Abstract
The neuroendocrine model of catch-up growth has been well studied in a number of animal models. During nutritional inadequacy, which invariably precedes catch-up growth, growth hormone (GH) levels increase under the influence of the oxytocic ‘hunger signal’ ghrelin. This increase in GH would usually be accompanied by an increase in IGF-1. However, malnutrition also induces the nutritionally responsive proteins sirtuin 1 (SIRT1) and fibroblast growth factor 21 (FGF21) that block GH signal transduction in the liver by blocking the JAK/STAT pathway, limiting IGF-1 production. The result is that GH’s action is shifted from hepatic effects to effects in other tissues (for example muscle and adipose) and shifted away from IGF-1-mediated effects and towards GH-mediated effects. Once nutrients become more available, SIRT1 and FGF21 levels, and hepatic GH sensitivity return to normal, and production of IGF-1 resumes. This shifts GH signaling away from GH-mediated effects, and towards IGF-1-mediated effects both in the liver and in other tissues. It presumably leads to greatly increased IGF-1 signaling that would have been expected without the prior episode of nutritional inadequacy. Although much work remains to be done, it does appear that ghrelin is increased in in utero and postnatal malnutrition, that elevations in ghrelin may be prolonged after malnutrition resolves, and that higher ghrelin levels are associated with increased rates of catch-up growth. Prolonged increases in circulating ghrelin and GH, combined with a rapid return in hepatic GH sensitivity would provide an elegant mechanism to drive catch-up growth after periods of nutritional insufficiency.

Introduction

Catch-up growth usually refers to a process that follows a period of growth failure, whereby the specific growth rate increases above the rate that would have been expected had the preceding growth deficit not have occurred. It leads
to a reduction in the growth deficit between the subject and his/her expected body size. Usually, catch-up is incomplete (a growth deficit remains), but sometimes overcompensation can occur and a greater than expected body size result.

The process has been recognized for almost 100 years [1], although the term originated in 1963 in a paper by Prader and Tanner [2]. Tanner described two types of catch-up: type A is a brief period of rapid growth followed by a normalization of specific growth rate; type B is seen when growth continues longer than would be expected [3]. Both forms of catch-up may be seen simultaneously in the same patient [3]. Small for gestational age and preterm infants clearly demonstrate catch-up growth [4], although most studies have considered type A catch-up rather than type B catch-up.

Models of Catch-Up Growth

It is not difficult to imagine why reduced nutrient availability would reduce growth, or why reestablishment of nutrient supply would increase growth back to normal. What is more difficult is to explain why subsequent growth would be greater than normal. Three main hypotheses have been described that seek to explain this [3].

_Tanner’s Time Tally Hypothesis_

In his early writings on catch-up growth, Tanner speculated on a mechanism that is now known as the ‘time tally’ model [3, 5]. He hypothesized the presence of a central marker of ideal body size (the time tally) that increases at a developmentally determined rate. Body tissues produce a counteracting ‘inhibiting substance’. Growth rate is determined by the difference between the central time tally and the inhibiting substance. During periods of growth failure, the time tally would continue to increase at its developmentally programed rate, but the level of the central inhibitor would not increase (as body size was not increasing). At the end of the period of growth arrest, the difference between the time tally and the inhibiting substance is greater than prior to the growth arrest, so growth rate (once sufficient nutrients become available) would also be greater than before the growth arrest, and greater than if that period had not have occurred [3, 5]. Although it is tempting to consider leptin as a potential inhibiting substance, this model suffers from the lack of an obvious mechanism for the central time tally.
**Epiphyseal Growth Plate Hypothesis**

This model sees the regulation of growth rate being controlled in peripheral tissues (specifically in the epiphyseal growth plate) rather than centrally, and is based on studies of catch-up growth in isolated bones [3, 6]. Explanted rat metatarsals continue to grow in culture, but growth slows dramatically if they are exposed to dexamethasone [6]. In metatarsals taken from rats on postnatal day 8, the specific growth rate after dexamethasone is withdrawn exceeds the rate of metatarsals of the same age that were not exposed to dexamethasone. In other words, catch-up growth occurs [6]. Catch-up does not occur with metatarsals taken on embryonic day 20, or after prolonged courses of dexamethasone. This effect has been explained by delayed senescence of the growth plate [3, 6] and is most similar to type B catch-up, while the time tally mechanism is more similar to type A catch-up [3].

