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Review

Mini-review: Retarding aging in murine genetic models of neurodegeneration

Roger L. Albin [a,b,c,d,*], Richard A. Miller [e]

[a] Neurology Service & GRECC, VAAAHS, Ann Arbor, MI 48105, USA
[b] Dept. of Neurology, University of Michigan, Ann Arbor, MI 48109, USA
[c] University of Michigan Udall Center for Parkinson's Disease Research, Ann Arbor, MI 48109, USA
[d] Michigan Alzheimer Disease Center, Ann Arbor, MI 48109, USA
[e] Dept. of Pathology & Geriatrics Center, University of Michigan, Ann Arbor, MI 48109, USA

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ABSTRACT

Retardation of aging processes is a plausible approach to delaying the onset or slowing the progression of common neurodegenerative disorders. We review the results of experiments using murine genetic models of Alzheimer disease and Huntington disease to evaluate the effects of retarding aging. While positive results are reported in several of these experiments, there are several discrepancies in behavioral and pathologic outcomes both within and between different experiments. Similarly, different experiments yield varying assessments of potential proximate mechanisms of action of retarding aging. The anti-aging interventions used for some experiments include some that show only modest effects on lifespan, and others that have proven hard to reproduce. Several experiments used aggressive transgenic neurodegenerative disease models that may be less relevant in the context of age-related diseases. The experience with these models and interventions may be useful in designing future experiments assessing anti-aging interventions for disease-modifying treatment of neurodegenerative diseases.

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Contents

1. Introduction

Neurodegenerative disorders such as Alzheimer disease (AD), Parkinson disease (PD), Frontotemporal dementias (FTDs), Huntington disease (HD), Amyotrophic Lateral Sclerosis (ALS), and Spinocerebellar Ataxias (SCAs) are common causes of morbidity and premature mortality. Incidence of the most common and debilitating neurodegenerative diseases is strongly age-related. This is true also for the less common Mendelian forms of AD, PD, FTDs, and ALS, as these variants exhibit age-related penetrance. Similarly, HD and SCAs exhibit age-related penetrance. With the number of elderly individuals now rising dramatically in both developed and developing nations, prevalence of neurodegenerative diseases is expected to soar. Efforts to find disease-modifying treatments have been largely unsuccessful. These efforts focus mainly on identifying pathogenic mechanisms specific to each disease process. The relative lack of progress with these approaches and the age-related nature of neurodegenerative disease incidence suggests that modulation of aging per se may be a useful alternative approach for delaying the onset or retarding the progression of neurodegenerative diseases

* Corresponding author at: 5023 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI 48109-2200, USA.
E-mail address: ralbin@umich.edu (R.L. Albin).
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Table 1
Anti-aging interventions in murine Alzheimer disease models.

Study	Intervention	Neurodegeneration model	Genetic background	Endpoints	Results	Endpoint age(s)	Statistical analysis
Patel et al., Neurobiol Aging 26:995–1000, 2005	Caloric restriction (started at 14–15 weeks)	$APP_{swe/ind}$(J20) transgenic APP mice (K670N/M671L/V717F mutations — PDGF promoter) Mucke et al., J Neurosci 20:4050–4059, 2000	Not stated	Amyloid plaque number & size by IHC	APP + PS1 — decreased cortical, but not dentate or CA1 plaque area. $APP_{swe/ind}$ — decreased cortical and hippocampal plaque #; decreased plaque size.	24 weeks	One-way ANOVAs
				Astrocytosis by IHC			
		APP + PS1 transgenic mice (PS1M146L — PDGF promoter) bred to Tg2576 APP mice — prion promoter Holcomb et al., Nat Med 4:97–100, 1998.		Microglial Activation by IHC	APP + PS1 — non significant effect on astrocytosis area; some effect close to astrocytes.		
			Not stated	APP mRNA levels	Microglial effect inconclusive.		
					No effect on APP mRNA		
Wang et al., FASEB J 19:659–651, 2005	Caloric restriction (started at 3 months)	Tg2576 mice Hsiao et al., Science 274:99–102, 1996	C57B6/SJL	Aβ IHC & stereology	Stable weight, decreased fat pad, improved GTT	12 months	Two-Way ANOVAs
				Aβ ELISA	Markedly decreased Aβ by IHC, ELISA		
				APP processing	Normal total APP		
					Possible increased α — secretase		
Halagappa et al., Neurobiol Aging 26:212–200, 2007	Caloric restriction (started at 3 months) Intermittent fasting (started at 3 months)	3xTgAD (APP_{swe}/Tau_{P301L}/$PS1_{M146V}$) Oddo et al., Neuron 39:409–421, 2003	129/C57BL6	Open Field & Water Maze	CR: improved open field & water maze; reduced Aβ peptides; reduced pTau	10 & 17 months for behavior	Two-way ANOVAs & One-way ANOVAs
				Aβ ELISA		17 months for biochemistry	
				Tau immunoblotting	IF: Improved open field & water maze; no change in Aβ peptides or pTau		
Cohen et al., Cell 139:1157–1169, 2009.	IGF1-R heterozygotes	APP_{swe}PS1ΔE9 mice Borchelt et al., Neuron 19:939–945, 1997	C3H/HeJ/C57Bl6-J/129	Water maze & Rotorod	Improved water maze & Rotorod	11–15 months	Two-way ANOVAs & One-way ANOVAs
				Astrocytosis IHC	Less gliosis & neuronal loss		
				Neuronal density & synaptophysin IHC	More synaptophysin		
				Aβ IHC & ELISAs	Plaque burden similar but plaques smaller & denser		
				EM	More Aggregated Aβ & Less Soluble Abeta		
				In vitro Aβ aggregation assay			