CHAPTER 6

RAMPs AS DRUG TARGETS

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Abstract: The receptor activity-modifying protein (RAMP) family of membrane proteins regulates G protein-coupled receptor (GPCR) function in several ways. RAMPs can alter their pharmacology and signalling as well as the trafficking of these receptors to and from the cell surface. Accordingly, RAMPs may be exploited as drug targets, offering new opportunities for regulating the function of therapeutically relevant RAMP-interacting GPCRs. For example, several small molecule antagonists of RAMP1/calcitonin receptor-like receptor complexes, which block the actions of the neuropeptide calcitonin gene-related peptide are in development for the treatment of migraine headache.
INTRODUCTION

G protein-coupled receptors (GPCRs) are the largest single grouping of proteins which are considered “druggable”. GPCRs represent the major signalling system in mammalian cells and are subdivided into three groups: Family A, the largest family, containing receptors for prototypical neurotransmitters and hormones; Family B, incorporating receptors for peptide hormones such as calcitonin (CT) and secretin; and Family C, which includes receptors for small molecules such as glutamate and GABA. GPCRs, like other signalling proteins, can form oligomeric protein arrays which may be critical to many aspects of their function. For many GPCRs it is likely that constitutive dimers or oligomers act as the core functional unit. Furthermore, these receptors, as either a monomer or oligomeric complex, may also interact with other proteins that regulate their function. Interactions such as these create novel opportunities for drug discovery and development as exemplified by the receptor activity-modifying protein (RAMP) family. This chapter will initially consider the range of GPCRs which can interact with RAMPs. The consequences of these interactions will then be reviewed, to indicate the range of functions that could be modulated by targeting RAMPs. Finally, mechanisms for directing drugs towards RAMPs and their complexes will be considered.

RAMPs AND THEIR INTERACTIONS WITH RECEPTORS

As comprehensively described elsewhere in this book, RAMPs are a family of 3 proteins initially shown to regulate the glycosylation, transport and pharmacology of the CT receptor-like (CL) receptor (CLR). RAMP1/CLR constitutes a CT gene-related peptide (CGRP) receptor, whereas RAMP2/CLR and RAMP3/CLR exhibit distinct adrenomedullin (AM) receptor phenotypes. RAMPs revealed a novel mechanism for producing diversity in receptor response. RAMPs were also shown to interact with the related CT receptor to create amylin receptors, with each RAMP/CT receptor complex displaying a distinct phenotype.

CLR and the CT receptor are Family B peptide hormone receptors; subsequent analysis of other members of this receptor family for potential interactions with RAMPs, revealed additional RAMP-receptor partners. There were different degrees of specificity in these interactions. The VPAC1 receptor interacted with all 3 RAMPs, like the CT receptor and CLR. However, the PTH1 and glucagon receptors interacted specifically with RAMP2, and the PTH2 receptor specifically with RAMP3. There was no measurable translocation of RAMPs with the VPAC2, GHRH, GLP-1 or GLP-2 receptors. There is some evidence that the VPAC1/RAMP2 interaction