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Conserved regulators of cognitive aging: From Worms to Humans

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Abstract

Cognitive decline is a major deficit that arises with age in humans. While some research on the underlying causes of these problems can be done in humans, harnessing the strengths of small model systems, particularly those with well-studied longevity mutants, such as the nematode *C. elegans*, will accelerate progress. Here we review the approaches being used to study cognitive decline in model organisms and show how simple model systems allow the rapid discovery of conserved molecular mechanisms, which will eventually enable the development of therapeutics to slow cognitive aging.

Keywords

aging; longevity; cognitive aging; model systems; cognitive decline

1. Introduction

Over the past century, the population of elderly individuals has greatly increased, leading to the emergence of age-related cognitive decline as a significant public health threat. Memory impairments are exhibited in many neurodegenerative diseases in which age is a risk factor, such as Alzheimer's disease (AD), Parkinson's disease (PD), and several forms of dementia. Additionally, cognitive decline is a prominent feature of normal aging, with decreased cognitive function beginning in mid-life and worsening with advanced age. In order to prevent these deficits, it is imperative to gain an understanding of how nervous system function is altered by the process of aging. Work in both vertebrate and invertebrate model systems has uncovered many features of neuronal aging and has determined how they are linked to age-related cognitive decline. More recent studies in model organisms have revealed that pathways that regulate lifespan may also play a role in the maintenance of cognition with age. Here we review features of neuronal and cognitive aging, and highlight how work in model systems has uncovered evolutionarily conserved pathways that regulate both longevity and age-related changes in learning and memory.

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2. Model systems and assays of cognitive function

Studies of human cognitive function and aging are often difficult to carry out, and are typically limited to epidemiological studies, genome-wide association studies, or the identification of changes in regional activity or neuroanatomical structure with aging. Longitudinal studies can identify both genetic and environmental factors that are linked to cognitive aging, as well interventions that may slow cognitive aging, but this wealth of information can take decades to collect, and usually cannot determine causation. While these studies can provide information regarding correlates of cognitive aging, humans are an unsuitable system to directly test the role of specific genes and molecules by knockout or overexpression in cognitive aging. Furthermore, researchers cannot use humans to rapidly screen chemical libraries of compounds that may ameliorate age-related cognitive defects. Thus, the development of model systems has been invaluable in the discovery and analysis of the conserved mechanisms underlying learning, memory, and other neuronal abilities. Interestingly, analyses of both vertebrate and invertebrate systems have revealed that the pathways that regulate cognitive function are highly conserved [17].

The ability to study aging in a simple, short-lived system is extremely useful. Aging studies in primates are generally impractical because they have decades-long lifespans and are not genetically tractable (Figure 1). Other mammalian systems that have genetic and molecular tools available, such as mice and rats, still live for years, making it difficult to rapidly perform aging studies (Figure 1). Even zebrafish, a relatively simpler non-mammalian vertebrate model, has a lifespan of 2–3 years (Figure 1). Recently, the African turquoise killifish has been identified as a promising model for aging. With a lifespan of only 4–6 months, it is the shortest-lived vertebrate that can be bred in captivity and will be useful for aging studies (Figure 1).

Invertebrate models such as *Drosophila* and *C. elegans* are excellent genetic models to study the process of aging, due to their lifespans of three months and three weeks, respectively (Figure 1). This short lifespan enables the rapid identification of genes that affect longevity [58, 65, 88, 101, 105, 118, 144, 158, 186, 207]. Moreover, a vast number of genetic techniques and tools are available that allow precise spatial and temporal control of genetic perturbations [38, 129]. Other invertebrate species, such as ants and bees, show promise for future studies in aging and cognition, but in the present review, the focus will be on more commonly used, genetically tractable organisms [4, 8, 36, 37, 66]. Though these features make invertebrate models attractive in the study of aging, there are some obvious caveats when working in such a simple system. They lack the analogous neuroanatomy that can be found in vertebrate models, and cannot fully recapitulate features of complex human diseases associated with neuronal dysfunction, such as AD. However, invertebrates remain useful for the rapid identification of genes that may be of interest for studies in higher organisms, and even more critically, can be used to determine the underlying molecular and genetic mechanisms before embarking on experiments in slower, more laborious systems. In the following section, we will review assays of cognitive and neuronal function across model systems, with a focus on evolutionarily conserved molecules and mechanisms.

2.1 Assays of cognitive and neuronal function in vertebrates

An obvious advantage of mammalian systems is that the nervous systems of rodents and non-human primates are well mapped and more closely resemble that of humans than do invertebrate systems, and age-related morphological changes in these have been determined [26, 138, 182]. Furthermore, there are many behavioral tasks developed to assess the function of these brain regions [9, 26, 221, 231]. This includes the circuits that control the cognitive processes that are most vulnerable to aging, the hippocampus and the prefrontal cortex (PFC) [138]. Moreover, these circuits and their activities that correlate to cognitive function can be easily measured by electrophysiological techniques, so the effects of age or interventions on these neuronal ensembles can be determined, even in behaving animals [69, 70, 96, 131]. Additionally, these circuits can be manipulated with precise spatiotemporal control using optogenetic techniques or Designer Receptors Exclusively Activated by Designer Drugs (DREADDS) [179, 229]. Furthermore, mammals can more closely model neurodegenerative diseases such as AD, PD, and other dementias due to similarities in brain structure with humans [115, 151]. However, a caveat to studying age-related neuronal dysfunction is that the subjects must be aged for more than a year even in rodents, while invertebrate models only require weeks to months to be considered “old”. Genetic manipulations are also laborious in mammals, although the use of techniques such as CRISPR may eventually help circumvent these difficulties.

