Somatomedin and the Regulation of Skeletal Growth

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ABSTRACT

Somatomedin is a polypeptide(s) which "mediates" the actions of growth hormone. This pituitary dependent hormone was previously called "sulfation factor," a term derived from the bioassay technique which measures the incorporation of radioactive sulfate into cartilage glycosaminoglycans. Somatomedin has a more general effect upon cartilage; it is necessary for the cell multiplication and cartilage maturation which results in the growth of long bones.

Somatomedin is not found in the plasma in growth hormone deficiency and appears following growth hormone administration. A genetic defect in somatomedin synthesis has been identified in the Laron's dwarf. Growth hormone is present in excess in the plasma and growth hormone administration does not stimulate somatomedin synthesis in this syndrome.

Insufficient data are available to delineate the role for somatomedin in other growth disturbances. It has been demonstrated that glucocorticoid hormones interfere with both somatomedin synthesis and its biological activity.

Purification of somatomedins in plasma has been achieved and radioreceptor or radioimmunoassays will be available in the future for study of growth problems in children.

Introduction

Disorders of growth are the most common problems relating to the skeletal system encountered in children. Many of these problems can be shown to be either nutritional, constitutional, or genetic in origin. After having ruled out these factors, the problems which are left are those relating to the endocrine system. Early in life, thyroid hormone is perhaps the most important hormone regulating long bone growth. After the second year, growth hormone is preeminent in regulating growth while the sex hormones begin to play a major role at or about the time of puberty. The growth of long bones involves an ordered sequence of events which include multiplication of cartilage cells, glycosaminoglycan (GAGS) biosynthesis, collagen biosynthesis and calcification.

The major determinants in this system,
assuming adequate nutritional and normal thyroid function, are depicted in figure 1. Included is a functioning hypothalamus capable of releasing growth hormone releasing hormone in response to an appropriate stimulus. Growth hormone releasing hormone is secreted into the portal venous system which connects directly to the anterior pituitary gland and stimulates the secretion of growth hormone. Growth hormone then acts on the appropriate target organ to stimulate the secretion of a small polypeptide which mediates the action of growth hormone on cartilage. This peptide was formerly called “sulfation factor” to describe its action of stimulating sulfate uptake by the cartilage cell. As more information became available on the action of somatomedin, it was apparent that this term was too restricted. The presently accepted term for this factor is somatomedin. “Somato” designates a hormonal relationship to somatotrophin (growth hormone) and “soma” indicates the target tissue. The suffix “medin” was chosen to indicate that this hormone mediates the action of growth hormone.

Somatomedin is transported via the plasma, from its site of synthesis, to the cartilage cell where a number of anabolic events are initiated. These include the stimulation of mitotic activity, deoxyribo- nucleic acid (DNA) synthesis, DNA dependent ribonucleic acid (RNA) synthesis, protein synthesis, the biosynthesis of GAGS, collagen synthesis and increased thickness of the epiphyseal growth plate with resultant long bone growth. The somatomedin bioassay in plasma is based on sulfate incorporation into cartilage glycosaminoglycans (GAGS). Although sulfate incorporation is the final step in GAGS biosynthesis, an alteration at any step in the biosynthesis could result in decreased sulfate uptake. At present it is not known which of these steps somatomedin specifically stimulates or which may be altered by other factors. GAGS is known to be synthesized by the stepwise addition of sugar residues onto a protein acceptor.

Xylose is transferred from UDP-xylose by the enzyme xylosyltransferase to serine residues of the protein acceptor, thereby initiating the biosynthesis of the polysaccharide chains. Synthesis of GAGS continues by sequential addition of two galactose residues and one glucuronic acid residue. These additions occur in sequence and require specific glycosyltransferase enzymes for the transfer of the sugar from the respective uridine diphosphate(UDP)-derivative. Sulfation of the growing chain occurs simultaneously with polymerization of the polysaccharide chain. Polymerization occurs as the repeating units of hexuronic acid and amino sugar are added.

In figure 2 is depicted, graphically, the process of GAGS biosynthesis in cartilage. GAGS are long polysaccharide residues of approximately 50 dimer units attached to a protein core. This protein core is 3700 Angstroms in length. All GAGS have a com-
mon linkage region of xylose-galactose-galactose-glucuronic acid between serine and the dimer units. The individual proteoglycan molecules have a molecular weight of approximately 4 million. In addition to the protein core (acceptor protein), a covalently linked protein, molecular weight approximately 200,000 provides secondary structure to the GAGS.

