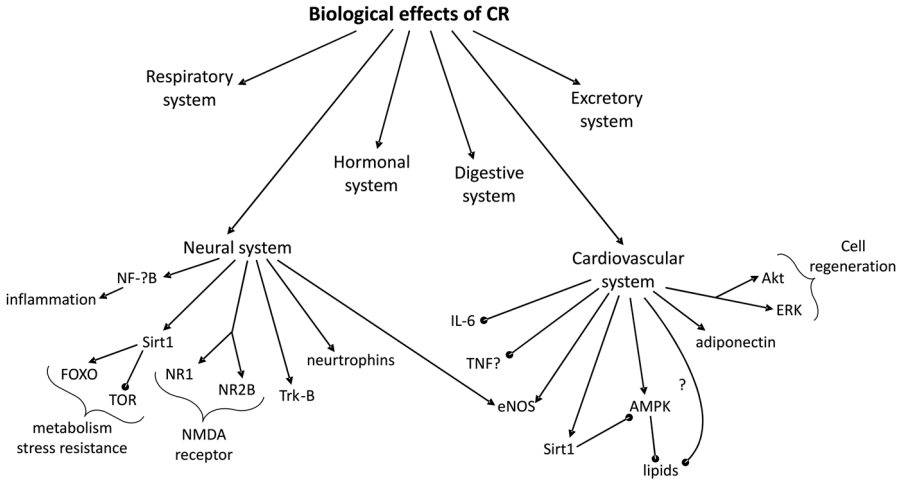

Figure 10.2 Key molecular pathways affected by CR in the cardiovascular and neural systems. Transcription regulators: NF-κB: nuclear factor κB; FOXO: forkhead box O. Modifying enzymes: TOR: target-of-rapamycin kinase, AMPK: AMP-activated protein kinase; ERK: extracellular signal-regulated kinase; Trk-B: tropomyosin receptor kinase B; Akt: pro-carcinogenic protein kinase B; Sirt1: sirtuin, histone/protein deacetylase. Metabolic enzymes: eNOS: endothelial nitric oxide synthase. Receptors/ligands: NMDA: *N*-methyl-D-aspartate; NR1 and NR2B: subunits of NMDA receptor; TNFα: tumor necrosis factor α; IL-6: interleukin 6.

10.3.3 Hormonal Regulation

Aging significantly affects the endocrine system. Both decreased hormone secretion and responsiveness of endocrine tissues to stimuli are observed in aging.[121] Aging causes decreases in the levels of estrogen (menopause), testosterone (andropause), growth hormone and insulin-like growth factor-1 (IGF-1) (somatopause), and dehydroepiandrosterone sulfate (adrenopause). In addition, the response of targeted tissues may induce development of pathologies and diseases. For example, the level of fasting insulin increases because of the development of resistance to it in peripheral tissues due to increased adiposity, decreased physical activity, and loss of muscle mass.[122] Thus, insulin, IGF-1, and growth hormone are key mediators of life span extension by CR.

The insulin concentration in plasma may serve as a biomarker for aging since it increases with age. Lower levels of insulin were observed in calorie restricted rodents and monkeys.[69] Increased longevity was observed in people with lower than median plasma insulin levels.[123] In CRONies (*CR* with *O*ptimal *N*utrition) study, restriction for about 6 years decreased serum insulin and glucose concentrations.[75] A randomized controlled trial for 12 months where aged individuals were subjected to 20% CR showed decreased concentrations of fasting insulin but increased sensitivity to this hormone.[124]