Growth Hormone Releasing Hormone: Therapeutic Potentials

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Introduction

A new chapter in hypothalamic-pituitary growth hormone physiology was opened with the isolation, characterization and synthesis of growth hormone releasing hormone (GHRH) in 1982. Multiple factors regulate growth hormone secretion. Somatostatin inhibits and GHRH stimulates GH secretion. Many of the metabolic effects of growth hormone are effected by generation of somatomedin C (IGF-1) by the liver and other tissues. IGF-1 inhibits growth hormone secretion and closes the feedback loop for growth hormone, probably by both a direct inhibitory effect on the pituitary and by stimulating hypothalamic somatostatin secretion (Figure 1). In this chapter we will review our work on the effects of GHRH in dynamic testing and as therapy in man.

Growth hormone is secreted in man, as in other species, in a pulsatile fashion. The significance of this pattern is unknown, but in animal experiments growth hormone is more potent in stimulating growth if it is administered in a pulsatile fashion than given as a continuous infusion (Clark *et al.*, 1985). The mechanisms subserving pulsatile growth hormone secretion are poorly understood. However, studies in man and in the rat (Vance *et al.*, 1985; Tannenbaum and Ling, 1984;) suggest that intermittent growth

hormone release is mediated by pulsatile GHRH secretion associated with intermittent withdrawal or reduction of hypothalamic somatostatin secretion (Figure 2). Somatostatin apparently tonically inhibits growth hormone secretion between secretory episodes of GHRH. This mechanism will be important to recall when considering the variable responses to exogenous GHRH administration in normal subjects and in children with growth hormone deficiency.

Fig. 1. Schematic representation of the control of GH secretion. Growth hormone secretion is regulated by two hypothalamic hormones, somatostatin, and GRF; these inhibit and stimulate growth hormone secretion, respectively. The release of GH results in the generation of IGF-1 (somatomedin C) from peripheral tissues which produces some of the metabolic effects of growth hormone. IGF-1 exerts a negative feedback directly at the pituitary and also hypothalamus by stimulating somatostatin secretion and possibly by inhibiting GRF secretion. Reprinted with kind permission from Thorner *et al.* (1986b).

Growth Hormone Deficiency

Only a small proportion of short children actually are deficient in growth hormone. This pathologic condition may arise either as a result of an organic lesion, usually a hypothalamic tumor or infiltration of the hypothalamus, e.g., by Histiocytosis X.

Fig. 2. Schematic representation of the postulated rhythmic secretion of SRIF and GRF into hypophyseal portal blood, with the net result on GH secretion, as observed in plasma. Reprinted with kind permission from Tannenbaum and Ling (1984).

With the advent of longer term survival of children with leukemia, a larger number are seen who suffer from arrested growth possibly secondary to inadequate growth hormone secretion as a result of the cranial irradiation or intrathecal chemotherapy. In addition a group of children have congenital (idiopathic) growth hormone deficiency. In the past this was considered a primary pituitary defect, but as will be described below, these children almost certainly display a hypothalamic defect in hypothalamic function since they secrete growth hormone

in response to exogenously administered GHRH. Studies of adults, who had growth hormone deficiency in childhood and of children with growth hormone deficiency, reveal that GHRH, either acute or chronic administration, increases growth hormone and somatomedin C levels (Borges *et al.*, 1983; Wood *et al.*, 1983; Rogol *et al.*, 1984; Thorner *et al.*, 1985; Gelato *et al.*, 1986). Thus many patients do not have a defect of the somatotrope, but instead have a hypothalamic disorder resulting in absolute or functional GHRH deficiency.

We initially evaluated 40 children with short stature with varying etiologies and examined the effects of an acute intravenous bolus of 3 μ g/kg of hGRH (1-40) (Rogol *et al.*, 1984). These children were subdivided into four diagnostic clinical subcategories based on their response to the standard provocative tests of arginine and L-dopa. Children with constitutional delay of growth and adolescence had by definition normal responses to arginine and L-dopa and responded to GHRH in a variable manner similar to normal adults. This variability may well be due to the administration of GHRH when hypothalamic somatostatin secretion fluctuated. Thus, the responsivity of the somatotrope to GHRH varies depending upon the local somatostatin concentration. In children with intra-uterine growth retardation the responses were similar to those with constitutional delay of growth and adolescence, while in children with idiopathic growth hormone deficiency, GH secretion was subnormal following arginine and L-dopa administration. The response to GHRH was variable. Most children, however, had a good response to GHRH although there were two who did not respond. Our final category is a group of children who had hypothalamic tumors. All had previously had either surgery and/or irradiation therapy. They responded poorly to arginine and L-dopa and also a diminished response to GHRH. However, some

children did respond with a small rise in circulating growth hormone. Those who did not respond may have developed somatotrope deficiency as a result of their therapy.

Our results are similar to those observed by other groups (Takano *et al.*, 1984; Schriock *et al.*, 1984; Gelato *et al.*, 1986). Takano *et al.* (1984) originally reported that a minority of GH deficient children responded to GHRH with a rise in growth hormone concentration; however, as Dr. Takano

Fig. 3. Cumulative linear growth rate before and during 6 months of GRF therapy in 2 GH-deficient children. Note acceleration of the growth rate in both children, which was sustained in Patient 2 but waned after 16 weeks in Patient 1. The normal ($\pm$ SD) growth rate is shown for an 8-year-old boy. Reprinted with kind permission from Thorner *et al.* (1985).

stated at a recent meeting to discuss GH deficiency, more than 80% of the children responded when their serum samples were re-assayed in a more sensitive GH immunoradiometric assay. Thus, it appears that a majority of these children have somatotropes responsive to GHRH.

