CHAPTER 1

INTRODUCTION TO RAMPs

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Abstract: Receptor activity modifying proteins (RAMPs) are single transmembrane proteins discovered for their role in the regulation of translocation of certain G-protein coupled receptors (GPCRs) to the plasma membrane. Since its discovery in 1998, several pivotal advances have been made in understanding the function of this family of proteins. This chapter provides a basic introduction to RAMPs as well as details on the various chapters in this book.
INTRODUCTION

In 1998, Foord and his colleagues ended years of frustration among adrenomedullin (AM) and calcitonin gene related peptide (CGRP) receptor biologists by discovering a single transmembrane accessory protein called receptor-activity modifying proteins. Using an expression cloning strategy in Xenopus Oocytes, a 148-amino acid RAMP1 was identified initially and this protein was shown to regulate proper translocation of calcitonin receptor-like receptor (CLR) to the plasma membrane. In addition, this protein was shown to regulate CGRP responsiveness of this receptor. Data base search revealed two additional and related RAMPs, RAMP2 and RAMP3 (Fig. 1). It was then determined that RAMP1 and CLR combination gives rise to a CGRP responsive receptor whereas RAMP2 or RAMP3 and CLR combinations give rise to an adrenomedullin receptor. Prior to McLatchie et al’s discovery of RAMPs, adrenomedullin/CGRP receptor biologists were frustrated because heterologous expression of CLR alone gave rise to a CGRP receptor only in specific cell types. McLatchie et al’s report clarified that the presence of a particular RAMP in a specific cell line dictated whether CLR expression would give rise to a CGRP receptor or an adrenomedullin receptor, thus ending the confusion.

Subsequent studies have found that of the two peptides, amylin and calcitonin (both of which signal via Calcitonin receptor (CTR)), amylin’s interaction with CTR is dependent on RAMPs, while that of calcitonin is not (For a review, see ref. 4). Taken together, this unique diversity in receptor interaction (four ligands, three RAMPs, two GPCRs) provided a paradigm shift in our understanding of GPCR biochemistry (Fig. 2). Recent findings suggest that RAMPs may diversify ligand-receptor interaction to a much larger scale within the Class II GPCRs. In this regard, Christoupoulos et al showed that, VPAC1 receptor (vasoactive intestinal polypeptide/pituitary adenylate cyclase-activating peptide receptor) interacts with all three RAMPs, whereas the glucagon and PTH1 (parathyroid hormone receptor) interact only with RAMP2. Interestingly PTH2 receptor was shown to interact with RAMP3. In a recently published study, Harikumar et al present further evidence that another member of the Class II GPCR, namely the secretin receptor associates with RAMP3, but not RAMP1 or RAMP2. Together these studies not only expand the repertoire of GPCRs that RAMPs interact with, they also provide evidence for selectivity of GPCRs for certain RAMP members. In addition to interaction with members of Class II GPCRs, previous studies from Dr. Henley’s group have shown that Calcium Sensing receptor (CaSR), which belongs to the Class III GPCR, is also regulated by RAMPs. The role of RAMPs in regulating a variety of GPCRs is only expanding and this book provides a detailed account of