Published in final edited form as:

Behav Brain Res. 2017 March 30; 322(Pt B): 191–205. doi:10.1016/j.bbr.2016.05.008.

Molecular and cellular aspects of age-related cognitive decline and Alzheimer's disease

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Abstract

As the population of people aged 60 or older continues to rise, it has become increasingly important to understand the molecular basis underlying age-related cognitive decline. In fact, a better understanding of aging biology will help us identify ways to maintain high levels of cognitive functioning throughout the aging process. Many cellular and molecular aspects of brain aging are shared with other organ systems; however, certain age-related changes are unique to the nervous system due to its structural, cellular and molecular complexity. Importantly, the brain appears to show differential changes throughout the aging process, with certain regions (e.g. frontal and temporal regions) being more vulnerable than others (e.g. brain stem). Within the medial temporal lobe, the hippocampus is especially susceptible to age-related changes. The important role of the hippocampus in age-related cognitive decline and in vulnerability to disease processes such as Alzheimer's disease has prompted this review, which will focus on the complexity of changes that characterize aging, and on the molecular connections that exist between normal aging and Alzheimer's disease. Finally, it will discuss behavioral interventions and emerging insights for promoting healthy cognitive aging.

Graphical abstract

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Keywords

Aging; Alzheimer's disease; Cognition; Hippocampus; Molecular mechanisms

1. Introduction

In almost every country around the globe, the proportion of people aged 60 and older is growing faster than any other age group [1]. In 2013, persons 65 years or older represented 14.1% of the U.S. population, or about one in every seven Americans; by 2040, older persons are expected to represent 21.7% of the population [2]. This growth represents a demand to continue our studies on the molecular mechanisms of aging in order to understand the basis of disease vulnerability and improve the quality of life in older individuals. One area of vast importance for our society is that of cognitive aging. Normal aging is most typically accompanied by slower processing speed and changes to memory and executive functions. Aging is also the most important risk factor for mild cognitive impairment (MCI) and Alzheimer's disease (AD). MCI is defined as problems with memory, language, thinking, and judgment that are serious enough to be recognized by the patient, but not serious enough to interfere with daily life. A diagnosis of dementia instead is made when cognitive and behavioral problems interfere with daily activities. The incidence of MCI and dementia has risen over the course of the past decade, with an estimated 75% of people 60 and older expected to have dementia by 2050 [1,3]. To optimize healthy cognitive aging and deal with the increasing burden of age-associated diseases that affect cognitive functions it is important to understand the molecular mechanisms underlying aging and cognitive decline.

Many cellular and molecular aspects of brain aging are shared with other organ systems (e.g., oxidative stress, mitochondria dysfunction; dysfunctional protein homeostasis, etc.). However, due to its unique molecular and structural complexity, there are age-related changes that are only observed in the brain. The most prominent changes of the aging brain are summarized in Table 1.

The hippocampus has been at the forefront of “memory research” for the last sixty years. It integrates sensory, emotional and cognitive components of many memory inputs coming from the entorhinal cortex while performing fundamental activities related to formation, storage, and retrieval of episodic memories [4–7]. The hippocampus is particularly susceptible to detrimental age-related changes in function [8,9]. In this review we will focus on events that occur within the hippocampus and that are associated with cognitive decline over the aging process. We will also briefly introduce AD neuropathology and discuss signaling pathways that regulate the progression of aging in mammals and show how they impact on the pathogenesis and progression of AD. The fact that common pathways can regulate both aging and AD neuropathology demonstrates that a clear understanding of aging biology is likely to provide answers for development of interventions and treatments to offset and correct cognitive decline and AD.

Due to space limitations, we had to refrain from a more comprehensive analysis of available research. For example, we will not discuss the growing body of research focused on proteostasis and metabolism. These processes play fundamental roles in the brain, and investigation of their contribution to aging and AD is rapidly expanding [10–18]. Indeed, there is compelling evidence that brain aging is accompanied by changes in protein homeostasis that lead to accumulation of toxic protein aggregates [10–13]. Therefore, dissection of the molecular mechanisms that regulate proteostasis will help us prevent age-associated diseases that are characterized by the accumulation of toxic protein aggregates (i.e., AD, Parkinson’s disease, Lewy body dementia, frontotemporal dementia) [10–13]. Similarly, new research has revealed that the brain is metabolically very active. Although many pathways are shared with peripheral tissues, the brain does display unique metabolic features. Topics of high interest that are influenced as a function of age and that impact on different neurological diseases include glucose uptake, acetyl-CoA biosynthesis and flux, metabolism of fatty acids, sphingomyelins and major glycosphingolipids, and mitochondria energy production rates [14–18]. The integration of knowledge that is obtained by dissecting the above highly interconnected metabolic pathways will likely give us information that will impact on several age-associated diseases.

Another important area of research that we will not discuss in this review is the role of aging in regulating neurotrophin signaling. The expression levels of the ligands (neurotrophins) and associated receptors (neurotrophin receptors) change as a function of age, resulting in different signaling pathways being activated. Although much has been learned on the underlying mechanisms, we still need to gather more biochemical information and determine the different layers of cross-talk between neurotrophin signaling pathways if we wish identify possible therapeutic strategies.

2. The hippocampus

The hippocampus is part of the limbic system, a series of highly interconnected structures involved in a variety of functions, which include emotion, behavior, motivation, memory, and olfaction. In humans, it is found within the medial temporal lobe while in rodents it is found just beneath the neocortex. It consists of four Cornu Ammonis (CA) areas, CA1, CA2, CA3, and CA4 [19]. In the literature, the hippocampus is frequently associated with the

dentate gyrus and the subiculum; together, these three structures are referred to as the hippocampal formation. Three major neuronal pathways relay information within the hippocampal formation: the perforant pathway projects from the entorhinal cortex to the dentate gyrus, area CA3, and area CA1; the mossy fiber pathway projects from the dentate gyrus to area CA3; the Schaffer collateral pathway projects from CA3 to area CA1 [4,7]. Hippocampal output is also sent back from CA1 to the entorhinal cortex, forming an axonal loop [20]. Recent anatomical tracing studies have also revealed complex connectivity within the hippocampus and hippocampal formation with multiple processing and feedback circuits [4,7].

As mentioned above, the hippocampus has been at the forefront of memory research. The identification of complex circuitry connecting to the entorhinal cortex, the characterization of hippocampal-dependent long-term potentiation, and, more recently, the identification of place cells, head direction cells, and grid cells have further consolidated the role of this structure in memory formation [4–6,21]. Importantly, the entorhinal cortex receives inputs from spatial processing areas, such as the post-subiculum and the retrosplenial cortex, and high-order areas, such as the perirhinal cortex [4–7]. Therefore, in addition to performing fundamental activities related to formation, storage, and retrieval of episodic memories, the hippocampus also integrates sensory, emotional and cognitive components of memory inputs [4–7].

