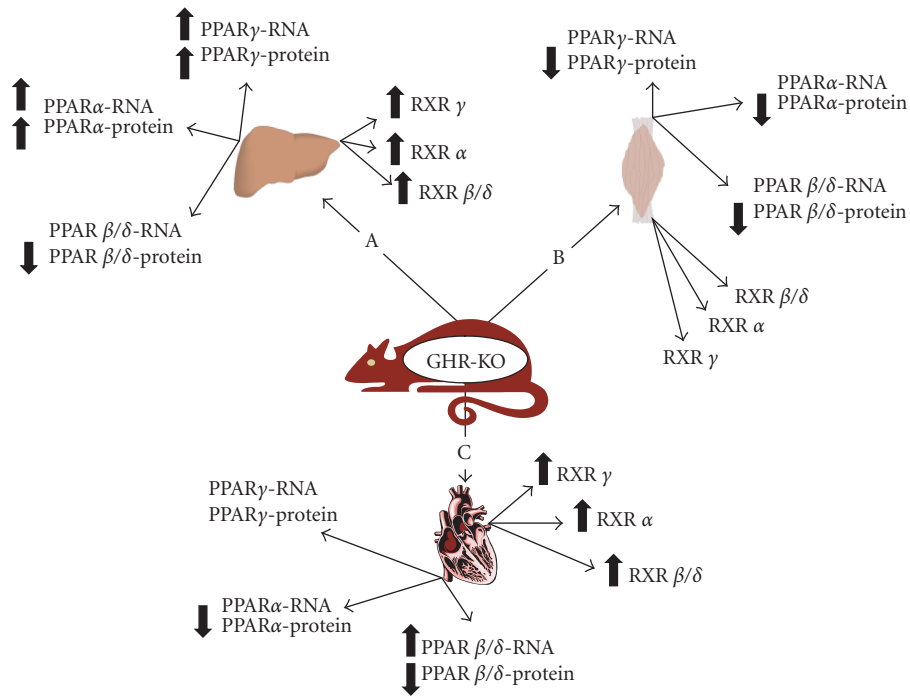


FIGURE 2: Effects of growth hormone receptor/binding protein knockout (GHR-KO) on the expression of PPARs family genes in mouse: (A) liver, (B) skeletal muscle, and (C) heart. Arrows pointing up or down indicate statistically significant increases or decreases ($P < .05$). Lack of arrow means no alteration.

skeletal muscle of CR mice [21]. It is well known that CR promotes fat depletion and prevents obesity. Studies in PPARδ-deficient mice on HFD revealed reduced energy uncoupling and obesity [21]. This would predict that reduced levels of PPARδ in the muscles of CR mice may lead to increased lipid accumulation and promote obesity. However, reduced dietary fat intake in CR animals may alter these relationships. It was suggested that CR down-regulates the pathway of lipid metabolism and accommodates it to the circumstances of restricted food intake [21]. This may serve to prevent disruption of fatty acid homeostasis in CR animals. In addition to its effects on PPARs expression, CR reduced mRNA levels of RXRα and RXRβ/δ [21]. Altered expression of these genes important to PPARs activation correlated with the changes in the expression of the corresponding members of the PPAR family (Figure 1B) [21].

### *PPARs, CR, and the white adipose tissue*

PPARγ is mainly expressed in white adipose tissue (WAT). As mentioned previously, the deficiency of PPARγ in adipose tissue is protective against obesity and insulin resistance caused by HFD [16, 23]. However, CR increases insulin sensitivity in mice, without altering PPARγ mRNA levels in WAT (Figure 1C) [24]. It can be speculated that under conditions of reduced calorie intake diminished PPARγ would not be beneficial, or that limited fat storage does not allow increased PPARγ activation in this tissue. At the time of this writing no data are available on the effects of CR on PPARα and PPARβ/δ in WAT.

## PPARs IN GENETICALLY LONG-LIVED AND SHORT-LIVED MICE

### *Growth hormone receptor/binding protein knockout (GHR-KO) mice*

GHR-KO (Laron dwarf) mice have their GH receptor/binding protein gene disrupted and thus are deficient of GHR. Consequently these mice are GH resistant or insensitive and have greatly reduced plasma IGF-1 and insulin levels, and low glucose level [25, 26]. GHR-KO mice are also characterized by markedly extended lifespan in comparison to normal controls [27, 28].

In comparison to normal animals, GHR-KO mice also have significantly elevated PPARγ mRNA and protein level in the liver (Figure 2A) [19]. We speculated that increased level of PPARγ in the liver of those long-lived animals may be responsible for or contribute to their exceptionally high insulin sensitivity. This correlates with findings in PPARγ-adiposeKO mice, which indicated that PPARγ deficiency in WAT is compensated for by increased expression of this nuclear receptor in the liver to promote insulin sensitivity [16, 19]. The findings in the muscle also suggest that in GHR-KO mice PPARγ in the liver contributes to high insulin sensitivity, because the level of PPARγ mRNA in skeletal muscle of KO mice was not altered, while the PPARγ protein level was decreased in comparison to normal controls (Figure 2B) [21].

The increased level of PPARα measured in the liver of KO mice [19] could be suspect of exerting to negative