INTERNATIONAL SYMPOSIUM
GENEVA, SWITZERLAND
MAY 27-28 / 2017

CURRENT APPROACHES TO TESTING ANTI-AGING DRUGS

Anisimov V.N.
Department of Carcinogenesis and Oncogerontology, N.N. Petrov Research Institute of Oncology, Pesochny-2, St.Petersburg, 197758, Russia, E-mail: aging@mail.ru

Relevance. Extending the human healthy lifespan is one of the main purposes of gerontology and modern preventive medicine. Researchers managed to slow down aging and to prolong healthy lifespan using genetic, dietary and pharmacologic approaches in many model organisms: yeasts, worms, fruit flies, insects, short-living fishes, birds, rodents (mice, rats and hamsters), minipigs, dogs, and monkeys. Recent experimental studies demonstrate that medications targeting aging (antioxidants, calorie restriction mimetics, autophagy inductors, etc.) can substantially promote health and extend lifespan [1-3]. Pharmacologically targeting aging appears to be more effective in preventing age-related pathology compared with treatments targeted to particular pathologies. The development of new anti-aging drugs represents a great opportunity for the pharmaceutical and healthcare industries. However, if people will better survive into later life and live longer, the increase in incidence of age-associated diseases including cardiovascular diseases, diabetes type 2 and cancer will be a great challenge for the mankind. The search for adequate selection models of effective and safe methods of life extension became the most urgent matter in biology of aging.

There are at least two accepted definitions for compounds applicable to pharmacological intervention into the aging: a) *anti-aging drugs*, which presumably are able to reverse the aging process (rejuvenation) and b) *geroprotectors,* which being administered lead to prevention of premature aging and/or slow down or postpone aging. Spindler [2] introduced term “longevity therapeutics” for drugs that intervene in the process of aging to extend mean and/or maximum life span, maintain physiological function, and mitigate the onset and severity of a broad spectrum of age-associated diseases in mammals. Vaiserman et al. [3] subdivided potentially geroprotective agents into several groups: those demonstrating anti-aging effect, but without any evidence of life span increase; drugs which increase life span reducing incidence of age-associated pathology, and agent which extend lifespan because they suggested to reverse the aging process itself. While laboratory animals are similar to humans in some respects (such as patterns of aging at the molecular, cellular/tissue, and physiological levels, responses to hazardous exposures), there is a growing pool of experimental evidence indicating important differences (genetic, metabolic, ontogenetic etc.) among mammalian species that make valid interpretation and extrapolation of the animal experiments to humans difficult. Issues of concordance of responses between rodent species and between rodents and humans – as well as repeatability and site-specificity – are important considerations in evaluating laboratory animal results [4].

In 2003 the U.S. National Institute of Aging (NIH) started the Aging Interventions Testing Program (ITP), which proposed to test compounds with the potential to extend lifespan and to delay (postpone) age-associated diseases and dysfunctions. Among such means are pharmacological drugs, nutriceutics, food products, diets, food additives, plant extracts, hormones, peptides, amino acids, chelating agents, antioxidants, etc. In the framework of the ITP aspirin, nordihydroguaretinic acid, nitrofluorodiprophen, rapamycin, resveratrol and some other drugs were studied. Priority was paid to preparations which are easily available, have a reasonable price and can be administered with food (preferentially) or with drinking water. An ITP protocol includes two phases. During the first phase the

capability of the drug to increase lifespan is studied. In addition, other parameters, such as the animal's activity in young and old age, metabolic hormone levels, and T-lymphocyte levels are also studied. During the second phase, drugs that show promising results are studied more intensively to reveal candidates for further clinical studies. Behavioral and cognitive experiments, measurement of the oxidation level and pathomorphological studies of the dead animals take place during the second phase.

In 2000, an international program (project) on the assessment of efficacy and safety of geroprotectors has been suggested. Its activity could be carried out under the control of the United Nations Program on Aging, World Health Organization and the International Association of Gerontology and Geriatrics. The aim of this program is the preparation of international critical reviews by an expert working group providing systems and guidance of evidence relating to the activity and efficacy of geroprotective drugs. Experts could give recommendations for additional studies, if required. The categorization of agent is a matter of scientific judgment that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The drug is geroprotector for *humans*. This category includes drugs with *sufficient evidence of lifespan increase* in humans. Evidence is confirmed by epidemiological multicenter randomized studies;

Group 2: This category includes drugs for which, on the one part, the degree of evidence of geroprotective activity in humans is almost *sufficient*, as well as those for which, on the other part, there are no human data, but for which there is evidence of lifespan extension in model animals.