The biosynthesis of these compounds takes place in the endoplasmic reticulum and Golgi apparatus of the cartilage cell. Enzymes responsible for their biosynthesis are bound to the membrane in a sequential fashion.

The acceptor protein is synthesized in the rough endoplasmic reticulum and transported to the Golgi where the UDP-sugar transferases are found. The biosynthesis of GAGS in cartilage both in vivo and in vitro has been shown to be growth hormone dependent. Sulfate incorporation into cartilage is reduced by hypophysectomy and is restored by the administration of growth hormone. This action of growth hormone, however, is indirect since the stimulation of sulfate uptake in cartilage cannot be achieved by the addition of growth hormone in vitro. In the initial studies by Salmon and Daughaday, it was found that the serum of normal rats contained a factor which stimulated sulfate uptake into hypophysectomized rat rib cartilage in vitro. Serum from hypophysectomized rats had decreased ability to stimulate sulfate uptake. Treatment of the hypophysectomized rats with growth hormone restored the capacity of the serum to stimulate sulfate uptake, but the addition of growth hormone in vitro failed to restore activity.

These studies form the basis of the bioassays of plasma somatomedin which is presently used by many investigators.

Bioassay for Somatomedin

Several modifications of the original hypophysectomized rat rib cartilage bioassay for somatomedin are presently in use. These may vary as to the type of cartilage used in the in vitro assay system, i.e., hypophysectomized rat rib cartilage, embryonic chick pelvic rudiments, porcine rib cartilage, or the rib cartilage of normal rats following prolonged fasting. The incubation medium also varies, but all include an enriched nutrient mixture suitable to maintain cell growth in culture. The basic procedure is depicted in figures 3 and 4.

### BASIC SOMATOMEDIN ASSAY PROCEDURE

1. Wash repeatedly
2. Digest cartilage
3. Take aliquots for:
   a. radioactivity
   b. protein
   c. uronic acid

Figure 3. Schematic representation of the basic somatomedin assay procedure.
The cartilage is removed from its source and preincubated in an enriched tissue culture medium for 4 to 24 hours prior to the addition of serum or plasma containing somatomedin. Serum or plasma is then added to the incubation medium. Incubation is allowed to proceed for 24 hours following which $^{35}$SO$_4$ is added and the incubation continued for an additional 24 hours. The concentration of serum or plasma used may vary from 1 percent to 20 percent of the incubation medium depending upon the amount of somatomedin in the serum or plasma. The cartilage is boiled for two minutes to stop the reaction, then washed repeatedly before digesting and weighing. Following digestion, aliquots are taken for counting of radioactivity, protein, uronic acid or sulfate determinations. For each assay, a symmetrical 4 or 6 point design is used with equal number of pelvic rudiments for each concentration of the reference and test serum. Statistical analysis of validity, regression and precision are carried out on each assay to insure parallelism.  

The hypophysectomized rat rib cartilage assay has the greatest sensitivity but the least precision. The embryonic chick cartilage assay and the porcine rib cartilage assay have the greatest simplicity and precision, but are less sensitive.  

Van Wyk et al. have recently developed a competitive placental membrane binding assay for somatomedin which has excellent precision and is extremely sensitive. The activity has been found to be low in patients with growth hormone deficiency, high in patients with acromegaly and also to vary with stature in patients with normal growth hormone secretion. Insulin and proinsulin compete with somatomedin for binding, but at high concentrations. Binding is not affected by other growth factors studied. At the present time, purified somatomedin is very difficult to prepare. However, this assay or a radioimmunoassay appears to be the assay of choice for future studies with this hormone.