3. Behavioral assays of hippocampal decline

Studies from humans, non-human primates, and rodents reveal age related changes in cognition across many species. In rodents, some aged animals develop severe cognitive impairments whereas others retain normal cognitive abilities [22–24]. In particular, hippocampal-dependent tasks, such as spatial memory, appear to be significantly affected. Performance on spatial navigation tasks as well as the ability to quickly encode changing environments is also affected [8,24].

Several behavioral assays have been developed to assess spatial learning and memory in rodents. Some of them are briefly described below. The Morris water maze is perhaps the most commonly employed measure of hippocampal-dependent spatial memory formation and retention in the rodent. In this procedure, the animals are placed in a large pool of water and trained to use visual cues around the room to locate a platform hidden from view within the pool. It has been established that performance on the Morris water maze declines with age for both rats and mice [8,23–27].

The Barnes circular platform task is another commonly used hippocampal-dependent test of spatial learning and memory. In this task, rodents learn which of 18 holes lead to a dark escape tunnel. Aged rats and mice are impaired in learning the location of the tunnel, and demonstrate difficulties retaining the memory of the location. Furthermore, when the location of the escape tunnel is changed they struggle to learn the new location [8,28–30].

Spatial working memory can be tested with the eight-arm radial maze, and the similar radial arm water maze. In these tasks, rewards are available at the end of arms and animals must

learn which arms lead to specific rewards. Numerous studies have demonstrated that aged rodents require significantly more trials to learn the location of rewards, and make more errors of spatial working memory than adult or young counterparts [31,32].

In the object recognition memory task, rodents are exposed to two identical objects in the first training session, and one of the objects is replaced with a novel object in the second training session. The amount of time spent investigating the novel vs familiar object is recorded. The task takes advantage of rodents' innate preference for novelty, and tests the ability to discriminate between novel and familiar objects. Object recognition memory also appears to be deficient in aged rodents [33,34].

Contextual fear conditioning is another frequently used hippocampal-based test. It was developed by pairing a footshock with a cue such as a light or a tone. When exposed to the same context (location) after the shock, the animal will exhibit a startle response, otherwise known as freezing behavior, which is indicative of fear. Aged animals tend to display significant deficits in this type of conditioning [35,36].

In conclusion, a series of different and independent behavioral tests show significant decline of hippocampal-dependent functions with age. A more severe decline is observed in certain AD mouse models (discussed later).

4. Synaptic plasticity and cognition

Synaptic plasticity, or the ability of the brain to reorganize, develop, and prune neural pathways, is essential for the development and maintenance of memories [37,38]. Two key components of synaptic plasticity, which underlie learning and memory formation are long term potentiation (LTP) and long term depression (LTD). Both LTP and LTD are typically recorded in isolated hippocampal slices. LTP, which involves a rapid influx of calcium into the cell, leads to the enhancement of cell excitability by the activation of intracellular signaling cascades that increase protein transcription, translation, and the insertion of new receptors into the cell membrane [39–42]. LTD has the opposite effect, modulating transcription, translation, and the induction of receptors back into the cell, which leads to decreased cell excitability [43–46]. It is commonly believed that LTP and LTD are the cellular correlates of learning and memory [37,38,47–51]. Detailed information of the different cell surface receptors and down-stream signaling cascades that regulate LTP and LTD can be obtained elsewhere [8,42,52–61].

Interestingly, robust, high intensity stimulation protocols do not reveal differences in LTP between aged and young rats [8,62–64]. In contrast, stimulation paradigms with fewer stimuli or lower amplitude currents reveal that aged rats have deficits in LTP induction in CA1 and in the dentate gyrus [62–64]. Studies in rats and mice have also shown that aged animals display deficits in LTP maintenance and that the durability of LTP correlates with performance in hippocampal dependent tasks [65–67]. Furthermore, LTP is reduced in the hippocampus of aged rats that demonstrate cognitive impairments relative to aged unimpaired rats [68,69]. Studies have also demonstrated that aged impaired rodents are more susceptible to LTD. Interestingly, the stimulus threshold for the induction of LTD appears to

be lower in the aged animal, perhaps making it easier to erase memories [70,71]. How this specific feature impacts on the reduced ability to encode new memory of events and facts that is typically observed in old individuals remains to be determined.

5. Changes in the aging hippocampus

5.1. Synapse structure

In addition to age-related alterations in hippocampal LTP and LTD, several studies have indicated that changes in synaptic function are accompanied by age-dependent changes in synapse structure. Most studies indicate that aging does not entail a substantial loss of total neurons in the hippocampus or the prefrontal cortex [72]. However, several studies indicate that neurogenesis decreases as a function of age [73,74]. In addition to decreased neurogenesis, evidence suggests that aging is accompanied by the loss of synapses. The extent of synaptic loss correlates with the severity of learning impairment, supporting the notion that the loss of hippocampal synapses directly contributes to age-related cognitive impairment [75–77]. The synaptic loss observed in the hippocampus of aged rats may be due to the loss of both presynaptic [78] and postsynaptic terminals [79]. Presynaptic terminals may be single-synapse boutons, multiple-synapse boutons, or boutons that do not make synaptic contacts (nonsynaptic boutons) [80]. Importantly, hippocampal-dependent associative learning is accompanied by selective synaptogenesis that results in formation of multiple-synapse boutons [81]. This process has been linked to preservation of input specificity during interneuronal spread of LTP and, ultimately, to successful learning under hippocampal-dependent paradigms [82]. Studies using electron microscopy have revealed age-related changes in the type of terminals formed. Specifically, aged female monkeys (Rhesus macaque) with memory impairment have fewer multiple-synapse boutons and twice as many nonsynaptic boutons in the dentate gyrus [80,83]. Finally, aged rodents and monkeys also display significant loss of postsynaptic spines in the hippocampus and cortex [84,85], associated with reduced cognitive performance [75,86].