Zebrafish have been traditionally been utilized in the study of developmental biology, but recent studies have demonstrated that they can also display associative learning. These learning tasks include association of food or images of conspecifics (other zebrafish) in a spatial location on a maze or in a shuttle-box [160, 189, 235]. The association of images with conspecifics with a location on a maze requires NMDA-type glutamate receptors, as treatment with MK-801, a non-competitive NMDA receptor antagonist, impairs this behavior [190]. Killifish also display associative learning on a modified version of the shuttle-box task, which pairs side of a tank with a visual cue (red light) and aversive stimulus (shock). Learning is measured by the success rate of escaping the side of the tank associated with the shock following presentation of the visual cue [219]. It still remains to be determined how well memory can be modeled in fish, though recent studies suggest that the shuttle-box task produces a short-term memory in zebrafish [50, 93]. The circuits and molecules that regulate associative learning in fish also remain largely unknown.

2.2 Assays of cognitive and neuronal function in invertebrates

Drosophila exhibit several types of learning, but olfactory learning is the form that has been most valuable in identifying required molecules and circuits, and has been applied to the study of aging, as well [74]. Briefly, flies learn to associate an odor (the conditioned stimulus) with a positive reinforcement (food reward), or negative reinforcement (mild electrical shock) [40, 216]. These training paradigms result in mechanistically and quantitatively different forms of performance, as measured by the memory expression at defined times post-conditioning. A single conditioning trial generates a memory that decays over the course of 24 hours [14, 108, 159, 208, 215]. Massed conditioning, which consists of multiple cycles with no rest between cycles, produces a robust initial memory that decays over a few days. By contrast, the memory formed after spaced conditioning lasts for 4–7

days and requires both protein synthesis and CREB activity at the time of conditioning, which are features of long-term associative memory in higher organisms [162, 188, 215, 233, 234]. The circuits that are responsible for olfactory memory formation are fairly well understood, and the Mushroom body (MB), a symmetrical structure that is composed of ~2500 neurons in each hemisphere, is thought to be the primary center for olfactory memory storage [47, 108, 128]. The memory circuit is modulated by the biogenic amine neurotransmitters dopamine and octopamine [74]. Microarray analysis of *Drosophila* mutants with defects in short-term, medium-term, and anesthesia-resistant memory identified differentially-expressed genes with putative roles in membrane excitability, synaptic transmission, cytoskeletal regulation, cell adhesion, and cell signaling, suggesting that these functions are involved in *Drosophila* learning and memory [73].

The position and connectivity of all 302 of *C. elegans*' neurons have been mapped, and these nematodes carry out many complex behaviors despite having a relatively simple nervous system [220, 225]. The 302 neurons include sensory neurons, interneurons, and motor neurons [84], which together function to integrate sensory stimuli and exhibit both associative and non-associative behavioral plasticity. The fact that *C. elegans* has a very short lifespan (~21 days), is genetically tractable, and 80% of its genes have human orthologs [111] makes it a particularly attractive model for cognitive aging, as the effects of age on behavior can be rapidly assessed.

Although it has long been an established model for aging [58, 88, 101, 105], synaptic function [116, 170, 225], and behavior [42, 84], *C. elegans* is a relatively new model organism in the study of age-related cognitive decline [5, 100, 195]. Forms of non-associative behavioral plasticity include adaptation to inherently attractive odors [33] and habituation in response to multiple taps [171]. Associative behaviors include the ability to associate feeding state with a pathogen [236], temperature [82], salt concentration [181], and odor [33, 100, 181, 199, 212]. *C. elegans* is also able to form both short-term and long-term memory, lasting up to 24 hours [3, 33, 68, 99, 100, 171, 196, 199, 222]. The associative behaviors that have been used in the study of age-related learning and memory are described in more detail below.

C. elegans can be conditioned to associate a training temperature with the presence or absence of food [82, 107, 135]. After training, worms move to the training temperature that had been associated with food, or avoid a temperature associated with starvation, a behavior is termed isothermal tracking (IT). This conditioning can last for several hours [68], and is dependent on diacylglycerol kinase, a known memory regulator in mice [187], though it still remains unclear whether it requires the other known processes involved in long-term memory (transcription, translation, and cAMP response element-binding protein (CREB) activity).

Both positive and negative associative plasticity assays have been developed using olfactory cues. One form of negative associative plasticity, referred to as benzaldehyde starvation associative plasticity, occurs when worms avoid an attractive concentration of benzaldehyde after experiencing starvation in the presence of an aversive concentration of the same odor (benzaldehyde) [148]. Pairing the neutral odorant butanone at low concentrations with food

induces positive association, termed “butanone enhancement” [203]. Brief starvation before food-butanone conditioning induces a stronger learning response, inducing a 60% increase in their chemotaxis towards butanone [100]. Massed training of food associated with butanone results in short-term associative memory (STAM), while spaced training induces long-term associative memory (LTAM) [100]. STAM, which worms exhibit following a single conditioning session, declines within two hours [100]. STAM is transcription-independent, and can be broken down into translation-independent (30 minutes post-training) and translation-dependent (1 hour post-training) stages, suggesting that massed training can be used to test both short-term and intermediate-term memory [196]. LTAM lasts 16–24 h after training, and is dependent on transcription, translation, and CREB activity [100], factors that are required for long-term memory in other organisms, such as flies, *Aplysia*, and mice [188]. A similar paradigm has been developed for negative associative olfactory learning and memory [199, 222], in which worms are starved in the presence of the attractive odorant diacetyl. This training paradigm also results in STAM or LTAM after 1 or 3 training cycles, respectively [199, 222].

