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REVIEW ARTICLE

Interactions between GH, IGF-I, Glucocorticoids, and Thyroid Hormones during Skeletal Growth

HELEN ROBSON, THOMAS SIEBLER, STEPHEN M. SHALET, AND GRAHAM R. WILLIAMS

Department of Clinical Research [H.R.], Department of Endocrinology [S.M.S.], Christie Hospital National Health Service Trust, Manchester, U.K.; University Children's Hospital, University of Leipzig, Leipzig, Germany [T.S.]; IC Molecular Endocrinology Group, Division of Medicine and MRC Clinical Sciences Centre, Faculty of Medicine, Imperial College School of Science Technology and Medicine, Hammersmith Hospital, London, U.K. [G.R.W.]

ABSTRACT

Linear growth occurs during development and the childhood years until epiphyseal fusion occurs. This process results from endochondral ossification in the growth plates of long bones and is regulated by systemic hormones and paracrine or autocrine factors. The major regulators of developmental and childhood growth are GH, IGF-I, glucocorticoids, and thyroid hormone. Sex steroids are responsible for the pubertal growth spurt and epiphyseal fusion. This review will consider interactions between GH, IGF-I, glucocorticoids, and thyroid hormone during linear growth. It is well known from physiologic and clinical studies that these hormones interact at the level of the hypothalamus and pituitary. Interacting effects on peripheral tissues such as liver are also well understood, but we concentrate here on the epiphyseal growth plate as an important and newly appreciated target organ for convergent hormone action. **(*Pediatr Res* 52: 137–147, 2002)**

Abbreviations

5'-DI, 5'-iodothyronine deiodinase
FGF, fibroblast growth factor
FGFR, fibroblast growth factor receptor
GC, glucocorticoid
GHR, GH receptor
GR, glucocorticoid receptor
HSPG, heparan sulfate proteoglycan
11βHSD, 11β-hydroxysteroid dehydrogenase
IGF-IR, IGF-I receptor
IGFBP, IGF binding protein
Ihh, Indian hedgehog
JAK-2, Janus-activated kinase-2
PTHrP, PTH-related peptide
RTH, resistance to thyroid hormone
STAT, signal transducers and activators of transcription
T3, 3,5,3'-L-triiodothyronine, thyroid hormone
T4, L-thyroxine TR, thyroid hormone receptor

PREPUBERTAL GROWTH

GH and IGF-I. Disruption of the GH/IGF-I axis causes an IGF-I deficiency syndrome that is characterized by growth retardation due to failure of GH production or GH resistance. Failed production results from genetic abnormalities (1–4), hypothalamic or pituitary malformations (5), trauma, inflammation, tumors (6), radiation (7), psychosocial disorders (8), and neurosecretory abnormalities (9). GH resistance results from GHR mutations (10), postreceptor signaling defects, and defects of IGF-I synthesis, or may be secondary to chronic disease, malnutrition (11), or circulating GH or GHR antibodies. Defects in genes encoding GH (2), the Pit-1 transcription factor (1), and GH releasing hormone receptor (4) cause severe GH deficiency, but the associated growth retardation results from predominant postnatal growth failure. Similarly, mild growth retardation is apparent at birth in GH insensitivity and other causes of congenital GH deficiency. In contrast, intrauterine growth retardation was severe in the single reported case of IGF-I gene deletion (12), suggesting that IGF-I exerts

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Correspondence and reprint requests: G.R. Williams, Imperial College Molecular Endocrinology Group, 5th Floor, Medical Research Council Clinical Sciences Centre, Hammersmith Hospital, Du Cane Road, London W12 0NN, U.K.; e-mail: graham.williams@ic.ac.uk
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major influences during fetal growth. In neonates, growth failure due to GH deficiency is established by 6 mo and may result in short stature 3 or 4 SD below the mean.

Glucocorticoids. Excess glucocorticoids enhance bone resorption, inhibit osteoblast activity, and reduce bone matrix production to cause growth retardation in children (13, 14) and osteoporosis in adults (15). These effects are related to duration of GC excess and occur irrespective of its etiology. Long-term GC excess also interferes with GH pulsatility and decreases total GH secretion by elevating hypothalamic somatostatin tone (16). Nevertheless, growth impairment due to excess GC is associated with normal circulating GH and IGF-I concentrations, suggesting there is peripheral insensitivity to both hormones, an interpretation supported by the requirement for pharmacological doses of GH, which only partially overcome growth retardation in GC excess (17). Furthermore, GC inhibit calcium absorption and reabsorption in the gastrointestinal tract (18) and kidney (19), and may cause secondary hyperparathyroidism. They induce sex hormone deficiency and alter vitamin D metabolism, leading to deleterious effects on growth and skeletal integrity (20). Growth retardation resulting from excess GC is dose-related, may be severe, and is difficult to treat. Exposure to excess hormone should be corrected early or GC treatment can be limited by intermittent dosing, although this may not prevent bone loss (21). Treatment with GH in the presence of continuing GC therapy or after correction of GC excess often fails to achieve target height, suggesting that deleterious effects of GC on the growth plate are persistent and resolve only partially after steroid withdrawal (22).

Thyroid hormones. Childhood hypothyroidism causes growth failure, but other features of adult hypothyroidism are often absent. Growth failure may develop insidiously, but is severe once established. In untreated hypothyroidism, complete growth arrest occurs with delayed bone age, epiphyseal dysgenesis, and immature body proportion (22). A proportion of patients with T3 resistance, caused by mutant T3 receptor β proteins, suffer from growth retardation and developmental abnormalities of bone (23) that reflect tissue hypothyroidism. T4 replacement induces rapid catch-up growth, although this may be incomplete because bone age advances faster than the increase in height (24). The deficit in final height after treatment correlates with the duration of hypothyroidism. Catch-up growth may be especially compromised if treatment is required at or around the onset of puberty, when it may be appropriate to treat with lower T4 replacement doses and add therapy to delay puberty and epiphyseal fusion. In accord with this, childhood thyrotoxicosis causes accelerated growth and advanced bone age, which may lead to craniosynostosis, premature growth plate closure, and short stature (24, 25).