5.2. Calcium conductance

Despite these changes in synapse structure, the basic properties of the cell membrane such as resting potential, input resistance, amplitude and duration of action potentials, etc. are unchanged in aging rodents [8]. However, several studies have revealed changes in calcium transmission across the membrane as a function of age. The influx of calcium is the final step in synaptic transmission, which triggers LTP or LTD. Therefore, changes in calcium conductance across the cell membrane could have significant effects on synaptic plasticity in aged animals. Aged rats display an increased density of L-type Ca^{++} channels in CA1 pyramidal cells, leading to increased L-type Ca^{++} currents [87,88]. Performance on the Morris water maze was inversely related to the density of L-type calcium channels, demonstrating that this change has significant downstream effects on learning and memory [88]. In addition, CA1 pyramidal cells from aged rodents show an increased duration of calcium-mediated action potentials [89,90]. The inward flux of calcium in response to an action potential activates a calcium mediated inward potassium current. The potassium channels are slower to open and close than calcium channels, which leads to a temporary after-hyperpolarization (AHP) of the cell following an action potential. This phenomenon is

increased in aged rodents and rabbits, leading to less frequent firing of action potentials in response to a prolonged depolarizing current [91–93]. Subsequent studies demonstrated that these age-related deficits were eliminated when slices were bathed in low Ca^{++} artificial cerebrospinal fluid (ACSF), or when the membrane permeable calcium chelator 1,2-bis(2-aminophenoxy)ethane- N,N,N',N' -tetraacetic acid tetrakis(acetoxymethyl ester) (BAPTA-AM) was added to the ACSF prior to stimulation [94,95]. In addition, when the L-type calcium channel agonist Bay K8644 was added to the ACSF, slices from adult (unimpaired) animals demonstrated increased AHP and subsequent impairments in frequency potentiation [96]. Several studies have also examined the relationship between altered calcium transmission and the aberrant LTD seen in aged animals. As discussed previously, aged rats demonstrate increased vulnerability to LTD and have a lower LTD induction threshold than adult rats. This deficit is eliminated when slices are bathed in low Ca^{++} ACSF, whereas bathing slices from adult rats in high calcium ACSF increases susceptibility to LTD [71,97]. Taken together, these data demonstrate that age-related changes in calcium transmission underly detrimental changes in synaptic plasticity and may partially explain the deficits in plasticity seen over the course of aging.

5.3. mGluRs

In addition to calcium transmission, it has been proposed that changes in activity and expression of metabotropic glutamate receptors (mGluRs) may partially explain age related cognitive decline. mGluRs are a family of group C G-protein-coupled receptors that participate in the modulation of synaptic transmission and neuronal excitability within the central nervous system. They bind glutamate on their extracellular domain and transmit signals to intracellular signaling partners (see Fig. 1). The mGluR family includes eight different members (referred to as mGluR1 to mGluR8) clustered into three groups, group I, II and III. Mice lacking mGluR5 show impaired learning on the Morris water maze and contextual fear conditioning tasks [98], and display exacerbated impairments in a reversal learning paradigm of the maze [99]. Cognitive performance in aged rodents can be rescued by positive allosteric modulators of mGluR5, whereas mGluR5 antagonists have the opposite effect [100–103]. Finally, aged rats that demonstrate superior memories have higher levels of mGluR5 in the post synaptic density than aged rats with learning and memory deficits [102].

Whereas young rats rely on N -methyl-D-aspartate (NMDA) receptor-dependent mechanisms for LTP and LTD, successful cognitive aging appears to be associated with a transition to NMDA receptor-independent forms of LTP. This includes mGluR-dependent and voltage-dependent calcium channel (VDCC)-dependent LTP [51,101,104]. Successful cognitive aging has also been correlated with a transition to mGluR-dependent LTD [103,105]. Taken together, these results provide compelling evidence that mGluRs are essential for synaptic plasticity and memory performance in aged animals. Downstream signaling cascades are discussed in the next chapters (see also Fig. 1).

5.4. Intracellular signaling cascades

The inward flux of calcium following an action potential triggers various intracellular signaling cascades that lead to global changes in cellular activity. Differential calcium

conductance in aged impaired animals will mount a cellular response to synaptic input that may inappropriately activate intracellular signaling pathways, thus contributing to synaptic dysfunction and cognitive impairment in the aged animal. Several of these cascades (discussed below) have been proven to be essential for LTP/LTD, learning, and memory to occur and, therefore, are attractive targets to ameliorate age-related cognitive decline (see Fig. 1).

PKC—Protein kinase C (PKC) is a large family of serine/threonine kinases that are highly expressed in the brain. A number of these are already known to play an essential role in synaptic plasticity, learning, and memory [106–108]. One example is the conventional PKC gamma, which is highly expressed in hippocampal neurons and appears to be required for the regulation of synaptic plasticity downstream of ionotropic and metabotropic glutamate receptors [109–113] (see Fig. 1). In addition to this role in synaptic plasticity, PKC is known to be essential for learning and memory. Training in a spatial memory task has been shown to increase expression of PKC gamma [114]. Furthermore, PKC activity is reduced in aged rats compared to middle-aged and young counterparts [115]. PKC activity has also been linked to individual differences in cognitive aging: increased activation of PKC promotes successful cognitive aging whereas animals with diminished PKC activity demonstrate cognitive impairments [102,116,117]. Additionally, PKC activators improve spatial learning [118], whereas PKC inhibitors impair performance on spatial tasks [119]. The activation of PKC in small groups of hippocampal or cortical neurons has been shown to improve the performance of aged rats in the Morris water maze [108]. Finally, PKC gamma activity may protect against neurodegeneration, promote synaptogenesis, and increase neuronal interconnections [120], making PKC an attractive target for therapeutics against age-related cognitive decline.

ERK—The extracellular signal related kinase (ERK), a subclass of mitogen-activated protein kinases (MAPKs), is an important regulator of transcription, translation, and receptor trafficking [121–123]. The activation of group I mGluRs leads to the phosphorylation of ERK, activating the kinase pathway and inducing subsequent phosphorylation of several downstream targets [124,125] (see Fig. 1). Activation of ERK by phosphorylation (pERK) induces p90 ribosomal S6 kinase 1 (RSK1) to translocate to the nucleus and phosphorylate transcription factors such as cAMP response element binding protein (CREB) and ETS domain-containing protein 1 (Elk1), which regulate transcription [126,127]. mGluR induced activation of the ERK pathway can also directly regulate protein translation through activation of MAP kinase interacting kinase 1 (Mnk1) and subsequent formation of the eukaryotic initiation factor 4F complex (eIF4F) [128,129], or through the phosphorylation of S6 Kinase (S6K) [130].

