THE ROLE OF CGRP-RECEPTOR COMPONENT PROTEIN (RCP) IN CGRP-MEDIATED SIGNAL TRANSDUCTION

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The calcitonin gene-related peptide (CGRP)-receptor component protein (RCP) is a 17-kDa intracellular peripheral membrane protein required for signal transduction at CGRP receptors. To determine the role of RCP in CGRP-mediated signal transduction, RCP was depleted from NIH3T3 cells using antisense strategy. Loss of RCP protein correlated with loss of cAMP production by CGRP in the antisense cells. In contrast, loss of RCP had no effect on CGRP-mediated binding; therefore RCP is not acting as a chaperone for the CGRP receptor. Instead, RCP is a novel signal transduction molecule that couples the CGRP receptor to the cellular signal transduction machinery. RCP thus represents a prototype for a new class of signal transduction proteins that are required for regulation of G protein-coupled receptors.

A receptor named the calcitonin receptor-like receptor (CRLR) has been identified that functions as a CGRP receptor when coexpressed with an accessory protein named receptor activity modifying protein-1 (RAMP1). RCP, CRLR, and RAMP1 are expressed in NIH3T3 cells, and CRLR coimmunoprecipitates with RCP from cell extracts. This interaction between RCP and CRLR has been confirmed by yeast two-hybrid studies where we have mapped the interactive sites between CRLR and RCP. Thus, we hypothesize that a functional CGRP receptor is a trimer of proteins: a ligand binding protein (CRLR), an accessory protein that determines pharmacologic specificity (RAMP1), and a protein that couples the receptor to the cellular signal transduction pathway (RCP). This work was supported in part by AHA Awards 9920180V (BEB), 9810018FL (IMD), and NIH DK52328 (IMD).