Role of the New Growth Hormone–Releasing Secretagogues in the Diagnosis of Some Hypothalamopituitary Pathologies

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Growth hormone (GH)–releasing hormone (GHRH) and somatostatin have a dominant role in regulating GH secretion. However, results of studies using the new class of GH secretogogues, particularly GHRP-6, indicate that there may also be other, as yet undefined, hypothalamic mechanisms involved. Studies in adults with hypothalamopituitary disconnection (functional pituitary stalk transection), show GHRP-6–mediated GH release to be completely blocked, indicating a main action at the hypothalamic rather than the pituitary level. The synergistic effect of GHRH plus GHRP-6 administration on GH release seen in normal adults (and virtually unaffected by age, obesity, or sex) is also absent in these patients, providing further support for this conclusion. Studies of the effects of GHRP-6 in children with GH deficiency due to perinatal pituitary stalk transection have produced similar findings. It is suggested that the combined GHRH plus GHRP-6 test should be a promising tool for diagnosing GH deficiency states in both children and adults, and may identify a subgroup of patients with GH deficiency caused by interruption of the hypothalamopituitary connection.

THE WIDELY ASSUMED dominant roles of both growth hormone (GH)–releasing hormone (GHRH) and somatostatin in the regulation of GH secretion[1,2] by no means exclude other operant hypothalamic factors. Considerable interest has recently been directed towards the so-called nonclassical GH secretagogues, a group that comprises different artificial compounds such as GHRP-1, GHRP-2, GHRP-6, hexarelin, new benzolactam derivatives, and so on, all of which are able to release GH in vitro via non-GHRH mechanisms.[3,4] Of these compounds, GHRP-6 (His-D Trp-Ala-Trp-D Phe-LysNH_2), synthesized by C. Bowers, is the most representative.[5] Like GHRH, GHRP-6 releases GH specifically, in a dose-related manner, and is active in humans, as well as in all species so far tested.[5] This hexapeptide possesses unusual characteristics: it activates not only pituitary, but also hypothalamic receptors; it does not operate through GHRH receptors or by modulating endogenous GHRH release; and there is some suggestion that it may not operate through the modulation or action of somatostatin.[5] Although its exact mechanism and point of action for releasing GH are unclear, the new and unusual properties of GHRP-6 may be useful for the study of some pathological states in humans. We have used GHRP-6 with two aims: (1) to further understand the mechanism of action of these small peptides, and (2) to evaluate whether they can be used as diagnostic tools in the clinical setting.

PATHOLOGICAL STATES LEADING TO HYPOTHALAMO-PITUITARY DISCONNECTION IN ADULT PATIENTS

The GH-releasing activity of GHRP-6 alone or in combination with GHRH was assessed in 12 adult patients with tumoral pathologies that had resulted in a state of hypothalamopituitary disconnection, also called functional pituitary stalk section. In all patients, the primary process (craniopharyngioma, nonfunctional adenoma, or suprasellar metastasis) maintained the pituitary intact while altering the flux of messages from the hypothalamus. In fact, the patients who were unresponsive to hypothalamic stimuli were responsive, after a delay, to synthetic hypothalamic hormones, and they all required end-organ hormone replacement therapy. By definition and in contrast with control subjects, in these patients any GH-releasing agent that mainly acts through hypothalamic structures will be non operandi.

As Fig 1 shows, patients with hypothalamopituitary disconnection displayed a normal, although delayed, GHRH-mediated GH release, a result providing evidence for a well-preserved somatotroph pool, as well as GH stores. Normal subjects showed the expected GHRP-6–mediated GH release, with this being higher than when tested with GHRH. By contrast, in patients with hypothalamopituitary disconnection, GHRP-6–induced GH secretion was completely blocked.[6] This is the first direct indication that the new GH-releasing peptides act mainly at hypothalamic structures, with the direct activation of the pituitary being minimal; this is a curious property for compounds that were developed for their in vitro GH-releasing capabilities.

One peculiar finding is that GHRP-6 and GHRH, when administered together, act synergistically, ie, the GHRH-plus GHRP-6–induced GH discharge is significantly higher that the arithmetic sum of the GH released by GHRH alone plus the GH released by GHRP-6 alone.[7] In patients with hypothalamopituitary disconnection, the synergistic effect of GHRH plus GHRP-6 was absent (Fig 1), again suggesting that this potentiating activity implies the activation of structures located at the hypothalamic level.

