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Preface

During the past decade there has been an emerging interest in growth hormone secretagogues (GHSs) not only as research tools, but as diagnostic, prophylactic, and therapeutic agents. This heightened interest resulted in large part from two events: the expanding public demand for growth hormone (GH) replacement during aging, and the development of receptor-specific, orally active secretagogues. Historically, GHS research intensified during the late 1960s and early 1970s. At that time, research teams at the Salk Institute and Tulane University were vying for the honor of being first to describe the molecular structure of growth hormone–releasing hormone (GHRH) and other hypothalamic neuropeptides as part of an effort to understand the functional relationship between the brain and pituitary. A significant obstacle to these efforts was the lack of sufficient material in hypothalamic tissue to facilitate sequencing the peptides by technology of the day. Thus, it was not until the discovery that some patients with pancreatic tumors displayed acromegalic characteristics owing to the production of GHRH that sufficient material derived from these tumors became available for sequencing. Eventually, the competing sides tied in their race and the structure for GHRH was simultaneously published by Drs. Roger Guillemin and Andrew V. Schally. In 1977 they shared the Nobel Prize in Physiology for their work on hypothalamic peptides.

During the time that Guillemin and Schally were taking a traditional approach to describing the amino acid sequence of GHRH, another research team headed by Dr. Cyril Bowers was using a more novel approach to the problem. Working under the assumption that hypothalamic peptides might be similar in structure, Bowers's team modified those whose structures were known and screened them for bioactivity. One family of compounds resulting from this effort was derived from enkephalin and proved to have weak GH-releasing activity in vitro. The prototype molecule was a hexapeptide, His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2, which was subsequently named GH-releasing hexapeptide or GHRP-6. Further work with the molecule showed that it potentiated GHRH activity, especially in vivo, and that the molecule worked through specific, saturable receptors and intracellular second messengers that were distinctly different from GHRH. Work on these xenobiotics accelerated in the 1990s when nonpeptidyl mimics of GHRP were developed within the pharmaceutical industry. The new molecules were orally active and readily bioavailable. A rapidly growing base of information on the efficacy of these molecules suggested that they were potentially cosecretagogues of GHRH, and the search for an endogenous ligand was initiated. As a result of this effort, a 28 amino acid molecule produced by the gut was isolated. The report was published late in 1999 and later expanded at the Third International Symposium on Growth Hormone Secretagogues during February 2000. The endogenous compound was named ghrelin.

In 1994, recognizing the rapid and progressive expansion of interest in GH regulatory physiology, we organized the First International Symposium on GH Secretagogues, which was sponsored by Serono Symposia and held in St. Petersburg, FL. Befitting the theme of this first meeting, special recognition was awarded to Dr. Roger Guillemin for his noteworthy accomplishments in the field that had earned him the Nobel Prize. Because of the widespread interest in developing these compounds by the pharmaceutical industry, we held a Workshop Conference on Growth Hormone Releasing Secretagogues immediately following the symposium at the Food and Drug Administration in Bethesda, MD. Because GHRP research was still in a state of relative infancy, the first meetings focused mainly upon the relationship between GHRH and somatostatin for maintaining GH homeostasis. However, by 1997 it was becoming very obvious that the GHRPs represented a real component of that regulatory axis so that the Second International Symposium on Growth Hormone Secretagogues, which was held in Tampa, FL, included more discussion of these compounds. Accordingly, the investigators from Tulane including the Nobel Laureate Dr. Andrew V. Schally and his colleague Dr. Cyril Bowers were formally recognized for their work. Dr. Schally received commendation for his earlier work, as well as for his efforts to discover new therapeutic applications for structural modifications of GHRH. Dr. Bowers was honored for his distinguished work in the discovery and development of GHRP.

The Third International Symposium on GH Secretagogues was held in Keystone, CO, during February 2000, at which state-of-the-art talks were presented on all aspects of GHRH and GHRP physiology and pharmacology. The proceedings from this meeting serve as the basis of the Virtual Symposium published herein. With slight modification of the original meeting organization, published articles have been organized into three main categories. The first focuses on the influence of secretagogues upon GH neuroendocrine physiology. Specifically, topics range from central loci and hypothalamic networks in which GHRH and GHRP operate to sites in peripheral tissues that they directly influence. The complex functional interactions of

GH secretagogues with somatostatin, its synthetic analogs, leptin, and gonadal steroids are also examined. Finally, articles that evaluate the properties of secretagogues that influence functional dynamics of pituitary GH secretion as well as the somatic responses to those effects are presented. Following the discussion of secretagogues on GH physiology, the subject of this symposium shifts to the topic of aging and disease in which normal function of the GH neuroendocrine axis becomes impaired. The value of secretagogues as diagnostic and therapeutic agents are discussed both in the context of their actions on GH secretion and as unique and direct effectors of somatic function, specifically that of the heart. Finally, progress in new product development within the pharmaceutical industry is discussed.

As a result of the success of these meetings in the past and considering the logarithmic growth in research on and application of GHSs, a fourth conference is planned for the fall of 2002. Considering the monumental strides that have occurred in this field over the short course of the past decade, it is impossible to predict the advances that will be reported at that conference. However, they will undoubtedly supersede our expectations as our understanding of GHSs and their potential applications in medicine are put to practice.

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