Kauffman et al. (2010) determined that LTAM performance also correlates with levels of activated CREB protein [100]. At Day 1 of adulthood, mutants of the *C. elegans* insulin receptor homolog, *daf-2*, have significantly extended LTAM performance when compared to wild-type animals. Examination of CREB expression and levels of activated protein in *daf-2* and wild-type worms revealed that higher levels of active CREB correlates with *daf-2*'s enhanced LTAM performance [100]. Similarly, overexpression of CREB solely in neurons also improves and extends wild-type's LTAM [100]. The downstream targets of CREB following LTAM training were recently identified [113]; while the basal targets of CREB primarily regulate growth and metabolism, many of the mammalian homologs of the CREB targets induced during LTAM training are involved in memory formation and neuronal functions in other organisms, as well [113]. The large set of CREB/memory induced genes (>750) includes indirect downstream targets of CREB, and identifies new mechanisms and novel components that warrant future study in cognitive function in higher organisms. Although many of the tested CREB/LTAM targets are required for long-term memory [113], *C. elegans*' decline in memory with age correlate with declining levels of CREB itself [100], suggesting that the major intervention to prevent memory loss could be maintenance of CREB levels and activity.

3. Features of the aging nervous system

It was initially believed that there was significant neuronal loss with advanced age in humans [22, 34]. However, after the development of stereological principles, which allow objective counting of the number of objects in a three-dimensional space independent of the size of the objects [223], it was determined that significant cell death in the neocortex and hippocampus were not characteristic of normal aging in rodents [133, 173, 175], non-human primates [62, 102, 134, 163], or humans [152, 224]. More recently, it was reported that there is significant neuronal loss in area 8a of the dorsolateral prefrontal cortex of non-human primates, while studies in rodents regarding neuronal loss in the dorsal and ventral prefrontal cortex have yielded conflicting results [191, 201, 232]. This highlights a difference between normal aging and neurodegenerative disorders, such as Alzheimer's disease, Parkinson's

disease, and Huntington's disease, which are characterized by a significant decline in cell number [224]. Instead, small, region-specific changes in dendritic branching and spine density are more commonly observed effects of aging on neuronal cell morphology.

Some of these age-dependent alterations at the dendritic level include increased branching and length of dendrites in projections both to and within the dentate gyrus itself in aged individuals, which is distinct from the changes observed in brains of individuals with senile dementia, where there is extensive dendritic loss [23, 24, 54, 55]. This change in branching is not exhibited in all areas associated with memory formation, as there is no difference with age in other subregions of the hippocampus, such as areas CA1 and CA3 and the subiculum [56, 79], although some synaptic loss is observed in individuals with mild cognitive impairment [147]. Studies of hippocampal dendritic morphology and length in rodent models have also reported no regression of dendritic length with age, but there is some evidence of an increase in dendritic length in small subsets of neurons [167, 217]. Interestingly, neurons of the prefrontal cortex (PFC) appear to be more vulnerable to age-related morphology changes than hippocampal neurons are. Reduced dendritic branching is observed in aged pyramidal neurons in superficial cortical layers and the anterior cingulate in the rat, and in the medial PFC in humans [43, 71, 123]. It remains to be determined whether fish models also display age-related changes in neuron morphology, although the similarities between vertebrates and invertebrates, discussed below, suggests that such morphological changes may be an evolutionarily conserved feature of aging.

Drosophila models have been used extensively to study neurodegenerative disorders [6, 46, 52, 213], but neurological changes that occur in the fly brain as a result of normal aging remain mostly unknown. However, age-related changes are observed in circadian rhythms, sleep patterns, and olfactory acuity, suggesting there are aging-specific changes in the neural circuits controlling these processes [72, 178]. Studies of morphological changes in the aging brain have primarily focused on the number of dopaminergic neurons with age, because of their role in locomotion, which declines with age [226]. No significant changes in the number of dopaminergic neurons have been observed in aging flies [226]. More recent studies have examined other age-related neuronal alterations in *Drosophila*. Normal aging results in a progressive accumulation of neural aggregates containing insoluble ubiquitinated proteins, which may correlate with impairments in olfaction that result in abnormal courtship activity during the night [12, 176]. A recent study by Haddadi et al. (2014) more closely examined the neurons of the MBs in young and aged flies. More vacuolated areas were observed in the MBs of 50-day-old flies when compared to 5-day-old animals, indicating neurodegeneration in the area, although it remains to be determined whether there is any significant loss of neuronal number in the region [76]. Electron microscopy of MBs revealed a reduction in the number of synapses and decreased numbers of mitochondria [76], which also tended to be irregular in size and shape in aged flies [76]. These mitochondrial abnormalities were also accompanied by a significant reduction in the activity of catalase and superoxide dismutase, two antioxidant enzymes [76].

