid forgetting in the aged animal following NMDAR blockade are due to inhibition of LTD-like processes, which are enhanced during aging.

Importantly, the memory-enhancing effects are observed for lower doses of NMDAR antagonists, suggesting that the effects are due to a reduction in receptor activity rather than complete receptor blockade [128]. The requirement for limiting NMDAR activity may explain why adult animals treated with the low-affinity non-competitive NMDAR antagonist, memantine, exhibit improved performance on the spatial version of the water-escape task [12]. In this regard, it is important to note that, unlike other NMDAR antagonists, memantine treatment does not block LTP induction, and acts to increase the durability of LTP [12,30]. The benefits of memantine appear to be due to the fact, that memantine is a strongly voltage-dependent, low-affinity NMDAR antagonist and, as such, has properties similar to $Mg^{2+}$, reducing rather than blocking NMDAR activity [153]. Interestingly, increasing the level of $Mg^{2+}$ in the plasma also improves cognitive function in aged rats [103]. Furthermore, a shift in the $Mg^{2+}$ level can alter synaptic function in an age-dependent manner [104], including amelioration of differences in susceptibility to LTD induction [143]. The data are consistent with the idea that activity-dependent processes underlie forgetting. However, the corollary prediction remains to be tested, whether enhanced NMDAR function, following training, can increase forgetting. Thus, the model of altered synaptic plasticity thresholds may contribute to our understanding of the qualitative features of memory improvement or impairment following pharmacological treatments.

### *5.4. Altered synaptic plasticity thresholds underlie deficits in learning and memory*

Physiological studies indicate that, for aged animals, L-channel function is fundamental in regulating neuronal excitability [27,135,179,182] and adjusting synaptic plasticity thresholds [144]. Blockade of the L-channel in aged rats ameliorates the increased susceptibility to LTD and lowers the threshold for NMDA-dependent LTP. Therefore, according to the model of altered synaptic plasticity

thresholds in mediating age-related memory deficits, L-channel blockade should improve both learning and retention. In aged animals, pretraining treatment with L-channel antagonists has been shown to improve learning on hippocampal-dependent tasks including eye blink conditioning [49], maze learning [97], spatial-reversal learning [124], and working memory [106,169]. L-channel antagonists, such as nimodipine, also improve retention when treatment is delivered after training [161,175]. While anatomical evidence suggests that chronic treatment with L-channel antagonists may be beneficial for synaptic transmission [43,125], no study has demonstrated that L-channel antagonists increase basal synaptic strength in aged animals.

Research on treatments that promote L-channel activity supports the idea that changes in L-channels underlie both the shift in synaptic plasticity and the decline in hippocampal-dependent memory. Increased L-channel function due to L-channel activators, stress, or glucocorticoids, increase the AHP amplitude, reduce the susceptibility to LTP induction, facilitate induction of LTD, and impair learning on spatial discrimination tasks (for a review, see Refs. [66,95]). Interestingly, proteins related to β-amyloid, a protein associated with Alzheimer's disease, also increase $Ca^{2+}$ channel activity [5,68,108]. The change in $Ca^{2+}$ channel activity may explain the ability of β-amyloid to influence LTP induction [41,140,195], alter the frequency–response function [89], and decrease synaptic strength [40]. Finally, injections of β-amyloid into the brain impair memory function, in a manner unrelated to neurodegeneration and cell loss [4,31,176,178]. Together, the results support the idea that age-related memory impairments are due to altered $Ca^{2+}$ homeostasis and changes in $Ca^{2+}$-dependent processes involved in regulating synaptic modifiability.

## 6. Relationship of synaptic plasticity threshold to other hypotheses of brain aging

Cognitive deficits and brain aging likely are not due to a single factor. Indeed, because of the multiple steps within the model, from $Ca^{2+}$ entry to synaptic plasticity, it is likely that other neurological markers of brain aging will interact with these processes. Thus, a shift in synaptic plasticity thresholds may underlie neural anatomical correlates of brain aging (e.g., see Refs. [75,76]). Differences in specific neurotransmitter systems have been long regarded as indications for age-related memory decline [42,168]. Changes usually involve a loss of a marker for specific neurons that release the transmitter of interest or a loss of postsynaptic responsiveness to the transmitter. The AHP can be modulated by a number of extraneous factors and is a key target for several neurotransmitters including acetylcholine, serotonin, dopamine, norepinephrine, and glutamate metabotropic receptor activation [2,105,156,187,198]. Moreover, these transmitters can influence the susceptibility to synaptic modification possibly through regulation of the AHP [35,36,86,90,91,148,186]. In some cases, the reduction in the AHP may be a secondary outcome to transmitter-mediated inhibition of L-channel function [35] or altered activity of protein kinases and protein phosphatases [156,157,167,187]. Nevertheless, the ubiquitous nature of AHP regulation implies the importance of this $Ca^{2+}$-dependent process. Barring dysfunction of the underlying $K^+$ channel, the redundancy of pathways for regulating the AHP would seem to suggest that surviving neurotransmitter systems may compensate for a change in any single transmitter system. However, reports appear to indicate that aging is associated with a decrease in hippocampal responsiveness to multiple neurotransmitters [8,22,173], signaling an overall reduction in the capacity to regulate the AHP and perhaps ultimately, synaptic plasticity.

Finally, many of the age-related changes observed in the hippocampus would be expected to act in concert to decrease transmission through this structure. A loss of neural substrate, a decrease in synaptic strength, an increase in the AHP with commensurate changes in the activity and pattern of cell firing, combined with a loss of neural modulators, would limit the ability to transfer information through the hippocampus. A decrease in information transfer would, in turn, reduce the influence of the hippocampus on cognitive processes such as memory [70].

## 7. Conclusions

Aging is associated with a decline in hippocampal-dependent memory, and the general hypothesis, that age-related memory deficits are associated with changes in the hippocampus, has been widely confirmed. A challenge for the $Ca^{2+}$ hypothesis of brain aging is to determine the key elements which relate altered $Ca^{2+}$ homeostasis with memory impairment. This review lays out a framework for linking age-related changes in $Ca^{2+}$ regulation to cognitive decline through altered thresholds for synaptic modifiability. The relationship between synaptic plasticity and memory function is far from clear; however, the available data suggest that aged memory-impaired animals exhibit changes in hippocampal morphology, biochemistry and physiology that are linked to synaptic plasticity. In some cases, the age-associated changes may manifest as a direct result of altered synaptic plasticity processes. For example, the characteristic decrease in synaptic strength may be due to increased phosphatase activity through an LTD-like process.

In other cases, changes may involve a reorganization of mechanisms involved in regulating synaptic modifiability, such as the loss of neurotransmitter, increased L-channel activity or growth of the AHP and associated reduction in neural excitability. Research indicates that during aging, there is a shift in the mechanisms that regulate the induction or maintenance of $Ca^{2+}$-dependent synaptic modification rather than the loss of mechanisms for expression of synaptic plasticity. Thus, experiments directed at manipu-

lating the regulatory mechanism for synaptic plasticity are expected to reveal the nature of the interaction between synaptic plasticity and memory.

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