SRT1720, was shown to extend both mean and maximal lifespan of mice fed a standard diet.[108] The lifespan extension caused by SRT2104 was accompanied by enhanced motor coordination and performance, bone mineral density, insulin sensitivity, and decreased inflammation in the treated mice.[108] Further studies will need to be carried out on synthetic STACs to see if their effects are conserved in higher organisms such as non-human primates.

11.4.2 Obesity, Metabolism, and Type II Diabetes

One of the most well studied effects of STACs on healthspan is their ability to regulate metabolic parameters and type II diabetes.[15] In mice fed a high-fat diet, dietary supplementation with resveratrol not only reduces the risk by death by 31% but also protects against obesity, fatty liver disease, and insulin resistance.[15,109] In addition, resveratrol reverses transcriptional changes associated with HFD feeding, and improves mitochondrial function by increasing the activity of AMPK and PGC1α, two key regulators of mitochondrial biogenesis.[105] The beneficial effects of resveratrol treatment in the HFD model appear to depend on both SIRT1 and AMPK, a kinase that is activated by resveratrol in a dose-dependent manner.[105] Studies in conditional SIRT1 knockout mice have demonstrated that a low dose of resveratrol (~24 mg kg^{-1}) stimulates AMPK *via* SIRT1-dependent deacetylation of LKB1, while at higher doses (~240 mg kg^{-1}) AMPK is activated in a SIRT1-independent manner.[110]

The effects of resveratrol on metabolism and obesity have also been examined in rhesus monkeys and humans.[27] In monkeys fed a high fat (HF)/high sucrose (HS) diet that mimics the typical Western diet, supplementation with resveratrol was shown to improve adipose insulin signaling and decrease inflammation in the adipose tissue.[111] Subsequent studies have demonstrated that resveratrol also decreases arterial wall inflammation and stiffening,[112] improves muscle function,[113] and confers neuroprotection in monkeys fed a HF/HS diet.[114] In humans, SRT501, a proprietary formulation of resveratrol, has been shown to improve glucose tolerance in type II diabetes.[115] Moreover, 30 day supplementation with resveratrol (150 mg day^{-1} resVida™) in healthy humans was shown to induce a CR-like phenotype consisting of a decrease in intrahepatic lipids, circulating glucose levels, triglycerides, inflammatory markers, and systolic blood pressure.[116] These results have been supported by independent studies demonstrating a therapeutic benefit of resveratrol in patients with type II diabetes[115] and nonalcoholic fatty liver disease.[117] However, other studies have shown conflicting results. One study reported that 12 week supplementation with 75 mg day^{-1} of resveratrol in non-obese healthy women did not improve metabolic performance,[118] and a more recent clinical trial reported that resveratrol dosed twice daily at 500 mg for 5 weeks had no effect on glucagon-like peptide (GLP-1) secretion, or on glycemic control in type II diabetic patients.[119] Further studies will need to be performed in order to resolve the factors underlying these discrepancies.