

THE EFFECT OF CALORIC RESTRICTION AND METFORMIN ON INSULIN PATHWAY GENES IN GROWTH HORMONE (GH) TRANSGENIC MICE

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Growth hormone, insulin like growth factor 1 (IGF1), and insulin sensitivity are likely mediators of life span and seem to play a regulatory role in the aging process. PEPCK-bGH transgenic (TG) mice overexpressing the bGH gene fused to control sequences of the rat phosphoenolpyruvate carboxykinase (PEPCK), are characterized by markedly shortened life span in comparison to their normal siblings. Caloric restriction (CR) increases longevity and sensitivity to insulin, in keeping with the hypothesis that insulin and its signaling pathway play key roles in aging. In this study, we subjected TG and normal mice to 30% caloric restriction and/or treatment with anti-diabetic drug, Metformin (250 mg/kg body weight/day) for a period of 2 months. After 6 weeks we performed an insulin tolerance test (ITT) by injecting the mice with insulin (1IU/ kg of body weight) and measuring plasma glucose level at 0, 10, 20, 40, 60, 90, 120, and 180 minutes. Both Metformin and CR improved responses to insulin in normal and Tg animals and their effects were additive. Two weeks after ITT, the animals were killed and tissues collected. The expression of PPAR γ , PPAR α , PGC1 α , Sirt1, Foxo1, Akt1 and Akt2 genes was analyzed by real time PCR. The expression of AKT2 and Sirt1 were increased in normal mice in comparison to their Tg siblings with no effect of CR. Akt1 mRNA expression was increased by CR. Caloric restriction also increased the expression of PPAR γ , PPAR α , PGC1 α and Foxo1, with a statistically significant interaction between CR and phenotype. Metformin treatment, which increased the response to insulin in both N and Tg mice did not induce any changes in the expression of the examined genes. We conclude that CR alerts sensitivity to insulin in N and Tg mice through different mechanisms.