Abstract—Historically, calcitonin gene-related peptide (CGRP2) receptors were first detected in 1989, when it was shown that the truncated CGRP antagonist, CGRP_{12–37}, preferentially antagonized the chronotropic and ionotropic actions of CGRP on the guinea pig atrium but not its ability to inhibit contraction of the electrically stimulated rat vas deferens. In contrast, the linear CGRP agonist, Cys(ACM)_{2,7}-hCGRP, selectively activated CGRP receptors on the vas deferens (Dennis et al., 1989). Based on these data, it was suggested that the CGRP_{1} receptor was a complex between CLR and RAMP1. It is now apparent that the CGRP_{2} receptor phenotype is the result of CGRP acting at receptors for amylin and adrenomedullin. Accordingly, the term “CGRP_{2}” receptor should no longer be used, and the “CGRP_{1}” receptor should be known as the “CGRP” receptor.

I. Introduction

Heterogeneity among calcitonin gene-related peptide (CGRP) receptors has been divided into two classes, CGRP_{1} and CGRP_{2}. After the cloning of calcitonin receptor-like receptor (CLR) and receptor activity-modifying proteins (RAMPs), it became clear that the CGRP_{1} receptor was a complex between CLR and RAMP1. It is now apparent that the CGRP_{2} receptor phenotype is the result of CGRP acting at receptors for amylin and adrenomedullin. Accordingly, the term “CGRP_{2}” receptor should no longer be used, and the “CGRP_{1}” receptor should be known as the “CGRP” receptor.

II. Studies on Cloned Receptors

A. Calcitonin Gene-Related Peptide and Adrenomedullin Receptors

The best characterized CGRP receptor has two transmembrane-spanning components; a G protein-coupled receptor-like protein, CLR, and also an accessory protein, RAMP1. This receptor has the pharmacological...
profile of a CGRP₁ receptor (McLatchie et al., 1998). Coexpression of CLR with RAMP2 and RAMP3 gives receptors that preferentially bind AM (McLatchie et al., 1998). These are the AM₁ and AM₂ receptors (Poyner et al., 2002). The AM₂ receptor, in particular, can have significant affinity for CGRP and therefore might be activated by this peptide at pharmacological concentrations (Hay et al., 2003). CGRP₈–₃₇ can antagonize AM₁ and AM₂ receptors with estimated pA₂ values in the range of 6.0 to 7.0 (Fig. 1a); BIBN4096BS has no appreciable affinity at either of these receptors (Hay et al., 2003). Therefore, under conditions of high receptor expression, the AM₂ receptor could be activated pharmacologically by CGRP and antagonized by CGRP₈–₃₇ with low potency; the characteristics of a CGRP₂ receptor.

B. Calcitonin and Amylin Receptors

CT receptors are activated only very weakly by CGRP so need not be considered here. On the other hand, AMY receptors can show significant affinity for CGRP. In particular, the AMY₁(a) receptor (insert negative CT receptor [CT (a)] plus RAMP1), at least in transfected cells, may potentially be activated by this peptide at pharmacological concentrations (Hay et al., 2003). CGRP₈–₃₇ can antagonize AM₁ and AM₂ receptors with estimated pA₂ values in the range of 6.0 to 7.0 (Fig. 1a); BIBN4096BS has no appreciable affinity at either of these receptors (Hay et al., 2003). Therefore, under conditions of high receptor expression, the AM₂ receptor could be activated pharmacologically by CGRP and antagonized by CGRP₈–₃₇ with low potency; the characteristics of a CGRP₂ receptor.

III. Conclusions

There are now clear molecular correlates for CGRP receptors identified pharmacologically. The CGRP₁ receptor corresponds to the CLR/RAMP1 complex. The pharmacological profile of the CGRP₂ receptor can be generated by the AMY₁ receptor and, to a lesser extent, by the AMY₃ and AM₂ receptors. Accordingly, it is recommended that the “CGRP₁” receptor should now be called the “CGRP” receptor and the term “CGRP₂” receptor should not be used. There remain significant differences between antagonist affinities found on cell lines and tissues for the same receptor subtype (Fig. 1). These complicate the pharmacological identification of receptors and may relate to accessibility or stability issues of the currently available antagonists.

REFERENCES


Edvinsson L, Nilsson E, and Jansen-Olesen I (2007) Inhibitory effect of BIBN4096BS, CGRP8–37, a CGRP antibody and an RNA-Spiegelmer on CGRP...


