REJUVENATION RESEARCH
Volume 18, Number 6, 2015

DOI: 10.1089/rej.2015.1774

Healthspan Pharmacology

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Abstract

The main goal of this paper is to present the case for shifting the focus of research on aging and anti-aging from lifespan pharmacology to what I like to call healthspan pharmacology, in which the desired outcome is the extension of healthy years of life rather than lifespan alone. Lifespan could be influenced by both genetic and epigenetic factors, but a long lifespan may not be a good indicator of an optimal healthspan. Without improving healthspan, prolonging longevity would have enormous negative socioeconomic outcomes for humans. Therefore, the goal of aging and anti-aging research should be to add healthy years to life and not merely to increase the chronological age. This article summarizes and compares two categories of pharmacologically induced lifespan extension studies in animal model systems from the last two decades—those reporting the effects of pharmacological interventions on lifespan extension alone versus others that include their effects on both lifespan and healthspan in the analysis. The conclusion is that the extrapolation of pharmacological results from animal studies to humans is likely to be more relevant when both lifespan and healthspan extension properties of pharmacological intervention are taken into account.

Introduction

Aging is a complex and multi-factorial process that is not well defined. The majority of evolutionary biologists, like Michael Rose, characterize aging as a decline or loss of adaptation with increasing age, caused by a time-progressive decline of William D. Hamilton's forces of natural selection.[1] Although there are a number of variants of this definition, we can all agree that as we age, we will experience a progressive accumulation of cellular damage and a degradation of repair and maintenance mechanisms, leading to a gradual deterioration of physiological functions. This process, which is highly conserved across species throughout evolution, creates progressive dysfunction associated with frailty and age-related diseases and eventually leads to the death of the organism.

Over recent decades, improvements in medical diagnostics and procedures, as well as improvements in hygiene, have resulted in a steady increase in human lifespan,[2–10] but this increase has unfortunately been accompanied by ever-growing occurrences of diseases of aging, such as diabetes, neurodegenerative diseases, cancer, and cardiovascular diseases.[11] Therefore, understanding the mechanisms of aging, defining the most important risk factors for the development of chronic diseases of aging, and identifying pharmacological interventions to ameliorate the aging process are more important today than ever. Over the last two decades, using several model systems, such as yeast, fruit flies, worms, and mice, numerous evolutionarily conserved pathways that regulate longevity have been identified, and the modification of these pathways either intrinsically (*e.g.*, genetic modifications for deletion, down-regulation or over-expression) or extrinsically (*e.g.*, environmental factors, use of pharmacological agents) have been shown to extend the lifespan of the model organisms.[12–30]

Most of pharmacological intervention studies have focused on lifespan extension of animals, but very little attention has been given to the aspect of pharmacologically induced healthspan extension, which I refer to as healthspan pharmacology. Clearly, this omission is a serious one if results from animal studies are to be relevant to humans, many of whom consider their quality of life with advancing age to be just as important as their longevity. There appears to be an emergence of assays in animal models to evaluate healthspan. One of the tests that can be used to evaluate age-related changes in mice, in an effort to quantify the impact of pharmacological interventions on healthspan, is the frailty index (FI), also known as the index of cumulative deficits.[31,32] A recent study with the goal of evaluating the utility of FI as a tool to evaluate the impact of caloric restriction and resveratrol on healthspan showed that these interventions reduced FI.[33] There is no obvious reason that this tool could not be used

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Table 1. Studies Focusing on Lifespan Pharmacology Only