It was originally believed that *C. elegans* neurons did not display age-related morphological decline at either a cellular or subcellular level, because EM studies indicated that axons of motor neurons appeared to remain intact with age, in contrast to other tissues, such as skin

and muscle [61, 83]. This did not correlate with a preservation of neuronal function with age, as many sensory behaviors and motility decline with age, and more recent studies have further characterized neuronal morphology with age [5, 195]. Although the soma are still intact, age-related changes are observed in neuronal processes and subcellular structures [153, 206, 214], and neuronal activity [30, 141]. This is similar to findings in mammals and *Drosophila*, which also do not display gross neuronal loss with age, but instead exhibit age-related morphological abnormalities; some abnormalities begin to appear as early as Day 8 of adulthood [153, 206, 214]. These structural alterations include ectopic neurite branching from the soma and processes, bubble-like lesions and GFP beading within the process, and blebbing that results in a “wavy” process [153, 206, 214]. The extent and type of morphological changes that occur vary somewhat between neurons. In addition to morphological abnormalities, neuronal mitochondria progressively fragment with age in *C. elegans* [94], and mitochondria are found within some of the beaded processes and bubble-like lesions [94, 214]. A decrease in gentle touch response and mobility correlates with excess ectopic neurites, suggesting that the age-related morphological changes either cause or are correlated with impaired neuronal function [206]. Using electron microscopy, Toth et al. (2012) found that synapses in the nerve ring and ventral ganglion exhibit vesicle depletion at Day 15 of adulthood, and the severity of depletion of synaptic vesicles correlates with the overall condition and mobility of the worm.

4. Declines in cognitive function with age

In addition to changes in neuronal morphology, synaptic function appears to decline with age in mammals. Reductions in synapse number in the dentate gyrus [64] may account for the reduced field excitatory postsynaptic potentials recorded in this region [9, 10]. This reduction in synapse number also correlates with spatial memory deficits in aged rats [63]. In other areas, such as Schaffer collateral – CA1 synapses, there is no difference in total synapse number, but instead there is a reduction in postsynaptic density area of rats with age-related learning impairment compared to learning-unimpaired animals [147]. Additionally, electron microscopy studies have reported substantial synapse loss (~32%) in the PFC of primates [48, 164]. Further investigation into the types of synapses that are most vulnerable to aging revealed that most of the synapses lost in the PFC with age are thin spines, which have a high degree of plasticity, are associated with learning new information, and may represent immature ‘silent synapses’ [21, 27, 48, 85, 238]. This loss of functional synapses results in changes in long-term potentiation (LTP) and long-term depression (LTD), such as deficits in both the induction and maintenance of LTP and increased susceptibility to LTD [26, 182].

Gene expression and protein synthesis, two processes that are required for the maintenance of LTP, also change in aged animals. Blalock, et al. (2003) performed microarray analysis of area CA1 of aged rats following behavioral testing to identify gene expression alterations that correlate with age-related cognitive decline. Downregulated genes included the Immediate early genes *Arc* and *Narp* and many genes associated with energy metabolism, biosynthesis, and activity-regulated synaptogenesis, while upregulated genes are associated with inflammation and intracellular Ca^{2+} release [18]. It is therefore unsurprising that age-related declines are observed in tasks that require information processing in the

hippocampus and PFC, which show age-related changes in synaptic function. Deficits in retrieving contextual details of episodic memories are present in aged humans when compared with younger adults [130, 194]. Additionally, aged mice [7], rats [9, 59, 125], dogs [81], monkeys [112, 174], and humans [227] all display deficits in tasks designed to test spatial navigation, indicating that hippocampal function is impaired with age. There are also deficits in humans [53], rabbits [193, 209], rats [106], and mice [104] in trace eyeblink conditioning, an associative learning task that requires the hippocampus as well as other brain structures, such as the cerebellum. While the hippocampus is involved in spatial episodic memory, the PFC is required for working memory and episodic function. Rats [49], non-human primates [139, 140, 172], and humans [120] show working memory impairments with age. Executive function has also been shown to decline in aged humans and monkeys when compared to young adult controls [136, 177].

Age-related cognitive phenotypes have been less well characterized in fish, but also show declines. Zebrafish exhibit decreased associative learning with age, with defects in spatial learning evident at around 18 months [180, 235, 237]. Inhibitory avoidance is also reduced by 24 months of age [122], and there is a corresponding reduction in the expression of plasticity-associated genes in the zebrafish telencephalon, such as *bdnf*, *cart4*, and *pcna* [122]. Killifish also display reduced performance on an active avoidance task by 9 weeks of age [218, 219]. Interestingly, this decline can be prevented by interventions that prolong lifespan, such as reducing the temperature of the fish's habitat or by resveratrol treatment [218, 219].

There have been relatively few studies investigating the effects of aging on olfactory associative memory in *Drosophila*, though various forms of memory have been shown to decline with age [205, 210, 211]. A slight defect in associative learning is observed after 10 days of age, although no further decline at later days was reported [205]. Intermediate-term memory, which is defined as the physiological changes that occur in neurons as a result of learning, shows a progressive decline with age [205], and is associated with decline in the ITM cellular memory trace [41, 210]. More recently, protein synthesis-dependent long-term memory, along with an age-dependent disruption in the long-term memory trace in the Mushroom Body, were also found to decline with age [211].

Neuronal aging phenotypes appear rapidly in *C. elegans*, long before the animals start to die [5, 195]. These include simpler behaviors such as motility and maximum velocity, which decrease by more than 50% by day 10 [77, 90], midway through life. Sensory behaviors, such as odor chemotaxis, decline several days before motility, suggesting that separate mechanisms of molecular decline regulate these behaviors [67, 100]. Non-associative learning (e.g., habituation to a tap stimulus) also changes with age. Worms at Day 9 of adulthood respond to a tap with smaller reversals, and recover from habituation more slowly than worms at age Day 1 or Day 4 [13].

