Central Actions of Peptide and Nonpeptide Growth Hormone Secretagogues

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INTRODUCTION

For some time now, the authors have been investigating the neuroendocrine events leading to increased growth hormone (GH) secretion following administration of GH secretagogues, including GH-releasing peptide (GHRP-6). It is now well established that these compounds act both at the pituitary (1–5) and within the central nervous system (CNS) (6,7). The recent cloning of the GHRP-6 receptor has paved the way for the localization of the receptors at both pituitary and hypothalamic sites (8).

In most species, GH is secreted in a highly pulsatile pattern that is believed to reflect a balanced alternation in the output of two neuroendocrine systems, the GH-releasing hormone (GHRH) neurons and the inhibitory somatostatin neurons. The effects of GH secretagogue administration on the pattern of GH secretion are complex and may be mediated, at least in part, by modification of the output of the central GHRH-somatostatin pulse generator. However, to date, no endogenous ligand for GH secretagogues has been
identified, and hence, it is not clear whether such a ligand participates in the normal physiological control of pulsatile GH secretion. In conscious male rats, a GHRP-6 infusion causes an initial GH peak followed by a sustained elevation of plasma GH concentrations during which pulses occur, but the normal three hourly pulsatile rhythm is disrupted (9). Similar responses have been observed in pigs infused with the nonpeptide secretagogue L-700,653 (10) and in guinea pigs infused with L-692,585 (11). Here we will review what is known about the central site and mechanism of action of the GH secretagogues to consider how an endogenous GH secretagogue ligand might influence the GHRH-somatostatin pulse generator network; and to consider the physiological circumstances in which such a ligand might be released will be reviewed.

**ACTIVATION OF CELLS IN THE ARCULATE NUCLEUS FOLLOWING GH SECRETAGOGUE ADMINISTRATION**

In 1993 it was shown that an iv injection of GHRP-6 causes activation of cells in the rat hypothalamic arcuate nucleus as reflected by increased electrical activation in a subpopulation of neurosecretory neurons (Fig. 1) and an increased expression of Fos-immunoreactivity in a subpopulation of cells in this region (Fig. 2) (6). Similar central activation follows administration of related, nonpeptide mimetics (7). The arcuate nucleus is the only hypothalamic region to show such a response, though the authors now know that Fos expression is also induced by GHRP-6 in some neurons in the area postrema and of the neighboring nucleus tractus solitarii (12). Fos is the protein product of the immediate early gene (IEG) c-fos, and is thought to be involved as a transcription factor linking electrical activity to changes in gene expression. Fos is expressed in many neuronal systems following activation. In the magnocellular neurosecretory system regulating neurohypophysial hormone secretion, Fos expression has been extensively characterized (13–15), and is established to be, for some systems at least, a reliable and sensitive indicator of neuronal activation in a very wide range of physiological and experimental circumstances. In oxytocin neurons, c-fos mRNA is induced within 10 min following stimuli that increase neuronal activity by a mean of only about 1 spike/s (15).

The GHRP-6-induced activation of Fos expression in arcuate neurons is the consequence of a direct central action since injection of low doses of GHRP-6 (0.1 μg) into the third ventricle induces a selective Fos expression similar in distribution and equivalent in extent to that induced by an iv injection of 50 μg of this compound (7). Thus, either GHRP-6 penetrates the blood–brain barrier readily following systemic administration, or its primary central site of action is at specialized brain sites where the blood–brain barrier is relatively permeable. Although the median eminence is known to be one such specialized site, the arcuate nucleus itself is not. In the hypothalamus as at the pituitary, GHRH does not act in the same way as GHRP-6, and central administration of GHRH does not induce Fos expression in the arcuate nucleus.

**IDENTIFICATION OF THE ARCULATE CELLS ACTIVATED BY GH SECRETAGOGUES**

That the central action of the GH secretagogues includes increased GHRH release was first suggested by the observation that, in the rat, the administration of GHRH antiserum attenuates the GH response to GHRP-6 (9). Direct measurement of GHRH release into the portal blood of sheep has confirmed that GHRH is released following GH secreta-