

be suggested that newly developed PPAR agonists with minimum adverse side effects will have beneficial effects on aging and age-related diseases, and it is important to evaluate their anti-aging effects experimentally and clinically.

16.6 Effects of Anti-Aging Calorie Restriction on PPAR Modulation

One interesting aspect of PPARs is their involvement in calorie restriction (CR), which is well known as an effective anti-aging treatment. It was firmly established that CR markedly increases median and maximum life span in several species including mammals.¹³⁶ Although the precise mechanisms of the action of CR on aging and longevity are not fully established, several plausible mechanisms have been proposed. Generally, CR is known to alter various physiological functions, including lipid and carbohydrate metabolism, the immune system, and inflammation.¹³⁷ Among the many changes occurring during CR, various metabolic processes are known to be changed most substantially. CR reduces overall energy expenditure and also alters insulin sensitivity and insulin signaling, neuroendocrine functions, and stress response.¹³⁸ In addition, CR also exerts its benefits through inducing the antioxidative defense mechanisms to suppress age-related oxidative stress. Interestingly, some changes occurring during CR seem to be similar to those induced by PPAR activation. Several pieces of evidence suggest the possibility that PPARs mediate the effects of CR by modulating similar signaling pathways.

Although PPARs are regulated by CR and mediate some beneficial effects of CR, the effects are organ-specific.¹³⁹ Furthermore, depending on the experimental designs and animals used, a decrease, an increase, or no changes are observed in the expression of PPARs in response to CR.¹³⁹ One most reasonable explanation of the relationship between CR and PPAR comes from changes of hepatic PPAR α levels by CR in comparison to *ad libitum* (AL, free access to food)-fed mice.^{140,141} Increased hepatic PPAR α expression may play an adaptive role in regulating glucose homeostasis to prevent hypoglycemia during CR.³⁶ In addition, Corton and Brown-Borg demonstrated that 19% of genes (mostly involved in metabolism and inflammation) changed by CR were dependent on PPAR α ¹⁴² as the protective effects of CR were lost in PPAR α null mice. These findings indicate that PPAR α plays an important role in mediating the action of CR and suggest that PPAR α agonists may act as plausible CR mimetics.

CR experiments in aged rats also suggest the relationship with PPAR. Sung *et al.* first reported that the levels of PPAR α and PPAR γ decreased in aged rat kidneys.¹¹³ They found that in young healthy rats, CR did not have any effects on the levels of PPAR α and PPAR γ expression. However, CR in aged rat kidneys increased PPAR α and PPAR γ expression compare to *ad libitum*-fed