Chemical Properties of Somatomedin

Somatomedin circulates in the plasma associated with a high molecular weight protein of 50,000 daltons or greater. Cold acid-ethanol will extract 20 to 40 percent of the somatomedin from plasma while precipitating 99 percent of the other plasma proteins. After acid-ethanol extraction, further purification is achieved using gel filtration and carboxymethyl cellulose ion-exchange chromatography. The greatest resolution has been obtained using isoelectric focusing. When this procedure is utilized, somatomedin activity is recovered in an acid, neutral, and/or basic pH range. All have molecular weights of 6,000 to 11,000 daltons. The neutral peptide has been termed somatomedin A and has been found to be most active in the chick embryo assay system. The acidic peptide, termed somatomedin B, has a molecular weight of approximately 6,000 daltons, slightly less than somatomedin A. It stimulates thymidine incorporation by human fibroblasts and glial-like cells. The basic peptide has been
termed somatomedin C. It is an arginine-rich peptide of about 50 amino acid residues and is very active in stimulating $^{35}$SO$_4$ and $^3$H-thymidine uptake in hypophysectomized rat cartilage. The molecular weight is very similar to somatomedin A. It has a mobility slightly greater than insulin by preparative gel electrophoresis at pH 2.3 in a 15 percent polyacrylamide gel.

At present it is not known if these are different peptides or if they appear unique because of different methods of isolation and/or assay systems. They all, however, meet the criteria established for a somatomedin, that is: (1) they are to some extent under the control of growth hormone; (2) they have been shown to be insulin-like in their activity; (3) they stimulate cell growth in one or more tissues; and (4) they stimulate $^{35}$SO$_4$ uptake in cartilage in at least one species. Other growth factors have also been isolated from various tissues. These include insulin from the pancreas, non-suppressible insulin like activity (NSILA) from liver, multiplication stimulating activity (MSA) from calf serum, nerve growth factor and epidermal growth factor from mouse submandibular gland, and erythropoietin from plasma and urine.

Somatomedins have only been partially purified from plasma and as yet the specific site of synthesis has not been determined. Several tissues may be able to synthesize somatomedin but current evidence can only suggest that the liver may be the primary site of synthesis. Although somatomedin has not been purified, it is stable in plasma. It can be stored for long periods of time at $4^\circ$ C and is unaffected by repeated freezing, thawing or lyophilization. Plasma can be acidified and heated to $100^\circ$ C for one hour without destroying the activity. However, somatomedin activity is destroyed by proteolytic enzymes.

**Biological Actions of Somatomedin**

A comparison of the *in vitro* effects of somatomedin with those of growth hormone on the growth hormone sensitive tissues, such as cartilage, muscle, adipose tissue and liver, are shown in table I. Perhaps the best known biological effects of somatomedin are the effects of somatomedin on the cartilage cell. It is now well accepted that all of the known actions of growth hormone on cartilage are attributable to somatomedin. Somatomedin stimulates the incorporation of $^3$H-thymidine into DNA and $^3$H-uridine into RNA, increases the incorporation of $^{14}$C-leucine into protein-polysaccharides complexes, increases the incorporation of $^{35}$SO$_4$ into chondromucoprotein, and provides the conversion of $^{14}$C-proline into hydroxyproline of collagen. These biological effects were previously ascribed to growth hormone; however, it has now been amply demonstrated that the growth hormone effects are mediated by somatomedin. Growth hormone *in vitro* is without effect on cartilage.

In the rat epididymal fat pad, somatomedin stimulates glucose oxidation. In isolated fat cells, somatomedin stimulates lipid synthesis and opposes the effect of epinephrine on stimulating lipolysis. It inhibits the rise in adenylcyclase production by epinephrine in lymphocytes and fat cells. It also inhibits the rise in adenylcyclase in chondrocytes produced by parathormone. Somatomedin competes with insulin for binding to the plasma membrane receptors, cell-free liver membranes and chondrocytes. Only insulin and pro-insulin have previously been shown to compete for the insulin receptors. Furthermore, somatomedin can compete effectively with insulin for binding to a common receptor on the cell membrane of adipose tissue lymphocytes and placenta. However, in cartilage membranes, the two hormones do not compete for the same primary receptor site. The cartilage cell is much more sensitive to somatomedin than to insulin.