GROWTH PLATE STRUCTURE

The epiphyses and metaphyses of long bones originate from independent ossification centers and are separated by a growth plate (Fig. 1*A*). The growth plate becomes ossified after puberty and epiphyseal fusion occurs. In the normal growth plate, immature cells lie toward the epiphysis, with mature chondrocytes adjacent to the primary spongiosum, which lies in continuity with the bone marrow. The reserve zone contains small clusters of progenitor cells within a matrix of type II collagen and proteoglycans. Flattened chondroblasts undergo clonal expansion in the proliferative zone and form organized columns. Proliferative chondrocytes secrete matrix and enlarge as they mature. The largest proliferative cells differentiate to form hypertrophic chondrocytes, which secrete type X collagen. Hypertrophic chondrocytes enlarge by five times their volume and eventually undergo apoptosis to leave lacunae separated by cartilaginous septae that become calcified and form a scaffold for new bone formation (Fig. 1*B*). New blood vessels enter from the primary spongiosum and osteoblasts invade from the bone marrow to lay down trabecular bone and complete the endochondral ossification process. These processes have been reviewed in detail (26, 27).

Recent experiments have established that chondrocyte differentiation during bone development and growth is regulated by a negative feedback loop involving the paracrine factor Ihh (28, 29) and PTHrP (30, 31). Ihh is secreted by prehypertrophic chondrocytes and stimulates production of PTHrP from the periarticular region of the epiphysis (28–32). PTHrP acts on PTHrP-receptor expressing prehypertrophic chondrocytes to maintain cell proliferation, reduce Ihh production, and complete a feedback loop in which PTHrP exerts a negative signal that inhibits hypertrophic differentiation (Fig. 2). The physiologic importance of other autocrine, paracrine, or systemic factors to influence bone formation *via* this pathway must also now be considered with the demonstration that retinoic acid stimulates Ihh expression in primary cultured growth plate chondrocytes (33), our finding that expression of growth plate PTHrP and PTHrP receptor mRNA is sensitive to thyroid status *in vivo* (34), and evidence that bone morphogenetic proteins influence expression of its signaling components (35, 36). The importance of this feedback loop has also been demonstrated in man by the rare inherited conditions Jansen's metaphyseal and Blomstrand chondrodysplasias, which are characterized by delayed or advanced endochondral ossification, respectively. Jansen's metaphyseal dysplasia results from constitutively active PTHrP-receptors (37), whereas, in Blomstrand chondrodysplasia, the mutated receptor is nonfunctional (38), thus confirming the requirement for correct PTHrP signaling in the programming of human endochondral ossification.

HORMONE ACTION IN SKELETAL CELLS

GH and IGF-I. The growth-promoting actions of GH and IGF-I have been reviewed recently (39). The original somatomedin hypothesis (40) proposed that GH stimulates hepatic production of IGF-I, which in turn promotes growth directly at the epiphyseal plate. Subsequently, the dual somatomedin hypothesis (41) proposed that local IGF-I promotes chondrocyte maturation and longitudinal growth in an autocrine/paracrine fashion (42), while hepatic IGF-I exerts feedback control on pituitary GH secretion (43). However, this does not account for the additional direct actions of GH on bone. Thus, GH induces unilateral epiphyseal growth when injected (44) or infused locally (45) and promotes chondrocyte proliferation *in vitro* (46). Furthermore, IGF-I neutralizing antibodies block the proliferative effects of GH (17), to suggest an additional local

