10.3.2 Brain Function

An interesting interrelationship occurs between brain functioning and CR. On the one hand, CR affects the brain by enhancing cognitive function and preventing age-related changes and neurodegeneration.[97] On the other hand, the brain plays an important role as a mediator of the response to CR by activating nutrient-sensitive hypothalamic circuitries.[98] The beneficial effects of CR on the brain mostly include impact on neurogenesis, synaptic plasticity, and neuroprotection, and are mediated by induction of mild stress.[99] This mechanism, called hormesis, modulates key pathways regulating neuronal activity and cell resistance in response to stronger stress.[100] CR affects neurogenesis by maintaining neuronal stem cells.[101] These cells can proliferate and differentiate into either neuronal or glial cells to recover tissue after damage.[102] The ability to produce new cells is also important for learning and memory consolidation.[103]

Synaptic plasticity is the ability of synapses to transmit stronger or weaker signals between cells. Both regulation of neurotransmitter release from presynaptic cells and the amount of receptors in postsynaptic cells define the strengths of a signal. Production, release and reabsorption of neurotransmitters require energy for synthesis and active transport. Thus, an increased mitochondrial biogenesis to support energetic needs could be among the beneficial effects of CR.[104] Additionally, it was shown that more mitochondria are accumulated in the synapses[105] and their damage impairs learning and memory consolidation.[106] Mitochondrial biogenesis is partially activated by a higher concentration of NO, which is also involved in the formation of synapses in hippocampus.[107] This fact is also supported by results obtained with Sirt1-deficient mice, which have weaker synaptic plasticity, impaired memory and upregulation of eNOS.[108,109] CR affects the expression levels of many genes encoding receptors by preventing age-dependent decrease in expression.[110,111] Neurotrophins, Trk-B, NR1 and NR2B subunits of the *N*-methyl-D-aspartate-sensitive receptor are among them. This mechanism prevents the loss of synaptic plasticity and increases cognitive functions that rely on hippocampus-dependent memory tasks.

CR induces pro-longevity and anti-aging mechanisms in various cells, including neuronal ones. Altered mitochondrial biogenesis[112] and an increased level of free radical species were observed in aged brain and in several models for neurodegeneration.[113,114] Respiration capacity and biogenesis of mitochondria are regulated primarily by ***p***eroxisome proliferator-activated nuclear receptor ***g***amma ***c***oactivators (PGC-1α and PGC-1β), regulators of gene transcription whose activation is mediated by NO.[94,115,116] Furthermore, the activity of PGC-1α is regulated by Sirt1-driven deacetylation.[117] Being an important regulator of brain health and mediator of response to CR, Sirt1 targets the transcription factors such as FOXO1 and NF-κB, which, in turn, regulate metabolism, stress resistance and inflammation.[118–120] Thus, brain Sirt1-deficient mice did not properly respond to CR by increasing locomotor activity and insulin sensitivity.[118] The key molecular pathways affected by CR in cells belonging to cardiovascular and neural system are summarized in Figure 10.2.