It has been demonstrated that activation of ERK is vital for the expression of LTP (see Fig. 1). Inhibitors of ERK activation lead to suppression of hippocampal LTP [131,132] and LTP induction has consistently been shown to lead to phosphorylation of ERK in the dentate gyrus [126,131]. ERK activation is also important for formation of long term memories, specifically in tasks that are known to be hippocampal dependent such as the Morris water maze [84,133,134]. ERK is also known to be important for LTD. Application of

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dihydroxyphenylglycine (DHPG), an agonist of group I mGluRs, to hippocampal slices causes LTD, hereby referred to as DHPG-LTD; this is accompanied by a robust phosphorylation of ERK and inhibitors that disrupt activation of the ERK pathway significantly reduce DHPG-LTD [135]. Furthermore, selective activation of mGluR5 enhances phosphorylation of ERK1/2 in striatal neurons, and mGluR5 mediated ERK1/2 phosphorylation is almost completely eliminated by disrupting the interactions of mGluR5 and the scaffolding protein Homer1b/c (see later) [136]. The phosphorylation of ERK has been linked to successful cognitive aging. Aged animals demonstrate diminished levels of pERK relative to their young counterparts and pERK levels correlate with performance in the Morris water maze. Additionally, aged rats that demonstrate superior cognitive abilities have elevated pERK levels within the hippocampus compared to aged animals with inferior learning and memory [102].

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PI3K-Akt-mTOR—The PI3K-Akt-mTOR pathway has emerged as essential for learning and memory and synaptic plasticity (see Fig. 1). In this pathway, activation of mGluRs leads to dissociation of their g-proteins and activation of the protein kinase phosphoinositide 3 kinase (PI3K) [124,125]. PI3K phosphorylates second messengers that activate the protein kinase Akt [137]. Akt activates many targets, including mammalian target of rapamycin (mTOR), a protein kinase that is thought to be important for LTD, LTP, and memory formation. Phosphorylation (activation) of mTOR leads to two events that are important for translational regulation (see Fig. 1): phosphorylation of S6K causes enhanced translation of mRNAs [138], while phosphorylation of eukaryotic initiation factor 4E binding protein (4EBP) allows for the formation of the translation initiation factor eIF4F, which regulates translation of proteins [139]. Proper translational control via mTOR is required for LTP [129,140] and for formation of hippocampal dependent long term memories [129,141]. It has also been demonstrated that mTOR is activated during DHPG induced mGluR-LTD and that blocking activity of mTOR by the antagonist rapamycin can prevent DHPG-LTD in the hippocampal area CA1 [142].

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Aged animals with superior performance in the Morris water maze task were reported to have increased phosphorylation (and activation) of mTOR within the hippocampus compared to aged inferior learners, suggesting a role for mTOR activity in successful cognitive aging [102]. However, mTOR regulates a wide range of biological functions including autophagy, mitochondrial function, lipogenesis, ketogenesis, and glucose homeostasis [143]. mTOR complexes also regulate the cellular response to growth factors such as insulin and insulin like growth factors (IGFs) and, therefore, connect growth to glucose metabolism [143]. Interestingly, reduced signaling through the IGF1 receptor (IGF-1R), which leads to decreased mTOR activity, is linked to increased lifespan and delayed progression of age-associated events ([144]; discussed later). However, IGF-1R also plays an essential role in learning and memory. Various studies have demonstrated a central role for IGFs in memory formation, consolidation, enhancement, and extinction [145] as well as in the generation of LTP [146–148]. In light of this delicate balance between cognition, longevity, and metabolism, the therapeutic potential of IGF-mTOR signaling for age-related cognitive decline may be limited.

CREB—The transcription factor cAMP response element-binding protein (CREB) regulates gene transcription and has been shown to be essential for multiple forms of learning and memory [145,149–153] (see Fig. 1). Aged animals with cognitive impairments demonstrate significantly lower levels of CREB [102,154]. However, CREB is ubiquitously expressed and thus it is likely that modulation of CREB activity will have widespread health consequences for the animal. Therefore, it may be more beneficial to target genes downstream of CREB for cognitive enhancement therapeutics.

When taken together, the information reported above clearly shows the complexity of the molecular pathways that control different aspects of synaptic plasticity, learning and memory. Indeed, multiple independent – but also overlapping-signaling pathways relay fundamental information. It is likely that cross-talk between the individual players and pathways provide balance and specificity to ensure proper formation of memory. Dysregulation of this balance may be at the basis of several aspects of cognitive decline observed during aging.

5.5. Immediate early genes

Synaptic plasticity and subsequent memory formation require experience-induced activation of neuronal transmission, which leads to activation of transcription factors such as CREB and Elk1 to induce transcription of several key immediate early genes (IEGs) that rapidly mount a widespread cellular response to a variety of stimuli (see Fig. 1). These IEGs, such as BDNF, Arc, Zif268, cfos, and CREB are essential for LTP, LTD, and for long-term memory formation and consolidation [155,156]. Given their significance for synaptic plasticity and memory, IEGs are potential gene targets that may be differentially activated and expressed in aging animals. Indeed, decreased IEG expression has been reported in normal aging [157,158], and is seen in some models of memory disorders, including AD [159–161]. Several microarray studies have been conducted to investigate whether aged animals with cognitive impairment display differential activation patterns of these IEGs compared to aged unimpaired counterparts [23,157,159,162]. These studies separated aged animals into impaired and unimpaired learners, typically by testing in the Morris water maze, and then conducted microarray analysis to determine which genes were differentially expressed between groups. They revealed that aged impaired animals display reduced expression of IEGs relative to aged unimpaired and young counterparts [23,157,159,162]. This reduction in IEG activation can have widespread cellular consequences given the central role of IEGs in coordinating the neural transmission program. Many IEGs are transcriptional activators and DNA binding proteins, thereby exerting a broad influence over the expression of other downstream proteins. Therefore, dysregulation of one IEG might have broader amplification. Again, cross-talk and partial overlap is likely fundamental for neuronal activity and learning.

5.6. The homer family of proteins

In addition to changes in IEG activity and intracellular signaling cascades discussed above, another important event that may underlie cognitive deficits in some old animals is deficient expression or activity of scaffolding proteins. Scaffolding proteins create anchors between receptors and their intracellular signaling partners and thus facilitate signal transduction.

One example of scaffolding proteins that may be differentially activated in aged animals is the Homer family of adaptor proteins, which consists of three members: Homer1, Homer2, and Homer3 [163].

Due to alternative splicing, each member results in several isoforms of various lengths. For example, the *HOMER1* gene encodes a short isoform (Homer1a) and two long isoforms (Homer1b and Homer1c). Homer1c was identified as a protein that is upregulated in aged animals that were superior learners, and therefore has been targeted for research focused on the molecular basis of learning and memory [23]. Homer 1c has been shown to bind mGluRs and to enhance trafficking of group I mGluRs to the cell membrane in hippocampal neurons [164,165]. Furthermore, Homer1c links mGluRs to other cell surface receptors, such as N-type calcium and M-type potassium channels [166], thus regulating cell signaling following activation of mGluRs. Homer1c also connects mGluRs to intracellular signaling complexes by interacting with phosphoinositide 3 kinase enhancer (PIKE), and regulates calcium homeostasis by interacting with IP3 and Ryanodine receptors [136,167]. Additionally, Homer1c has been shown to interact with NMDA through Shank, and to participate in the formation of functional connections between mGluRs and ionotropic glutamate receptors at the post synaptic density [168]. Finally, Homer1a is an IEG that is activated following synaptic stimulation and appears to disrupt the connections mediated by the long Homer isoforms, thus having effects opposing those of Homer1c [169].