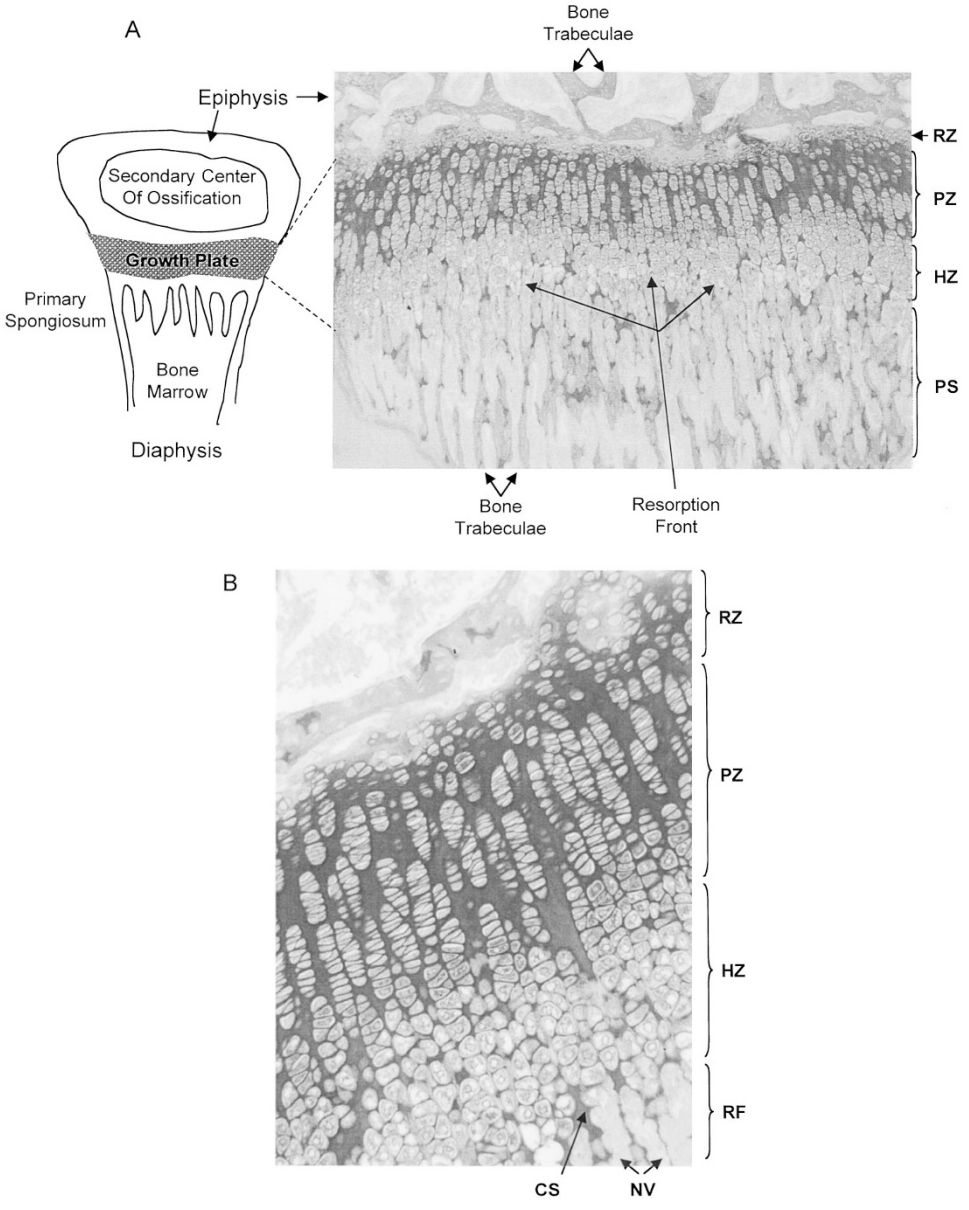

Figure 1. Structure of the growth plate. (*A*) Diagram of the growth plate in relation to the upper end of a long bone alongside a section of normal growth plate from a 3-wk-old mouse stained with Alcian blue/van Gieson. *RZ* indicates reserve zone; *PZ*, proliferative zone; *HZ*, hypertrophic zone; *PS*, primary spongiosum. The resorption front is the region where cartilage is ossified by invading osteoblasts. (*B*) High-power view of the growth plate. *RF* indicates resorption front. Small, rounded progenitor cells are present in the RZ, columns of flattened proliferating chondrocytes in the RZ, and enlarging hypertrophic cells in the HZ. Cartilaginous septae (*CS*) are seen in the RF, where osteoblasts invade *via* new vessels (*NV*) that invade from the underlying bone marrow.

somatomedin hypothesis, in which GH actions in chondrocytes are mediated by local IGF-I production (Fig. 3).

Infusion of GH or IGF-I shortens stem and proliferating cell cycle times in the growth plate of hypophysectomized rats and decreases the duration of the hypertrophic differentiation phase, with GH being more effective. GH or IGF-I treatment restores mean cell volume and height, but the growth rate is not normalized by either hormone (47). The rats in this study were hypothyroid, and treatment with infused GH or IGF-I for 8 d did not alter thyroid status. Furthermore, the GC axis was not investigated, and it is likely, therefore, that incomplete recovery after GH or IGF-I replacement resulted from uncorrected hypothyroidism and altered GC signaling. Nevertheless, it was concluded that both IGF-I and GH stimulate growth plate chondrocytes at all stages of differentiation, and that GH actions are mediated predominantly *via* IGF-I but also by direct IGF-I independent effects (47). This has since been described as the "dual effector theory" (41), in which GH acts selectively on stem cells but also promotes chondrocyte proliferation *via* local IGF-I production. IGF-I is proposed then to stimulate clonal expansion of proliferating cells in an autocrine/paracrine manner (48).

GHR and IGF-IR are expressed at all stages of growth plate chondrocyte differentiation in many species (47, 49–54) (Fig. 2). Distribution of the GHR varies with age. It is only present in hypertrophic chondrocytes in neonatal rabbits, but becomes more widespread at 20–50 d and appears in reserve zone and proliferative cells. In 3- to 8-mo-old humans, GHR protein is

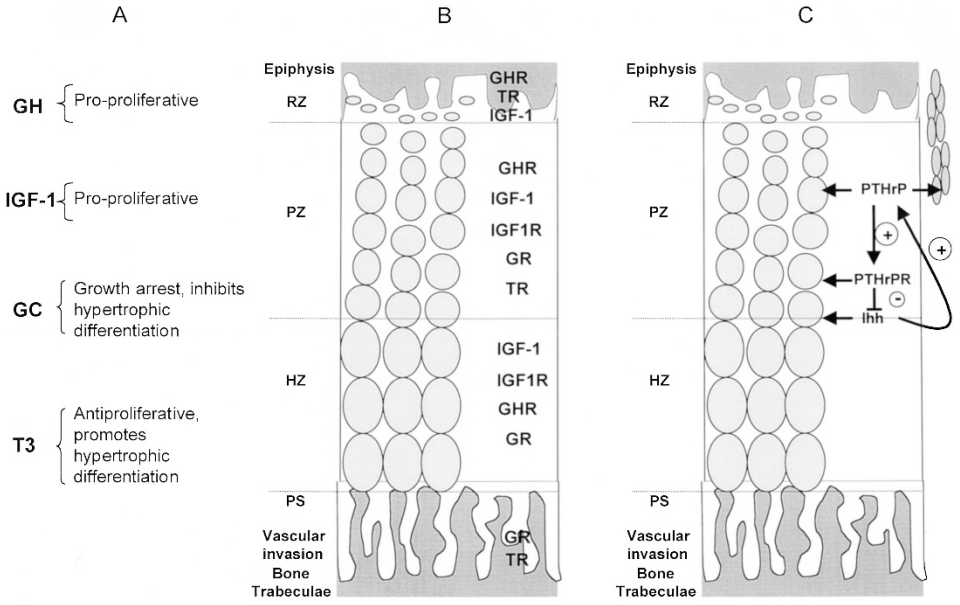

Figure 2. Hormone action in the growth plate. *A* indicates the effects of GH, IGF-I, GC, and T3 on growth plate chondrocytes. *B* demonstrates regions of the growth plate in which IGF-I and GHR, IGF-IR, GR, and TR are expressed. *RZ* indicates reserve zone; *PZ*, proliferative zone; *HZ*, hypertrophic zone; *PS*, primary spongiosum. *C* shows the Ihh/PTHrP feedback loop, which regulates the pace of endochondral ossification. Ihh is secreted by prehypertrophic chondrocytes and acts on perichondrial cells during development, or on proliferative chondrocytes during postnatal growth, to stimulate release of PTHrP. PTHrP acts on PTHrP receptors (*PTHrPR*) that are expressed in uncommitted prehypertrophic chondrocytes to delay differentiation and maintain cell proliferation.

expressed in proliferative and hypertrophic chondrocytes and immunostaining has been documented in fetal growth plates of 12–16 wk gestation.

