effects is that of whether melatonin can really extend lifespan, particularly in humans, or whether its value may predominantly be seen in the maintenance of health during aging.

19.2 Overview of Melatonin's Actions in Relation to Aging

Aging is associated with numerous changes. Some of them gave rise to assumptions concerning the primary reasons for aging and led to several partially competing theories of aging.[11] The main lines of argumentation include limitations of age by (i) energy expenditure, (ii) mitochondrial dysfunction that causes increasing damage by free radicals and, often, cell death, (iii) immune remodelling during senescence and mechanisms of inflammaging, (iv) reduction of cell division capacity by progressive telomere attrition and losses of stem cells. A closer look shows that all these processes are not suitable for monocausal explanations, but are, in fact, multiply interconnected. This insight has given rise to network hypotheses that underline the interconnections.[11–14] Moreover, a necessary distinction has to be made between (i) the basic, rather slowly progressing mechanisms of aging that lead to a steady, continuous decline in physical capacity and (ii) the step-wise, discontinuous deteriorations caused by diseases, which bear the potential of considerably accelerating aging.[15] This duality in the dynamics of aging is also relevant to the actions of melatonin because numerous effects have been described that concern either the slow, lingering basic processes or the disease-related, aging-promoting damage.[11]

19.2.1 Energy Balance and Metabolic Sensing

Although a comparison of equally sized endothermic vertebrates clearly demonstrates that energy consumption alone cannot explain the limits of lifespan,[11,15] energy metabolism, balance, sensing and disturbances thereof can certainly contribute to the velocity and course of aging. This may be particularly important for the avoidance of metabolic diseases, especially all aspects of insulin resistance, including obesity, metabolic syndrome and diabetes type 2. Interestingly, calorie restriction not only prolonged lifespan in rodents, but also preserved the functioning and circadian rhythmicity of the pineal gland.[16,17] However, it is still uncertain whether these findings are also applicable to humans because of profound differences to rodents, which continue to grow until senescence and are less facing the problem of malnutrition under food restriction as seen in primates. With regard to melatonin, its administration to rodents in the chow was shown to reduce food intake,[18] whereas intraperitoneal injections favoured carbohydrate consumption after a circadian phase shift.[19] This result indicates a role of the circadian system in the metabolic effects of melatonin. Although strengthening of the circadian system may be beneficial in both rodents and humans,[6] a frequently