

oxidation by ROS. It was recently found that a relatively slight increase in the ROS level may account for life span extension in fruit flies and nematodes.^{165,166} ROS production by respiratory complex I increased because of over-reduction of CoQ and thus leaking of electrons. In fruit flies, expression of non-proton-pumping rotenone-insensitive NADH dehydrogenase increased ROS production and extended the life span.¹⁶⁶ This effect was not observed when other complexes were affected. An explanation may come from the regulatory function of ROS as signaling molecules from mitochondria to other cellular compartments. ROS can affect the activity of specific MAP-kinase cascades and redox-sensitive transcription factors to increase antioxidant defense and capacity. Interestingly, co-treatment with antioxidants to inhibit ROS production reduces signal transduction and abolished life span extension under CR.^{167,168} Moreover, the hypothesis of mitohormesis assumes a potentially beneficial influence of moderate levels of mitochondrial ROS on organismal healthspan.¹⁶⁹ Furthermore, the oxidatively modified molecules may not cause death themselves.^{132,160,170}

An organism would deteriorate in case of oxidation of essential proteins, key metabolic enzymes, metabolite transporters, components of signaling machinery, *etc.* It becomes more evident that oxidation of relatively unessential proteins may instead protect essential ones.^{171,172} The oxidation and clearance of incorrectly translated proteins may also protect organisms.^{173,174} Oxidation of special susceptible amino acids, particularly methionine, may protect organisms from death.¹⁷⁵ There is also evidence that protein aggregation is necessary for homeostasis.¹³⁷ In some cases, oxidation of susceptible proteins may allow the re-direction of metabolism in order to withstand stressful conditions.¹⁷⁶ An increase in mitochondrial biogenesis may also not lead to a corresponding increase in ROS production: several works show that mitochondria are sinks for ROS rather than ROS generators.¹⁷⁷⁻¹⁷⁹

Finally, one can conclude that chemical compounds that would activate the same pro-longevity processes as CR, particularly mitochondrial biogenesis, autophagy and antioxidant response, may partially or completely mimic CR and extend life span.

10.5 Ways to Achieve CR

10.5.1 Decreased Food Consumption

Food consumption is regulated by many factors, both external and internal. Among external ones, food quality, visual and smell input signals are probably the most important. Internal factors primarily involve neuronal and hormonal regulation. Decreased food consumption is the easiest way to achieve CR. It is quite simple to decrease food consumption in mice, rats or humans by giving less food, but not in some other animals. For example, in budding yeast *S. cerevisiae*, the only way to give less food is to decrease the amount of carbohydrate within the initial medium. For the round worm *C. elegans* the dilution of the initial culture makes it possible to decrease the amount of