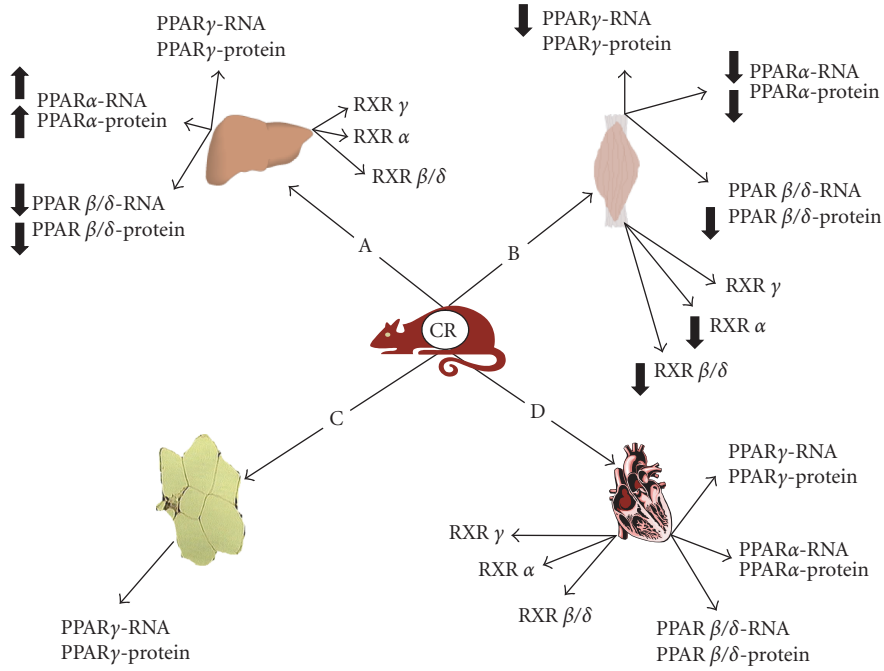

Figure 1: Effects of calorie restriction (CR) on the expression of PPARs family genes in mouse: (A) liver, (B) skeletal muscles, (C) white adipose tissue, and (D) heart. Arrows pointing up or down indicate statistically significant increases or decreases ($P < .05$). Lack of arrows means no alteration.

were significantly increased by CR in comparison to mice fed with unlimited (*ad libitum*; AL) access to food. This finding appears counterintuitive in view of the evidence that PPARα deficiency prevents insulin resistance in mice subjected to HFD [13]. However, the suggested involvement of PPARα in glucose homeostasis could imply that the increase of PPARα in mice subjected to CR is a mechanism protecting these animals from hypoglycemia [14, 15]. Perhaps under conditions of HFD the decrease of PPARα is adaptive, but when the animals are subjected to CR, PPARα increases to facilitate maintenance of normal glucose levels during the periods when food is not available. Additionally, a recent study conducted by Corton et al indicated that 19% of hepatic genes involved in lipid metabolism, inflammation, and cell growth which were altered by CR were dependent on PPARα. Interestingly, some of these genes were altered by CR only in normal mice but not in PPARα deficient animals. Results obtained in animals treated with a PPARα agonist indicated overlap of genes influenced by CR and by a compound activating PPARα [20]. These important findings indicated that PPARα plays an important role in mediating the action of CR [13, 20]. Corton et al also suggested that drugs activating the PPARα-RXR-LXR axis can be potential CR mimetics [20].

The expression of the remaining member of the PPAR family, PPARβ/δ, in the liver was significantly decreased by CR at both mRNA and protein levels [19]. Thus, the hepatic expression of three genes from the PPAR family is differentially altered by CR. However, CR did not alter hepatic RXRα, RXRγ, and RXRβ/δ mRNA (Figure 1A) [19].

PPARs, CR, and skeletal muscle

Similarly to the liver, the skeletal muscle is a major insulin target organ. In this tissue, the expression of PPARs and RXRs is altered differently by CR than in the liver [19, 21]. It was reported that 30% calorie restriction in mouse skeletal muscle decreased the level of PPARγ mRNA and the PPARγ protein level appeared to also be decreased [21]. We could speculate that the decrease of PPARγ in the muscle as seen in the adipose specific knockout for PPARγ is beneficial for insulin sensitivity [16]. However, muscle-specific knockout of PPARγ caused whole-body insulin resistance [22]. Interestingly, treating these knockout mice with TZD improved insulin sensitivity [22], suggesting the effect was due to PPARγ agonism in other tissues. This suggests that CR can increase insulin sensitivity through effects on PPARγ expression in tissues other than the muscle, and speculating further we could suggest that under the conditions of CR, a decreased rather than elevated PPARγ expression is beneficial.

PPARα mRNA and proteins were decreased by CR in skeletal muscle, an effect opposite to that observed in the liver [19, 21]. It was speculated that a decrease of PPARα in the muscle under CR slowed fatty acid oxidation, thus increasing the reliance on carbohydrates as the energy source. More importantly, consequences of reduced PPARα expression could prevent the muscle from using all of the FFA immediately after food intake and thus maintain a balance between energy availability and energy usage during the fasting period. The protein level of PPARβ/δ was also decreased in the