

SDS is greater for those who were born AGA. As noted by the authors, the study was retrospective and it would be important to perform prospective studies on the children born SGA. Performance of these studies on the AGA children with short parents might prove more difficult, but the information to be gathered from such a study might be extremely important in understanding the auxiological changes that occur in these children, and might lend support to therapies for improving final adult height.

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Second Editor's Comment: The body weight and growth progression of patients with FSS with or without constitutional growth delay (CGD) was studied by Dr. Vaquero-Solans and me.¹ The linear growth in infancy was similar in both groups of patients. Infants with FSS and CGD showed a sharp parallel fall from the 50th percentile to -1 SD by 3 months of age and a more gradual, but steady, deterioration in length to -2 SD between 3 to 27 months of age. The z scores of height for age remained 2.0 – 2.5 SD below the mean until 12 years of age. In contrast, the body weight progression differed among the 2 types of patients. The CGD patients exhibited a marked impairment

in body weight gain as compared with the FSS. Patients with CGD had body weight deficits for stature, whereas the FSS patients did not. The differences were more marked during infancy. The CGD patients attained an appropriate body weight for height by 9 to 10 years of age, whereas the FSS patients presented body weight excess after 4 years of age and remained progressively overweight until 12 years of age. The catch-down pattern of growth in CGD patients during infancy has been observed by others.² The growth data of SGA and AGA infants in the paper by Völkl et al was similar to the growth exhibited by FSS patients, though they did not assess bone development or weight and height progression after 4 years of age. The pattern of growth and weight gain during infancy and childhood has become more important as it may set the stage for obesity and adult-onset disease.^{3,4}

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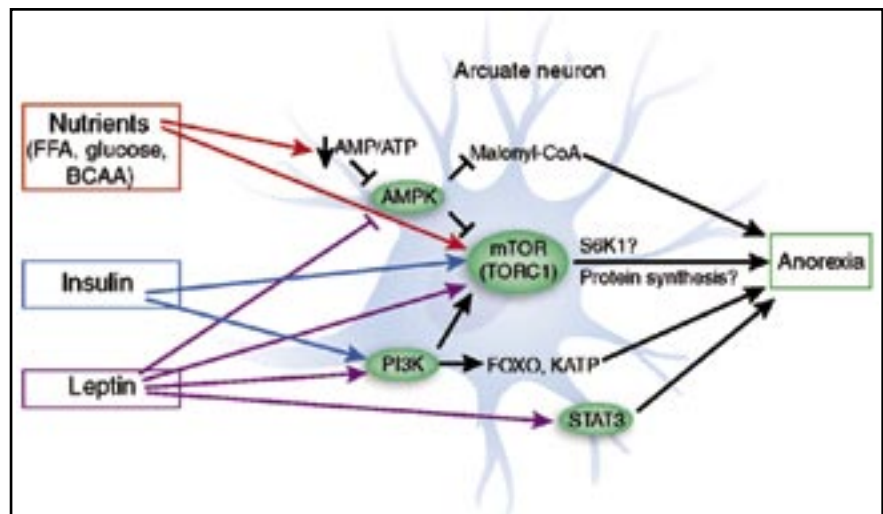
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Interleukin Deficiency Leads To Hyperphagia, Obesity, and Insulin Resistance

Serum concentrations of interleukin 18 ([IL-18] OMIM 600953, chromosome 11q22.2-q22.3), an interferon- γ inducing factor that augments natural killer cell activity and perhaps contributes to chronic inflammatory disorders such as Crohn's disease, are increased in patients with obesity, type 2 diabetes mellitus, and polycystic ovarian syndrome. Interleukin-18 is synthesized and secreted by hepatic Kupffer cells and macrophages. The biologic effects of IL-18 are mediated by its binding to a specific cytokine receptor (IL-18R1; OMIM 604494, chromosome 2q12) and receptor accessory protein (IL-18RAP; OMIM 604509, chromosome 2q12). The biologic activity of IL-18 is inhibited by binding to an IL-18-binding protein ([IL-18BP] OMIM 604113, chromosome 11q13) which prevents the interaction of IL-18 with IL-18R1.

Netea et al demonstrated in the mouse that loss ("knock out") of IL-18 (*IL-18^{-/-}*), or its receptor (*IL-18R^{-/-}*), or excessive ("knock in") production of *IL-18bp* (thus neutralizing endogenous IL-18) results in hyperphagia and obesity associated with hyperinsulinemia and insulin resistance primarily confined to muscle



Converting metabolic signals into anorectic (appetite-suppressing) responses in the hypothalamus. Major classes of anorectic signals in the hypothalamus include nutrients such as free fatty acids (FFA), glucose, leucine and other branched-chain amino acids (BCAA), and hormones such as insulin and leptin. Cota et al¹ show that BCAA potentially activates signaling through the mTOR complex (TORC)-1. FFA and glucose may also regulate TORC1 in the arcuate nucleus, either directly or indirectly (via cellular AMP/ATP levels and AMPK activity). The regulation of cellular malonyl-coenzyme A levels may mediate a component of feeding control by AMPK in parallel with AMPK effects on mTOR. In addition to potentially regulating TORC1 indirectly through the inhibition of AMPK, insulin and leptin may also control mTOR via the PI3K or other pathways. Regulation of FOXO-dependent transcription and ATP-dependent potassium (KATP) channels probably also contributes to PI3K-dependent anorexia. Activation of STAT3-dependent transcription by leptin is a crucial short- and long-term regulator of feeding. Although the mediators of TORC1-dependent anorexia are not clear, S6K1 and downstream events such as protein synthesis are likely to be involved.

