REVIEW

Microbial and nutritional influence on endocrine control of growth

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Abstract

The worrying number of children suffering from undernutrition and consequent stunting worldwide makes the understanding of the relationship between nutritional status and postnatal growth crucial. Moreover, it is now well established that undernourished children harbor an altered microbiota, correlating with impaired growth. In this review, we describe how murine models have been used to explore the functional relationships between endocrine regulation of growth, nutrition and gut microbiota. In numerous Mammalian species, postnatal growth is mainly regulated by the conserved GH/IGF1 somatotrophic axis that acts through endocrine and paracrine pathways, notably enabling longitudinal bone growth. Recent studies have demonstrated that the microbiota effects on growth could involve a modulation of GH and IGF1 circulating levels. Besides, the GH/IGF1 somatotrophic axis may regulate the gut microbiota composition and diversity. Studying the bidirectional relationship between growth hormones and the gut microbiome could therefore help developing microbiota-targeting therapies in order to reduce the long-term consequences of stunting.

Key Words

- ▶ microbiome
- ▶ IGF
- ▶ growth factors
- ▶ linear growth

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Introduction

The growth hormone (GH)/insulin-like growth factor-1 (IGF1) somatotrophic axis plays a crucial role in the regulation of growth. GH is known for its anabolic effects on the intestine, stimulation of catabolism in adipose tissue, as well as bone growth (Jensen *et al.* 2020b). Effects of GH occur independently or in synergy with IGF1 (Yakar & Isaksson 2016, Poinsot *et al.* 2018, Jensen *et al.* 2020b). Interestingly, circulating levels of IGF1 depend on the nutritional status of the organism. Indeed, during an acute phase of protein malnutrition, resulting in stunting, IGF1 secretion is strongly diminished (Fazeli & Klibanski 2014, Schwarzer *et al.* 2016).

In humans, as defined by the World Health Organization, undernutrition triggers stunting (low height-for-age), wasting (low weight-for-height)

or underweight (low weight-for-age) (<https://globalnutritionreport.org/reports/2020-global-nutrition-report/>). Undernutrition has been associated to alterations in the gut microbial communities, correlating with poor growth patterns (Subramanian *et al.* 2014). Moreover, colonization of mouse and pig gnotobiotic models with the microbiota of human undernourished patients reproduces the wasting and stunting phenotype observed in humans (Smith *et al.* 2013, Blanton *et al.* 2016b, Gehrig *et al.* 2019). Although the exact mechanisms underlying such phenotypes remain to be elucidated, expression levels of proteins involved in the GH/IGF1 axis strongly correlate with length-for-age z score (Chen *et al.* 2020).

In the past 15 years, the role of the gut microbiota has been widely studied, expanding into the understanding

of its impact on physiological processes such as growth, endocrine function and regulation of host metabolism. In this review, we explore associations between the gut microbiota, GH/IGF1 somatotrophic axis and systemic growth in mammals. Furthermore, we provide insight into the use of selected microbial strains for the management of undernutrition-related diseases.

Gut microbiota and regulation of mammalian growth

Involvement of the GH/IGF1 axis in growth

The mammalian somatotrophic axis is centrally regulated by GH, which is a 191-amino acid peptide secreted by the anterior pituitary gland. In the intestine, GH activates its receptor (GHR) (Delehay-Zervas *et al.* 1994), inducing proliferation of intestinal stem cells and improving nutrient absorption (Young *et al.* 2019). In the bone, GH regulates chondrocyte multiplication and hypertrophy (Mackie *et al.* 2011). While GH directly influences the growth of several organs (Jensen *et al.* 2020b), its most significant effects on growth are obtained by enhancing the production of IGF1, a potent growth

factor that stimulates growth and metabolism (Yakar & Isaksson 2016). GH secretion is promoted by GH releasing hormone, ghrelin and leptin, while being inhibited by IGF1 and somatostatin (Burgus *et al.* 1973, Carro *et al.* 1997, Kojima *et al.* 1999) (Fig. 1). Somatostatin, ghrelin and leptin are also known for their roles in appetite regulation and their secretion has been linked to the gut microbiota (Karsenty 2006, Pradhan *et al.* 2013).