GH binding to its receptor causes recruitment and activation of the receptor-associated JAK-2, which in turn activates members of the family of STAT (55). In particular, the growth retardation described in *STAT5ab*$^{-/-}$ mice suggests that STAT5 proteins largely mediate GH effects on bone growth (56), although a more recent study of GHR null mice suggested that bone homeostasis in these animals could be restored by IGF-I *via* a pathway that was independent of STAT5 (57). Importantly, FGF, which also play a major role in both endochondral and intramembranous ossification (58–60), have been shown to activate the STAT1 signaling pathway and mediate the inhibitory effects of FGF on chondrocyte proliferation that are mediated mainly by FGFR3 (61, 62). These results indicate an essential role for STAT signaling pathways in the control of chondrocyte proliferation during endochondral bone formation in the growth plate and suggest a point of convergence for interaction between GH and FGF signaling during growth.

IGF and IGFBP are also expressed in growth plate chondrocytes. In fetal bovine growth plates, IGF-I and IGF-II expression occurs mainly in proliferating chondrocytes, although others have identified IGF-I mRNA in hypertrophic and proliferating chondrocytes or in all zones of the postnatal rat growth plate (47, 63). IGF-I has important direct effects on proteoglycan synthesis and cell proliferation, however, these actions are modulated by noncovalent associations between IGF-I and IGFBP that limit the bioavailability of IGF-I. Furthermore, a range of factors, including IGF-I, IGF-II, insulin, and transforming growth factor β1, differentially modulate the expression and release of IGFBP from cultured fetal tibial growth plate chondrocytes, suggesting a role in the control of local IGF action (64). Surprisingly, other factors that are involved in the regulation of chondrogenesis, including GH, FGF2, and T4, had no effect on IGFBP expression and release in these experiments. High concentrations of IGFBP have also been associated with inhibition of IGF activity and impairment of longitudinal growth in children with chronic renal failure, although a recent study demonstrated differential effects of IGFBP to either stimulate or inhibit IGF-I-induced chondrocyte proliferation, depending on whether they were present as intact molecules or proteolysed fragments (65). This is further complicated by a recent report concerning mesenchymal chondrogenic RCJ3.1C5.18 cells, in which the antiproliferative effects of IGFBP3 were influenced by the stage of chondrocyte differentiation (66). IGFBP-3, -4, and -5 are expressed in proliferating cells and hypertrophic chondrocytes, whereas IGFBP-2 expression occurs throughout the growth plate (50), and IGFBP-1 inhibits the growth-promoting effects of IGF-I and GH in the growth plate in hypophysectomized rats (67). Taken together, these studies indicate that IGF-I action in bone is subject to complex and subtle regulation of its bioavailability by locally expressed IGFBP that are secreted in varying combinations and concentrations.

The activity of IGFBP has been shown further to be differentially regulated by GC (68), an observation that may be relevant to the growth-inhibiting effects of GC. Thus, dexamethasone inhibited IGFBP-5 expression, a potentiator of IGF-I action in chondrocytes (69, 70), but up-regulated IGFBP-3 mRNA and protein, which has been reported by some (71), but not others (72), to have an inhibitory effect on IGF-I action. Despite the *in vivo* and *in vitro* studies that have addressed the regulation of IGFBP by GC, the results have varied considerably between IGFBP, the types of cells studied, and the experimental conditions. Another level of interaction

that deserves consideration in this context is the effect of IGF-I on matrix proteoglycan synthesis. As indicated above, this may modulate IGFBP availability in the growth plate. Additionally, structural modifications to HSPG within the growth plate are likely to impact on FGF/FGFR signaling because binding of FGF to its receptor requires heparan sulfate (73, 74) and altered expression and structure of HSPG modulates FGFR signaling in a ligand- and receptor-specific fashion (75, 76). Furthermore, matrix HSPG act as a reservoir for delivery of FGF, indicating that modulation of matrix proteoglycan secretion and structure is likely to play an important role in dictating growth plate chondrocyte responses to both the IGF/IGFBP and the FGF/FGFR signaling pathways. Regulation of chondrocyte matrix secretion and proteoglycan structure by systemic hormones such as glucocorticoids (77, 78) and T3 (34) adds further complexity to the convergence of systemic hormones and local autocrine/paracrine factors at the growth plate.

Glucocorticoids. Evidence for a direct effect of GC in the growth plate came from a study in which local dexamethasone infusion markedly decreased tibial growth compared with the contralateral limb (79). The GR has since been identified in proliferating and hypertrophic chondrocytes and in osteoblasts and osteocytes in the rat (80). GR is also expressed in human growth plates, mainly in hypertrophic chondrocytes and in osteoblasts at sites of bone remodeling, but is not expressed in osteoclasts, suggesting that effects of GC on bone resorption are indirect (81). GC inhibit osteoblast proliferation, enhance their differentiation, and enhance bone resorption, probably *via* increases in collagenase expression with concomitant reduced expression of tissue inhibitors of matrix metalloproteinase (82, 83). GC also inhibit type I collagen gene expression so that there is a simultaneous decrease in bone matrix production with increased levels of proteases that degrade it. Furthermore, excess GC induce apoptosis of osteoblasts and osteocytes in rabbit trabecular bone (84), and in osteoblasts in rat long bones (85), resulting in an almost complete absence of new bone formation. In rats, GC excess also reduces growth plate width, possibly due to decreased numbers of proliferative chondrocytes and increased apoptosis in terminal hypertrophic chondrocytes (86). These results are also consistent with the dexamethasone-induced inhibition of chondrocyte proliferation and cartilage matrix production observed in 3-mo-old rats *in vivo* (87), suggesting that dexamethasone is a potent negative regulator of the progression of chondrogenesis. It is likely, however, that dexamethasone also acts as a stimulator of chondroprogenitor cell recruitment and supporter of chondrocyte viability (88, 89). Dexamethasone enhances expression of the Sox-9 transcription factor (90), which regulates expression of genes encoding markers of commitment to chondrogenesis, including Col2a1 and aggrecan, to further support the notion that dexamethasone is a maintenance factor for chondrogenic cells. This effect on Sox-9 mRNA and protein expression was observed within 24 h. Indeed, Murakami *et al.* (91) also reported that FGF-2 increased Sox-9 mRNA expression in primary cultures of chondrocytes as early as 30 min after its addition, an effect that lasted at least up to 24 h. FGF signaling in chondrocytes also results in an inhibition of proliferation (62) and thus it is possible that the effects of dexamethasone on Sox-9 are indirect and involve FGF signaling (91, 92). In addition, Sox-9 is a target of PTHrP signaling in prehypertrophic growth plate chondrocytes, suggesting a complex interplay between these factors to influence discrete early steps during chondrogenesis (92, 93).

