Octreotide: From Basic Science to Clinical Medicine

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It gives me much pleasure to dedicate this book to two great friends of mine, as a token of my deep appreciation of their constant encouragement and continuing support:

Mara Gioffré Florio Micali, MD,
Associate Professor of Surgical Oncology, School of Medicine and Dentistry, University of Messina, Italy

She helped me to make a dream, reality.

Jean-Paul Galmiche, MD, FRCP (Ed.),
Professor and Chairman, Department of Gastroenterology and Hepatology, Faculty of Medicine, University of Nantes, France, and President, European Association for Gastroenterology and Endoscopy (EAGE)

He gave me the stimulus to move from basic science to clinical medicine and to find out, over the years, the essential link between digestive clinical pharmacology and gastroenterology.

Carmelo Scarpignato

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In the age of biotechnology, the modelling of the somatostatin molecule to create an effective new therapy, octreotide, is a shining example of a practical success. It illustrates an effective synergy between industry and science. As you will see in this exciting book, the science has not stopped. Here recorded are numerous advances in both basic biology and clinical application. The future looks exhilarating, we have lucidly explained the new approaches and the new applications. This is a comprehensive account by all the experts in a fast-moving field. It is both good reading and a volume for reference. The editor and the authors are to be congratulated.

The D cell was first described by Bloom [1] in 1931. It lay alongside the cell in the islet of Langerhans and although full of granules, suggesting it synthesized a hormone, its product was unknown. In the search for the factor that controlled growth hormone release, Brazeau et al. [2], in 1973, identified within the hypothalamus a 14-amino acid peptide inhibitor of growth hormone release, somatostatin. Later this was shown to pharmacologically inhibit release of a great many
other hormones and indeed prevent their action on the target tissue as well. Somatostatin was nicknamed ‘endocrine cyanide’. Immunocytochemistry demonstrated somatostatin to come from both endocrine cells (for example this is the product of Bloom’s D cell in the islet) and also neurones. Somatostatin was shown to be particularly abundant in neurones in the hypothalamus. It was early shown that analogues of somatostatin could have differential effects in the rat, for example D-Trp8, D-Cys[4] somatostatin inhibited glucagon and growth hormone more than insulin [3]. This was pharmacological evidence of the possibility of multiple somatostatin receptors. Unfortunately these differential effects could not be shown in man [4].

Regulatory hormones do not have a singular function, rather they are the means of transmitting information from one cell to another. This information is spatially and temporally particular. Thus the biological role of somatostatin is dependent on circumstance and position. It is likely to, and does, differ greatly from instance to instance. However, evolution is by its nature parsimonious. Thus, somatostatin tends to be inhibitory, at least in endocrine tissue. This tells us little about its putative role in the CNS. Somatostatin’s post-receptor action includes inhibition of cAMP formation [5], increase of the inwardly rectifying potassium current [6] (though inhibiting it in oligodendrocytes [7]), activation of MAP kinase and induction of the phosphorylation of 85-kD cytosolic phospholipase A2 (cPLA2), in a PTX-sensitive manner [8].

Somatostatin was early thought likely to be useful in the treatment of endocrine tumours as these are often slow growing and produce most of their symptoms by the excess hormone secretion. Thus, suppression of this abnormal secretion could result in useful palliation of symptoms. This principle was tested and found successful. The short half-life of somatostatin made it impractical in the clinic and various tricks were tried, with limited success, to extend its effect [9]. The amount of peptide required was anyway enormous and uneconomic. The modelling of the molecule and production of a small analogue that preserved the active site while protecting it from degradation (octreotide) was immediately recognized as a major clinical breakthrough [10] which has brought considerable relief to very many endocrine patients. The recent development of a preparation acting over weeks will further improve patient acceptability.

Other therapeutic possibilities are well described in this book. The effect of somatostatin on cell growth, although seen in the test tube, has been less easy to demonstrate in the clinic. Endocrine tumour growth rate is probably slowed in patients on octreotide. More exciting is the possibility that endothelial and vascular smooth muscle growth may be inhibited [11, 12]. This would have major impact in angioplasty, where post-procedure vascular closure due to a hypertrophic reaction is a major clinical problem.

Future directions clearly include the development of nonpeptide (orally
active) receptor-specific agonists and antagonists. The biology and mechanism of action of each receptor type needs to be clarified. In view of the abundance of somatostatinergic circuits in the CNS, specific analogues may yield new psychoactive agents, while in the periphery an agent which suppresses glucagon and growth hormone release while leaving insulin unaffected (or even enhanced) would clearly be useful in treating diabetes mellitus.

Somatostatin is an exciting peptide in an exciting field. Read this book and learn.

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Preface

During the last decades a truly remarkable series of advances has taken place in our understanding of the biochemistry and physiology of the gastrointestinal (GI) peptides. Gut peptide receptor agonists and antagonists, however, have found limited application in the therapy of GI diseases because of lack of knowledge of the peptide receptor subtypes mediating particular physiologic events, and lack of specific agonists and antagonists at these various receptor subtypes. Furthermore, most peptides that act as agonists or antagonists have only a short duration of action that makes them unsuitable for long-term clinical use. Amongst the different peptides, somatostatin has been the one whose wide range of physiological and pharmacological actions has been exploited in clinical practice. Several long-acting analogues have been synthesized and, amongst them, octreotide has been introduced in clinical practice. This compound represents indeed a successful example of gut peptide receptor agonist that has found a role in the treatment of various (GI and non-GI) diseases. After 7 years of extensive clinical use, new exciting developments have been made and novel therapeutic applications are being tested. It is therefore a timely moment to review in this book of the prestigious series Progress in Basic and Clinical Pharmacology both present and future therapeutic applications of octreotide as well as the basic science behind it. Unlike some of the other publications in this field, this volume is not the result of any national or international symposium. It represents the collection of 21 commissioned monographic reviews generously offered by 43 internationally recognized scientists, all of whom have significantly contributed to this new
knowledge, in order to provide a glimpse of what may lie ahead. I am indebted to all the contributors for having accepted to share with us their knowledge and for providing us with excellent manuscripts despite the many daily commitments. The book has been organized into 5 different sections dealing with basic science, endocrine and digestive diseases, therapeutic perspectives and safety issues. It is expected that this format will facilitate use of the book by the different specialists and provide a deep insight into octreotide’s wide range of therapeutic applications. I sincerely hope that new thoughts or ideas may arise from a reading of the present volume. Its publication, and the efforts of both the authors and the editor, will then have been justified.

This volume would never have gone to press without the careful and thorough assistance I received from people at the Editing and Production Department, S. Karger AG Medical and Scientific Publishers, Basel. I wish here to express my appreciation to Ms. Denise Greder who carefully followed the development of the project and to Ms. Anke Rogal for her remarkable work of supervision and editorial production. In addition, I owe so much to my Secretary, Mrs. Sabina Cavagni, for her outstanding job of managing papers, corresponding with authors and referees and following every stage of editorial work. Last but not least, my sincere gratitude goes to Sandoz Pharma Italy for backing the production costs and rendering this publication possible. There, Dr. Maria Gabriella Camboni and Dr. Luigi Boano showed a never failing enthusiasm and made huge efforts to make this book available to the scientific and medical community.

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