IGF1 acts via a receptor which is widely expressed in most cell types (excepted hepatocytes) (Bartke *et al.* 2013), leading to the transcription of target genes (Papaconstantinou 2009). IGF1 is essential for growth at two periods: during the embryonic development in a GH-independent manner and during childhood and adolescence in a GH-dependent manner (Netchine *et al.* 2011). Stimulation of IGF1 production by GH elicits growth in two different ways. Indeed, liver-produced IGF1 can act as a hormone, while peripheral production leads to autocrine or paracrine signaling (Mohan & Kesavan 2012). IGF1 stimulates skeletal muscle mass development (Sharples *et al.* 2015) and bone growth by both pathways, since liver-specific deletion of *Igf1* (decreasing circulating

Figure 1

The reciprocal relationship between the GH/IGF1 somatotrophic axis, the gut microbiota and the nutritional status modulates systemic growth. GH (growth hormone) secretion in the pituitary gland is enhanced by GHRH (GH releasing hormone), leptin and ghrelin and inhibited by somatostatin. GH notably promotes intestine and bone growth and promotes IGF1 production in the liver and in other peripheral organs (not shown). IGF1 in turn reduces GH secretion and activates bone growth and skeletal muscle development. In the intestine, the microbiota can modulate IGF1 secretion and therefore bone growth. A possible mechanism for this modulation involves ghrelin inhibition by microbiota-derived short chain fatty acids (SCFA). Microbiota composition is also impacted by the nutritional status (e.g. undernutrition), which also affects IGF1 production. In turn, circulating GH modulates microbiota composition as well as bacteria translocation through the intestinal epithelium. Beyond the GH/IGF1 axis, microbiota could modulate systemic growth by interacting with human milk oligosaccharides (HMO). Created with biorender.com.

IGF1 by 70%) does not impair growth in the first weeks of life (Yakar *et al.* 2002).

IGF1 genetic deficiency is a rare autosomal recessive mutation but, in cases where it has been described, it leads to pre- and postnatal growth retardation and microcephaly. Patients with the mutation can benefit from recombinant IGF1. These observations show that IGF1 signaling is crucial for optimal growth and CNS development.

Gut microbiota influence on GH and IGF1

Interestingly, germ-free mice, which lack a gut microbiota, have impaired growth (Schwarzer *et al.* 2016, Yan *et al.* 2016, Novince *et al.* 2017). Previous work from our lab has shown that germ-free mice have reduced circulating IGF1 and insulin-like growth factor binding protein-3 (IGFBP3, IGF1 major binding protein), as well as reduced *Igf1* and *Igfbp3* expression in the liver (Schwarzer *et al.* 2016). Specifically, when germ-free mice were undernourished with a protein- and fat-depleted diet, they exhibit stronger stunting phenotype than their conventional counterparts, with decreased IGF1 levels and expression of *Igf1* and *Ghr* in the skeletal muscle and liver. Germ-free mice under chronic undernutrition exhibit a resistance to GH signaling, as is the case in undernourished humans (Blanton *et al.* 2016b, Hoffman *et al.* 2017). Moreover, administration of recombinant IGF1 to germ-free mice normalizes weight and bone length, suggesting a direct impact of the gut microbiota on IGF1 secretion (Schwarzer *et al.* 2016).

Yan *et al.* confirmed the link between gut microbiota, IGF1 secretion and bone growth using germ-free mice colonized with the microbiota of conventional mice. Despite no difference in circulating GH when compared to germ-free mice, colonized mice had increased IGF1 secretion. Besides, the effects of the gut microbiota on bone turnover is age dependent. Indeed, after 1 month, the authors observed a decrease both in bone formation and resorption, associated to decreased trabecular bone mass and body weight. However, after 8 months, colonization resulted in increased bone formation and growth (Yan *et al.* 2016). In a similar manner, fecal microbiota transplantation in suckling pigs increases body weight and plasma IGF1, associated to increased presence of *Lactobacillus* sp. and *Faecalibacterium* sp. (Cheng *et al.* 2019).

