Preface

The melanocortins have a fascinating history, first as pituitary peptide hormones, and more recently as neuropeptides. The study of the melanocortin peptides and their receptors has contributed many "firsts" to biomedical research. Based on the frog skin pigmentation assay, melanotropic activity was first identified in pituitary extracts early in this century; in many ways these experiments heralded the beginning of modern pituitary endocrinology. The melanocortin peptides were also among the first biologically active peptides to be purified and sequenced in the 1950s by Bell, Lerner, Li, Harris, and Geschwind. Cloning of the complete proopiomelanocortin precursor gene by Nakanisha and Numa in 1979 provided one of the first examples of a prohormone precursor encoding a variety of different neuropeptides and peptide hormones.

More recently, work in the field has largely been focused on the receptors for the melanocortin peptides. My own interest in receptors for the melanocortin peptides derived from a structural question rather than any knowledge of, or interest in, the biology of these peptides. In 1989, the structure of the luteinizing hormone receptor was published, and this made it clear that the large glycoprotein hormones were binding to a large extracellular domain attached to the canonical hydrophobic seven-membrane spanning domain known at the time to be the conserved structure for such G-protein coupled receptors as rhodopsin, the β-adrenergic receptor, and the substance K receptor. Though the substance K receptor clearly was capable of binding the hydrophilic substance P peptide without a large extracellular domain, I remember many discussions among scientists at the time, particularly John Potts and Henry Kronenberg at the MGH, that perhaps the extracellular motif of the glycoprotein hormone receptors was a conserved domain that could be involved in the binding of many large peptide hormones such as PTH and ACTH. Ultimately, Kathleen Mountjoy in my laboratory, with important reagents from Jeff Tatro and Seymour Reichlin, Vijay Chhajlani in Sweden, and Ira Gantz at the University of Michigan were able to disprove this hypothesis with the cloning of a family of five different receptors for the melanocortin peptides.

Around the time of the cloning of the melanocortin receptors, there was skepticism about whether many interesting biological findings would result from continued studies of the melanocortin receptors. The mechanism of action of the MSH-R and ACTH-R in pigmentation and adrenal steroidogen-

esis, for example, seemed to be fairly well understood. Happily, over the last eight years, around every corner a remarkable new finding has arisen regarding the melanocortin receptors, their mode of action, and their physiological roles. Continuing with the listing of "firsts," the MC1-R was the first example of a G-protein-coupled hormone receptor to be constitutively activated by naturally occurring mutations, the agouti and agouti-related proteins are the first examples of endogenous antagonists of the GPCRs, and the MC4-R is the first GPCR to be demonstrated to be involved in the central control of energy homeostasis. If the annual number of publications in the melanocortin field is any indicator, the tenfold increase over the last five years suggests a tremendous newfound interest in the remarkable complexity of action and function of the melanocortins.

Organizing *The Melanocortin Receptors* has given much pleasure owing to the many fine colleagues I have had the privilege of working with, quite a number of whom have provided chapters for this volume. I would like to express my sincere thanks to the authors, and to the editors at Humana Press for making this book happen. Finally, I thank my wife Midge and children Miriam, Anna, and David for their continued encouragement and patience, and for genuinely sharing in the excitement of scientific discovery.

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