

determining life span.^{3,5-9} So, isocaloric diets with different amounts of proteins may result in different life spans of model organisms.^{3,9} At nearly the same time, the life-prolonging effects of resveratrol, a low molecular phenolic compound, were discovered.¹⁰ It was first noticed that resveratrol mimics CR.^{11,12} The molecular mechanisms of resveratrol were found to be mediated by NAD⁺-dependent histone deacetylases, sirtuins.^{11,13-15} Parallels between the life-extending effect and mimicking physiological and molecular signs of CR were found for many anti-aging drugs, including glitazones¹⁶ and rapamycin.¹⁷ Simultaneously, a number of compounds that block catabolism of macronutrients or even ingestion were found to provide life span prolongation.¹⁸ For instance, acarbose and 2-deoxyglucose, which block glycogen breakdown and glycolysis, respectively, are among these compounds.¹⁸ It is suggested that some CR mimetics are not only inhibitors of catabolism but are signaling molecules shamming energy and/or nutrient sensors of cells. Indeed, a way of blockage of nutrient delivery to cells may not matter. The result is always either a lack of energy in the form of adenosine triphosphate (ATP) or deficiency of some building blocks for synthesis of proteins, polysaccharides and lipids. The question about the superiority of energy over plastic material or *vice versa* is still unresolved. In addition, it is still not clear whether we should take into account the number of calories in the diet, or dietary composition, or macronutrient balance, or even certain dietary components, which when taken away from the diet would provide life span extension. In this review we will try to provide a comprehensive picture for development of the CR concept, the tissue-specific and intracellular consequences of CR, a description of drugs that mimic CR outcomes, and suggest a mechanism explaining why a decrease in either energy or specific nutrients may lead to an increased life expectancy in particular biological species.

10.2 Aging and CR

The first evidence on the ability of CR to extend life span came from experiments performed in rats by McCay and colleagues.¹ Further studies showed that CR extended the life span by shifting mortality factors, such as diseases and tumors, to older age. Using different protocols, researchers revealed the life span extension by CR in many organisms like yeast, rotifers, spiders, nematodes, flies, fishes and mammals, including non-human primates (Figure 10.1).

10.2.1 CR in Yeast: *Saccharomyces cerevisiae*

Replicative and chronological life spans are described for unicellular yeast. The replicative life span is measured by the amount of formed daughter cells produced by a single cell. Reduction of the glucose concentration from 2% to 0.5% was the first CR intervention in yeast and this extended the replicative life span two-fold. The same study showed the importance of certain genes (*SIR2*, *FOB1*, *CYT1*) for mediating this phenotype. In addition, gene