Associative learning and memory is the most sensitive to the effects of aging [5, 100, 195]. Isothermal tracking, in which worms associate temperature with the presence of food, shows a modest but significant decline by day 6 of adulthood [143]. The fraction of worms that

display isothermal tracking after training decreases by half at Day 12, and is undetectable by Day 15 [143].

In order to determine how aging affects *C. elegans* olfactory associative memory in relation to other phenotypes, Kauffman et al. (2010) examined motility, chemotaxis, massed positive olfactory learning, spaced positive olfactory learning, and 16-hr long-term positive olfactory memory for the first week of adulthood [100]. Movement and chemotaxis were maintained during this time; however, 16-hr LTAM decreased by day 2 of adulthood, and was undetectable by day 5. Massed learning begins to decline on day 3 and is absent by day 6, while spaced learning is undiminished at day 3, but declined by day 7 of adulthood. These declines in olfactory associative learning and memory performance precede age-related changes in chemotaxis [67], isothermal tracking [143], habituation [13], and motility [77, 90], suggesting that these associative olfactory forms of learning and memory are most sensitive to age-related changes. Furthermore, these declines in cognitive function occur at timepoints prior to observable age-related morphological defects in neurons and muscles [5, 83, 153, 195, 206, 214]. It remains to be determined if negative associative olfactory behaviors or other associative behaviors such as taste avoidance learning show similar age-related declines. Kauffman et al. (2010) also determined that levels of active CREB are significantly reduced by day 4, suggesting that this decrease underlies the loss of the ability to form long-term memory with age [100]. At this age, STAM levels are still maintained, indicating that different molecular pathways maintain this behavior with age [100]. Together, these results suggest that the maintenance of each form of learning and memory is regulated independently, or at least that they are differentially susceptible to age-related declines.

5. Intersection of longevity pathways and cognitive function with age

5.1 Insulin Signaling

The insulin/IGF-1 (IIS) pathway was first found to regulate lifespan in *C. elegans* [101]. In worms, the IIS pathway consists of a single insulin receptor homolog *daf-2*, which has >30% amino acid identity to human insulin and IGF-1 receptors [103]. The effects of *daf-2* on lifespan require activity of the forkhead box O (FOXO) transcription factor, DAF-16 [101, 149]. In brief, signaling through DAF-2 activates phosphoinositide 3-kinase (PI3K), which leads to the Akt-1/2 and PDK-1-dependent phosphorylation of DAF-16 [155, 156] and its transcriptional inactivation by sequestration to the cytoplasm [119, 149]. In *daf-2* mutants, IIS is low, which allows DAF-16 to enter the nucleus and enact a transcriptional program that promotes longevity and stress resistance, through the expression of DAF-16 targets, many of which have been identified and characterized [144]. Though there is only one known insulin receptor homolog in *C. elegans*, the genome encodes approximately 40 insulin-like peptides that can act as either DAF-2 agonists or antagonists [144, 165]. *Drosophila*, like *C. elegans*, has a single insulin-like receptor that, when mutated, extends life span in a manner that is dependent on its *daf-16* homolog, *dFOXO* [207], and also expresses several different insulin-like peptides (dILPs) [98].

Reduction of insulin signaling by mutations in *daf-2* promotes longevity, extending the lifespan to more than twice that of wild type [101]. IIS is evolutionarily conserved, and components of the IIS pathway regulate lifespan in *Drosophila*, mice, and humans [19, 32,

203, 207]. Mice haploinsufficient for the IGF-1 receptor are long-lived, as are mice that have reduced levels of insulin receptor substrate 2, and adipose tissue-specific insulin receptor knockout mice also exhibit increases in lifespan [19, 86, 204]. Moreover, genetic variations in IIS pathway components are linked to long life in humans [161]. Mutations in a human *daf-16* homolog, *FOXO3a*, are linked to increased longevity [228]. In addition, IGF-1R mutations are highly represented in populations of centenarians [203].

In addition to having dramatic effects on lifespan, IIS regulates neuronal phenotypes with aging. Older *daf-2* worms display fewer neuronal abnormalities with age, when compared to similarly aged wild-type worms, and this reduction in age-related morphological defects is dependent on *daf-16* [153, 206, 214]. IIS also influences behavioral plasticity with age. Mutants of *age-1*, the catalytic subunit of PI3K downstream of *daf-2*, have increased isothermal tracking in young and old animals, and a 210% extension in “high IT” ability, which is defined as a period when more than 75% of the worms exhibit IT [142]. This extension is mediated directly by AGE-1 activity in the AIY interneurons, and is not merely a side effect of organism-wide lifespan extension, which involves other tissues [107, 142]. *daf-2* worms also have increased IT with age [142], and the effects of both *daf-2* and *age-1* depend on *daf-16* [142]. *daf-2* worms display significantly extended short- (STAM) and long-term associative memory (LTAM) on the first day of adulthood [100], as well as extended maintenance of learning and short-term memory with age (Arey & Murphy, unpublished) as compared to wild-type animals.

To determine the effects of insulin signaling pathway on learning and memory with age, worms’ massed learning performance was tested daily for the first 5 days of adulthood, and LTAM was tested at Day 4 of adulthood [100]. *daf-2* mutants maintained day 1 massed learning ability until Day 5, an age at which it is undetectable in wild-type worms [100]. In contrast, LTAM at Day 4 of adulthood was abrogated in both *daf-2* and wild-type animals, indicating that maintenance of these two behaviors occurs through different mechanisms. The limiting factor for LTAM is CREB: *daf-2* worms, like wild-type animals, exhibit decreases in CREB expression and activation with age that correlate with decreased LTAM activity [100].