Homer1c is a scaffolding protein that is localized to the postsynaptic density of neurons in hippocampal area CA1 [165,167]. Given its role as a scaffolding protein, it is not surprising that Homer1c expression is essential for normal synaptic plasticity in the hippocampus. The use of a blocking peptide that disrupts binding of Homer1c to mGluR5 prevents the induction of LTD in hippocampal neurons, thus providing direct evidence that Homer1c-mGluR5 interactions are vital for hippocampal LTD to occur [170,171]. These results have also been replicated in rat striatal neurons [136]. Overexpression of Homer1a has been shown to disrupt LTP maintenance, indicating that a balance between the long and short isoforms of Homer is essential for healthy synaptic plasticity. Homer proteins have also been linked to healthy cognitive aging. Homer1 knockout mice display drastic deficits in spatial memory and synaptic plasticity [172,173]. Furthermore, Homer1c is upregulated in hippocampal area CA1 of aged superior learners compared to aged animals that are impaired in hippocampal dependent memory tasks [23]. Homer1c gene delivery into the hippocampus of aged learning impaired rats can rescue learning deficits [174]. Similarly, aged rats with superior memories have been found to have an increased ratio of Homer1c:Homer1a bound to mGluR5 in hippocampal area CA1 [102]. In contrast, aged rodents with notable cognitive deficits demonstrate elevated levels of Homer1a within the hippocampus [102,103].

6. Aging and epigenetics

Our understanding of changes in synaptic structure, function, and cognition that occur as a function of age is further complicated by the complexity of epigenetic alterations that may occur over the lifespan. Epigenetic modifications of histones include the addition and removal of acetyl, ubiquitin, methyl, and/or phosphate groups. These modifications can alter

the structure and conformation of chromatin, thereby blocking or enhancing the transcription of the coded genes, and, ultimately, resulting in changes in gene expression [175,176].

Acetylation is one of the most commonly studied forms of histone modification. It promotes gene expression by disrupting histone-DNA interaction, thereby relaxing the chromatin structure and promoting transcription [177]. Deacetylation has the opposite effect and is associated with decreased gene expression [178,179]. Sustained histone acetylation has been shown to promote learning and memory, whereas lack of acetylation correlates with long-term memory deficits [177–180]. Furthermore, evidence suggests that histone hypoacetylation contributes to age-related cognitive decline. Indeed, aged mice with learning and memory impairments demonstrate hypoacetylation of H4K12; restoration of H4K12 acetylation by using histone deacetylase (HDAC) inhibitors ameliorates the memory deficits [181,182]. Epigenetic changes associated with aging have also been observed on other acetylated sites [183].

Another commonly studied form of epigenetic regulation is DNA methylation. In this process, cytosine residues are reversibly methylated at CpG sites in the DNA sequence. In general, methylation in promoter regions prevents transcription factors from binding and thereby reduces gene expression, whereas demethylation correlates with increased gene expression [184,185]. Studies of DNA methylation indicate that aged rats with learning and memory impairments display abnormal methylation of memory promoting genes [186]. Identified sites include H3K36me3, H4K20me1, H3K9me2/3, and H3K27me3 [183]. A recent study demonstrated that increased expression of DNA methyl transferase 3a2 (DNMT3a2) can rescue age-related memory impairment in aged mice. Additionally, downregulation of DNMT3a2 in young mice can result in memory deficits [187]. These experiments demonstrate a role for methylation in age-related cognitive decline, specifically postulating that differential expression of DNMT3a2 may underlie cognitive changes with the aging process.

The causative effect of described changes is unclear; collectively, they are thought to significantly affect gene expression of both neuronal and non-neuronal brain cells resulting in age-associated maladaptation [183]. However, clear mechanistic validation is impaired by the fact that epigenetic changes may occur at several different sites, and that the acetylation/methylation of different sites may have different effects depending on the area of the brain being examined [183]. For example, aged mice with spatial memory deficits display increased acetylation levels of H3 in the CA1 region, but decreased H4 acetylation in the dentate gyrus [188]. Nevertheless, several epigenetic-modifying compounds are currently being explored for translational purposes [183].

7. Aging and Alzheimer's disease: common pathways

7.1. AD neuropathology

Thus far, the changes in the aging hippocampus described in this review have focused on nonpathogenic age-related cognitive decline. However, aging is also the most common risk factor for late-onset AD, with prevalence increasing dramatically after the age of 60 and rising to affect roughly 50% of individuals 80 and older [3,144]. While typical age-related

cognitive decline includes changes in cognition that do not dramatically interfere with day to day life, AD is characterized by progressive and severe cognitive and behavioral changes that affect daily living. AD neuropathology is characterized by the accumulation of amyloid plaques (also referred to as senile plaques), neurofibrillary tangles (NFTs), and diffuse loss of neurons and synapses within the hippocampus, cortex, and other regions of the brain responsible for learning and memory formation [144]. Amyloid plaques and NFTs are also observed in the hippocampus and neocortex of aged individuals with normal cognitive functions [144,189].

Amyloid plaques are extracellular protein deposits consisting of a dense core of protein aggregates surrounded by dystrophic dendrites and axons, activated microglia, and reactive astrocytes [190,191]. The protein core consists primarily of amyloid β -peptide ($A\beta$), a small hydrophobic peptide generated through processing of the amyloid precursor protein (APP) in a two-step process [144]. First, APP is cleaved at the β site by β -site APP cleaving enzyme (BACE1) generating a large N-terminal fragment that is released to the extracellular *milieu* and a small, membrane-anchored, fragment called C99 (see Fig. 2A). This initial β -site cleavage by BACE1 is the rate-limiting step in the generation of $A\beta$. C99 is then cleaved by γ -secretase to form $A\beta$ and a small cytosolic fragment called APP intracellular domain (AICD) (see Fig. 2A). $A\beta$ can be generated both at the cell surface and on intracellular membrane compartments; as a result, $A\beta$ aggregates can form both outside and inside the neuronal cell body. Intracellular $A\beta$ aggregates can also be released to the extracellular *milieu* where they further aggregate to form amyloid plaques. In contrast, AICD is only released in the cytosol where it can bind to cytosolic mRNA:ribosome complexes (polysomes) to regulate initiation of translation [192] and/or translocate to the nucleus to regulate transcription [193–195]. Both $A\beta$ and AICD production are linked to the pathology of AD, and animals that do not express BACE1 (and therefore do not cleave APP) are resistant to the development of AD neuropathology [196].

