

THYROXINE REPLACEMENT THERAPY IN AMES DWARF AND GROWTH HORMONE RECEPTOR/ BINDING PROTEIN KNOCKOUT MICE AFFECTS CARBOHYDRATE METABOLISM

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We hypothesize that alterations in carbohydrate metabolism and extension of longevity in Ames dwarf (df) and Growth Hormone Receptor Knockout (GHRKO) mice are related to reduced levels of anabolic hormones during development. As the first step in testing this hypothesis, we have examined the effects of thyroxine (T4) therapy between 2 and 8 weeks of age on the expression of insulin-related genes in adulthood.

Groups of df and GHRKO mice were treated with T4 [0.1 mg/g body weight (BW)] or vehicle 3x week from 2 to 8 weeks of age using 10 animals per group. Animals were weighed weekly during treatment and monthly thereafter. At eight months of age, all mutant animals plus ten wildtype (WT) siblings from each strain were bled for determination of fasted blood glucose (BG) and insulin and killed. Liver tissue was collected for assessment of the levels of mRNA, by real-time polymerase chain reaction (RT-PCR), and proteins, by Western blots, for the following genes: insulin receptor (IR), Akt2, Foxo1, PPAR α , and PGC-1 α ; which were previously shown to be expressed differently in these mutants vs WT siblings; Treatment with T4 increased BW in male and female df and in female GHRKO. In T4 treated df males, BG was higher than in df controls ($p < 0.05$) and not different from WT male animals. PGC-1 α protein levels in T4 injected df male liver were higher than in df controls ($p < 0.01$) but lower than in WT animals ($p < 0.05$). In T4 treated GHRKO, plasma insulin was higher than GHRKO controls ($p < 0.05$) but numerically lower than in WT. IR mRNA was reduced by T4 in GHRKO of both sexes and Akt2 mRNA was reduced in females. These findings indicate that anabolic hormones during early development can have lasting effects on adult carbohydrate metabolism. (Supported by the Ellison Medical Foundation)