Recent studies in *Drosophila* have found that knocking down the insulin receptor substrate *chico* in the fly brain results in defects in negative olfactory associative learning and protein synthesis-dependent memory, although the effect of reduced insulin receptor function on positive associative learning has yet to be determined [28, 145]. The role of IIS in age-dependent changes in learning and memory in *Drosophila* has not yet been elucidated.

In addition to the insulin pathway, two other insulin-like peptides (ILPs), insulin-like growth factor 1 & 2 (IGF1 and IGF2), regulate neuronal function in mammals. IGF1 and IGF2 have specific receptors (IGF1R and IGF2R, respectively), but can bind with varying affinities to IGF1R, IGF2R, and to the insulin receptor IR [51]. All three ILPs have been examined for their roles in learning and memory. In young rodents, microinjection or intracerebroventricular administration of insulin improves memory performance [78, 132, 137, 157, 197]. Following intranasal delivery of insulin, humans also show enhanced cognitive function [15]. Injection of IGF1 into the hippocampus or amygdala has no

detectable effects on memory formation [197]. By contrast, systemic or hippocampal injection of IGF2 can enhance retention of hippocampal-dependent memories [2, 29, 198]. This enhancement is dependent on the actions of the IGF2R [29]. Interestingly, insulin does not bind IGF2R [95], so the enhancement of memory by these two ILPs must occur via distinct signaling mechanisms.

Despite insulin's ability to alter cognitive performance, loss of neuronal insulin receptor function does not result in obvious dysfunction, and the effects of the loss of IGF1R and IGF2R function have yet to be determined. When the brain/neuron insulin receptor knockout (BIRKO) mice were examined for neurological and behavioral abnormalities, they displayed no alteration in neuronal proliferation or survival or memory at seven weeks of age [184], but it remains to be determined if reduced neuronal insulin signaling may have beneficial or deleterious effects in aged mammals. Interestingly, a recent study determined that intracerebroventricular injection of insulin does not enhance spatial memory in the water maze test in old rats [75], unlike young rats, suggesting that the link between aging and the effects of IIS on cognition has yet to be fully elucidated.

Diabetes mellitus, in which individuals have absolute or relative insulin deficiency, is associated with cognitive dysfunction and dementia (reviewed in [16]), further suggesting that insulin response is required for proper cognitive function with age. However, reduced cognitive function in diabetes mellitus may be due to insulin resistance, as recent studies have suggested that superior health in old age is associated with maintenance of insulin sensitivity [150]. Therefore, diabetes and lowered insulin signaling as seen in long-lived IIS mutants are likely two independent pathways that may oppositely affect cognitive maintenance.

5.2 Dietary Restriction

Dietary restriction, in which caloric intake is reduced to about 60–70% of normal levels, has been shown to extend lifespan in many model organisms, including yeast, worms, flies, rodents, and primates [121, 126, 127]. *C. elegans* can undergo caloric restriction by feeding them diluted bacteria or in axenic media, by intermittent fasting, or via a genetic mutations that cause altered pharyngeal pumping and defective feeding, such as *eat-2* [87, 114, 168]. DR-mediated lifespan extension is at least in part independent of the insulin signaling pathway, as some dietary restriction treatments and *eat-2* mutations can extend the lifespan of *daf-2* mutants [39, 89]; instead, they depend on the PHA-4/FOXA1 transcription factor [154]. However, lifespan extension by intermittent fasting does require signaling through DAF-16 [87].

Although *eat-2* worms have an extended lifespan, they are not protected from age-related ectopic neurite branching [206], indicating that morphological defects with age are regulated by specific longevity pathways, and that a longer lifespan is not protective of all phenotypes. *eat-2* mutants have also been examined for positive olfactory associative memory performance, and were revealed to have normal STAM at Day 1. Young *eat-2* mutants worms displayed impaired LTAM (about 60% of wild-type levels) but this could be improved by increasing the number of training cycles [100]. This reduced performance is dependent on caloric restriction itself, as feeding *eat-2* animals smaller, easier to digest

bacteria, *Comamonas* sp., restores LTAM to wild-type levels [100]. Kauffman et al. (2010) also examined *eat-2* LTAM performance with age. Although *eat-2* animals exhibit reduced LTAM at Day 1 of adulthood, their memory ability is maintained until at least Day 4 of adulthood, in contrast to *daf-2* and wild-type animals, which have no detectable LTAM at the same age; CREB levels in *eat-2* mutants compared to wild-type again correlated with the maintained LTAM performance [100]. The differences between *eat-2* and *daf-2* mutants in STAM and LTAM performance demonstrate that longevity pathways differ in their regulation of learning and memory in early adulthood, which can be traced to their differential regulation of CREB levels and activation [100].

Dietary restriction also affects learning and memory performance in *Drosophila*. Following aversive olfactory conditioning, dietary-restricted young flies (5 days old), have enhanced memory when assessed for performance 60 minutes after training [25]. However, this effect is not maintained with age, as learning and memory performance decline to similar levels in old dietary-restricted and rich diet-fed flies [25].