In contrast to the amyloid plaques, NFTs form in the cytoplasm of neurons. NFTs are made of highly stable polymers of the microtubule-binding protein TAU. Importantly, the phosphorylation status of TAU inversely correlates with binding to microtubules. As a result, hyper-phosphorylated TAU dissociates from microtubules and tends to polymerize into filaments to form NFTs [144,196]. In line with this observation, several TAU kinases including tyrosine-regulated kinase 1A (DYRK1A), cyclin-dependent kinase 5 (CDK5), and glycogen synthase kinase-3 β (GSK3 β) have been linked to the pathogenesis of AD. Studies from different mouse models have shown that Tau plays an important role in the pathogenesis of the disease. Mutations in *MAPT*, the gene encoding TAU proteins, are associated with different forms of age-associated dementias (globally referred to as tauopathies). No mutation on *MAPT* has so far been identified in AD [144].

AD is normally divided into familial (also referred to as early-onset) and sporadic (also referred to as late-onset) AD. Familial AD accounts for ~3–5% of all AD cases and typically becomes manifest between the age of 35 and 55 years [144]. It has been associated with causative mutations on the *APP* gene (on chromosome 21), the *PSEN1* gene (on chromosome 14), and the *PSEN2* gene (on chromosome 1). Currently, about 39 mutations have been identified on *APP*, 211 on *PSEN1*, and 33 on *PSEN2* [197]. All identified

mutations are pathogenic and are associated with familial forms of the disease. *APP* gene duplications associated with familial/early-onset AD have also been reported [198,199]. Interestingly, a single-point genetic variation on *APP* that impairs β cleavage of APP and protects from AD has also been identified [200]. Globally, currently identified mutations in *APP*, *PSEN1* and *PSEN2* account for about 50% of all cases of familial AD, and, therefore, about 1–2% of all AD cases (familial and sporadic). Not all mutations affect the onset and/or progression of the disease equally. For example, the onset of the disease can occur as early as 25 years of age with some *PSEN1* mutations, and as late as 80 years of age with some *PSEN2* mutations. Disease manifestations also display significant variability, with *PSEN1* mutations causing some of the most severe forms of familial AD and *PSEN2* mutations causing some of the less severe forms [197].

Sporadic AD is a multifactorial disease with both genetic and environmental risk factors playing important roles. Although more than 20 loci have been associated with sporadic AD, the $\epsilon 4$ allele of the *APOE* gene (on chromosome 19) remains the most important genetic risk factor [197]. It increases the risk for sporadic AD approximately 3–5 fold in heterozygous carriers and approximately 15–20 fold in homozygous carriers. In contrast, the *APOE* $\epsilon 2$ allele displays protective effects. The *APOE* gene encodes three different isoforms, ApoE2, ApoE3, and ApoE4 that differ in only two amino acids. ApoE is a major cholesterol carrier protein and displays important trophic functions in the brain, where it is mostly secreted by astrocytes. The molecular basis of the ApoE-AD association is still a matter of discussion. However, some of the most studied aspects of ApoE biology include rate of A β generation, aggregation and clearance, as well as neuronal outgrowth and repair, and synaptic plasticity [201,202].

7.2. Mouse models of AD

Dissection of AD neuropathology in the mouse has proven to be problematic, mostly due to the fact that both mouse App and mouse Tau differ considerably from the human counterparts. Mice overexpressing human APP or a humanized version of mouse App (where the A β region of mouse App was replaced with human A β , leaving the rest of the protein untouched) have been generated. Both mice also had one or more familial AD-associated mutations incorporated into the *APP* gene. The resulting animals developed amyloid plaques, LTP/LTD defects, and a certain degree of synaptic loss. Cognitive changes were more elusive, being detected in certain models but not in others. Importantly, the Tau pathology (NFTs) and the neuronal loss appeared almost completely absent, suggesting that additional biochemical/molecular events are required to develop the full spectrum of AD [reviewed in [203,204]. Mice that overexpress PS1/PS2 in addition to APP display a more severe form of AD-like neuropathology. However, NFTs are only observed when animals are engineered to overexpress human TAU harboring mutations associated with human tauopathies [reviewed in Refs. [203,204]]. Again, this differential behavior is explained by significant differences that exist between mouse and human tau proteins (both in the splicing and in the amino acid sequence). Finally, mice overexpressing only the A β or the AICD fragments of APP have also been generated. The former develop amyloid plaques or amyloid angiopathy [204,205], while the latter develop synaptic deficits and increased neuronal susceptibility to exogenous stress [206,207]. Mice that were engineered to harbor

three or five familial AD-associated mutations (respectively called 3X and 5X mice) on two or more genes appear to offer the closest, albeit still incomplete, models of AD neuropathology [reviewed in Refs. [203,204]].

7.3. Aging and AD

As mentioned above, aging is the single most important risk factor for sporadic AD. The increased lifespan of the population across the globe is solely responsible for the dramatic rise in prevalence and incidence of AD and is transforming this disease into a global pandemic and economic threat. The last decade has seen the explosion of microarray studies in mice, rats, non-human primates, and humans that have fully characterized the transcriptional profile of both the aging and the AD brain. The results show that aging itself is accompanied by changes in expression levels that affect about 3–5% of all the genes expressed in the brain [157,208,209]. A similar profile was also found in late-onset AD; the only major difference was in the fact that AD displayed a slightly higher number of genes being altered and more significant changes [189,210,211]. This overlapping profile seems to support the notion that a continuum exists between aging and AD. Whether this is indeed the case, it remains to be clearly determined. Unfortunately, the complexity of the aging process interferes with our ability to dissect precise cellular and molecular mechanisms underlying the aging-AD connection. It is likely that different events contribute to the association. Possible contributing pathways identified by transcriptional profiling include: vesicular transport and synaptic transmission; Ca^{++} homeostasis; mitochondrial bioenergetics; glucose and lipid metabolism; stress and unfolded protein response; DNA repair; protein homeostasis; APP/A β metabolism; immunity and inflammation; neuronal outgrowth and regenerative mechanisms [189,202]. Overall, almost all the changes that we described in the previous sections on the aging brain are observed in the AD brain, with the latter being more severely affected. Importantly, while most of the changes that are observed in the aging brain are within a spectrum of “natural variability” those that are observed in the AD brain are outside this spectrum and clearly pathological.

