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Effects of Dietary Restriction on the Expression of Insulin-Signaling-Related Genes in Long-Lived Mutant Mice

Andrzej Bartke, Michal M. Masternak, Khalid A. Al-Regaiey, Michael S. Bonkowski

Geriatrics Research, Departments of Internal Medicine and Physiology, Southern Illinois University School of Medicine, Springfield, Ill., USA

Abstract

Hypopituitary Ames dwarf mice and growth-hormone-resistant (growth hormone receptor knockout, GHRKO) mice have reduced plasma levels of insulin-like growth factor 1 and insulin, enhanced insulin sensitivity and a remarkably increased life span. This resembles the phenotypic characteristics of genetically normal animals subjected to dietary restriction (DR). Interestingly, DR leads to further increases in insulin sensitivity and longevity in Ames dwarfs but not in GHRKO mice. It was therefore of interest to examine the effects of DR on the expression of insulin-related genes in these two types of long-lived mutant mice. The effects of DR partially overlapped but did not duplicate the effects of Ames dwarfism or GHR deletion on the expression of genes related to insulin signaling and cell responsiveness to insulin. Moreover, the effects of DR on the expression of the examined genes in different insulin target organs were not identical. Some of the insulin-related genes were similarly affected by DR in both GHRKO and normal mice, some were affected only in GHRKO mice and some only in normal animals. This last category is of particular interest since genes affected in normal but not GHRKO mice may be related to mechanisms by which DR extends longevity.

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Many of an animal's physiological responses to nutritional signals are mediated through insulin, insulin-like growth factor 1 (IGF-1) or homologous pathways. There is considerable evidence that dietary restriction (DR) reduces circulating levels of both IGF-1 and insulin, and diminished IGF-1/insulin signaling is among the mechanisms believed to link DR with delayed aging and extended longevity [1, 2]. In laboratory stocks of house mice (*Mus musculus*),