In the rat diaphragm, somatomedin has been shown to have a direct effect on membrane transport. It stimulates amino
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TABLE I

Biological Actions of Somatomedins and Growth Hormone on Selective Tissues In Vitro

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Somatomedin Effect</th>
<th>Growth Hormone Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage</td>
<td>Stimulates growth</td>
<td>Minimal to no effect on cartilage</td>
</tr>
<tr>
<td></td>
<td>Increases $^{35}$S uptake into glycosaminoglycan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increases $[^3]$H thymidine uptake into desoxyribonucleic acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increases $[^3]$H uridine uptake into ribonucleic acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increases $[^1]$C proline incorporation into hydroxyproline of collagen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increases $[^1]$C leucine uptake into protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increases amino acid transport</td>
<td></td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Stimulates glucose oxidation</td>
<td>Stimulates all effects seen with somatomedin but there is long lag phase and action can be blocked by puromycin and theophylline</td>
</tr>
<tr>
<td></td>
<td>Opposes effect of epinephrine on stimulated lipolysis or is anti-lipolytic</td>
<td>Lipolytic</td>
</tr>
<tr>
<td></td>
<td>Stimulates lipogenesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Competes with insulin for binding</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Stimulates protein synthesis</td>
<td>Increased somatomedin production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased protein synthesis but weak and delayed</td>
</tr>
<tr>
<td>Rat diaphragm</td>
<td>Direct effect on membrane transport</td>
<td>Stimulates all effects seen with somatomedin but there is long lag phase and action can be blocked by puromycin and theophylline</td>
</tr>
<tr>
<td></td>
<td>Stimulates amino acid transport, sugar transport and protein synthesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Action is immediate and not blocked by puromycin and theophylline</td>
<td></td>
</tr>
<tr>
<td>HeLa cells</td>
<td>Stimulate growth in tissue culture</td>
<td>Minimal effect</td>
</tr>
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</table>

acid transport, sugar transport and protein synthesis. These effects are not blocked by either puromycin, an inhibitor of protein synthesis, or theophylline, a phosphodiesterase inhibitor. It would appear, therefore, that the effect of somatomedin is not mediated through either protein synthesis or cyclic nucleotides. Significantly, both theophylline and puromycin block the action of growth hormone on the rat diaphragm. In addition, the growth hormone effect is delayed and requires relatively large doses of the hormone.

In muscle, somatomedin stimulates protein synthesis, the action is immediate and requires only minimal amounts of the hormone, whereas the action of growth hormone on muscle in vitro is very weak and delayed. The same situation is true for the effects of somatomedin on liver.

Factors Influencing Somatomedin Activity

Plasma somatomedin activity has been shown to be influenced by multiple factors, including age, nutritional status, constitutional factors and some as yet unidentified factors. These are shown in Table II. Van den Brande et al have shown that somatomedin activity is lowest in the very young and increases with age. The largest increase occurs before the age of six years and reaches adult levels about the time of puberty. No sex difference was found either before or after puberty. Nutritional status, however, does appear to alter somatomedin activity. Severe malnutrition or marasmus results in low somatomedin levels. Salmon et al showed that prolonged fasting in the rat caused low levels of somatomedin. The low levels appear to be due to the development of
somatomedin inhibitors in the plasma. Furthermore, children who are markedly underweight have very low levels of somatomedin which may also be related to the presence of inhibitors. In children with documented hypopituitarism, somatomedin levels are decreased. In response to growth hormone administration, there is a rise in plasma somatomedin levels which precedes any detectable increase in growth.65 Conversely, children with constitutional dwarfism often have normal to low levels of somatomedin but have normal levels of growth hormone.10

Normal plasma somatomedian levels are often seen in patients who have undergone surgery for a craniopharyngioma, in spite of low plasma growth hormone levels. These patients also have very high insulin levels and are usually obese.18 Likewise, somato-

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<table>
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<th>Factors Studied</th>
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<td>Somatomedin Activity</td>
<td>Growth Hormone Concentrations</td>
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<td>Deficiency</td>
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<td>Low</td>
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<tr>
<td>Limited responders</td>
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<td>Thyroid hormone</td>
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<tr>
<td>Excess</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Deficiency</td>
<td>Normal-low</td>
<td>Normal-low</td>
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<tr>
<td>Insulin</td>
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<tr>
<td>Deficiency</td>
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<tr>
<td>Androgens</td>
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<tr>
<td>Estrogens</td>
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<td>Sex</td>
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<td>Age</td>
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<tr>
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<tr>
<td>Turner's syndrome</td>
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<td>Noonan's syndrome</td>
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<tr>
<td>Cerebral gigantism</td>
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<td>Other</td>
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<td>Uremia</td>
<td>Decreased</td>
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</table>
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Medin activity is usually normal in obesity but growth hormone levels are frequently low.53 Thus, the increased somatomedin levels, relative to that growth hormone in both obese and post-operative cranio-pharyngioma patients, may be due to the same, although unknown, mechanism. However, in both cases, insulin is markedly increased. Quite possibly these paradoxical somatomedin levels may be related to the high insulin levels. Laron's dwarfism is associated with very low levels of somatomedin.30 These patients are extremely dwarfed but have very high levels of growth hormone. Significantly, they do not respond to administered growth hormone by increasing their somatomedin activity.29 This could be due to the absence of growth hormone receptors in the target tissue, or alternatively the inability of the target tissue to synthesize somatomedin.17 Presumably, these patients could successfully be treated with purified somatomedin.

