Belarusian State Medical University

PHARMACOLOGICAL AND NON-PHARMACOLOGICAL INTERVENTIONS FOR AGING

Department of Pharmacology

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The purpose and objectives

The purpose: to summarize information about pharmacological and non-pharmacological interventions for aging from different literature sources

Objectives:

• Understand potential mechanisms of aging

• Realize possible methods of interventions
Introduction

• Aging is a multi factorial process leading to the loss of physiological function
• It is associated with the development of numerous life threatening diseases such as cancer, cardiovascular diseases and neuro degenerative diseases
• Aging and its diseases cause a huge economic, medical and social burden worldwide
• Hence, development of interventions to slow down aging and the onset of the diseases is necessary
Mechanisms of aging

Fig. 1. Underlying mechanism of aging

Accumulation of unrepaired molecular damage, impaired cell signaling

Cellular defects, DNA methylation, stem cell exhaustion

Tissue dysfunction

Aging

Fig. 2. Interaction of various molecular mechanisms that lead to aging

DNA damage

Impaired signal transduction

Protein damage

Mitochondrial dysfunction

Oxidative stress
Possible Interventions for aging

Fig. 3. Different interventions to slow aging
Calorie restriction

- A dietary regimen that reduces the daily caloric intake without malnutrition or deprivation of essential nutrients
- One of the most established forms of intervention
- CR counteracts aging by regulating different pathways including:
  - Mechanistic target of rapamycin (mTOR)
  - AMP-activated protein kinase (AMPK)
  - Sirtuins
  - Insulin and insulin like growth factor 1

Fig. 4. Calorie restriction pathway and its effects
Fig.5. Results from Wisconsin National Primate Research Center

(A) The CR monkeys reported 80% survival rate compared to the 50% seen in the control fed group
(B) Less incidence of age related pathologies compared to the control fed group. Reduced CVD diseases, brain atrophy, diabetes and incidence of cancer were observed in the CR group.
mTOR pathway modulation

- mTOR is a protein kinase which forms the two complexes, mTORC1 and C2
- Regulates cell growth, autophagy, production of protein and energy storage
- Mutations or downregulation of this pathway increased longevity in many animal and yeast models
- **Rapamycin**, a pharmacological inhibitor of mTOR has also increased lifespan due to its inhibition of mTOR pathway

Fig. 6. mTOR pathway and its effects
<table>
<thead>
<tr>
<th>Study</th>
<th>Alteration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabrizio et al., 2001</td>
<td>Deletion of gene encoding for S6K in yeast model</td>
<td>Doubling of the yeast lifespan</td>
</tr>
<tr>
<td>Jia, Chen and Riddle, 2004</td>
<td>Mutations and RNA interference of mTOR</td>
<td>Extended lifespan in the nematode, C. elegans</td>
</tr>
<tr>
<td>Kapahi et al., 2004</td>
<td>Mutation in mTOR in fruit fly and yeast models</td>
<td>Increased life span in both models</td>
</tr>
<tr>
<td>Onken et al., 2010</td>
<td>Overexpression of AMPK in nematodes and cancer prone mice using Metformin</td>
<td>Down regulation and impaired mTOR pathway in C.elegans and cancer prone mice</td>
</tr>
<tr>
<td>Harrison et al., 2009; Miller et al., 2014</td>
<td>Rapamycin treated mice to disrupt mTOR</td>
<td>Extended lifespan in mice upto 30%</td>
</tr>
<tr>
<td>Johnson et al., 2013</td>
<td>Reduced mTOR signaling through genetic and pharmacological interventions</td>
<td>Extended lifespan in yeast, worms, flies and mice</td>
</tr>
</tbody>
</table>

Tab. 1. Overview of some studies carried out in mTOR regulation studies
Insulin/insulin like growth factor signaling modulation

- Insulin and insulin like growth factor 1 (IGF) signaling (IIS) pathway is responsible for energy metabolism and growth.
- Reduced IIS and plasma IGF-1 along with increased insulin sensitivity have increased lifespan in nematodes, fruit flies and mice models.