Intervention	*Model organism*	*Mean lifespan extension*	*Mechanism of action*
α-ketoglutarate Chin et al., 2014[47]	*C. elegans*	50%	Inhibition of ATP synthase and TOR signaling
Alpinia zerumbet Extract Upadhyay et al., 2013[48]	*C. elegans*	23%	Anti-oxidant
Aspirin Strong et al., 2008[49]	Mice	8% (male)	Anti-oxidant, anti-inflammatory
β-Guanidinopropionic acid Yang et al., 2015[50]	*D. melanogaster*	Increase in mean lifespan	Activation of AMP-activated protein kinase, autophagy
Black tea Peng et al., 2009[51]	*D. melanogaster*	9.8%	Anti-oxidant
Blueberry extract Wilson et al., 2006[52]	*C. elegans*	28%	Anti-oxidant
Blueberry extract Peng et al., 2012[53]	*D. melanogaster*	10%	Anti-oxidant
Caffeic acid phenethylester Havermann et al., 2014[54]	*C. elegans*	9–17%	Modulation of the insulin-like DAF-16 signaling
Chicoric acid Schlernitzauer et al., 2013[55]	*C. elegans*	Increase in mean lifespan	Activation of AMP-kinase
Cinnamon Yu et al., 2010[56]	*C. elegans*	12%	Regulation of Insulin/IGF-1 signaling
CoQ-10 Ishii et al., 2004[57]	*C. elegans*	6–18%	Anti-oxidant
Diallyl trisulfide (garlic) Powolny et al., 2011[58]	*C. elegans*	12–13%	Activation of SKN-1
Ethosuximide Collins et al., 2008[59]	*C. elegans*	17%	Regulation of chemosensation
EUK-8/ EUK-134 Melov et al., 2000[60]	*C. elegans*	44%	Anti-oxidant
Ginko biloba Wu et al., 2002[61]	*C. elegans*	8%	Anti-oxidant
Glaucarubinone Zarse et al., 2011[62]	*C. elegans*	Increase in mean lifespan	Induction of mitochondrial activity
Green tea Li et al., 2007[63]	*D. melanogaster*	16–19%	Inhibition of iron accumulation, anti-oxidant
L-Theanine Zarse et al., 2012[64]	*C. elegans*	Increase in mean lifespan	Anti-oxidant
Lipoic Acid Benedetti et al., 2008[65]	*C. elegans*	21%	Anti-oxidant
Lithium McColl et al., 2008[66]	*C. elegans*	46%	Modulation of histone methylation and chromatin structure
Lonidamine Schmeisser et al., 2011[67]	*C. elegans*	8%	Anti-oxidant
Mainserin Petrascheck et al., 2007[68]	*C. elegans*	31%	Activation of DR metabolism
Metformin Anisimov et al., 2008[69]	Mice	38%	Activation of DR metabolism, oxidative stress
Metoprolol Spindler et al., 2013[70]	Mice	10%	Inhibition of β-AR signaling
Myriocin Cutler et al., 2014[71]	*C. elegans*	24%	Decrease of ceramides
N-acetylcysteine Brack et al., 1997[25]	*D. melanogaster*	27%	Differential gene expression
Natto extract Ibe et al., 2013[72]	*C. elegans*	16%	Anti-oxidant
Oxaloacetic acid Williams et al., 2009[73]	*C. elegans*	25%	Regulation of FOXO/DAF-16
Propyl gallate Benedetti et al., 2008[65]	*C. elegans*	12%	Anti-oxidant

(*continued*)

Table 1. (Continued)

Intervention	*Model organism*	*Mean lifespan extension*	*Mechanism of action*
Pyrrolidine dithiocarbamate (PDTC) Moskalev & Shaposhnikov 2011[74]	*D. melanogaster*	20%	Inhibition of NF-κB
Quercetin Kampkotter et al., 2008[75]	*C. elegans*	15%	Anti-oxidant
Rapamycin Harrison et al., 2009[20]	Mice	9–14%	Inhibition of the mTOR pathway
Resveratrol Howitz et al., 2003[12]	*S. cerevisiae*	70%	Activation of NAD+ dependent protein deacetylases of the sirtuins
Resveratrol Viswanathan et al., 2005[76]	*C. elegans*	10–14%	
Rhodiola rosea Bayliak & Lushchak 2011[77]	*S. cerevisiae*	25%	Sensitization to oxidative stress
Rhodiola rosea Wiegant et al., 2009[78]	*C. elegans*	10–20%	Increased stress resistance
Rifampicin Golegaonkar et al., 2015[79]	*C. elegans*	60%	Activation of DAF-16
Spermidine Eisenberg et al., 2009[80]	*C. elegans* *D. melanogaster*	15% 30%	Autophagy
Thioflavin T Alavez et al., 2011[81] Tullet et al., 2008[82]	*C. elegans*	60%	Inhibition of SKN-1
Tocotrienols Adachi et al., 2000[83]	*C. elegans*	17%	Anti-oxidant
Trolox Benedetti et al., 2008[65]	*C. elegans*	31%	Anti-oxidant
Vitamin E Harrington & Harley 1988[84]	*C. elegans*	17–23%	Anti-oxidant

to quantify the effect of other pharmacological interventions on healthspan in animal model studies with the goal of extrapolating the results to humans.

