Behavioural Brain Research 322 (2017) 299–310

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Conserved regulators of cognitive aging: From worms to humans

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ARTICLE INFO

Article history:
Received 25 March 2016
Received in revised form 27 May 2016
Accepted 17 June 2016
Available online 18 June 2016

Keywords:
Aging
Longevity
Cognitive aging
Model systems
Cognitive decline

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.

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.

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 (Fig. 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 (Fig. 1). Even zebrafish, a relatively simpler non-mammalian vertebrate model, has a lifespan of 2–3 years (Fig. 1). Recently, the

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http://dx.doi.org/10.1016/j.bbr.2016.06.035
0166-4328/

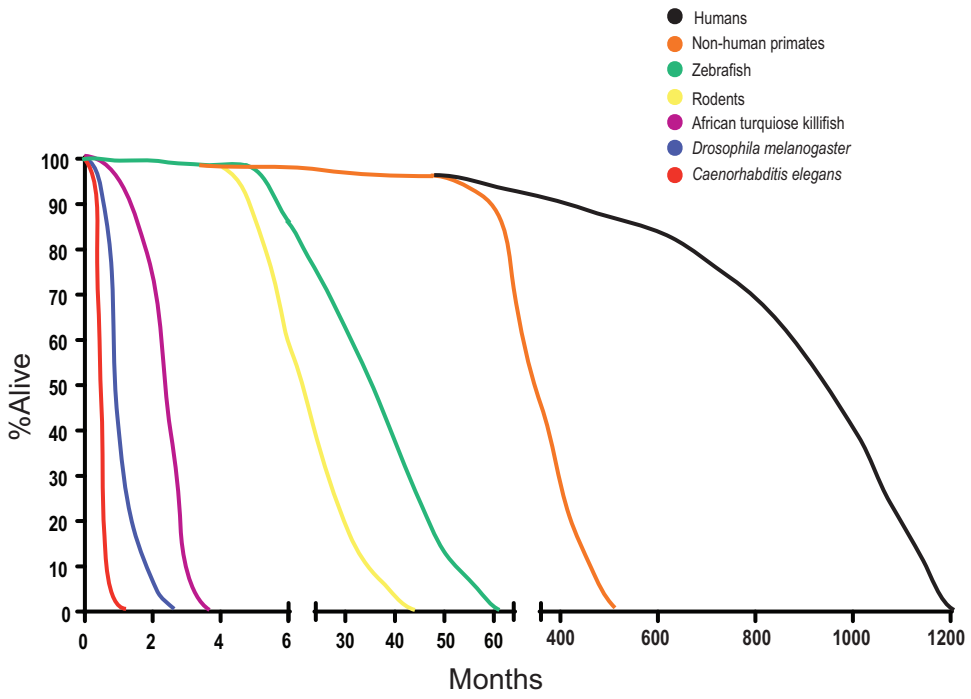

Fig. 1. Model systems allow for rapid study of longevity. Because of the long life of humans (black line), model systems are necessary to study regulators of aging. Non-human primates (orange line) still live for decades and thus are impractical for many aging studies. Simpler vertebrate models, such 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 (purple line) 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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 (Fig. 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 (Fig. 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