Receptor Activity-modifying Protein 1 Determines the Species Selectivity of Non-peptide CGRP Receptor Antagonists*

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The heterodimeric CGRP receptor requires co-expression of calcitonin receptor-like receptor (CRLR) and an accessory protein called receptor activity-modifying protein (RAMP) 1 (McLatchie, L. M., Fraser, N. J., Main, M. J., Wise, A., Brown, J., Thompson, N., Solari, R., Lee, M. G., and Foord, S. M. (1998) Nature 393, 333–339). Several non-peptide CGRP receptor antagonists have been shown to exhibit marked species selectivity, with >100-fold higher affinities for the human CGRP receptor than for receptors from other species (Doody, H., Hallermayer, G., Wu, D., Entzeroth, M., Rudolf, K., Engel, W., and Eberlein, W. (2000) Br. J. Pharmacol. 129, 420–423; Edvinsson, L., Sams, A., Jansen-Olesen, I., Tajti, J., Kane, S. A., Rutledge, R. Z., Koblan, K. S., Hill, R. G., and Longmore, J. (2001) Eur. J. Pharmacol. 415, 39–44). This observation provided an opportunity to map the determinants of receptor affinity exhibited by BIBN4096BS and the truncated analogs, Compounds 1 and 2. All three compounds exhibited higher affinity for the human receptor, human CRLR/human RAMP1, than for the rat receptor, rat CRLR/rat RAMP1. We have now demonstrated that this species selectivity was directed exclusively by RAMP1. By generating recombinant human/rat CRLR/RAMP1 receptors, we demonstrated that co-expression of human CRLR with rat RAMP1 produced rat receptor pharmacology, and vice versa. Moreover, with rat/human RAMP1 chimeras and site-directed mutants, we have identified a single amino acid at position 74 of RAMP1 that modulates the affinity of small molecule antagonists for CRLR/RAMP1. Replacement of lysine 74 in rat RAMP1 with tryptophan (the homologous amino acid in the human receptor) resulted in a >100-fold increase in antagonist affinity, similar to the K_i values for the human receptor. These observations suggest that important determinants of small molecule antagonist affinity for the CGRP receptor reside within the extracellular region of RAMP1 and provide evidence that this receptor accessory protein may participate in antagonist binding.

CGRP is a 37-amino acid neuropeptide that is expressed in a variety of cell types in both the central and peripheral nervous systems (5). In many tissues, CGRP-containing fibers are closely associated with blood vessels (6). Among the various physiological functions reported for CGRP, the most pronounced is vasodilation. CGRP is the most powerful of the vasodilator transmitters (7), and its vasoactive effects have been demonstrated in a variety of blood vessels (8), including those in the cerebral, coronary, and mesenteric vasculature.

Mounting evidence suggests that CGRP is involved in the pathophysiology of migraine headache (9). Migraine is thought to be associated with dilation of cerebral blood vessels and activation of the trigeminovascular system (10). During the headache phase of a migraine, CGRP levels are elevated in the cranial circulation (11, 12). Successful treatment of the headache with sumatriptan resulted in normalization of CGRP levels (12), thus implicating CGRP in the pathophysiology of this disorder. Moreover, intravenous administration of CGRP to migraineurs induced a delayed migraineous headache in some patients (13). These observations suggest that inhibition of CGRP-mediated vasodilation may have therapeutic utility in the treatment of migraine.

Research in the area of CGRP has intensified in recent years due in large part to the identification of its receptor, CRLR1 (14), and the cloning of the receptor activity-modifying proteins (RAMPs) (1) and receptor component protein (15). CGRP activity is mediated by the G_coupled G-protein-coupled receptor (GPCR), CRLR, which shares 55% homology with the calcitonin receptor. In an elegant study, McLatchie et al. (1) demonstrated that functional CGRP and adrenomedullin receptors are both derived from CRLR and that the phenotype is determined by co-expression with a particular RAMP. Co-expression of CRLR with RAMP1 results in CGRP receptor pharmacology, whereas RAMP2 or RAMP3 co-expression produces an adrenomedullin receptor. RAMPs are relatively small (148–175 amino acid) proteins containing a single predicted membrane-spanning domain, a large extracellular domain, and a short cytoplasmic domain. CRLR and RAMP1 form a 1:1 heterodimer that was recently shown to undergo internalization as a stable receptor complex in a -arrestin- and dynamin-dependent fashion (16). The molecular function of RAMPs includes cell surface targeting (17) and may involve direct ligand binding, indirect modulation of CRLR conformation, or both (18).