It is well established, however, that the effects of GC are transient and that, after their removal, there is a period of accelerated catch-up growth. It has been proposed that the mechanism governing catch-up growth after treatment of GC excess resides in the growth plate itself (94). This proposal was based on the observation that suppression of growth within a single rabbit growth plate *in vivo* by local administration of dexamethasone was followed by catch-up growth restricted to the affected limb. According to this model, growth inhibiting conditions of excess GC reduce the growth and maturation of growth plate stem cells, or chondroprogenitors, and conserve their proliferative potential (95). Our unpublished observation that the GR is expressed in germinal and proliferative zone chondrocytes of the rat tibial growth plate is consistent with this proposal and suggests that chondrocyte progenitors and proliferating cells are GC target cells in the growth plate. These hypotheses are further supported by our findings that dexamethasone-treated chondrogenic ATDC5 cells retain the capacity to re-enter chondrogenesis following withdrawal of GC. Thus, although dexamethasone arrests growth and differentiation of chondrocytes, the capacity for cells to undergo chondrogenesis is maintained in the presence of GC, even though progenitor cells are quiescent; the program is reactivated when dexamethasone is removed. Nevertheless, it is the additional action of dexamethasone on cells of the proliferative zone to decrease clonal expansion that, if prolonged, may contribute to the permanent height deficit observed in children treated for prolonged periods with GC (96).

The growth-suppressing effects of GC appear multifactorial, and some GC actions in bone may modify skeletal responses to GH and IGF-I. GC reduce IGF-I mRNA in growth plate chondrocytes (97) and inhibit basal and IGF-I-induced DNA synthesis (98). Some skeletal effects of GC may actually be mediated *via* decreased IGF-I expression, as evidenced by reduced expression of IGF-I, GHR, and IGF-IR in GC-treated chondrocytes (17, 99). In cultured osteoblasts, GC inhibit expression of IGF-I and IGFBP-1, -3, -4, and -5 (83). Thus, GC cause a generalized reduction in skeletal IGF-I expression in osteoblasts and chondrocytes. This correlates with observations that IGF-I and GC exert opposing actions in bone; IGF-I is mitogenic and GC inhibit proliferation. IGF-I also increases collagen synthesis and decreases collagenase 3 expression, whereas GC decrease and increase these parameters, respectively. It has also been reported that IGF-II overexpression in transgenic mice partially protects bone from the osteopenic effects of GC (100). Furthermore, GC prevent the induction of GHR and IGF-IR expression by GH and IGF-I in chondrocytes (17), although it has been shown previously that GC *per se* increase GH receptor mRNA expression in liver, growth plate, and osteoblasts (83, 101). Although variable effects of GC on GHR are evident between studies, the effects of GC on GHR and IGF-IR may account for peripheral GH insensitivity in patients with GC excess. Reduced numbers of peripheral GHR

and IGF-IR may also explain antagonism of the growth-promoting actions of GH by GC, although children with impaired growth due to GC excess may still respond to pharmacological doses of GH therapy. Importantly, and in contrast to chondrocytes, GC stimulate GHR in osteoblasts (102), suggesting that insensitivity to GH in conditions of GC excess is mainly applicable to the detrimental effects of GC on growth rather than bone mass.

Of additional interest is the observation that GH, *via* IGF-I, inhibits activity of 11βHSD1 in human adipose stromal cells (103). 11βHSD1 is principally a reductase *in vivo* that converts inactive cortisone to cortisol, mainly in liver and adipose tissue, to maintain circulating levels of GC. The type 2 enzyme, 11βHSD2, is a dehydrogenase that catalyzes inactivation of GC to protect the nonselective mineralocorticoid receptor from GC activation in target tissues such as the kidney, or to prevent the passage of maternal GC across the placenta and protect the fetus (104). Thus, local tissue GC concentrations are modulated by the 11βHSD2 enzyme, and 11βHSD2 activity has been demonstrated in osteoclasts and osteoblasts (105, 106), although its function in bone is unknown (107). If 11βHSD enzymes are expressed in growth plate chondrocytes, they may act as significant GH- and IGF-I-sensitive regulators of local GC concentrations in the growth plate.