A comprehensive description of AD neuropathology and possible associated events can be found in [144,189,202]. Here, we limit our attention to established aging pathways that affect the pathogenesis and/or progression of the disease (see also Fig. 2B).

7.4. The IGF-1R signaling pathway

Given that old individuals with normal cognitive functions can develop amyloid plaques and NFTs similar to those seen in the early phases of AD, it is not surprising that signaling pathways that are altered in normal aging are intimately linked to cognitive decline and AD pathogenesis. The IGF-1R signaling pathway is probably the most studied in the aging field. The IGF-1R is widely expressed throughout the body and the brain [212–214]. It is organized as two α and two β subunits. The two α subunits are largely extracellular, are linked by a disulfide bond, and contain the ligand-binding domain. In contrast, the β subunits are largely intracellular and contain the signal transducing domain. IGF1 binding to the IGF-1R causes the receptor to undergo autophosphorylation. This autophosphorylation enables the receptor to recruit insulin/IGF1 receptor substrates (IRS) and activate phosphatidylinositol 3-kinase (PI3K). PI3K subsequently catalyzes the conversion of PIP2

into PIP3, which recruits and activates the PKB/Akt pathway (upstream of the mTOR signaling pathway) and the Ras/MEK/ERK signaling cascade (Fig. 3). IGF-1R signaling is downregulated by the phosphatase and tensin homolog deleted on chromosome ten (PTEN) oncogene, which converts PIP3 back into PIP2 (Fig. 3) [190].

Increased IGF-1R signaling accelerates aging and shortens lifespan, whereas a reduction in signaling has the opposite effect [190,215,216]. This has been observed in worms, fruit flies, mice, and humans, indicating that the role of IGF-1R in aging is evolutionarily conserved [190,215–219]. In humans, genetic variations that result in overall reduced IGF-1R signaling appear to be beneficial for old age survival and preservation of cognitive functions [220–223]. IGF1-R expression levels increase as a function of age in both cortex and hippocampus; this event has been linked to learning deficits in aged rats [23,24,143]. Correlation studies in normally aged volunteers confirm that disturbances in the IGF1/IGF1-R pathway are associated with poor performance on neuropsychological tests evaluating different cognitive functions normally affected by age [145]. IGF-1R is also connected to AD. Indeed, down-regulation of IGF-1R can rescue AD neuropathology in the mouse [224,225]. However, in mammals, insulin and IGF1 are also neurotrophic factors that facilitate neuronal growth and promote learning and memory [146,226]. Therefore, there appears to be a dichotomy between neuroprotective and deleterious effects of IGF1 signaling on animal lifespan. As discussed above, the ERK and mTOR signaling pathways are vital for proper learning and memory to occur and thus may in part explain why IGF1 signaling is also important for proper cognitive function.

7.5. P44/p53 signaling

The p53 protein is best known for its tumor suppressor activity. In fact, a large number of mutations associated with human cancers are found in the p53 gene (*TP53*). Impaired p53 functions are also observed as a result of mutations in genes that act as immediate activators or inhibitors of p53 activity. The tumor-suppressor activities of p53 are activated in response to stress signals that can potentially lead to abnormal proliferation and transformation of mitotically competent cells. Under these conditions, p53 acts as a “gatekeeper” by inducing permanent withdrawal from the cell cycle (cellular senescence; also referred to as replicative senescence) and/or programmed cell death (most typically apoptosis) [reviewed in Refs. [144,227,228]].

It is now known that the common *TP53* gene generates at least twelve different p53 isoforms through a combination of alternative usage of promoters, alternative splicing, and alternative initiation of translation [229]. Of these, full-length p53 (simply known as p53) and 40p53 (also referred to as DeltaNp53, p44, or p47) are the most studied. 40p53 is an N-truncated form lacking the first 39 amino acids of full-length p53 and is intimately linked to the aging process. Transgenic animals that overexpress this isoform, referred to as p44^{+/+} animals, display reduced lifespan, accelerated aging, osteoporosis, type 2 diabetes, skin atrophy, synaptic deficits, and severe learning and memory impairments [230,231]. This progeroid phenotype requires the presence of endogenous p53 suggesting that the ratio of p53: 40p53 rather than the actual levels of 40p53 determines the observed phenotype [230]. Mechanistically, the phenotype of p44^{+/+} mice is intimately associated with the activation of

the IGF-1R signaling pathway. p44^{+/+} mice display increased activation of IGF-1R signaling and the synaptic deficits of p44^{+/+} animals are rescued by haploinsufficiency of IGF-1R [230,231].

In addition to an accelerated aging phenotype, increased activation of IGF-1R in p44^{+/+} mice has also been linked to increased processing of APP, overproduction of A β , and deficits in cognition and synaptic plasticity [231,232]. These features are commonly seen in the aging population and in the early phases of AD, suggesting a general role for p44 and IGF-1R. Murine A β does not display significant aggregation or neurotoxicity and thus p44^{+/+} mice under normal circumstances do not develop amyloid plaques or widespread neurodegeneration. However, when engineered to overexpress a humanized version of mouse App (described above), p44^{+/+} mice develop more classical symptoms of AD, including significant A β aggregation, synaptic loss, and severe degeneration of the afferent pathway (hippocampal formation) and corpus callosum [231]. In essence, p44 can accelerate the AD-like phenotype of APP_{695/swe} mice.

Recent work has also revealed a possible “amplification loop” connecting APP, p44 and Tau. In fact, AICD can bind to the second internal ribosome entry site (IRES) element on the p53 mRNA to regulate translation of p44, which in turn can bind to the promoter of key Tau kinases to regulate transcription [192,233]. Taken together, these data indicate that cross-talk between p53 and IGF-1R signaling influences key molecular and cellular pathways that drive both the general aging process and the pathogenesis of AD. Again, these findings indicate that a spectrum exists between normal cognitive aging and severe cognitive deficits associated with AD, which highlights the importance of understanding both processes in order to identify means of treating and preventing cognitive decline in aged populations.