In the pursuit of small molecule antagonists of the CGRP receptor, CRLR/RAMP1, Doody et al. (2) identified a potent and highly specific compound, BIBN4096BS (Fig. 1). BIBN4096BS

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§ The on-line version of this article (available at http://www.jbc.org) contains Tables S1–SIII and Fig. S1.

The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EBI Data Bank with accession number(s) AF424807.

1 The abbreviations used are: CRLR, calcitonin receptor-like receptor; hCRLR, human CRLR; rCRLR, rat CRLR; RAMP, receptor activity-modifying protein; hRAMP, human RAMP; rRAMP, rat RAMP; GPCR, G-protein-coupled receptor; hCGRP, human CGRP.
demonstrated high affinity for the human CGRP receptor, with a $K_d$ of 14 PM. Of particular interest was the observation that BIBN4096BS exhibited >100-fold lower affinity for CGRP receptors from rat, rabbit, dog, and guinea pig, although the affinity for the marmoset receptor was reported to be similar to that for human. These authors utilized marmoset for in vivo studies to evaluate the utility of BIBN4096BS as a potential anti-migraine agent. A related compound, Compound 1 (Fig. 1), was likewise shown to be a significantly more potent antagonist on human cerebral arteries than on guinea pig cerebral and porcine coronary arteries (3, 4).

To probe the species selectivity observed with the non-peptide antagonists BIBN4096BS and Compound 1, we chose to focus on the affinity differences seen for the human and rat CGRP receptors. In this report, we demonstrate that the small molecule antagonists, BIBN4096BS, Compound 1, and an analog, Compound 2, have different affinities for the human and rat receptors, and these differences are determined by the species origin of RAMP1 that is co-expressed with CRLR. Furthermore, through the use of chimeric RAMP1 proteins and site-directed mutagenesis, the exact residues responsible for the species selectivity have been identified. The results of this study may provide additional insight into the molecular basis of the CRLR-RAMP interaction and facilitate the future discovery of high affinity non-peptide antagonists.

**MATERIALS AND METHODS**

**Marmoset RAMP1 cDNA Cloning**—A partial marmoset RAMP1 cDNA was isolated from frontal brain cDNA using the PCR. The PCR primers were based upon human RAMP1 (5'-CTGCCAGGAGGCTACTAC-G and 5'-CACGATGAGGCTGTTAGAAGGAG). Amplification reactions consisted of 40 cycles of 45 s at 94°C, 45 s at 58°C, and 1 min at 72°C and were carried out according to the manufacturer’s recommended protocol for PLATINUM Taq PCR DNA polymerase (Invitrogen). Multiple subclones were sequenced to rule out potential errors.

**Expression Constructs, Chimeras, and Mutagenesis**—Human and rat cDNAs for CRLR and RAMP1 in the mammalian expression vector pcDNA3.1 were co-transfected in equal amounts. Control transfections included pcDNA3.1 vector alone, hCRLR/pcDNA3.1, rCRLR/pcDNA3.1, and pcDNA3.1/hRAMP1. The transfection mixture was added directly to the medium, and this mixture was replaced with fresh medium 24 h later. The cells were harvested for membranes 48 h after transfection.

**Membrane Preparation and Radioligand Binding Studies**—Transiently transfected 293 EBNA (Invitrogen) cells were cultured in Dulbecco’s modified Eagle’s medium with 4.5 g/liter glucose, 1 mM sodium pyruvate, and 2 mM glutamine supplemented with 10% fetal bovine serum, 100 units/ml penicillin, and 100 μg/ml streptomycin and maintained at 37°C, 5% CO₂, and 95% humidity. Cells were subcultured by treatment with 0.25% trypsin/0.1% EDTA in Hanks’ balanced salt solution.