**Neuroendocrine Hypothesis**

This model (see below) is probably the most popular model of catch-up growth, and has been examined in a number of animals including rodents, birds, pigs, and fish [3, 7]. It explains catch-up growth as resulting from two apparently conflicting actions of growth hormone (GH): (1) a stimulator of somatic growth; (2) a mediator of metabolic adaptation to fasting and two conflicting actions of ghrelin as (1) a stimulator of GH secretion and (2) an appetite-stimulating ‘hunger signal’.

The model has been extensively studied in fish [see 7] and is summarized below.

**Neuroendocrine Model of Catch-Up Growth**

**Overview of the Model**

A fundamental tenet of the neuroendocrine model is that catch-up growth (or hyperanabolism) can only follow a period of catabolism. It is not possible to move directly from a period of normal growth to one of catch-up growth (fig. 1) as endocrine changes that occur during poor growth are required to enable later catch-up growth [7].

**Normal Anabolism**

During normal anabolism (normal growth), GH is secreted from the pituitary at a rate determined by the balance between several factors. Ghrelin, produced systemically in the stomach and locally in the hypothalamus, stimulated GH se-
cretion both directly and indirectly. Leptin, derived from adipose tissues, reduces GH secretion. Ghrelin also acts via neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons to stimulate appetite (orexigenic), while leptin acts on the same neurons to reduce appetite (anorexigenic) [7].

Pituitary-derived GH interacts with receptors on the liver and signals via the Janus kinase/signal transduction and activators of transcription signal (JAK/STAT) pathway to stimulate the production of target genes including IGF-1, ALS (acid labile subunit) and IGFBP-3 (IGF-binding protein 3). These are secreted from the liver and bind to produce the tertiary complex. IGF-1 can affect target tissues (such as muscle and adipose) to stimulate growth via interactions with the IGF-1 receptor and its signaling pathways [7]. The GH/IGF axis therefore produces effects in hepatic and nonhepatic tissues directly via the GH receptor (GHR) and its signaling pathway, and indirectly via IGF-1 and its receptor [7].

Catabolism
During fasting, ghrelin increases as a response to reduced dietary intake, and leptin falls as a response to loss of leptin-producing adipose tissue. This leads to both an increase in appetite (via NPY/AgRP neurons) and an increase in GH

Fig. 1. Neuroendocrine model of normal anabolism, catabolism, and hyperanabolism (catch-up growth). Reproduced from Won and Borski [7].
secretion. Despite this increase in GH, hepatic production (and serum levels) of IGF-1 falls during fasting due to hepatic GH resistance. The basis for GH resistance is complex. Effects on GHR number and function are possible, but much of the effect appears to be postreceptor, probably within the JAK/STAT signaling pathway (see below). Target tissues now act in response to GH to increase production of free fatty acids and support other GH-mediated fasting adaptations. The action of IGF-1 on target tissues is, however, reduced [7]. The switch from hepatic to nonhepatic effects of GH may also be due to increases in GHR in muscle and adipose tissue during fasting.

**Hyperanabolism**

When refeeding occurs, hepatic GH resistance ends and the elevated GH levels result in elevated IGF-1 levels. These elevated levels act on target tissues to produce greater than normal protein synthesis and cell division, and catch-up growth occurs [7]. Gradually, leptin production rises as adipose stores increase, which leads to greater inhibition of central GH production. At the same time, ghrelin secretion by the stomach (and within the hypothalamus) falls and further decreases GH secretion [7].

In this elegant model, hepatic GH resistance is central to fasting adaptation. The rapid reestablishment of hepatic GH sensitivity (and hepatic GH signal transduction) in the face of persisting and prolonged GH secretion (driven by ghrelin) is responsible for catch-up growth following catabolic stresses.

**Hepatic GH Signaling and Resistance**

Hepatic GH resistance can occur in a variety of conditions including malnutrition, protein deficiency, and deficiency of specific nutrients (including zinc, magnesium, vitamin A and vitamin B_6_) [8]. Protein deficiency may also lead to resistance to IGF-1 in target tissues [8].

Fasting leads to hepatic GH resistance by a range of mechanisms, including downregulation of hepatic GHR number and postreceptor effects, for example within the JAK/STAT signaling pathway that mediates many of the effects of GH [8, 9].

