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A New Receptor for Growth Hormone–Release Peptide

P. Michael Conn and Cyril Y. Bowers

In 1984, a synthetic hexapeptide was developed that causes release of growth hormone from the pituitary gland. But even then there were hints that this synthetic peptide (called GHRP, for growth hormone release peptide) and the natural growth hormone–releasing hormone acted at distinct receptors in the pituitary, suggesting that GHRP was mimicking a second "endogenous factor or . . . hormone that regulates growth hormone release" (*1*, p. 1542). Now in this issue of *Science*, a group of researchers from Merck reports the cloning of the receptor for these synthetic growth hormone secretagogues (*2*), clinching the existence of a second route for growth hormone regulation, and opening the door for identification of the endogenous ligand for this receptor.

Until recently the typical path leading to the development of a drug has been to identify the active compound and then to make analogs that recognize the target (usually a receptor or an enzyme). But Howard *et al.* (*2*) have followed a different route: They identified a potential lead drug before the identification of either the endogenous active compound or the receptor. The scientific history that led to this development is a fascinating story of independent accomplishment by individuals whose efforts may now be resulting in a valuable new class of drug.

It was recognized for years that opiates can cause release of growth hormone; indeed, certain peptide analogs of the opiate Met-enkephalin actually lack opiate activity but still cause release of growth hormone (*3*). The best of these early compounds GHRP-6 (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2) was interesting, because it had the biological activity of a hypothalamic growth hormone–releasing hormone (*1*). However, it contains two uncoded D–amino acid residues and so is clearly not naturally present in mammals.

At about the same time, a natural 44–amino acid protein from the hypothalamus was identified that causes release of pituitary growth hormone (GHRH) (*4*). Defying a number of predictions, GHRP-6 did not compete with GHRH for its receptor (*5*). Likewise, a proposed mechanism of action in which GHRP-6 caused growth hormone release by inhibiting the binding of somatostatin (which inhibits growth hormone release) to its receptor was excluded. In fact, GHRP-6 could synergize with GHRH to release growth hormone in animals and humans (*5*, *6*).

GHRP-6 and its chemical descendants were licensed to a series of drug companies whose researchers prepared peptidic analogs in the hope of identifying some that might promote growth hormone release in humans or be useful for veterinary purposes. And GHRP-6 and its analogs did show potent growth hormone–releasing activity by intravenous, subcutaneous, intranasal, and oral routes in humans and topically in mice (*7*–*9*).

In 1990, recombinant human growth hormone (rhGH) was shown to increase the quality of life for otherwise healthy men aged 61 to 81 with low plasma concentrations of insulin-like growth factor–1 (IGF-1) of 350 units per liter (the "youthful" range is 500 to 1500 units per liter) (*10*). In the experimental group, who received rhGH three times weekly for 6 months, the IGF-1 value moved into the youthful range, accompanied by an increase in lean body mass, a decrease in adipose tissue mass, and an increase in average lumbar vertebral bone density. Skin thickness also increased. But thrice weekly self-administration of rhGH would be expensive as a routine treatment, and aging patients would likely have difficulty with compliance. Clearly, a drug that would cause release of the individual's own growth hormone would be preferable, especially if a version with oral activity were available. Physicians treating short-statured children, as well as veterinarians, would find such compounds useful. Another advantage would be that the GHRP-like compounds increase growth hormone secretion in the normal pulsatile pattern and so, in contrast to rhGH administration, might be less likely to have any adverse clinical effects in older subjects.

The Merck group has now identified compounds that may fulfill the criteria of useful agents and has used them to clone the receptor for this class of compounds (*2*, *11*–*13*). Their findings demonstrate the existence of an endogenous system, distinct from GHRH and somatostatin, that participates in the regulation of growth hormone release. This "reverse pharmacology" then gives us access to the receptor, as well as (presumably) agonists for it, even before we know the endogenous ligand or the precise physiological role of the receptor. Identification of the receptor unequivocally establishes a novel target of action for this drug class.

P. M. Conn is with the Oregon Regional Primate Research Center, Beaverton, OR 97006–3499, USA, and in the Department of Physiology and Pharmacology, Oregon Health Sciences University, Portland, OR 97201, USA. E-mail: connm@ohsu.edu. C. Y. Bowers is in the Department of Medicine, Tulane Medical School, New Orleans, LA 70112, USA. E-mail: rjabower@tmcpop.tmc.tulane.edu

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