The precise mechanisms underlying microbial stimulation of the somatotrophic GH/IGF1 axis remain to be elucidated. Microbial by-products such as short-

chain fatty acids (SCFAs), produced by the fermentation of dietary fibers, have been shown to modulate IGF1 and GH secretion (Wang *et al.* 2013, Yan *et al.* 2016). *In vitro*, SCFAs inhibit GH production in bovine anterior pituitary cells, through activation of the cAMP/PKA/CREB pathway (Wang *et al.* 2013). Furthermore, Yan *et al.* showed that SCFAs, when co-administered with antibiotics to deplete the microbiota, resulted in elevation of IGF1 in serum, adipose tissue and liver (Yan *et al.* 2016). One way through which SCFAs may modulate the somatotrophic axis is *via* the secretion of ghrelin, which is a GH secretagogue (Fig. 1). Administration of an oligofructose prebiotic (thus increasing SCFA secretion by the microbiota) results in decreased ghrelin levels in obese individuals (Parnell & Reimer 2009). SCFAs also decrease ghrelin secretion in humans (Rahat-Rozenbloom *et al.* 2017). Furthermore, SCFAs, lactate and bacterial strains including *Bifidobacterium* and *Lactobacillus* are able to attenuate ghrelin-mediated signaling in an embryonic kidney cell line (Hek293a) stably expressing the ghrelin receptor (Torres-Fuentes *et al.* 2019).

Taken together, these data show that the gut microbiota is a potent positive regulator of GH and IGF1 signaling, stimulating host growth and development.

Bidirectional relationship effect of GH and IGF1 on the gut microbiota

A 2016 study by Chen *et al.* explored the role of GH/IGF1 on the gut microbiota community using a female mouse model of anorexia nervosa (i.e. nutrient-restricted mice). When compared to controls, anorexic BALB/c mice showed decreased microbial diversity (Chen *et al.* 2016). When anorexic mice received subcutaneous injections of IGF1, this led to restoration of body weight, accompanied by normalization of the microbiota composition (Chen *et al.* 2016). Furthermore, specific deletion of IGF1 in intestinal epithelial cells in mice decreases proliferation of the intestinal epithelium, along with increased bacterial translocation to the mesenteric lymph node and liver, and alteration of the cecal microbiota of mice (Zheng *et al.* 2018).

A direct role of GH on the gut microbiota of mice came from the study of Ames dwarf mice, a mouse model of hypopituitarism with deficiencies in several pituitary hormones, including GH (Wiesenborn *et al.* 2020). Ames mice at 2 months of age exhibited increased Bacteroidetes/Firmicutes ratio, when compared to WT littermates. Unlike control mice, Ames mice show minor

microbiota shifts when put on caloric restriction. The authors thus concluded that GH deficiency resulted in a distinct microbial composition. However, Ames mice have multiple hormone deficiencies (including TSH and prolactin), so it does not allow the study of GH specifically. Another study by Jensen *et al.* confirmed that GH signaling is associated with altered gut microbial composition. Two mouse models were generated: one with a full knockout of GH (GH^{-/-}) and one with ectopic expression of bovine transgenic GH (bGH) (Jensen *et al.* 2020a). Both mouse models exhibit altered microbiota composition when compared to littermate controls, in opposing directions. GH^{-/-} mice have reduced abundance of proteobacteria, campylobacteria and actinobacteria, whereas bGH mice exhibit an increase in those phyla. In line with that, several bacterial metabolic functions, such as SCFA, folate and heme B biosynthesis, also correlate with the presence of GH. Finally, GH is associated with altered intestinal length and morphology.

Overall, these studies show that there is a bidirectional relationship between gut microbiota and GH/IGF1 signaling (Fig. 1).