In contrast to the patient with Laron's dwarfism, patients with acromegaly have very high levels of growth hormones and also have high levels of somatomedin.31 This is due to overproduction of growth hormone, which in turn stimulates increased production of somatomedin.

 Constitutional factors have also been shown to be associated with alterations in plasma somatomedin activity. Patients with short stature usually have normal or minimal growth hormone as well as low somatomedin activity. In contrast, tall stature is associated with normal growth hormone and a high somatomedin activity.65

Genetic factors also influence somatomedin activity. Patients with Turner's syndrome, XO chromosomal abnormality, usually have normal growth hormone levels and high somatomedin activity, yet they have very short stature.2 This is also true of the patients with Noonan's syndrome,13 suggesting a possible peripheral defect or a defect in responsiveness of the peripheral tissue to somatomedin. Van den Brande et al85 recently demonstrated that patients with achondroplasia also have very high somatomedin activity. It is thought that this high somatomedin activity may be related to the cartilage hypertrophy seen in these patients.

Patients with chronic renal disease and elevated blood urea nitrogen or nephrectomized patients also have decreased somatomedin levels, suggesting the kidney may have a role in the synthesis of somatomedin or, alternatively, elevations of the blood urea nitrogen may inhibit the effect of somatomedin at the cartilage level.45

Elevations of plasma free fatty acids have been shown to be inhibitory to plasma somatomedin in vitro, suggesting a role for free fatty acids in the control of cartilage metabolism.14

Thyroid hormone has been shown to have an influence on growth hormone. Patients who are severely thyroid hormone deficient usually do not release growth hormone in response to stimulation test. However, when treated with thyroid hormone, they frequently respond. It is somewhat puzzling that the somatomedin activity is normal in patients with thyroid hormone deficiency.65

Androgens have little effect on somatomedin activities. Estrogens in large doses, however, have been shown to decrease plasma somatomedin activity74 and, thereby, provide a rational basis for therapy in some patients with acromegaly.

The chronic administration of adrenal glucocorticoids universally causes inhibition of growth. Possible mechanisms for this growth retardation have included inhibition of protein synthesis, suppression of growth hormone release, inhibition of growth hormone action at the peripheral level and the suppression of somatomedin generation.4,38

In figure 5 is shown a summary of the proposed possible sites of cortisol action which may inhibit long bone growth. The hypothalamus which is responsible for releasing growth hormone releasing hormone
under appropriate stimuli appears to be intact as previous workers have shown that growth hormone synthesis and release from the anterior pituitary are probably adequate (Site 1).46,52 Both our data4 and Phillips et al38 suggest that cortisol does inhibit somatomedin synthesis and/or release from (Site 2) the somatomedin factory.416,38 In addition, an effect at the level of the cartilage cell has been demonstrated by us. The major action of glucocorticoids on the cartilage cell appears to be inhibition of glycosaminoglycan biosynthesis. The glucocorticoid effect appears to be early in the pathway at the point where xylose is incorporated into preformed acceptor protein (Site 4). Initial studies showed xylosyltransferase activity to be greatly decreased.4 Assays of xylosyltransferase, using an exogenous acceptor, suggested that enzyme was not limiting, but the available acceptor sites for xylose were decreased.36

It has been concluded by us that the formation of the acceptor protein was decreased by glucocorticoid therapy, either because glucocorticoids inhibited the generation of somatomedin which may be essential for the stimulation of biosynthesis of this protein or because the acceptor protein is uniquely sensitive to glucocorticoids as compared to proteins in general. Inhibition of synthesis of this acceptor protein would inhibit GAGS biosynthesis at the first step unique to the synthetic pathway causing a decrease in the extracellular matrix with resultant inhibition of long bone growth. Inhibition of sulfation by cortisol, although unlikely, is shown at Site 5.

References


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