Growth hormone releasing hormone, therefore, has the potential to stimulate growth hormone secretion in most hypopituitary children. We initially administered

Fig. 4. Growth velocity in 7 GH-deficient children treated with GRF in the United States by the University of Virginia group, by Dr. Georgeanna Klingensmith (Denver Children's Hospital, Denver, Colorado) and Drs. Seymour Reichlin and Boris Senior (Tufts New England Medical Center). All children demonstrated accelerated growth rate. One child (asterisk) grew at the same rate during GRF therapy as on growth hormone. During the 6 months prior to GRF therapy, this child did not take growth hormone and did not grow (data not shown). Note that 4 children were treated with subcutaneous injections every 3 hours administered by Pulsamat pump (Ferring) and 3 received GRF, 4 $\mu\text{g}/\text{kg}$, subcutaneously twice daily. Reprinted with kind permission from Thorner *et al.* (1986b).

GHRH to two children at a dose of 1 to 3 $\mu\text{g}/\text{kg}/\text{dose}$ every 3 hr using a mechanical pump (Pulsamat, courtesy of Ferring, Inc., Ridgewood, NJ). Both responded to therapy with accelerated growth velocity (Figure 3) to GHRH (Thorner *et al.*, 1985). We have now treated 24 growth hormone-deficient children for 28 six-month treatment cycles (Thorner *et al.*, 1986a). They re-

Fig. 5. GH serum profiles from 2100 to 0900 h in a normal subject and in a GH-deficient child pretreatment and while receiving GHRH every three hours overnight at 1 $\mu\text{g}/\text{kg}/\text{pulse}$ or 2 $\mu\text{g}/\text{kg}/\text{pulse}$ for five months. Reprinted with kind permission from Smith *et al.* (1985).

Fig. 6. Serum GH (ng/ml) and plasma immunoreactive GHRH (IR-GRF) levels in a patient with acromegaly and ectopic GRF secretion. ●, GH; ○, IR-GRF. Reprinted with kind permission from Vance *et al.* (1985).

Fig. 7. Serum GH levels measured every 20 minutes in a normal young adult male prior to (A), on day 14 of a 14 day intravenous infusion of (GHRH-40) (10 ng/kg/minute) (B), and 14 days after stopping the GHRH infusion (C). Note basal growth hormone levels are higher during the 14th day of the infusion and the greater number and amplitude of pulses during the nighttime hours. Following withdrawal of GHRH the pattern of growth hormone secretion returned to that seen prior to the infusion. Reprinted with kind permission from Thorner *et al.* (1986b).

ceived GHRH subcutaneously either by a pump which delivered a dose ($1-3 \mu\text{g/kg/dose}$) every three hours or by twice daily injections. Ten treatment cycles were given with a pump overnight only and 13 with a pump throughout the 24 hour period. All children who received the GHRH by pump throughout 24 hours and all five with twice daily injections ($4 \mu\text{g/kg/dose}$) had acceleration of growth velocity which was similar to children treated with growth hormone (Thorner *et al.*, 1986a). Examples of the type of growth responses to GHRH, administered subcutaneously by pump or twice daily injections, are shown in Figure 4. In Figure 5 the pattern of GH in a normal child is compared with that of a GH-deficient child before and during pulsatile GHRH administration (Smith *et al.*, 1985). Eight of ten children who received GHRH by pump overnight had an acceleration of growth velocity. Six children developed antibodies to GHRH. These were of low titre and disappeared either during continuation of treatment or after cessation. There was no evidence to suggest that these antibodies inhibited the growth hormone response to GHRH or impaired the children's growth rate.

Future Developments

In Figure 6 are shown the growth hormone and immunoreactive GHRH (IR-GRF) levels in a patient with ectopic GRF secretion. This patient had harbored a GHRH-secreting bronchial carcinoid tumor for 20 years. It should be noted that the immunoreactive GHRH levels greater than 5 ng/ml throughout, more than 10 fold those necessary to stimulate GH release. Thus, the pituitary was continuously stimulated by supramaximal quantities of GHRH (Vance *et al.*, 1985). In spite of that, growth hormone was still secreted in a pulsatile fashion. One might, therefore, surmise that a slowly

released preparation of GHRH which allows the somatotrope to be permanently stimulated might mimic the physiologic condition and result in pulsatile growth hormone secretion. To address this issue, we have performed experiments administering 24 hour (2 ng/kg/min) and 14 day (10 ng/kg/min) intravenous infusions of GHRH in normal subjects (Figure 7). In both sets of trials we found augmentation of pulsatile growth hormone secretion. Very recently we have studied a growth hormone deficient child with a similar 14 day infusion. This boy also had demonstrated a three-fold increase in circulating somatomedin C levels from 0.2 to 0.6 U/ml and an increase in pulsatile growth hormone throughout the 24 hour period on the 14th day of the infusion. Two weeks after stopping the infusion this child's somatomedin C levels fell back to the pre-treatment (hypopituitary) levels. We, therefore, believe that development of a delayed release preparation is urgently needed and offers the hope of a therapy which may only need to be administered infrequently to children and adolescents with hypothalamic GH deficiency. Not only would this provide a convenient means of therapy for the child but also might lead to a more physiologic pattern of growth hormone delivery to the peripheral tissues and, thus, better growth than the currently available therapy-three times a week injections of pharmacologic doses of growth hormone.

Conclusions

GHRH has therapeutic potential in children with growth hormone deficiency. The current methods of administration, either intermittently by pump or by twice daily administration have demonstrated that it is efficacious in stimulating growth hormone secretion and in providing supranormal, catch-up growth. However, longer term studies need to be performed to optimize

the dose and route of administration. The advent of delayed release preparations will greatly simplify its administration and acceptability as long-term therapy.

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