Dietary restriction attenuates age-related memory deficits in tests of mouse and rat hippocampal-dependent memory [91, 92, 124, 166, 200], and more recently was shown to preserve working memory in mice [110]. Improved spatial memory performance in aged dietary-restricted rats correlated with protection against age-related decreases in AMPA and NMDA-type glutamate receptors in the CA3 region of the hippocampus [1]. Deep sequencing carried out on the CA1 region of the hippocampus revealed that dietary restriction reduces age-dependent changes in gene expression [183]. Enriched pathways of these “protected” genes include calcium, long-term potentiation, and CREB signaling, though aged calorically-restricted gene sets still differed significantly from young ones. Suppression of age-related gene expression changes may provide some mechanistic insight into how dietary restriction prevents age-related cognitive decline in rodents.

Older people (mean age 60.5) subjected to 3 months of caloric restriction (30% reduction) were subsequently tested for verbal memory (recall of a word list after 30 minutes); the CR group had significantly improved memory performance when compared to controls or to those fed an unsaturated fatty acid-enriched diet [230]. This suggests that the benefits of caloric restriction may be evolutionarily conserved from invertebrates to humans.

5.3 APOE

Another gene that has been linked to lifespan, healthspan, and cognitive aging in humans is Apolipoprotein E (APOE). APOE is a polymorphic gene, with 3 common alleles, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The initial study linking APOE to age-related phenotypes identified the $\epsilon 4$ allele as a risk factor for the development of AD [202] while the $\epsilon 2$ allele is protective [35]. The APOE incidence of the $\epsilon 2$ allele was found to be increased in centenarians [185], and APOE is associated with longevity in a number of human genetics studies [44, 45, 57, 60, 146]. This is unlike other longevity pathways discussed here, which were known to affect lifespan before their effects on cognitive function with age were examined. Interestingly, a recent study found that APOE genotype does not modify the rate of change in cognition with age, and may only affect age of AD onset [192], suggesting that normal age-related cognitive

decline and cognitive dysfunction in neurodegenerative disease are two very distinct processes.

5.4 CREB and other molecules involved in cognitive aging downstream of longevity pathways

As discussed previously, Kauffman et al. (2010) uncovered a link between CREB levels and memory performance with age. *daf-2* animals have higher levels of active CREB than wild-type animals on Day 1 of adulthood, correlating with their enhanced LTAM performance. Conversely, *eat-2* animals have lower levels of active CREB and reduced LTAM on day 1 of adulthood. When CREB levels were examined with age, *daf-2* and wild-type worms both displayed a reduction in active CREB by day 4, while *eat-2* animals maintained day 1 levels of CREB activity, correlating with maintenance of LTAM activity in *eat-2* worms on day 4. The increased level of active CREB in *daf-2* animals is an example of tissue-specific regulation of phenotypes by IIS [97]; Kaletsky et al. (2016) found that CREB (*crh-1*) is specifically up-regulated in the neurons of *daf-2* (reduced IIS) animals, while *crh-1* is downregulated in other tissues [97]. (Worms with loss-of-function mutations in *crh-1*, the *C. elegans* homolog of CREB, are defective in long-term memory, but their lifespan and STAM are unaffected [113].) Kaletsky et al. (2016) also identified the full suite of adult neuronal IIS/FOXO targets. Several of these genes are required for the extension of STAM observed in *daf-2* animals in early adulthood; these targets included ion channels, transcription factors, G-proteins, and vesicle fusion proteins, suggesting that IIS regulates a broad number of processes to extend memory [97]. Many of these genes are required for wild-type STAM performance in young adult worms [97], and it will be interesting to determine if these molecules also have a role in the enhanced STAM performance with age in *daf-2* animals.

The differential effects of these longevity mutants on various types of memory performance can be attributed to different mechanisms. LTAM performance correlates with levels of active CREB, and maintenance of CREB expression and activity could be predictive of memory performance with age. Indeed, CREB and CREB binding protein levels decrease in the hippocampus with age in rodents [31, 80, 169], and correlate with impaired performance in contextual fear conditioning [109]. A recent study in humans also supports this hypothesis, as single nucleotide polymorphisms in the CREB-dependent histone deacetylation pathway, CREB-binding protein and RbAP48, are associated with episodic memory performance in healthy elderly subjects [11].

Recently, *daf-2*'s enhanced STAM memory performance with age was discovered to also be due to maintenance of synaptic integrity [117]. The anterograde kinesin motor UNC-104/KIF1A regulates synapse distribution, synaptic transmission, and motility with age in *C. elegans* [117]. Li et al. (2016) determined that UNC-104 levels are increased in *daf-2* animals, that UNC-104 functions downstream of IIS, and that UNC-104 is required for the memory extension of *daf-2* animals at Day 1 as well as their maintenance of STAM performance with age [117]. The loss of synaptic integrity is a conserved feature of cognitive aging. In aged mammals, deterioration in synapse number and structure is associated with impaired memory in both the hippocampus and cortex [20, 48, 138, 164].

Thus, molecules that preserve synaptic integrity are promising targets for the development of treatments for age-related cognitive decline.