7.6. Klotho

Klotho is a cell-surface membrane protein that is also released in the blood and cerebrospinal fluid following proteolytic shedding of the extracellular domain [234,235]. The cleaved and secreted form appears to have endocrine, paracrine and autocrine functions; its levels and enzymatic activity decline during aging [236–238]. Genetic variants of *KL*, the gene that encodes Klotho, are associated with human aging [239] and klotho-deficient mice display a progeroid phenotype resembling an accelerated form of aging [236]. The phenotype includes atherosclerosis, skin atrophy, osteoporosis, reduced fertility, emphysema, memory defects, and reduced lifespan [236]. In contrast, mice overexpressing Klotho display increased lifespan and increased resistance to several age-associated features [237]. In humans, polymorphisms of *KL* have been associated with life span and several age-associated diseases, including atherosclerosis, hypertension, osteoporosis, chronic kidney failure, and cancer [239–243]. A possible connection between Klotho and IGF-1R has also been delineated [237,244,245]. Human variations that lead to increased circulating levels of Klotho are associated with greater cortical volumes in the brain [246]. Finally, overexpression of Klotho in the mouse enhances cognition and rescues some of the defects that characterize AD [247]. These include propensity to seizures, deficits in synaptic plasticity, and cognitive decline [247]. Although the above studies support a role of Klotho in aging and, perhaps, AD, the mechanistic components remain to be fully dissected.

8. Non-medical interventions for age-related cognitive decline

A better understanding of the molecular mechanisms underlying age related cognitive decline is expected to lead to a better ability to prevent and treat cognitive deficits associated with aging and is therefore of vital importance to the field. In addition to developing therapeutic targets of cognitive decline, several behavioral interventions have proven to be effective in ameliorating or preventing cognitive deficits associated with the aging process.

A wide breadth of evidence in monkeys and humans suggests that, when applied in middle-age, a 20–40% reduction in food intake without malnutrition promotes healthy brain aging [248–250]. Caloric restriction has been shown to reduce motor deficits, improve metabolic functions, and reduce the likelihood of tumor development and cardiovascular disease [251–253]. Furthermore, caloric restriction has been shown to reduce cognitive deficits associated with aging, improve synaptic plasticity, reduce spine loss, and increase neurogenesis within the hippocampus [254–257]. Caloric restriction has also been shown to be protective in various disease states, including AD, Parkinson's disease, and other neurodegenerative disorders [258,259]. A recent 20-year longitudinal study in Rhesus macaques showed that a 30% reduction in daily calorie intake reduced the rate of age-related deaths as well as the incidence of typical age-associated diseases, including brain atrophy [251,260]. The mechanism whereby caloric restriction increases the resistance of neurons to the adverse effects of aging is not entirely known. However, studies in yeast, worms, flies, and rodents suggest that the reduced calorie intake causes a comprehensive metabolic reprogramming that involves key nutrient-responsive signaling pathways [261–263].

Frequent aerobic physical exercise is another well-established method of maintaining healthy synaptic plasticity and preserved cognition throughout the lifespan [264–266]. Animal research suggests that exercise has the capacity to stimulate neurogenesis in the hippocampus and enhance learning, synaptogenesis, and angiogenesis [27,252]. These beneficial outcomes of exercise appear to be mediated by neurotrophic factors such as BDNF, nerve growth factor, and fibroblast growth factor. BDNF has specifically emerged as one of the most relevant mediators for synaptic plasticity and neuronal connectivity and is considered an essential component for mediating the beneficial neuroprotective effects of physical exercise on the brain [252].

Numerous lines of evidence also indicate that environmental enrichment promotes learning and memory, and successful cognitive aging in human and animal models. Animals living in enriched conditions with enhanced social and cognitive stimuli have improved learning and memory, reduced cellular response to stress, enhanced neurogenesis in the dentate gyrus, increased brain size and weight, increased dendritic branching, and increased synaptogenesis [267–269]. Likewise, among humans, factors such as higher education and other markers of cognitive resilience appear to buffer older individuals against cognitive decline and development of dementia, and provide increased cognitive flexibility, perhaps via similar mechanisms as those observed in animals [270,271].

9. Concluding remarks

Ensuring a high level of cognitive functioning and independence is essential as the population of elderly people continues to expand worldwide. This review highlighted changes in hippocampal structure and function that contribute to cognitive impairment over the course of the aging process as well as in AD, the most common form of age-associated dementia. We propose that investigation of aging brain biology is likely to yield exiting new avenues for the development of intervention and treatments to offset and correct cognitive decline as a function of age.

Acknowledgments

We wish to thank Dr. Rozalyn M. Anderson and Dr. Barbara B. Bendlin for critically reviewing an early version of this manuscript. This work was supported by VA Merit Award (BX001638) and NIH (NS094154, AG033514). R.H. was supported by a National Science Foundation Graduate Research Fellowship.

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HIGHLIGHTS

- Aging is accompanied by structural changes of the brain.
- Aging affects synaptic plasticity at multiple levels.
- Partial overlap exists between aging and Alzheimer's disease.
- Aging pathways impact on pathogenesis and/or progression of Alzheimer's disease.

Fig. 1.

Aging and Hippocampal Signaling Pathways. Group 1 mGluR stimulation leads to subsequent activation of the downstream kinases including PKC, ERK, and mTOR. Subsequent activation of transcription factors such as CREB and ELK-1 within the nucleus induces transcription of immediate early genes such as Homer1a, Arc, and Zif268. Homer1a is released into the cytosol and disrupts Homer1c/mGluR5 binding, whereas the IEGs Arc and Zif268 promote expression of genes essential for learning and memory to occur. Changes in the expression ratio of Homer1a:Homer1c, cell surface expression of mGluR5, and activity of PKC, ERK, and mTOR are thought to play a role in successful cognitive aging.

Fig. 2.

APP Processing and AD-Aging Pathways. (A) APP is a type 1 membrane protein consisting of a large extracellular domain, a single membrane-spanning domain, and a small cytoplasmic tail. APP cleavage occurs in a 2-step process. First, BACE-1 mediated cleavage at the β site generates a large N-terminal fragment that is secreted into the extracellular milieu and a small C-terminal fragment (C99) that remains membrane-bound. In the second step, C99 is cleaved at the γ site by γ -secretase to produce A β and AICD. Both A β and AICD have been shown to promote various aspects of Alzheimer's disease pathology. (B) Possible impact of established aging pathways in the pathogenesis and/or progression of AD. Description is in the text.

Fig. 3. IGF-1R Signaling. Schematic view of the IGF-1R signaling pathway. Description is in the text.

Table 1

Most prominent structural changes of the aging brain.

Amyloid Plaques (progressive accumulation in the parenchyma; main component: Aβ)
Astrocytes (increased number of activated astrocytes)
Microglia (increased number of activated microglia)
Mitochondria (changes in morphology)
Neurofibrillary Tangles (progressive accumulation within neurons; main component: phospho-tau)
Neurons (reduced neurogenesis)
Neuronal Morphology (changes tend to affect dendritic branches and spines)
Synapses (reduced number and morphological changes)
Vascular (increased atherosclerosis and arteriosclerosis)
Volume (reduced white and gray matter volume and increased CSF volume)

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