Group 3: The drug is *not classifiable as to its geroprotective effect in humans*. This category is used most commonly for agents for which the evidence of geroprotective effect is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Group 4: The drug is probably *not a geroprotector* in humans. This category is used for drugs for which there is *evidence suggesting lack of lifespan extension in* humans and in experimental animals.

Publication of the results received by the expert group would assist national and international health institutions to plan and perform programs of rehabilitation and prevention of premature aging, as well as to make a decision about risk-benefit ratios of such programs. Experts in the working groups need to develop a scientific report about the evidence of geroprotector efficacy and safety of the drugs. They should not give any recommendations directly to national or international health institutions about regulation or legislation of drug usage, this remains the exclusive priority of this organizations. Currently, there is no substance which could be evaluated as a group 1 agent (i.e. geroprotector activity of the drug had been proved in humans). Drugs that could be in group 2 are probably metformin, rapamycin, melatonin, pineal peptide preparations Epithalamin and Ala-Glu-Asp-Gly (Epitalon). There are numerous data confirming the geroprotective effect of these drugs in animal experiments and, in some cases, in clinical studies (Table 1). These drugs are probably the most reliable candidates for testing in multicenter randomized clinical studies. The evaluation of safety of a drug in rodents is a crucial aspect of its preclinical trials. Long-term assays for carcinogenicity in rodents are an integral method which evaluates toxicity and some adverse effects of the drug being tested.

Table 1. Summary on some most significant effects of promising geroprotectors observed in rodents

Parameters	Metformin	Rapamycin	Melatonin	Epitalon*
Lifespan	↑	↑	↑	↑
Antioxidant potential	↑	↑	↑	↑
Susceptibility to insulin	↑	↑	↑	↑
Low-density lipids	↓	↓	↓	↓
Resistance to stress	↑	↑	↑	↑
Reproductive function	↑	↑	↑	↑
Cognitive and learning capacity	↑	↑	↑	↑
Physical endurance	↑	↑	↑	↑
Age-related pathology	↓	↓	↓	↓
Cancer risk	↓	↓	↓	↓

↑ - increase; ↓- decrease; *Ala-Glu-Asp-Gly.

Combination in one study of both safety and geroprotective potential of drugs significantly decreases the cost of the study. GeroScope is an *in silico* project that can aid prediction of novel anti-aging drug from existing human gene expression data. The design of the majority of studies in the field was found to suffer from confounds and defects.

Conclusion. Accordingly, there is the need to create standard guidelines for testing such drugs and for evaluation of life extension potential as well as other late effects including tumor development. Guideline for the testing should include such significant points as animal models, regime of testing, and biomarkers/endpoints. The system of experimental preclinical study of such drugs could include a study on their effects on biomarkers of aging, lifespan and the development of various age-associated pathologies, especially tumors. The study should be conducted in rats and mice (inbred, outbreed or genetically-modified animals) treated by drugs in different doses for their whole life [5]. The ultimate goal in this field is the choice of geroprotectors for studies in humans. To achieve these goals, the international standards for preclinical and clinical studies of agents for pharmacological interventions into the aging, as well as for evaluation of results of such studies, should be developed. In the coming years, the perspective direction could be the development of new biomarkers, based mostly on biochemical and genetic methods, for short-term screening of such drugs. At present, cooperative studies on anti-aging drugs and geroptotectors conducted in various laboratories could be promising.

References:

1. Anisimov V.N. Current Drug Res 2006;7:1485-504.
2. Spindler S.R. Age (Dordr). 2012;34:111-20.
3. Vaiserman A.M., Lushchak O.V., Koliada A.K. Ageing Res Rev. 2016;31:9-35.
4. Anisimov V.N., Ukraintseva S.V., Yashin Nature Rev Cancer. 2005;5:807-19.
5. Anisimov V.N., Popovich I.G., Zabezhinski M.A. Methods Mol Biol. 2013;1045:145-60.