6. Conclusions

In summary, age-related cognitive decline is a part of the normal aging process across phyla; in all invertebrate and vertebrate model organisms that have been examined for alterations in learning and memory with age, decreases in cognitive function have been observed (Figure 2) [26, 100, 182, 195, 205, 210, 211]. These changes in normal aging are not due to gross neuronal cell loss, but instead are the result of subtle changes in neuronal morphology, synaptic integrity, cellular connectivity, gene expression, and other factors that result in altered plasticity of circuits that regulate learning and memory (Figure 2) [26, 94, 138, 153, 182, 214]. There is a growing body of evidence that the major signaling pathways that regulate longevity are also important for the maintenance of cognitive function with age. Recent work in *C. elegans* has begun to elucidate the targets of these pathways that are necessary for the preservation of cognitive function with age; CREB function correlates with enhanced long-term memory performance in longevity mutants and the maintenance of long-term memory performance with age [100]. Maintaining CREB activity may be a way to preserve cognitive function with age in higher organisms, because CREB levels correlate with cognitive performance in mammals [31, 80, 109, 169], but the exact location and levels of this CREB maintenance will be important to avoid deleterious effects. Loss of short-term memory with age is less studied than long term memory, but several IIS targets have been identified that are required for normal STAM performance [97], and IIS mutants maintain STAM performance with age due to preserved pre-synaptic function [117]. Future work in model systems, both vertebrate and invertebrate, will be invaluable in the study of these targets in age-related cognitive decline. The identification and characterization of new molecules that regulate the loss of cognitive function with age will enable the development of treatments that ameliorate this growing health problem.

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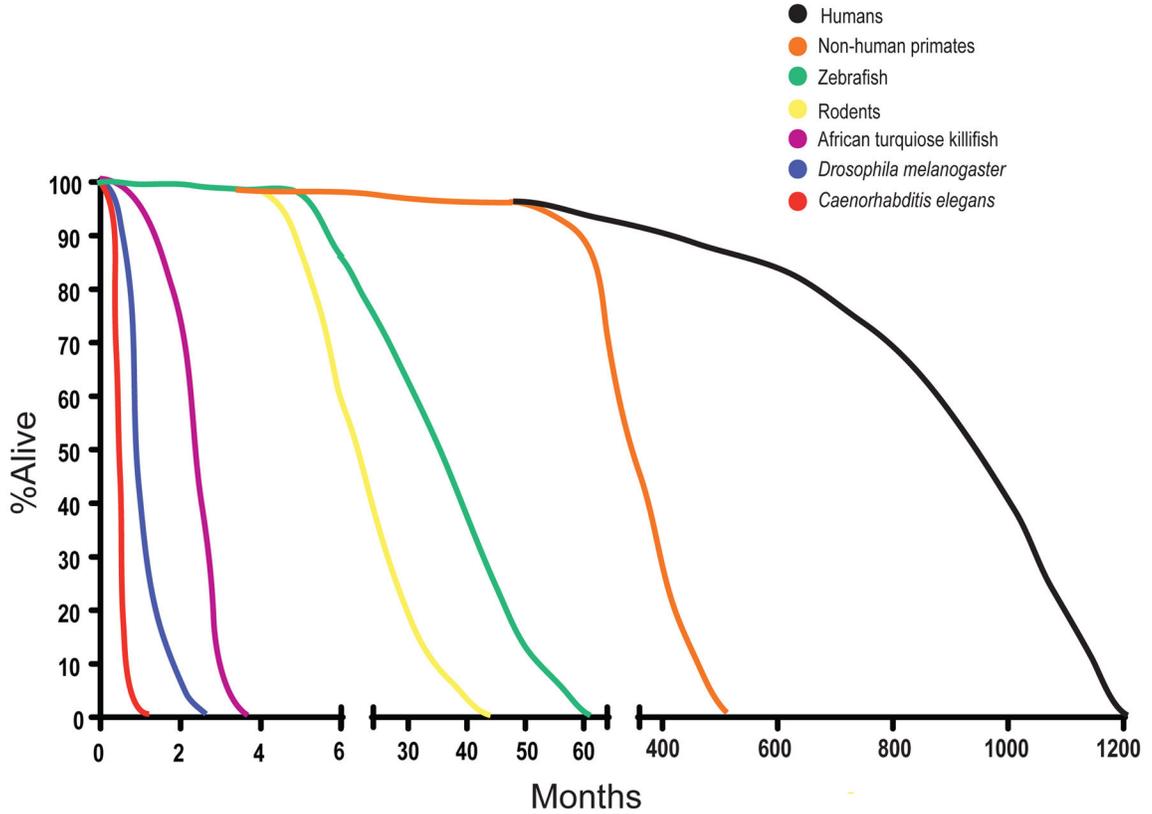


Figure 1. Model systems allow for rapid study of longevity. Because of the long life of humans (black line), model systems are necessary to study regulators of aging. Non-human primates (orange line) still live for decades and thus are impractical for many aging studies. Simpler vertebrate models, such as rodents (yellow line) and zebrafish (green line), are short-lived relative to humans and non-human primates, but take years to reach an “aged” state. Turquoise killifish live for about 3 months, which is significantly shorter than other vertebrate models. Invertebrate models such as *Drosophila* (blue line) and *C. elegans* (red line) live for 3 months or 3 weeks, respectively, making them ideal systems for the rapid identification of genes and molecules involved in aging and age-related cognitive decline.

					
# Neurons	302	10 ⁶	10 ⁸	~10 ⁸⁻¹¹	10 ¹¹
Tests of learning and memory available	+	+	+	+	+
Exhibits age-related cognitive decline	+	+	+	+	+
Exhibits AD/PD pathology	-, Tg Available	-, Tg Available	-, Tg Available	-, Tg Available	+
Exhibits altered neuron morphology and function with age	+	+	Unknown	+	+
Longevity pathways affect cognitive function	+	+	Unknown	+	+

Figure 2. Summary of neuronal aging phenotypes across model organisms. Despite having simpler nervous systems than humans, features of neuronal aging and age-related cognitive decline are evolutionarily conserved across model systems. Transgenic (Tg) models allow for the study of complex human neurological disease, even if the pathology does not normally occur in the model organism. Longevity pathways affect cognitive function in all organisms in which they have been examined.