Twenty-four h before transfection, the cells were seeded at 2.0×10⁷ cells/dish in 500-cm² dishes. The following day, the cells were refed with fresh growth medium 1 h before transfection. Transfections were performed by combining 60 μg/dish DNA with 180 μl LipofectAMINE 2000 (Invitrogen). cDNAs for CRLR and RAMP1 in the mammalian expression vector pcDNA3.1 were co-transfected in equal amounts. Control transfections included pcDNA3.1 vector alone, hCRLR/pcDNA3.1, rCRLR/pcDNA3.1, and pcDNA3.1/hRAMP1. The transfection mixture was added directly to the medium, and this mixture was replaced with fresh medium 24 h later. The cells were harvested for membranes 48 h after transfection.

**Cell Culture and DNA Transfection**—hRAMP1 was produced by Dr. Douglas MacNeil (Merck Research Laboratories, Rahway, NJ) and subcloned as a 5' NotI and 3' NotI fragments into pcDNA3.1 Zeo (+) (Invitrogen). Human RAMP1 (hRAMP1) was provided by Dr. Bruce Daugherty (Merck Research Laboratories, Rahway, NJ) in the expression vector pcDNA3.1 (+) (Invitrogen). Rat RAMP1 (rRAMP1) cDNA was subcloned into a 5' NheI and 3' BamHI fragment into pcDNA3.1 Hyg (+) (Invitrogen).

Two human/rat chimeric RAMP1 cDNAs were constructed by using restriction fragments of the corresponding native cDNAs. Chimera 1 was created by replacing the nucleotides coding for the first 66 amino acids of rRAMP1 with the corresponding nucleotides of hRAMP1 by using the BstB restriction site along with a NheI site located in the cloning vector. Chimera 2 was created by replacing the nucleotides coding for the first 112 amino acids of rRAMP1 with the corresponding nucleotides of hRAMP1 by using the SapI restriction site along with a NheI site located in the cloning vector.

Rat RAMP1 site-directed mutagenesis was performed by using the QuickChange site-directed mutagenesis kit (Stratagene) according to the manufacturer’s instructions. Lysine at position 74 of rRAMP1 was replaced with the corresponding human/marmoset amino acid tryptophan utilizing two complementary mutant oligonucleotide primers (5'-CTCTACTCAGCAGGAGGCTGTTAGAAGGAG and 5'-CTCTTCGACGGAGGCTGTTAGAAGGAG) and the RAMP1 expression vector construct as template. This mutation was accomplished by substituting the codon TGG corresponding to tryptophan (rK74W RAMP1). All constructs were sequenced bidirectionally with 100% coverage in each direction.

**Chemical structures of BIBN4096BS, Compound 1, and Compound 2.**

![Chemical structures of BIBN4096BS, Compound 1, and Compound 2.](image-url)
**RESULTS**