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and adipose tissues, hyperglucagonemia, hyperglycemia and impaired glucose tolerance, increased hepatic glucose output, hyperlipidemia, and vascular atherosclerosis. Thus, *IL-18*^{-/-} mice had characteristics of metabolic syndrome. In *IL-18*^{-/-} mice, relative to wild-type (wt) mice, body weight was normal at 3 months of age but substantially elevated by 6 months, and became progressively greater thereafter. The increased weight of the *IL-18*^{-/-} mouse was due to excessive caloric intake and augmented fat accumulation, while basal metabolic rate remained normal. Peripheral administration of leptin and central injection of recombinant IL-18 decreased appetite; peripheral administration of IL-18 restored glucose homeostasis in the *IL-18*^{-/-} mouse. The increase in hepatic glucose production in the *IL-18*^{-/-} mouse was due to decreased phosphorylation of the transcription factor—signal transducing and activation of transcription (STAT)3—that resulted in accentuated gluconeogenesis due in part to increased expression of phosphoenolpyruvate carboxykinase (PEPCK-1). The investigators concluded that IL-18 is another component of the complex of factors that regulate appetite and energy metabolism.

Netea MG, Joosten LA, Lewis E, et al. Deficiency of interleukin-18 in mice leads to hyperphagia, obesity and insulin resistance. *Nature Med.* 2006;12:650–656.

Editor's Comment: *To the enlarging list of anorexigenic factors (insulin, leptin, α -MSH, cocaine and amphetamine regulated transcript [CART], branched chain amino*

acids, and other nutrients) that regulate appetite and energy expenditure, IL-18 may now be added. One could speculate that an analogue of this cytokine might be an effective therapeutic agent for the management of patients with obesity and/or metabolic syndrome. Recent studies have further defined cellular mechanisms involved in appetite regulation. The serine-threonine kinase mTOR (mammalian target of rapamycin) has been identified as a critical regulatory factor in the integration of peripheral hormonal and nutritional (glucose, fatty acids, amino acids) signals (Figure) that decrease appetite.^{1,2} Leptin, insulin, and various nutrients suppress appetite in part by activating mTOR. This protein is a component of the multi-protein complex TORC1 that senses energy availability; when energy is sufficient, TORC1 permits cell growth and enables leptin production by the white fat cell. The TORC1 is particularly active in the arcuate nucleus, the site in which the central regulation of energy balance is present. Leptin also decreases appetite and energy utilization by inhibiting synthesis of orexigenic agouti-related peptide (Agrp) in the arcuate nucleus, an activity mediated through phosphatidylinositol 3 kinase (PI3K) but antagonized by the forkhead box-containing protein of the O subfamily (FOXO1), a DNA binding protein.³

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Insulin and Sulfonylureas in Diabetic Patients with Kir6.2 Mutations

Neonatal diabetes mellitus is a rare disorder and about half of those diagnosed before 6 months of age develop permanent diabetes. The most frequently identified genetic cause is related to heterozygous activating mutations in the *KCNJ11* gene encoding the Kir6.2, a subunit of the ATP-sensitive potassium (K_{ATP}) channel. The activity of this channel in the pancreatic beta cell regulates insulin secretion. These activating mutations cause 30% to 58% of the cases of diabetes mellitus diagnosed in infants. Diabetes results from a failure of this channel to close in response to increased intracellular ATP, leading to impaired insulin secretion. Sulfonylureas, a class of drugs used to treat type 2 diabetes mellitus, close this potassium channel by an ATP-independent route, causing insulin secretion. Thus, this drug represents an alternative therapy to insulin in these patients. The first cases treated with sulfonylureas were reported 2 years ago; this study by Pearson et al is the first to assess the sustained response to sulfonylureas in a large cohort of patients who were initially treated with insulin.

A total of 49 consecutive patients who had been diagnosed at less than 6 months of age with Kir6.2 mutations were switched from insulin to sulfonylurea therapy. An adequate dose of sulfonylureas was defined

as a dose of glyburide (also known as glibenclamide) of at least 0.8 mg/kg/day. The change was considered to be successful if the patient was able to stop insulin treatment completely. Additionally, insulin secretory responses were assessed in subgroups receiving intravenous or oral glucose, a mixed meal, or intravenous glucagon before and after treatment with glyburide.

Switching was successfully accomplished in 44 patients regardless of the type of sulfonylurea used, suggesting a class effect. The oldest patient was 36 years of age and the youngest was 3 months of age. The mean glycated hemoglobin level improved in all subjects and fell from 8.1% during insulin therapy to 6.4% after a mean of 12 weeks of sulfonylurea treatment and cessation of insulin. The initial improvement was sustained in the 12 patients who were insulin-independent for more than one year. The longest duration of insulin independence was 2.0 years, with a glycated hemoglobin level of 5.7%.

Switching to sulfonylureas was unsuccessful in only 5 patients (10%). Of these patients, 4 (80%) had severe neurological features, including severe developmental delay, epilepsy, and neonatal diabetes, known as DEND syndrome. These neurological features occurred in only 6 patients (14%) who were successfully treated with