Thyroid hormones. The hypothesis that GH mediates T3 effects on growth was tested in thyroparathyroidectomized rats treated with GH, T4, or both (108). T4 reversed all the effects of hypothyroidism, which reduced growth plate width, articular cartilage, and trabecular bone volume. GH had no effect on the growth plate or metaphysis but partially restored epiphyseal trabecular bone. GH and T4 in combination increased growth plate width and metaphyseal trabecular bone above the value of T4-treated animals. Hypertrophic features of chondrocytes were absent in hypothyroid rats and were only restored by treatment with T4 or T4 plus GH, but not GH. Thus, three sites of T3 action were identified in which GH exerted no influence. GH did not affect stimulation of resting zone cells to differentiate. GH accomplishes this in the intact animal, but these studies indicate the action requires T3 (108). Secondly, T3 is indispensable for chondrocyte hypertrophy; and, thirdly, T3 is required for vascular invasion of the growth plate and metaphyseal trabecular bone formation (108). In contrast, reduced epiphyseal trabecular bone volume in hypothyroidism may result partly from associated GH deficiency. A similar study in mandibular condyle cartilage came to the same conclusion that abnormal bone formation in hypothyroidism can be restored by T4 but not GH (109). Immunohistochemical analysis demonstrated expression of GHR throughout the mandibular condyle, regardless of thyroid status. IGF-I was also expressed throughout the condyle, but in hypothyroidism and GH-treated rats, it was absent from reserve and proliferating chondrocytes and present only in some hypertrophic cells. These data were interpreted to indicate that chondrocyte IGF-I is down-regulated in hypothyroidism and that hypothyroid cartilage is compromised in its GH responsiveness by a lack of IGF-I (109).

Although the effects of T3 and IGF-I on growth plate chondrocytes can be separated, T3 influences expression of several components of IGF-I signaling in bone. T3 increases IGF-I mRNA in osteoblastic cells, and stimulates IGF-I release from bone organ cultures (110). T3 also stimulates IGF-I protein accumulation in conditioned medium of cultured rat bone tissue (111), IGF-IR mRNA in chondrocytes (112), and IGFBP-4 in osteoblastic cells (113). IGFBP-4 is an inhibitor of cell proliferation, and this may be a mechanism that contributes to the antiproliferative effect of T3 in osteoblasts. T3 also stimulates IGF-I and IGFBP-2 expression in primary rat calvarial osteoblasts, whereas GH has no effect (114).

Current data suggest that the two phases of chondrocyte growth are regulated separately; IGF-I stimulates proliferation, whereas T3 induces hypertrophic differentiation (115). The fact that T4 is also active in this system is noteworthy. T4 is a prohormone that is converted to T3 by 5'-DI type 1 in peripheral tissues. GH stimulates conversion of T4 to T3 (116, 117), suggesting that some effects of GH may involve this pathway. Additionally, GC regulate deiodinase activity in renal tubular cells and the liver whereas T3 regulates 11βHSD1 in liver (118–120). The activity of T4 to promote chondrocyte hypertrophy in serum-free cultures suggests that expression of deiodinase in chondrocytes may be an important determinant of ligand supply to the growth plate that is physiologically significant and could be modulated by GH. Indeed, a recent study has confirmed that growth plate chondrocytes express deiodinase enzymes that may serve to regulate intracellular T3 concentrations during thyroid hormone-inducible hypertrophic chondrocyte differentiation (121). In view of interactions in other tissues, GC may modulate the supply of T3 in chondrocytes, and *vice versa*, indicating that local control of intracellular hormone concentrations might be an important mechanism for hormone interactions in the growth plate (Fig. 3).

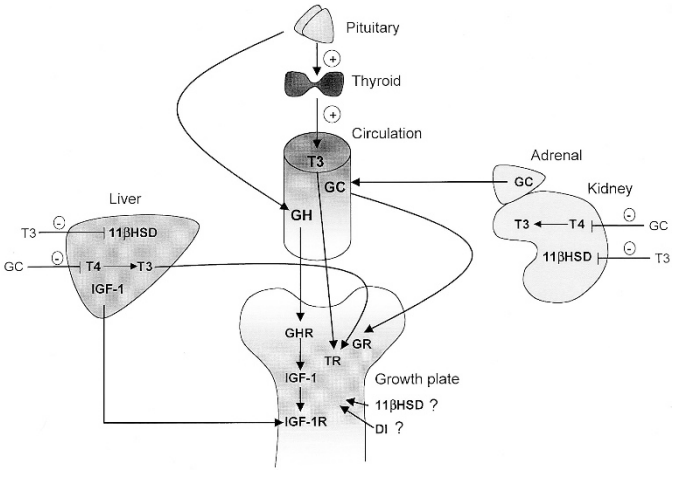

Figure 3. Interaction between GH, IGF-I, T3, and GC. GH stimulates hepatic IGF-I secretion and local production of growth plate IGF-I, and exerts direct actions in the growth plate. Circulating T3 is derived from the thyroid gland and by enzymatic deiodination of T4 in liver and kidney to act on growth plate chondrocytes. GC are secreted by the adrenal glands and circulating concentrations are modulated by activity of the 11βHSD enzyme in liver and adipose tissue (type 1 isoform). The regulatory 5'-DI and 11βHSD type 2 enzymes may also be expressed in chondrocytes to control local supplies of intracellular T3 and GC. Receptors for each hormone (GHR, IGF-IR, TR, GR) are expressed in growth plate chondrocytes.

TR-α1, -α2, and -β1 mRNA and -α1 and -β1 proteins have been identified in rat growth plate by reverse transcriptase PCR and Western blotting (122). High-affinity nuclear T3 binding sites are present in human fetal epiphyseal chondrocytes (123) and TR-α1, -α2, and -β1 proteins have been identified in chondrocytes at sites of endochondral ossification (124). Until recently, the locations of T3 target cells within the growth plate were unknown. In our studies (34, 125), TR-α1, -α2, and -β1 were expressed in reserve and proliferating zone chondrocytes but not in hypertrophic cells. These data suggest that progenitor cells and proliferating chondrocytes are primary T3-target cells but that differentiated chondrocytes lose the ability to express TR and are unresponsive to T3. Primary suspension cultures of rat tibial growth plate chondrocytes express TR-α1, -α2, and -β1 mRNA and T3 inhibits clonal expansion and cell proliferation directly while simultaneously promoting hypertrophic chondrocyte differentiation (125). These findings are supported by data that show T3 regulates chondrocyte proliferation and the organization of proliferating chondrocyte columns and is required for terminal hypertrophic differentiation (112, 115, 123, 126–132). This terminal differentiation process is associated with induction of the cyclin-dependent kinase inhibitors p21 and p27 (133), the expression of which was recently shown to be associated with rat epiphyseal chondrocytes induced to terminally differentiate with T3 (134).