Gut microbiota and altered growth

Juvenile microbiota and malnutrition

Nutrient deficiency, particularly dietary protein, leads to growth retardation during pregnancy (Gluckman & Pinal 2003). Stunting (as defined in the introduction) is characterized by reduced secretion of IGF1, but increased GH levels characteristic of a GH resistant state. The 2020 Global Nutrition Report (<https://globalnutritionreport.org/reports/2020-global-nutrition-report/>) estimates that over 150 million children aged 0–59 months (representing 22.2% of children globally) are stunted. The first 1000 days of life are crucial for growth. After that time, stunting is usually irreversible and leads to growth delay in adulthood (Shrimpton *et al.* 2001).

Decreased microbial diversity and delayed microbiota maturation are well-described features of severe acute malnutrition (SAM) (Blanton *et al.* 2016a). Microbiota immaturity correlates with childhood stunting and wasting (Subramanian *et al.* 2014, Blanton *et al.* 2016b) and is only partially improved by nutritional intervention, suggesting that altered microbial composition may contribute to the low success rates of nutritional rehabilitation programs. Transplantation of stool from Malawian twins discordant for kwashiorkor (a severe form of protein malnutrition) into germ-free recipient mice maintained on a low-protein,

low-fat diet showed that mice receiving fecal microbiota from severely malnourished children lose more weight than mice colonized with stool from healthy siblings (Smith *et al.* 2013).

Chen *et al.* studied the microbiota of stunted Bangladeshi children, who had not benefited from a nutritional intervention. Bacterial taxa from duodenal aspirates were negatively correlated with linear growth and positively correlated with inflammation. Moreover, colonization of germ-free mice with the duodenal aspirates led to enteropathy, showing a causal relationship between growth stunting and components of the duodenal microbiota (Chen *et al.* 2020).

Microbiota-targeting therapies

Despite evidence that malnutrition severely alters the microbial community of the gut, interventional trials using microbiota-targeting therapies have not shown any significant improvement on the growth phenotype. For instance, administration of a synbiotic product (containing several bacteria from the Lactobacillales order in combination with prebiotics) did not improve SAM outcomes in Malawian hospitalized children when compared to placebo treatment (Kerac *et al.* 2009). In the same manner, administration of a probiotic formula containing *Lactocaseibacillus* (formerly *Lactobacillus*) *rhamnosus* GG ATCC 53103 and *Bifidobacterium animalis* ssp. *lactis* Bb12 to children with SAM increases microbiota diversity but does not improve nutritional recovery and weight gain upon refeeding (Castro-Mejía *et al.* 2020).

The choice of the bacterial strains used in these trials was empiric (for a discussion on the matter, see Edwards *et al.* 2020). However, restoring the growth function upon severe malnutrition requires targeting an agent that goes beyond modification of the microbiota, which involves understanding the mechanisms underlying the interactions between the microbial strain(s) and the host.

Efforts have been made in this direction to identify growth-stimulating bacteria in preclinical models. Several studies have confirmed the capacity of a single bacteria to stimulate the GH/IGF1 somatotrophic axis, a finding conserved among animal species as evolutionary distant as insects and mice (Shin *et al.* 2011, Storelli *et al.* 2011, Schwarzer *et al.* 2016). Particularly, administration of the specific strain of *Lactobacillus plantarum* WJL to germ-free mice on a protein- and fat-depleted diet abrogates GH resistance and improves IGF1 and IGFBP3 secretion, resulting in overall growth (Schwarzer *et al.* 2016). Importantly, this phenotype is strain-specific, since a

second strain of *L. plantarum* did not confer such effects on growth. Similarly, oral supplementation of three different strains of *L. plantarum* to broiler chickens exposed to heat stress led to improved growth performance and increased expression of hepatic *Igf1* (Humam *et al.* 2019).

The main challenge to translating this approach to malnourished children is the incomplete knowledge of microbiota composition among large populations and of its variations between healthy and malnourished kids (who also differ in genetics, diets, and lifestyle). Additionally, probiotics-based approaches need to be monitored carefully, given that the immune system of severely malnourished children is constantly challenged.