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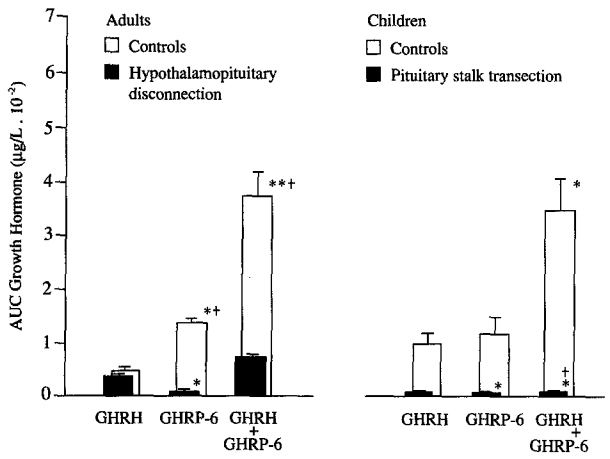

Fig 1. Areas under the curve (AUC) of GH secretion in adults with hypothalamopituitary disconnection, in children with neonatal pituitary stalk transection, and in their respective controls. Subjects were tested on 3 different occasions with either GHRH (1 μg/kg, intravenously [IV]), GHRP-6 (1 μg/kg, IV), or GHRH plus GHRP-6. *$P < .05$ v. GHRH. Redrawn from Popovic et al[6] and Pombo et al.[12]

CHILDREN WITH PERINATAL PITUITARY STALK TRANSECTION

The syndrome of idiopathic GH deficiency is composed of several distinct pathological entities, of which the main contributors are secondary GH deficiencies generated by altered secretion of hypothalamic hormones controlling GH. Alternatively, these deficiencies could be the result of structural alterations that impede the delivery of the hormones to the pituitary. One group of GH deficiencies based on such structural alterations consists of childhood pituitary stalk transection resulting from perinatal damage due to breech delivery or asphyxia suffered at birth, or low birth weight.[8,9] Children with neonatal pituitary stalk transection usually develop pan-hypopituitarism of variable degree, but GH deficiency is present in all of them and is the first hormonal deficiency to appear.[10] Magnetic resonance image (MRI) scans from such children show transection of the pituitary stalk and formation of an ectopic posterior lobe.[11] A simple and reliable dynamic test for the diagnosis of GH deficiency in such patients would be desirable.

When children with GH deficiency due to pituitary stalk transection were tested with GHRH, GHRP-6, or GHRH plus GHRP-6, a severely blunted GH release was observed (Fig 1). The blunted response after GHRP-6 was similar to that observed in adults. Furthermore, this group showed a near-absent GHRH- plus GHRP-6–mediated GH release.[12] The latter finding is interesting considering that, for example, the combined administration of both peptides is the most potent GH releaser found to date, and of the patients studied here, none attained a level of 5 μg/L. On a biochemical basis, this result immediately distinguishes patients with stalk interruption from patients with other causes of GH deficiency, in whom the GH response is always higher than 10 μg/L.[13] Although further tests with a larger group of patients are needed before reaching firm conclusions, the data presented here suggest that GHRH plus GHRP-6 administration could be a simple, cost-effective test for an immediate diagnosis of hypopituitarism due to pituitary stalk transection. These results further support the view that the new releasing peptides need an operational hypothalamus to exert their effects.

One of the most interesting findings is the very low GHRH-induced GH secretion observed in the patients with stalk interruption, which is in contrast with observations in adult patients. It seems that one hypothalamic factor, probably GHRH, is crucial for developing or maintaining the normal somatotroph population in the neonate and in early childhood, but its absence in adult life does not introduce any change in somatotroph number and responsiveness. This hypothesis is inferentially supported by results of studies in rats, which have shown that pretreatment of neonates with anti-GHRH serum induces permanent damage to GH secretion and growth, while being devoid of long-term effects in adults.[14]

In conclusion, both the acute GH-releasing capability of GHRP-6 and the synergistic action exerted by the combined administration of GHRH plus GHRP-6 were se-

