17.4 Effect of Antidiabetic Biguanides on Aging and Life Span in Mice

In the National Cancer Institute Bioassay of Phenformin for Possible Carcinogenicity, B6C3F1 mice of both sexes were used.[30] Similar to the rat study, the matched control groups included 15 animals each whereas groups exposed to phenformin comprised 35 animals each. Phenformin was given in low and high doses (400 and 800 ppm) in diet for 78 weeks starting at the age of 8 weeks. The treatment was followed by an observation period of 26 weeks, than all surviving animals were sacrificed. The mean body weights of both male and female B6C3F1 mice were markedly lower than those in controls during the first 60–78 weeks of administration of phenformin at the low and high doses. Until the age of 105 weeks, 13% controls, 19% low-dose and 29% high-dose treated male mice and 33%, 59% and 52% of female mice, respectively, were surviving. The incidence of hematopoietic tumors was 33% of the matched controls of both male and female mice, compared to only 1.5% hematopoietic tumors in the male and 5.4% of the female controls. The conclusion was that there is no evidence that under these conditions phenformin was carcinogenic. It's worthy to note that in female B6C3F1 mice the survival was rather increased in the phenformin-treated groups. The treatment with this drug also decreased the incidence of lymphomas in male and female mice. Unfortunately, since this study was terminated after the age of 112 weeks, animals could not survive until their natural death and it did not allow the evaluation of the effect of phenformin on the mean and maximal life span.

The geroptotector effect of biguanides was first demonstrated in our studies with phenformin orally given to mice.[16,17] Long-term administration of phenformin to female C3H/Sn mice (2 mg day^{-1} $mouse^{-1}$ orally) started at the age of 3.5 months was followed by a 21% increase in mean life span and a 26% increase in the maximum life span (Table 17.1). The incidence of spontaneous mammary adenocarcinomas as well as leukemias was reduced by four times under the treatment with phenformin as compared with control mice given tap water. It is worthy to note that the treatment with phenformin significantly—to more than 6 months (+53.9%)—increased the mean life span of tumor-free C3H/Sn mice.

Available data on the effects of antidiabetic biguanides in rodents are summarized in the Table 17.2.

In two sets of our experiments, administration of metformin with drinking water (100 mg kg^{-1} 5 times a week starting at the age of 2 months) to transgenic HER-2/neu female mice slightly increased the mean life span by 4–8%, and decreased the size and multiplicity of mammary adenocarcinomas.[24,32] The treatment reduced food consumption but did not have influence on the dynamics of body weight. In tumor mice treated with metformin, the expression of mRNA coding for lymphocyte-associated proteins granzyme-b and perforin mRNA was explored. Expression of these cytolytic molecules was not detected in the control, but it was significantly increased in mice treated