survived up to 800 days of age, and the same age was achieved by 54.3% of mice in the control female group and 30% of metformin-treated females ($p < 0.03$; Fischer's exact test). According to the log-rank test, the life span distribution of 129/Sv mice treated with metformin differed significantly from the control population. The difference was much more significant in male mice ($p = 0.0006$) than in females ($p = 0.0555$). The Cox's regression model has shown that neonatal metformin treatment increased the relative risk of death in female mice and decreased it in males compared to the respective intact control groups. Thus, neonatal metformin exposure slows down aging and prolongs life span in male but not in female mice.[29]

17.5 Antidiabetic Biguanides in Prevention of Age-Associated Diseases in Mouse Models

Transgenic mice with Hungtington's disease (HD) (the R6/2 line expressing exon 1 of the Huntington protein including ~130 glutamine repeats) were given metformin in drinking water (2 or 5 mg ml^{-1}) starting from the age of 5 weeks.[37] Metformin treatment significantly prolonged (by 20.1%) the survival time of male (but not female) HD mice at the 2 mg ml^{-1} dose (~300 mg kg^{-1} day^{-1}) without affecting the fasting blood glucose level. This dose of the drug also decreased hind limb clasping time in 11 week-old mice. The higher dose of metformin did not prolong life span, and neither dose was effective in female HD mice. Recently, additional evidence of a protective effect of low-dose metformin on neuronal dysfunction has been reported in mouse model of Huntington's disease.[38]

In another study, $SOD1^{G92A}$ mice of both sexes with a transgenic model of amyotrophic lateral sclerosis (ALS) were given metformin with their drinking water in various doses (0.5, 2, and 5 mg ml^{-1}) starting from the 35th day of age.[39] Administration of metformin failed to have any effect on the disease onset, progression or survival in male $SOD1^{G92A}$ mice at any doses. Moreover, in females authors observed a dose-dependent negative effect of metformin on neurological response. All groups exposed to metformin exhibited weight loss and significant life extension. The authors noted, however, a trend toward increased survival with a decreasing dose of metformin.[39]

17.6 Antidiabetic Biguanides as Anti-Carcinogens and Inhibitors of Tumor Growth in Rodents

The available data on the results of *in vivo* studies of effects of biguanides involving more than 20 experimental models of carcinogenesis were recently analyzed.[22,23,40] They included models of spontaneous carcinogenesis (in rats and mice), chemical carcinogenesis induced by 18 different agents, 4 viruses, 2 dietetic modifications, and 2 types of ionizing radiation (X-rays and gamma-rays) (Table 17.3). Antidiabetic biguanides were given with diet, drinking