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Survival in good health? Part II - Small molecules and red wine

Longevity has increased almost everywhere in the world, but especially in the developed countries. At older age, however, quality of life is often greatly impaired by chronic age-associated diseases such as cardiovascular diseases, stroke, kidney diseases, cancer, sarcopenia, osteoporosis, and arthrosis. Many of these conditions can be alleviated by dietary restrictions, as shown in mammals.

In animal experiments, caloric reduction to 30% to 50% below the libidum level, or feeding only every other day, can delay age-associated diseases, improve stress resistance, and alleviate functional decline.[1] Using surrogate end points these beneficial effects could likewise be demonstrated in humans.[2] (see part I).

Almost all observations and studies in primary and secondary prevention indicate that generally diet consisting only of a modification of food intake is poorly accepted. It can be anticipated that this will be even more the case for diets with marked caloric restrictions. Furthermore, such a diet may not be without risk, eg, in the frail, the elderly, or the critically ill. As a consequence, research has focused on the development of small molecules that provide a similar benefit but without caloric restriction. The first attempts were made by inhibition of glycolysis with 2- deoxyglucose or by enhancing insulin action by glucophage/metformin.[3]

Another strategy proposed includes activation of SIRT 1 (sirtuin 1), an enzyme which deacetylates proteins that contribute to cellular regulation. Sirtuins extend lifespan in yeast, worms, and flies. At least some of the effects of caloric restriction are suggested to be sirtuin-mediated in simple organisms and in mammals.[4,5]

A new approach uses resveratrol, which induces expression of sirtuin genes similar to the action of caloric restriction. Resveratrol is present in several plants, but predominantly in the skin of red grapes. It is concentrated in red wine (30 mg to 50 mg/L), the content in white wine and rosé is minor. Resveratrol has been shown to extend life span in *S. cerevisiae*, drosophila, and vertebrate fish. In mice on a fat diet, resveratrol reduces weight gain and improves endurance. In obese mice the substance improves several health parameters, such as glucose haemostasis and survival. At least partially, these beneficial effects are due to activation of SIRT 1.[6]

Gene expression in multiple tissues of mice after resveratrol application paralleled that of diets with either caloric restrictions or every-other-day feeding. The resveratrol-fed mice showed a marked improvement of signs of ageing: eg, albuminuria was reduced, inflammation decreased, as was apoptosis in the vascular endothelium. As a consequence, increased aortic elasticity, restored acetylcholine-induced responsiveness, greater motor coordination, reduced cataract formation, and preserved bone mineral density were observed. However, in contrast to caloric restriction, mice at the age of 12 months did not live longer if treated with resveratrol.[5]

The antiaging action of caloric restriction is nowadays related to attenuation of age-associated increase in oxidative stress. Likewise, the changes observed in resveratrol-fed animals involved a generalized reduction in oxidative stress and inflammation. For example, in the aorta a reduction of superoxide production was observed and transcripts related to inflammation were repressed.[5] There were, however, also marked differences in the effects of caloric restriction and resveratrol treatment. Whereas caloric restriction strongly upregulated the protective glutathione metabolism, resveratrol did not. Likewise, increased protein synthesis in skeletal muscle as one of the major effects of caloric restriction is not present following resveratrol treatment. These differences may well explain the different effects of caloric restrictions and resveratrol, with antiaging properties of both interventions but no effect on longevity of resveratrol.

Diets with caloric restriction are certainly not very popular in the western countries— in contrast to red wine. This tasty beverage in moderate amounts prolongs life. According to the results of animal experiments this may even achieved in good health, as resveratrol, which is present in high concentrations in red wine, has pronounced antiaging effects. If this notion could be confirmed in human studies, for many of us it would be good news.

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