**JAK/STAT Signaling and SOCS**

The GHR is a cytokine I receptor and lacks an intrinsic kinase, so it uses the JAK2 to phosphorylate downstream signaling molecules [9]. GH action is mediated via a number of downstream mediators including IRS-1, protein kinase C and STAT proteins (signal transduction and activators of transcription). STAT5
is especially important for GH action. It forms dimers that interact with DNA to upregulate expression of GH target genes including IGF-1, IGFBP-3, ALS, and suppressors of cytokine signaling such as SOCS1, SOCS2, SOCS3, and CIS [cytokine inducible SH2 (Srpi-homolog 2)] [9]. The SOCS proteins are critical negative feedback regulators of GH signaling, and the time courses of production of different SOCS proteins vary and are tissue specific. SOCS proteins inhibit GH signaling via a range of mechanisms including inhibition of JAK2, and by marking JAK2 and GHR for proteolytic degradation [9].

Several of the SOCS proteins appear to be associated with GH resistance during sepsis [10], but their role in GH resistance during fasting is less clear. In rats with IUGR without catch-up growth, hepatic IGF-1 production in response to GH is reduced (i.e. they have hepatic GH resistance), JAK/STAT signaling is decreased, and levels of SOCS and CIS are increased [11]. SOCS proteins are also important negative regulators of IGF-1 signaling via the JAK/STAT pathway, and perhaps also via the ERK and PI3K pathways [12].

However, more evidence suggests that the nutrient-sensitive regulators sirtuin (silent mating type information regulation 2 homolog) type 1 (SIRT1) and fibroblast growth factor 21 (FGF21) have important roles in fasting-induced hepatic GH resistance.

**Sirtuin 1**
Sirtuins are class III deacetylases that require nicotinamide adenine dinucleotide (NAD+) as a cofactor [13]. SIRT1 is the prototypical sirtuin and is involved in the regulation of many transcription factors. SIRT1 is involved in epigenetic deacetylation of histone proteins, and may mediate the effect of calorie restriction on longevity [13]. During periods of malnutrition, NAD+ levels rise and increase the activity of SIRT1 [13]. Low energy levels, and increasing cellular adenosine monophosphate (AMP) concentrations, activate AMP-activated protein kinase (AMPK) and further increase NAD+ and SIRT1 activity [14]. Increased SIRT1 activity leads to deacetylation and inactivation of STAT3 (reducing gluconeogenesis), deacetylation and degradation of CRTC2 (preventing glucagon-stimulated hepatic gluconeogenesis) and deacetylation and degradation of SREBP-1 (reducing lipogenesis and cholesterol synthesis). SIRT1 also deacetylates and activates several transcription factors leading to increased gluconeogenesis (via Fox01 and PGC-1α) and increased fatty acid oxidation (via PGC-1α and peroxisome proliferator-activated receptor-α, PPARα) [13].

SIRT1 also deacetylates and inactivates STAT5 and leads to reduced GHR/JAK/STAT signaling and hepatic GH resistance [8]. SIRT1 knockdowns show elevated hepatic expression of IGF-1, IGFBP-3, ALS and SOCS2 [15], and fail to
develop appropriate GH resistance during fasting [15]. Fasting reduces STAT phosphorylation and acetylation in mice treated with GH, but administration of a SIRT1 antagonist prevents these fasting-induced reductions in acetylated STAT5, and phosphorylated STAT5 were increased back to fed levels [15].

SIRT1 therefore leads to fasting-mediated inactivation of STAT5, and provides a mechanism by which malnutrition (via increased cellular NAD+ and AMP/ATP ratios) can lead to hepatic GH resistance (via inactivation of STAT5).

**Fibroblast Growth Factor 21**

Fasting also leads to increased production of FGF21 under the control of PPARα [16]. PPARα is stimulated by fasting and is responsible for a number of metabolic adaptations including increasing fatty acid oxidation and stimulating ketogenesis [17]. FGF21 is an immediate downstream target of PPARα and is responsible for both increased fatty acid oxidation and increased gluconeogenesis (via PGC-1α) [8]. FGF21 also leads to fasting-induced GH resistance, including downregulation of IGF-1 production in the face of increased GH levels, by reducing phosphorylation (and inactivating) STAT5 [8] via a SOCS2-dependent mechanism [18]. Transgenic mice that overexpress FGF21 have significantly decreased serum IGF-1 concentrations despite elevated GH concentrations [18]. FGF21 transgenic mice also have decreased expression of GH target genes including IGF-1, ALS, IGFBP-1 and SOCS2 [18]. Increased levels of FGF21, either due to overexpression of FGF21 in a transgenic model, or due to pharmacological PPARα activation, lead to similar effects as does fasting, including decreasing hepatic IGF-1 mRNA, decreasing serum IGF-1 protein, decreasing phosphorylation and activation of STAT5 and increasing levels of the JAK/STAT negative feedback regulator SOCS2 [18].

