Catch-Up Growth: Basic Mechanisms

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Catch-up growth follows a variety of nutritional or nonnutritional insults that slow the normal rate of growth, and is characterized by faster than expected growth once the insult is over. There are many explanations for catch-up growth, but the most widely accepted model is the 'neuroendocrine hypothesis'.

Nutritional insufficiency and reduced growth are an essential requirement for, and prelude to, subsequent catch-up growth. During nutritional insufficiency, increased ghrelin levels, and decreased leptin levels, stimulate appetite via Neuropeptide Y and agouti-related protein neurons in the hypothalamus. The changes in ghrelin and leptin also act directly (e.g. via the growth hormone, GH, secretagogue receptor) and indirectly to increase GH secretion which is required for normal metabolic adaptations to fasting.

GH signaling via the JAK (Janus kinase)/STAT (signal transduction and activators of transcription) signaling pathway leads to increased IGF-1 production in the liver (fig. 1). However, during fasting, IGF-1 levels fall despite the increase in GH, a condition known as hepatic GH insensitivity. This appears to be due in part to upregulation of two nutrient sensors (SIRT1 and FGF21) that inhibit JAK-STAT signaling and prevent coupling of higher GH levels to higher IGF-1 production. SIRT1 is upregulated in malnutrition due to increased cellular NAD+ levels and by increased cellular AMP levels (either directly or indirectly via AMPK). FGF21 is upregulated by the nutritional sensitivity transcription factor PPARα which is stimulated by fasting. SIRT1 and FGF21 reduce JAK/STAT signal transduction by deacetylating and dephosphorylating STAT5 and inactivating it. Despite the elevated GH levels therefore, IGF-1 production remains low.

Once nutrient availability improves, and cellular levels of NAD+ and AMP normalize, SIRT1 and FGF21 levels fall. This leads to reestablishment of normal JAK/STAT signaling, normal hepatic responsiveness to GH, increased IGF-1 production, and increased growth, as long as elevated levels of ghrelin and GH persist.
Fig. 1. A model of catch-up growth combining the effects of the ghrelin/GH/IGF-1 axis and the actions of the nutrient-regulated proteins FGF21 and SIRT1 on hepatic GH signaling. The width of lines reflects the degree of upregulation. Normal anabolism: GH is secreted from the pituitary under the influence of stimulator factors (including ghrelin secreted from the stomach in response to decreased nutrient intake) and inhibitor factors (including leptin secreted from adipose tissue). It binds to hepatic GH receptors (GHR) and IGF-1 production via the JAK/STAT signaling pathway. The actions of the GH/IGF-1 axis are due to the effects of GH and IGF-1. Fasting (catabolism): Ghrelin secretion increases, and leptin secretion decreases leading to increased GH secretion. However, low cellular nutrient levels (increased NAD+ and decreased NAHD, increased AMP and decreased ATP) stimulate SIRT1 and FGF21 production. These block the JAK/STAT signaling pathway and lead to hepatic GH resistance. IGF levels are low, and the GH/IGF-1 axis is shifted towards effects in nonhepatic target tissues and towards GH-mediated effects rather than IGF-1-mediated effects. Catch-up (hyperanabolism): Normalization of nutrient supply and cellular NAD+ and AMP levels leads to a reduction in SIRT1 and FGF21 and return of normal hepatic GH sensitivity. However, persisting elevations of ghrelin (and depression of leptin) continue to stimulate higher than normal GH production. This leads to increased GH and IGF-1 levels, increased GH and IGF-1 signaling in liver and other target tissues (such as muscle and adipose), and catch-up growth.
This model has been well studied in animal models, but the evidence in humans is less extensive. In preterm, and small for gestational age infants, it seems that (a) ghrelin is increased following in utero and ex utero (postnatal) malnutrition, (b) elevations in ghrelin can persist for prolonged periods of time, and (c) higher ghrelin levels are associated with greater degrees of catch-up growth. The possibility that a prolonged increase in ghrelin levels (and hence GH levels) following a period of nutritional inadequacy may lead to enhanced growth (catch-up) once the period of inadequacy is over is a plausible explanation for catch-up growth in preterm and SGA infants [1–5].

References