Fig.7. IGF1 modulation effects
Sirtuin pathway activators

- Sirtuins (SIRT1-7) promotes longevity and is capable of mediating many beneficial effects
- Resveratrol, a SIRT1 activator has improved function and extended lifespan in organisms such as *S. cerevisiae*, *C. elegans*, *D. melanogaster*, *N. furzeri* and *A. mellifera* (Hubbard and Sinclair, 2014)
- Additionally, it also showed increased lifespan in mice on a high-fat diet

Fig.8. Resveratrol and its effects
Targeting autophagy

- Rate of autophagy declines with age and is a potential cause of several neurodegenerative diseases
- The administration of natural polyimide extended the lifespan of mice and had a cardio protective effect
- Life span was extended up to 25% by lifelong administration of spermidine and also showed reduced liver fibrosis and hepatocellular carcinoma
- Also induced neuronal autophagy thereby decreasing the development of a number of neurological pathologies

Fig.9. Autophagy targeting pathways
Co-enzyme NAD+ boosters

• A decline in the levels of NAD+ is observed in aging animal models
• NAD + boosters such as NAD+ precursors, synthesis enhancers and inhibitors of NAD+ consuming enzymes have shown the ability to extend lifespan of mice
• Thus, NAD+ boosters are one of the highly promising drugs to slow aging and improve the quality of life

Fig.10. Benefits of NAD+ boosters
The table below summarizes some of the effects of NAD+ boosters seen in aging studies:

<table>
<thead>
<tr>
<th>NAD+ Booster</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Nicotinamide riboside</td>
<td>Rejuvenation of intestinal stem cells and 5% increase in lifespan</td>
</tr>
<tr>
<td>NAD+ precursor</td>
<td>A wide range of beneficial effects: improved glucose homeostasis, maintenance of genomic integrity, prevention of heart failure, steatosis and glaucoma</td>
</tr>
<tr>
<td>Extracellular nicotinamide phosphoribosylasetransferase (eNAMPT)</td>
<td>Extended lifespan in old mice</td>
</tr>
<tr>
<td>Nicotinamide and nicotinamide mononucleotide</td>
<td>Improved lifespan and health span in aging models caused due to deficiency of DNA repair</td>
</tr>
</tbody>
</table>

Tab.2. Types of NAD+ boosters and their effects
Senolytic elimination

- Accumulation of senescent cells causes the onset of deterioration and age related diseases
- Treatment with a senolytic cocktail, Dasatinib plus Quercetin alleviated numerous age related features in mice and restored neurogenesis
- Furthermore, the senolytic AP20187 extended the median lifespan of mice by about 25% and prevented bone deteriorations in aging mice
- Nevertheless, the safety and efficacy of these drugs should be well evaluated before introducing as an anti-aging treatment for humans
Proper lifestyle

• Diet, physical activity, alcohol intake and smoking plays a major role in health as well as in the development of many diseases
• Regular exercises along with reduced intake of alcohol, sugar and saturated fats have increased lifespan by two or more years
• Furthermore, the adaptation of a Mediterranean diet has shown countless benefits such as increased longevity, improved cognition in elderly, prevention or slowing down of metabolic syndromes
• Inclusion of antioxidant rich food has been shown to reduce oxidative stress and inflammation and has a protective action against free radicals and DNA damage

Fig.11. Diet (A) and exercise (B)
Conclusion

• Main strategies to prolong lifespan include:
  – Dietary interventions
  – Proper lifestyle

• Promising interventions, that could slow down aging is:
  – Drugs that inhibit GH/IGF-1 axis
  – Drugs that inhibit mTOR-S6K pathway
  – Drugs that activate AMPK or specific sirtuins
  – NAD+ boosters
  – Senolytics
THANK YOU