

Metabolic Modulation of the Growth Hormone-Releasing Activity of Hexarelin in Man

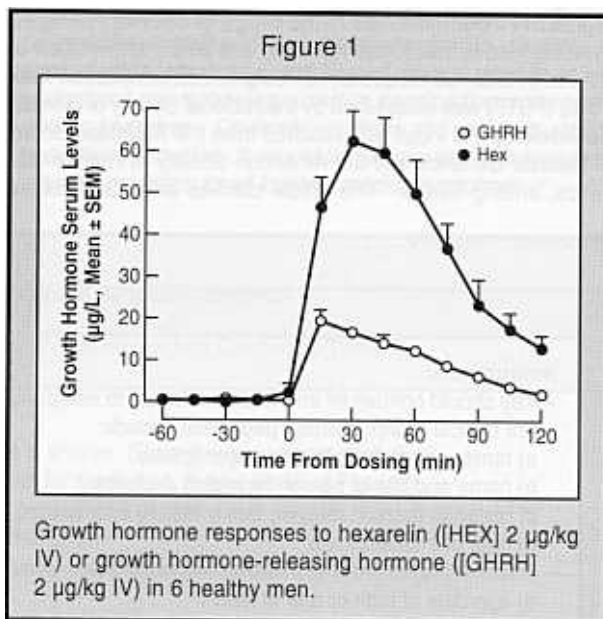
Maccario and colleagues studied the mechanism of action of hexarelin by investigating its interaction with glucose and free fatty acids. They specifically questioned whether the growth hormone (GH)-releasing effect of hexarelin could be reduced by factors known to inhibit basal and GH-releasing hormone (GHRH)-stimulated GH secretion. Six normal men participated in the study and underwent 6 treatment sessions separated by washout periods of at least 3 days. All subjects participated in each of the 6 different protocols, which included: (1) hexarelin, 2 µg/kg IV at 0 minutes; (2) GHRH, 2 µg/kg IV at 0 minutes; (3) hexarelin, 2 µg/kg IV at 0 minutes plus glucose (100 g orally at -45 minutes); (4) hexarelin, 2 µg/kg IV at 0 minutes plus lipid-heparin infusion (250 mL of a 10% lipid solution plus 2,500 U heparin from -30 to +120 minutes); (5) GHRH, 2 µg/kg IV at 0 minutes plus glucose; and (6) GHRH, 2 µg/kg IV at 0 minutes plus lipid-heparin infusion. Blood samples were taken every 15 minutes from -60 to +120 minutes. Serum GH, plasma glucose, and plasma free fatty acid levels were measured.

No significant decreases in basal GH were observed during the study. Hexarelin induced a much higher GH peak than did GHRH (62.6 ± 8.0 µg/L vs 19.8 ± 2.4 µg/L). The increase in plasma glucose after the oral load was similar during hexarelin and GHRH testing, but the GH-releasing effect of GHRH was more inhibited by glucose (peak, 5.6 ± 0.9 µg/L vs 38.4 ± 7.9 µg/L) than that of hexarelin. The lipid-heparin infusion increased plasma free fatty acids similarly during both hexarelin and GHRH treatment and basal GH levels were reduced similarly during both studies. The GH released by stimulation with GHRH was reduced to 4.9 ± 1.0 µg/L ($P < 0.01$) while that of hexarelin was reduced to 34.2 ± 4.5 µg/L ($P < 0.05$). The GH response to hexarelin after glucose was similar to that during lipid-heparin infusion and much higher than the GH response after GHRH alone ($P < 0.05$).

This study demonstrates a greater effect of oral glucose and lipid-heparin infusion on the GH-releasing effect of GHRH than that of hexarelin. The authors state that the results showing that the GH response to hexarelin is blunted but not abolished by glucose indicate that the stimulating effect of GHRP is partially resistant to an increase in endogenous somatostatin. The potential inhibitory effect of free fatty acids on basal and GHRH-induced GH secretion may be explained by a direct action on the pituitary. The GH-stimulating effect of hexarelin is partially resistant to the inhibitory effect of free fatty acids. Thus, unlike GHRH, the GH-releasing effect of hexarelin is partially resistant to the inhibitory effects of both glucose or free fatty acids. This resistance may be due to antagonism of somatostatinergic activity within the hypothalamus or directly at the pituitary. The authors caution that other unknown mechanisms cannot be ruled out.

Maccario M, et al. *Metabolism* 1995;44:134-138.

Editor's comment: More and more information is rapidly becoming available regarding the actions of GH-releasing peptides. As the authors point out, GH-releasing peptides release more GH than GHRH, and apparently have some action on specific non-GHRH, nonopiate receptors in both the pituitary and hypothalamus. The present study provides information with regard to the mechanism of action of these hormones and the level at which these hormones may act. Hexarelin is one of



the most recently and most frequently studied GH-releasing peptides in humans. It can be given either IV, subcutaneously, intranasally, or orally. We anticipate reports of the use of this hormone to treat patients with GH deficiency due to hypothalamic abnormalities. It is realistic to assume that such data should soon be forthcoming and that GH-releasing peptides may provide a new and potentially more practical method than GHRH for treating some children with growth failure.

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