Dietary approaches might thus represent a promising therapy to target the stunted microbiota. Gehrig *et al.* monitored metabolic parameters in healthy Bangladeshi children and those recovering from SAM, as they transitioned to moderate malnutrition with persistent microbiota immaturity. Diets were designed using pig and mouse models to drive the microbiota into a mature post-weaning state, expected to stimulate growth. These microbiota-directed complementary food (MDCF) prototypes were tested in gnotobiotic mice and piglets with immature microbiota (from children recovering from SAM). The authors determined the most efficient MDCF in a randomized double-blind controlled feeding trial, which drove plasma proteome profiles toward those of healthy children (Gehrig *et al.* 2019). In particular, this MDCF increased the abundance of age- and growth-discriminatory microbial taxa. An ongoing clinical trial will determine if these microbiota changes translate into stimulation of growth in stunted children (Mostafa *et al.* 2020).

Another approach has been the study of the properties of human milk oligosaccharides (HMOs) in the context of juvenile growth. HMOs act as prebiotics that help colonization of the infant gut with bacterial taxa (such as *Bifidobacterium* spp.) associated to beneficial functions on growth and immune function (Charbonneau *et al.* 2016). It is noteworthy that HMOs are significantly depleted in breast milk of Malawian mothers with children suffering from SAM. Germ-free mice were colonized with a microbial community characteristic of stunted Malawian children and then fed with prototypic Malawian diet with or without supplementation with HMOs. Gnotobiotic mice fed HMOs showed increased lean mass gain, associated to increased bone volume and density. In a similarly designed study, Cowardin *et al.* colonized germ-free mice with the microbiota of stunted infants and fed a diet mimicking that consumed by the microbiota donor.

Adding purified bovine sialylated milk oligosaccharides to the diet resulted in reduced osteoclastogenesis while increasing femoral trabecular bone volume and cortical thickness (Cowardin *et al.* 2019). Interestingly, the addition of milk oligosaccharides did not increase circulating IGF1, suggesting that stimulation of growth by the gut microbiota can also happen independently of GH/IGF1 pathway.

Such advances in the clinical literature regarding microbiota-directed therapies for malnutrition represent a promising strategy to tackle this worldwide problem. The first intention when treating malnutrition is refeeding but as pointed before, SAM can have long-lasting deleterious consequences despite nutritional restoration. Thus, understanding how the gut microbiota regulates growth and IGF1 secretion will help develop robust strategies with selected bacterial strains and/or prebiotics in the management of malnutrition and stunting.

Conclusion

The GH/IGF1 somatotrophic axis is central during mammalian development through its influence on the growth of numerous organs. Studies in germ-free mice under normal and depleted diet have demonstrated the ability of the gut microbiota to directly modulate IGF1 circulating levels. The idea that a bidirectional relationship between the GH/IGF1 axis and the gut microbiota could exist emerged from studies in GH^{-/-} mice demonstrating the ability of GH signaling to modulate the gut microbiota composition and intestinal physiology. Undernutrition has been associated with decreased microbial diversity and delayed microbiota maturation. Thus, microbiota interacts with both nutrition and the GH/IGF1 axis. Further research needs to be conducted to understand to what extent this tripartite relationship regulates systemic growth.

In the context of undernutrition, the first line of treatment should of course be refeeding with proper macronutrient balance. However, since interventional studies have shown this is not enough to fully counteract the deleterious effects of protein depletion in early life, microbiota-targeting therapies that allow not only microbiota maturation but also growth reestablishment could be promising treatments for undernourished children. Understanding the molecular mechanisms governing growth hormones-microbiota interactions using preclinical animal models is thus required. This would help identify promising probiotic candidates and therefore develop therapeutic strategies for stunted

children. Despite a putative function of microbiota-derived short-chain fatty acids in inhibiting ghrelin secretion and thus GH production, the exact molecular mechanisms underlying the effects of microbiota on growth remain poorly understood. Notably, microbiota could stimulate growth independently from the GH/IGF1 axis through interactions with human milk oligosaccharides.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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