Small molecule antagonists of the CGRP receptor such as Compound 1 and BIBN4096BS exhibit species-selective pharmacology (2–4). For example, BIBN4096BS was reported to exhibit >100-fold higher affinity for the human CGRP receptor than for the rat receptor (2). This observation led us to examine the sequences of CRLR and RAMP1 from different species. Protein sequence alignment revealed that whereas human and rat CRLR are 91% homologous, human and rat RAMP1 share only 71% homology. This observation suggested that the pharmacological differences could be a result of the sequence dissimilarity of either protein or may result from a combined effect of differences in both CRLR and RAMP1 sequences. To determine whether the species selectivity is derived from either CRLR itself or its accessory protein, RAMP1, hybrid human/rat CGRP receptors were created by transiently transfecting cDNAs coding for human CRLR with rat RAMP1 and vice versa in 293 EBNA cells. The cells were harvested, and cell membranes were prepared for subsequent competitive ligand binding experiments. As expected, the small molecule antagonists Compound 1 and BIBN4096BS had lower affinity for rCRLR/rRAMP1 than for the transfected human CRLR receptor, hCRLR/hRAMP1 (Table I). To confirm that these transiently transfected receptors exhibited physiologically relevant pharmacology, comparisons were made to native human and rat CGRP receptors found in SK-N-MC cells (20) and rat brain, respectively. As seen in Table I, similar $K_0$ values for values were obtained for both Compound 1 and BIBN4096BS on native and transiently expressed receptors. In 293 EBNA membranes expressing rCRLR/rRAMP1, $125^I$-hCGRP binding was inhibited by Compound 1 and BIBN4096BS with $K_0$ values of 8670 and 2.1 nM, respectively. In contrast, co-expression of rCRLR with hRAMP1 resulted in a dramatic increase in antagonist affinities, essentially yielding human-like pharmacology with $K_0$ values for Compound 1 and BIBN4096BS of 123 and 0.032 nM, respectively. Likewise, co-expression of hCRLR with rRAMP1 resulted in $K_0$ values that were similar to those observed for the pure rat receptor. These results demonstrated that RAMP1 determined the affinity of BIBN4096BS and Compound 1 for human and rat CGRP receptors. By contrast, the peptide antagonist CGRP$_8$-$37$ was not species-selective, resulting in $K_0$ values of 1.3 and 1.2 nM for the human and rat receptors, respectively (data not shown), consistent with previous reports (2, 21). The $K_0$ of the radioligand $125^I$-hCGRP also was similar for both human and rat receptors, as well as for the mixed-species receptors (Supplementary Material Table S1). The species origin of CRLR in these hybrid receptors had little or no effect on the small molecule antagonist affinities.

One of the demonstrated functions of RAMPs is to ensure proper cell surface targeting of CRLR. In doing so, it was originally proposed that RAMPs also serve to influence the glycosylation state of the receptor (1). In our studies, the functional significance of glycosylation was therefore addressed because the glycosylation state of the rat CGRP receptor had not been characterized previously; furthermore, the possibility existed that co-expression of CRLR with either human or rat RAMP1 resulted in differential glycosylation of CRLR and that this effect determined the observed differences in antagonist affinities. Using an antibody to rCRLR and deglycosylation enzymes, the glycosylation state of rCRLR associated with rat or human RAMP1 was determined. The membranes from the competitive binding experiments (rCRLR/rRAMP1, rCRLR/hRAMP1, and control rCRLR/pDNA3.1) were treated with peptide-N-glycosidase F and endoglycosidase F1. Peptide-N-glycosidase F catalyzes the hydrolysis of mature glycoproteins, whereas endoglycosidase F1 cleaves N-linked high mannos and hybrid oligosaccharides, but not complex oligosaccharides. Thus, the molecular mass of a glycosylated receptor will decrease after treatment with peptide-N-glycosidase F, and a
receptor with complex glycosylation will resist endoglycosidase F1 cleavage. Co-expression of rCRLR with either human or rat RAMP1 produced species with molecular masses of 55 and 68 kDa, which were reduced to a single 42-kDa species after peptide-N-glycosidase F treatment (Fig. 2). Furthermore, the 68-kDa species represented a mature glycoprotein, as demonstrated by its resistance to endoglycosidase F1 cleavage. The negative control rCRLR alone resulted in background levels of the 55-kDa species, possibly resulting from interaction of transfected CRLR with low levels of endogenous RAMPs. The 55-kDa species likely represents a core glycosylated form of the receptor (18). These results indicated that the co-expression of either human or rat RAMP1 with rat CRLR resulted in similar levels of complex glycosylation.