We also examined growth plates in thyroid-manipulated rats (34). Hypothyroid growth plates were grossly disorganized and hypertrophic chondrocyte differentiation failed to progress. These effects correlated with absent collagen-X expression and increased PTHrP mRNA expression. In thyrotoxic growth plates, histology was normal but PTHrP receptor mRNA was undetectable. TR-α1, -α2, and -β1 proteins were localized to regions in which PTHrP and PTHrP receptor expression was altered by thyroid status. Thus, dysregulated Ihh/PTHrP feedback loop activity may be a mechanism that underlies growth disorders in childhood thyroid disease, which could result from alteration of the set-point controlling growth plate chondrocyte maturation. Furthermore, the expression of TR in osteoblasts that invade the growth plate (34) also suggests that T3 may integrate the activities of chondrocytes and osteoblasts during ossification.

GENETICALLY MODIFIED MICE

GHR knockout. GHR null mice exhibit severe postnatal growth retardation, proportionate dwarfism, markedly reduced IGF-I and elevated GH concentrations, and reduced serum-free T3 but normal PTH, testosterone, and estrogen concentrations (135, 136). Growth retardation is evident at 2–3 wk of age, is progressive, and its onset is associated with reduced chondrocyte proliferation and growth plate narrowing (57, 136). In contrast to the original report in which proportionate dwarfism was identified in $GHR^{-/-}$ mice (135), others report the presence of disproportionate growth retardation and reduced bone mineral density (136). Treatment with IGF-I almost completely restores growth and bone turnover in $GHR^{-/-}$ mice, suggesting that most of the effects of GH on growth result from direct actions of IGF-I. It is important to note also that reduced T3 concentrations in $GHR^{-/-}$ mice may contribute to impaired epiphyseal mineralization (136). Analysis of other mutant mice has further highlighted the physiologic interaction between the GH axis and thyroid status. The *lit/lit* mouse has isolated GH deficiency and displays a growth curve that is similar to Laron mice (137). However, the Snell and Ames GH-deficient dwarf mice are more growth retarded than *lit/lit* mice, probably because they are also hypothyroid (138, 139).

IGF-I knockouts. Two IGF-I null mice have been generated (140, 141). The mice are growth retarded to 60% of normal birth weight. Many IGF-I null mice die soon after birth; those surviving to adulthood become further growth retarded, with delayed bone development, and reach only 30% of normal adult weight. Thus, IGF-I is essential for pre- and postnatal growth and development, although survival of IGF-I null mice to adulthood is dependent on genetic background (141, 142), suggesting that unknown genes modify IGF-I action. The IGF-I null growth plate is narrow, with an expanded reserve zone but reduced width of the hypertrophic zone at postnatal d 20, the beginning of the GH/IGF-I-dependent growth spurt (143). The expanded reserve zone is considered to be due to increased GH levels. The hypertrophic zone is reduced 35% in length and individual chondrocyte diameter reduced by 30%, correlating with the degree of growth retardation observed and indicating that IGF-I is required for expansion of hypertrophic chondrocytes. Collagen X, alkaline phosphatase, and bone sialoprotein expression in IGF-I null hypertrophic chondrocytes was normal, suggesting that cells differentiate but do not attain full somatic growth (143). These data support the view that GH expands the pool of chondrocyte progenitors but contradict the hypothesis that IGF-I is responsible for clonal expansion of proliferating cells. The major and unique effect of IGF-I is to amplify hypertrophic chondrocyte size.

To test whether hepatic IGF-I contributes to growth, liver-specific deletion of IGF-I was performed by two groups who crossed the same IGF-I loxP strain with differing Cre recombinase liver-specific strains of mice (144, 145). Sjogren *et al.* (145) used interferon-induced Cre excision of hepatic IGF-I on postnatal d 24, 26, and 28, whereas Yakar *et al.* (144) used an albumin promoter-driven Cre recombinase to constitutively delete hepatic IGF-I. Circulating IGF-I was reduced by 75% in both, and hepatic IGF-I expression was abolished, with a marked compensatory increase in circulating GH concentrations. There was no effect on postnatal growth in either study, providing evidence to refute the somatomedin hypothesis (40) and support the view that autocrine/paracrine actions of IGF-I are major determinants of postnatal growth. Nevertheless, such conclusions can be challenged by the argument that circulating concentrations of IGF-I at levels that are 25% of normal may be sufficient to maintain growth in the presence of elevated circulating GH concentrations.

IGF-IR knockout. IGF-IR deletion is lethal (141, 142, 146). Neonatal mice die of respiratory failure and exhibit severe growth retardation, delayed ossification, and generalized organ hypoplasia (141). Surprisingly, IGF-IR and IGF-IIR double knockout mice are rescued, although postnatal growth is compromised. Triple mutants lacking both IGFR and IGF-II are not viable and growth is retarded to 30% of normal (146). The IGF-IR mediates signaling by IGF-I and -II, whereas the

IGF-II receptor regulates IGF-II turnover but does not mediate signal transduction. Thus, the double and triple knockout data are interpreted as indicating that IGF-II, as well as IGF-I, contributes to postnatal growth regulation and signals *via* an unidentified receptor (146). Subsequent evidence from *in vitro* and genetic studies indicates that the unidentified receptor may actually be the insulin receptor inasmuch as proliferative and growth-promoting actions of IGF-II may also be mediated, in part, by the insulin receptor (147, 148). Thus, in contrast to IGF-I, which acts exclusively *via* the IGF-IR, IGF-II stimulates both the IGF-IR and the insulin receptor.

GR knockouts. GR gene deletion is lethal and mice die of respiratory failure due to lung atelectasis within a few hours of birth (149). Mice with GR targeted for a point mutation that prevents receptor dimerization and abolishes DNA-binding-dependent transcriptional activation were generated (150) to allow analysis of GR signaling pathways that are independent of DNA-binding and require cross-talk with other transcription factors. Such pathways inhibit transcription *via* protein–protein interactions between GR and other transcription factors, including activator protein-1 or nuclear factor-κB, or cause activation of transcription in the case of GR and STAT5 (151). Although the skeletal phenotype of these mice has not been studied, the GC effects on collagenase-3 and gelatinase B gene expression are now known to be independent of DNA binding (150), suggesting that GC regulation of matrix metalloproteinases is highly complex and involves other signaling pathways.