The pharmacological agents that are known to extend lifespan in animal studies appear to act mainly through anti-oxidant defense, protein homeostasis, dietary restriction (DR) modulation, inhibition of kinases, or modulation of insulin/insulin-like growth factor (IGF) signaling. Among numerous agents that have been tested using multiple model systems over the last two decades, the spectrum includes anti-depressants (*e.g.*, mianserin), anti-convulsants (*e.g.*, valproic acid, lamotrigine), anti-diabetics (*e.g.*, metformin), immunosuppressants (*e.g.*, rapamycin), and natural products (*e.g.*, resveratrol, *Rhodiola rosea*, curcumin, green tea, blueberry). The mechanism of action and the extent of lifespan extension vary among each agent (Table 1), and most can be classified under the aforementioned groups. In addition to the widely known pharmacological interventions that prolong lifespan (*e.g.*, resveratrol, *Rhodiola rosea*, rapamycin, metformin) across species, high-throughput chemical screening approaches have been used to identify new candidate molecules that extend lifespan in *Caenorhabditis elegans* and *Drosophila melanogaster* model systems.[14,34–40] With the convenience of *C. elegans* and *Drosophila* as platforms to discover new lifespan–extending compounds, it is inevitable that the number of identified anti-aging compounds that extend lifespan will continue to increase dramatically.

Although the end point of prolonged longevity is clear (*i.e.*, the death of the organism), the physiological mechanisms of extending lifespan via anti-aging interventions have been elusive. The implicit assumption that increasing the mean lifespan of a model organism not only delays aging but also the onset of the age-related physiological effects is unsupported and should be re-evaluated to include measurements of health parameters to determine if an intervention has the potential to add healthy years to the life of the model organism and eventually to humans. Even though a given intervention may extend the lifespan of the organism, if it decreases overall health, it should not be tested in a clinical study to evaluate its potential for human life prolongation, which is the ultimate goal of the longevity research.

The list of studies reporting lifespan extension via pharmacological agents (Table 1) is rather extensive compared to studies where healthspan was also taken into consideration (Table 2). There is no doubt that it is important to identify anti-aging compounds because, aside from their impact on lifespan, they will assist us in elucidating molecular pathways that may impact aging as outlined in Table 1. However, evaluating the impact of such compounds on healthspan is just as important as knowing their impact on lifespan.

The reason for this assertion is rather subtle. Although lifespan and healthspan have been thought to be highly correlated, recent reports indicate that they may not be as closely linked as previously thought. A recent study that uncoupled

Table 2. Studies Focusing on Both Lifespan and Healthspan Pharmacology

Intervention	*Model organism*	*Mean lifespan extension*	*Healthspan parameters*	*Mechanism of action*
4-phenylbutyrate (PBA) Kang et al., 2002[85]	*D. melanogaster*	33%	Locomotion, reproduction	Increased histone acetylation
Caffeine Sutphin et al., 2012[86]	*C. elegans*	37%	Locomotion	Regulation of Insulin/ IGF-1 signaling
Catechin Saul et al., 2009[87]	*C. elegans*	12–14%	Reproduction, pharyngeal pumping	Stress resistance
Celecoxib Ching et al., 2011[88]	*C. elegans*	20%	Locomotion	Inhibition of PDK-1
Cinnamon Schriner et al., 2014[89]	*D. melanogaster*	12–24%	Reproduction, locomotion	Regulation of Insulin/ IGF-1 signaling
Curcumin Alavez et al., 2011[81]	*C. elegans*	45%	Locomotion	Activation of HSF-1 and SKN-1
Curcumin Lee et al., 2010[90]	*D. melanogaster*	16–19%	Reproduction, locomotion	
Dichloroacetate Schaffer et al., 2011[91]	*C. elegans*	Increase in mean lifespan	Locomotion	Inhibition of pyruvate dehy-drogenase kinase
Ethosuximide Evason et al., 2005[92]	*C. elegans*	17%	Reproduction, locomotion, pharyngeal pumping	Regulation of chemosensation
Green tea Lopez et al., 2014[93]	*D. melanogaster*	16–19%	Reproduction	Inhibition of iron accu-mulation, anti-oxidant
Icariin & Icariside II Cai et al., 2011[94]	*C. elegans*	21%	Locomotion	Regulation of Insulin/ IGF-1 signaling
Lamotrigine Avanesian et al., 2010[45]	*D. melanogaster*	12–17%	Locomotion	Metabolic rate depression
Metformin Onken & Driscoll, 2010[44]	*C. elegans*	40%	Locomotion	Activation of DR metab-olism, oxidative stress
Metformin Anisimov et al., 2008[69]	Mice	38%	Estrus, metabolic parameters	
Metoprolol Spindler et al., 2013[70]	*D. melanogaster*	23%	Locomotion	Inhibition of β-AR signaling
Nordihydroguaiare-tic acid (NDGA) Harrison et al., 2014[95]	Mice	12%	Metabolic markers	Anti-oxidant, anti-inflammatory
Quercetin Pietsch et al., 2009[96]	*C. elegans*	15%	Reproduction	Anti-oxidant
Rapamycin Bjedov et al., 2010[97]	*D. melanogaster*	Increase in mean lifespan	Reproduction	Inhibition of the TOR pathway
Rapamycin Zhang et al., 2013[98]	*Mice*	Decrease in mortality	Locomotion, reduced sleep fragmentation	Inhibition of the mTOR pathway
Rhodiola rosea Schriner et al., 2009[99] 2013[28]	*D. melanogaster*	24%	Reproduction, locomotion	Decrease in endogenous superoxide levels, DR-Independent lifespan extension