**Relevance to Preterm Infants**

The model combining the neuroendocrine effects of the ghrelin/GH/IGF-1 axis, and fasting-induced hepatic GH resistance (mediated by the nutrient sensors SIRT1 and FGF21) provides an elegant mechanism to explain how adaptations during fasting can allow the development of subsequent catch-up growth (fig. 2). Although evidence in animal models supports such a hypothesis, it is reasonable to ask what evidence exists in humans, and especially in infants.

**GH, IGF-1 and Malnutrition**

Malnutrition, for example in anorexia nervosa, leads to increased GH levels and decreased IGF-1 levels in humans [19]. The elevated GH levels seem to be the result of decreased negative feedback by IGF-1 and a direct effect on the hypothalamus...
In children, GH levels are high in kwashiorkor and fall with treatment, although they may be low in marasmus. However, the effects of nutrition on GH concentration may be misleading, as GH secretion is pulsatile, and intermittent low GH levels (as seen in males) seem to lead to increased phosphorylation and activation of STAT5 compared to more constant levels (seen in females).
Undernutrition leads to decreased IGF-1 levels, increased production of IGF-binding protein 1 (IGFBP-1, which reduces the effect of IGF-1) and decreased IGFBP-3 production (which increases the effect of IGF-1) [22]. These effects combine to reduce IGF-1 action in malnutrition, and the effect on binding proteins may be more marked in protein malnutrition than in energy malnutrition [22].

Preterm growth-retarded infants have higher GH at birth, and lower IGF-1 and IGFBP-3, than appropriately grown preterm infants, consistent with intrauterine GH resistance resulting from intrauterine malnutrition [23].

**Ghrelin in Preterm Infants**

Ghrelin levels are increased in children with protein energy malnutrition (both marasmus and kwashiorkor) [24]. They are higher in SGA than AGA infants at birth [23, 25], and are negatively correlated with birthweight [25]. At 3 months of age, SGA term infants have higher ghrelin levels than AGA or LGA infants [26], and ghrelin levels are positively correlated with weight, length and head circumference gains [26]. At 12 months of age, SGA and AGA term infants had similar ghrelin levels, and both groups demonstrate reductions in serum ghrelin after an i.v. glucose load [27]. However, among SGA infants, those with catch-up growth had higher ghrelin levels (i.e. failed to suppress ghrelin secretion) than did those without catch-up [27]. Ghrelin levels in the SGA infants 10 min after the i.v. glucose load were positively associated with weight and length at 1 year of age, and with the amount of weight catch-up between birth and 1 year [27].

These findings suggest that poor in utero growth leads to increased ghrelin levels, and that persisting high levels at 3 months, or impaired ability to suppress ghrelin at 12 months, are associated with greater catch-up growth. These findings would be consistent with the model of catch-up growth described in figures 1 and 2.

**IGF-1 in Preterm Infants**

IGF-1 concentrations are low in preterm infants and begin to increase when catch-up growth begins to occur [28]. Among 64 preterm infants, IGF-1 concentrations were significantly positively associated with rates of weight gain during the initial growth retardation phase (from birth to the time of the lowest weight SD score) and during the later catch-up growth phase (from the time of the lowest weight SD score to 35 weeks’ corrected gestational age) [28].

IGF-1 concentrations in former preterm infants at term-corrected age are correlated with weight and length gain between birth and term, and the same is seen for IGF-1 concentration at 3 months and weight and length gain between
birth and 3 months, and for IGF-1 concentration at 6 months and weight and length gain between birth and 6 months [29].
However, there is no difference between IGF-1 or IGFBP-3 in the first year of life between term SGA infants who did or did not demonstrate catch-up growth, although IGF-2 was higher in those with catch-up growth [30].

**Conclusions**

The neuroendocrine model and nutritionally mediated hepatic GH resistance provide a compelling mechanism to explain catch-up growth after poor growth caused by nutritional or nonnutritional factors. The model has been well studied in animal models, although more is known about the adaptations and time course of effects associated with the fasting/nutritional insufficiency period than during the catch-up growth period. Although the human data are much more limited, those which are available broadly support the model as a cause of catch-up growth in preterm or small for gestational age infants.

**Disclosure Statement**

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

**References**