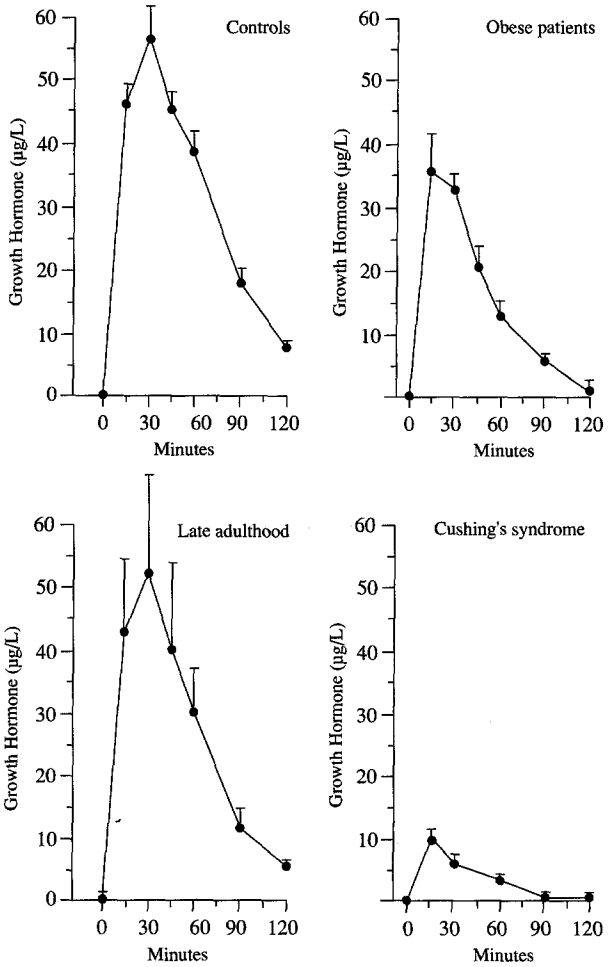

Fig 2. GH secretion after combined administration of GHRH plus GHRP-6 in control subjects, obese patients, normal elderly subjects, and patients with Cushing's syndrome. Redrawn from Leal-Cerro et al,[21] Cordido et al,[23] and Micic et al.[24]

verely impeded in patients with functional or organic pituitary stalk transection, whether children or adults. In these patients, GHRP-6 was always less effective than GHRH, suggesting that the main action of the hexapeptide is exerted at the hypothalamic level through an as yet undetermined mechanism.

GH DEFICIENCY IN ADULTS

A large number of patients with tumors of, or radiation- or disease-induced damage to, the hypothalamopituitary area, develop life-long GH deficiency. The problem of adults with GH deficiency has received considerable attention in the last few years, as it is associated with alterations in body composition, an increased prevalence of cardiovascular morbidity, and a shortened life expectancy.[15] Adults with GH deficiency greatly benefit from replacement therapy with GH.[16] However, the diagnosis of GH deficiency in adults shares some of the uncertainties of the diagnosis in children, and good and specific biochemical tests are still needed.[17] In contrast with children, additional confounding factors in adults with GH deficiency are adiposity and age—both being associated with decreased or absent GH secretion in normal adults.[18]

GHRP-6 may thus also be a new and promising tool for exploring GH secretory mechanisms in adults with suspected GH deficiency. In fact, in normal subjects, combined administration of GHRH plus GHRP-6 elicits a powerful GH discharge[6] (Fig 2), and this enhanced secretion is similar in men, women, and normal children.[13,19,20] Interestingly, while GHRH- plus GHRP-6–mediated GH secretion is blocked in patients with Cushing's disease,[21] the same stimulus elicits a near-normal GH discharge in obese patients[22,23] (Fig 2). Similarly, in elderly subjects, GHRH-plus GHRP-6–induced GH release is near normal[24] (Fig 2). It appears, then, that the combined test may be used for the diagnosis of GH-deficiency states in adults, as it is scarcely affected by age, obesity, or sex.

A group of GH-deficient adult patients, all diagnosed by the standard criterion of GH secretion less than 5 μg/l after an insulin tolerance test, was reassessed. Some presented normal levels of insulin-like growth factor-1 (IGF-1), a finding frequently observed in some patients labeled as GH-deficient, but with no clear cause. When these subjects were tested with the combined administration of GHRH plus GHRP-6, several showed a noteworthy release of GH.[25] Interestingly, most of these responders also had normal IGF-1 values and a diagnosis of isolated GH deficiency. In contrast, the vast majority of patients with blunted GH secretion due to either GHRH plus GHRP-6 administration or hypoglycemia, also showed low IGF-1 values and belonged to a group diagnosed as having multiple pituitary hormone deficiency. Though considerably more work is needed before reaching clear-cut conclusions, it appears that the combined stimulus of GHRH plus GHRP-6 may identify a subgroup of GH-deficient adults in whom the gold standard test of hypoglycemia is not truly diagnostic.

CONCLUSIONS

The new GH secretagogues, among which GHRP-6 is the most widely studied, may represent a new physiological system that participates in the regulation of GH secretion in humans. GHRP-6 and similar such compounds appear to be promising tools in the diagnosis of some pathological clinical states, and their role is likely to expand in the immediate future.

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