(*continued*)

TABLE 2. (CONTINUED)

Intervention	*Model organism*	*Mean lifespan extension*	*Healthspan parameters*	*Mechanism of action*
Rosa damascena Jafari et al., 2008[100] Schriner et al., 2012[101]	*D. melanogaster*	16% (males)	Reproduction	Heat shock proteins
Reserpine Srivastava et al., 2008[102]	*C. elegans*	31–64%	Locomotion, pharyngeal pumping	Increased stress tolerance
Resveratrol Wood et al., 2004[103]	*C. elegans*	10–14%	Reproduction, pharyngeal pumping	Activation of NAD+ dependent protein deacetylases of the sirtuins
	D. melanogaster	29%	Reproduction	
Resveratrol Baur et al., 2006[104]	Mice	31% reduction in the risk of death from a high-calorie diet	Organ pathology	
Trehalose Honda et al., 2010[105]	*C. elegans*	30%	Reproduction, pharyngeal pumping	Reduced Insulin/IGF-1 signaling
Trimethadione Evason et al., 2005[92]	*C. elegans*	47%	Reproduction, locomotion, pharyngeal pumping	Regulation of neural activity
Valproic acid Evason et al., 2008[106]	*C. elegans*	35%	Reproduction, locomotion	Regulation of Insulin/ IGF-1 signaling

lifespan and healthspan in *C. elegans* by examining wild-type and four long-lived mutants provided evidence that in a number of cases, where lifespan was extended, the health of the worms suffered drastically.[41] Given that life expectancy has been on the rise for humans, further extending lifespan alone without improving healthspan will have significant adverse outcomes, such as unmanageable health care costs due to declined quality of life and increased incidence of age-related diseases, which further underscores the importance of studying healthspan as opposed to just lifespan.

Healthspan Pharmacology

Despite the necessity of evaluating healthspan in the context of lifespan, a comprehensive definition of healthspan in the laboratory requires an all-inclusive approach defining and evaluating a number of physiological parameters that contribute to the state of health. Describing measurable parameters to determine healthspan is more challenging compared to lifespan, which is simply measured by the mean and maximum life expectancy of the organism. A few parameters for healthspan have been utilized for invertebrates model systems. For instance, movement and feeding behaviors have been used as healthspan markers for *C. elegans*,[41–44] whereas locomotion and reproduction serve as the indicators of health for *D. melanogaster*.[45] Not surprisingly, when it comes to a mammalian model system, such as mice, the definition of healthspan parameters becomes more complex. Even though there are a number of validated tests that measure behavior, locomotion, cognition, and metabolism in young mice, there is no uniform set of tests to measure healthspan in aging mice. A recent perspective article [46] put forward several recommendations for measuring healthspan in mice in an effort to provide a unified method of focusing on healthspan in aging research. Perhaps the FI that measures cumulative deficits in mice can also be incorporated to quantify the impact of pharmacological interventions on healthspan. Given the challenge of reproducibility of a specified connection between a compound and lifespan extension among different laboratories around the world, correlating the effects of pharmacological interventions with healthspan will be even more challenging.

In conclusion, to extrapolate the result of any potential anti-aging pharmacological agent from the laboratory model systems to humans, evaluation of healthspan absolutely needs to be part of the equation. This is why we now need to shift the focus of the scientific community studying aging and anti-aging from lifespan pharmacology to healthspan pharmacology.

Author Disclosure Statement

No competing financial interests exist.

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Received: September 14, 2015
Accepted: October 7, 2015