TR knockouts. The skeletal phenotypes of TR knockout mice (Table 1) (152–156) reinforce the view that T3 acts directly in growth plate cartilage. In TR-$\alpha^{-/-}$ mice there is growth arrest and disorganization of growth plate chondrocytes, with delayed cartilage mineralization and bone formation. These abnormalities result from severe hypothyroidism due to impaired thyroid hormone production at weaning, as the phenotype can be rescued by T4 (154). This suggests that TR-β can compensate for TR-α in the growth plate. Nevertheless, TR-β is not essential for bone development inasmuch as TR-β null mice (152, 153) show no evidence of growth retardation or developmental abnormalities in bone and cartilage. Furthermore, double knockout of both TR-α and -β genes fails to modify the skeletal phenotype seen in TR-$\alpha^{-/-}$ null mice (155). The TR-$\alpha^{-/-}$ mutation results in deletion of TR-α1 and -α2 proteins but preservation of two truncated isoforms, TR-$\Delta\alpha$1 and TR-$\Delta\alpha$2, that arise from a novel promoter in intron 7 (157). In contrast to TR-$\alpha^{-/-}$ mice, TR-$\alpha1^{-/-}$ mice (156, 158) do not exhibit skeletal abnormalities and retain expression of TR-α2 and -$\Delta\alpha$2 but lack TR-α1 and -$\Delta\alpha$1. Interestingly, TR-$\alpha1^{-/-}\beta^{-/-}$ double knockouts experience growth retardation (156) associated with an inhibition of the GH/IGF-I axis. However, GH substitution in these animals reverses the growth phenotype but not the defective ossification (159), suggesting that TR are important both for the regulation of the GH/IGF-I axis and for direct effects on cartilage. Furthermore, these animals suggest a role for TR-α2 in bone development. This argument, however, has been difficult to test by selective deletion of TR-α2 because TR-α1 is markedly overexpressed in TR-$\alpha2^{-/-}$ mice, thereby confusing phenotypic interpretation (160). To investigate this issue further, mice devoid of all known TR-α isoforms were generated (161). These TR-$\alpha^{0/0}$ mice exhibit all features of the previously described TR-$\alpha1^{-/-}$ mice (158), but also display retarded growth and delayed bone maturation. The skeletal phenotype of TR$\alpha^{0/0}$ mice includes retarded ossification, failed hypertrophic chondrocyte differentiation, and disorganized growth plate architecture. Importantly, TR-$\alpha^{0/0}$ mice are euthyroid and pituitary GH synthesis is normal. The data suggest that severe hypothyroidism may be more detrimental to endochondral ossification than deletion of all products of the TR-α gene and support the notion that there is functional redundancy between TR isoforms in the growth plate.

Table 1. *Genotypes and growth characteristics of TR null mice*

Genotype (reference)	Deleted TR mRNA	Expressed TR mRNA	Thyroid status	GH status	Growth retardation
TR-α mutants					
$\alpha1^{-/-}$ (158)	α1, $\Delta\alpha$1	α2, $\Delta\alpha$2, all β mRNA	Mildly hypothyroid	Normal	−
$\alpha2^{-/-}$ (160)	α2, $\Delta\alpha$2	α1,* $\Delta\alpha$1, all β mRNA	Mildly hypothyroid	GH normal, IGF-I deficient	+/− late onset
$\alpha^{-/-}$ (154)	α1, α2	$\Delta\alpha$1, $\Delta\alpha$2, all β mRNA	Grossly hypothyroid	Normal	++
$\alpha^{0/0}$ (161)	All α mRNA	All β mRNA	Euthyroid†	Normal	+
TR-β mutants					
$\beta2^{-/-}$ (162)	β2	All α mRNA, β1, β3, $\Delta\beta$3	RTH	Mildly deficient	−
$\beta^{-/-}$ (152)	All β mRNA	All α mRNA	RTH	Mildly deficient	−
TR-$\alpha\beta$ double mutants					
$\alpha1^{-/-}\beta^{-/-}$ (156)	α1, $\Delta\alpha$1, all β mRNA	α2, $\Delta\alpha$2	Severe RTH	GH & IGF-I deficient	++
$\alpha^{-/-}\beta^{-/-}$ (155)	α1, α2, all β mRNA	$\Delta\alpha$1, $\Delta\alpha$2	Severe RTH	Not determined	++
$\alpha^{0/0}\beta^{-/-}$ (161)	All α mRNA, all β mRNA	None	Severe RTH	GH deficient	++

RTH, resistance to thyroid hormone. GH status was determined by measurement of pituitary mRNA and/or protein or by GH concentration in serum. IGF-I was measured in serum.

* TR-α1 is overexpressed in $\alpha2^{-/-}$ mice, and presumed consequences of gene targeting on expression of $\Delta\alpha$1, $\Delta\alpha$2 mRNA were not tested in the original studies.

†TRα^{010} mice show mildly increased sensitivity to thyroid hormones following provocative dynamic testing.

CONCLUSIONS

We have reviewed the actions of GH, IGF-I, GC, and T3 during linear growth. Interactions between these hormones to regulate various hypothalamopituitary axes have long been understood, but recent interest from a variety of disciplines, including the broad fields of developmental biology, hormone action, and bone and cartilage metabolism, has led to a new appreciation of the epiphyseal growth plate. This organ is a point of convergence for interactions between circulating hormones and locally acting autocrine/paracrine factors that are achieved by mutual regulation of hormone availability and receptor expression in growth plate chondrocytes. We suggest that GH, IGF-I, GC, and T3 signaling pathways are integrated by such complex interactions to regulate, for example, the set point of the Ihh/PTHrP feedback loop to control the pace of growth plate chondrocyte differentiation and linear growth. A clearer understanding of the molecular basis for these interactions in humans will facilitate the design of new, targeted approaches to treat childhood growth retardation.

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