Abstract—Historically, calcitonin gene-related peptide (CGRP) receptors have been divided into two classes, CGRP1 and CGRP2. After the cloning of calcitonin receptor-like receptor (CLR) and receptor activity-modifying proteins (RAMPs), it became clear that the CGRP1 receptor was a complex between CLR and RAMP1. It is now apparent that the CGRP2 receptor phenotype is the result of CGRP acting at receptors for amylin and adrenomedullin. Accordingly, the term “CGRP2” receptor should no longer be used, and the “CGRP1” receptor should be known as the “CGRP” receptor.

I. Introduction

Heterogeneity among calcitonin gene-related peptide (CGRP) receptors was first detected in 1989, when it was shown that the truncated CGRP antagonist, CGRP12–37, 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-hoCGRP, selectively activated CGRP receptors on the vas deferens (Dennis et al., 1989). Based on these data, it was suggested that there were two subtypes of CGRP receptor, CGRP1 and CGRP2. Subsequent work with the antagonist CGRP8–37 confirmed these observations (Dennis et al., 1990). CGRP1 receptors were classified as being antagonized with high potency by CGRP8–37, whereas CGRP2 receptors were less sensitive to the effects of this antagonist. The interpretation of data with Cys(ACM)2,7-hoCGRP is complicated by the fact that it is a partial agonist (Waugh et al., 1999), but observations with CGRP8–37 have demonstrated that a broad range of CGRP8–37 affinities can be observed within a single species (Fig. 1a). A more limited range of studies with the nonpeptide antagonist BIBN4096BS also suggests heterogeneity in receptors responding to CGRP (Fig. 1b). Thus, there is good evidence that CGRP can act via more than one receptor when applied pharmacologically.

When the International Union of Pharmacology nomenclature subcommittee previously considered CGRP receptors, that status of the CGRP2 receptor was unclear (Poyner et al., 2002); this situation has now been clarified.

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, CGRP(8–37), a CGRP antibody and an RNA-Spiegelmer on CGRP FIG. 1. Antagonist affinities on CGRP receptors. a, apparent pA₂ values for CGRP8–37 on human cells and tissues. For CGRP receptors (CLR/RAMP1), data have been combined from studies on recombinant receptors and also 5K-N-MC cells. b, apparent pA₂ values for BIBN4096BS on rat (●) and human (○) cells and tissues. It should be noted that because BIBN4096BS is probably an allosteric antagonist (Hay et al., 2006), the apparent pA₂ values are simply to give a guide as to its affinity at the preparations illustrated here. Data for both figures from Hay et al. (2004), updated to 2008 (Sheykzhade et al., 2004; Springer et al., 2004; Kawase et al., 2005; Nodin et al., 2005; Verheggen et al., 2005; Bailey and Hay, 2006; Gupta et al., 2006a,b; Takushima et al., 2006; Edvinsson et al., 2007; De Mey et al., 2008; Wunder et al., 2008). In addition, an apparent pA₂ for BIBN4096BS of 14 on human pial arteries has been reported (Moreno et al., 2002). Where no error bar is shown, the result is from a single study; otherwise n = 2 to 12. HUVEC, human umbilical vein endothelial cells.


