

79. STUDYING THE GH/IGF/INSULIN AXIS USING KNOCKOUT AND TRANSGENIC APPROACHES

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Insulin-like growth factors (IGFs) are involved in normal growth and development. Initially, it was thought that IGF-I was produced solely by the liver in response to growth hormone (GH), and that this liver-produced, circulating IGF-I was the mediator of GH-effects on pubertal growth. More recently, it has been established that virtually all tissues produce IGF-I. Thus two distinct systems were recognized, the “endocrine” circulating IGF-I and the locally produced “autocrine/paracrine” IGF-I. Since the endocrine form of IGF-I is extremely sensitive to GH, it was believed that GH stimulates growth via the circulating IGF-I and locally produced IGF-I has some local tissue-specific effects. We have re-examined this hypothesis by ablating the liver production of IGF-I in a tissue-specific manner (LID mice), utilizing the cre/loxP system. Circulating IGF-I levels are significantly reduced (by 70%) and GH levels are markedly elevated; proving that circulating IGF-I is primarily derived from the liver and controls GH secretion. Surprisingly the (LID) mice had normal growth and development. However, when we crossed these mice with acid-labile subunit knockout (ALSKO) mice, we were able to reduce circulating IGF-I levels even further and these mice showed postnatal growth retardation and osteopenia, suggesting that circulating IGF-I is important for post-natal growth and development. Circulating GH levels were elevated in the LID mice and this was associated with insulin resistance as determined by hyperinsulinemia in the face of normoglycemia and using the hyperinsulinemic-euglycemic clamp technique. The insulin resistance could be corrected by injecting rhIGF-I, a GHRH antagonist, and most convincingly by crossing these animals with a GH antagonist transgenic mouse. Thus it appears that, at least in the case of this mouse model, GH is the most proximal cause for the insulin resistance seen in the face of low circulating IGF-I levels.