RAMPs are accessory proteins predicted to contain a large extracellular amino-terminal domain and a single transmembrane-spanning domain (1). To elucidate the region of RAMP1 that is directly involved in determining the affinities of BIBN4096BS and Compound 1, human/rat RAMP1 chimeras were constructed. Chimera 1 was created by replacing the first 66 amino acids of rRAMP1 with the corresponding hRAMP1 sequence. Conversely, replacement of the first 112 amino acids of rRAMP1 with the human sequence produced Chimera 2. These constructs were then used for transient transfections in similar experiments as described above. In membranes expressing rCRLR with Chimera 1, 125I-hCGRP binding was inhibited by Compound 1 and BIBN4096BS with $K_i$ values of 4704 and 2.0 nM, respectively (Table II). These results were similar to those obtained for rCRLR/rRAMP1 sequence homology of CRLR between these species is >90%.

**FIG. 2.** Western blot analysis of rCRLR co-expressed with rRAMP1 and hRAMP1. The membranes from the competitive binding experiments, including rCRLR transfected with empty vector (pcDNA3.1), were treated with peptide-N-glycosidase F (F,) endoglycosidase F1 (F1), or no enzyme. Samples were separated by SDS-PAGE, followed by Western blot analysis with anti-rat CRLR antibodies. The molecular masses (in kDa) are listed on the right.

**FIG. 3.** A, alignment of amino acids 66–112 of RAMP1 from human, marmoset, rat, mouse, and pig. A partial marmoset RAMP1 clone was generated as described under "Materials and Methods" and deposited in GenBankTM with accession number AF424807. B, species conservation. ClustalX version 1.81 alignment quality score, demonstrating that amino acid 74 is the least-conserved residue among these species.

| Species       | BIBN4096BS | Compound 1 | Compound 2 |
|---------------|------------|------------|------------|
| hCRLR/rK74W   | 0.013 ± 0.0015 | 48 ± 4    | 108 ± 12   |
| rCRLR/rRAMP1  | 2.9 ± 0.14   | >10,000    | 12,033 ± 824 |
| rCRLR/rK74W   | 0.036 ± 0.0013 | 52 ± 7    | 10 ± 0.46  |

**DISCUSSION**

The CGRP receptor is an atypical GPCR in that it requires heterodimerization of CRLR, a classical seven transmembrane domain receptor, with the accessory protein RAMP1. RAMPs confer agonist specificity to both CRLR and the calcitonin receptor. CRLR in combination with RAMP1 binds CGRP with high affinity, whereas co-expression of CRLR with RAMP2 or RAMP3 results in high affinity adrenomedullin binding (1). RAMPs also regulate the interaction of the calcitonin receptor with calcitonin and amylin, such that co-expression of calcitonin receptor with RAMP1 or RAMP3 results in amylin receptor pharmacology (22). It was recently demonstrated that the peptide agonists CGRP and adrenomedullin could be cross-linked to both CRLR and the respective RAMP, an observation that suggests that RAMPs may participate directly in the agonist binding site (18). An alternative explanation would be that RAMPs indirectly influence agonist binding sites by altering the conformation of CRLR.

Certain small molecule CGRP receptor antagonists display remarkable species selectivity, exhibiting up to 100-fold higher affinity for the human receptor than for the rat receptor. This observation is intriguing, considering the fact that the sequence homology of CRLR between these species is >90%. However, RAMP1 homology is only 71%. Using this informa-
RATION and Species-selective CGRP Receptor Pharmacology

We sought to determine whether the observed differences in pharmacology between the rat and human Cgrp receptors for small molecule antagonists resulted uniquely from either CRLR or RAMP1. The results of the present investigation demonstrated that the pharmacology was directed exclusively by RAMP1. Moreover, through the use of human/rat chimeric RAMP1 constructs and site-directed mutagenesis, we have determined that tryptophan 74 of RAMP1 is responsible for the high affinity binding of BIBN4096BS and Compounds 1 and 2 to the human receptor.

These observations have important implications for further understanding of the heterodimeric Cgrp receptor. CRLR is a member of the class B family of GPCRs that includes parathyroid hormone, corticotropin-releasing hormone, calcitonin, secretin, and glucagon receptors (23). It is well established that the large amino terminus of class B GPCRs plays a key role in agonist binding, although additional interactions with extracellular loops are still required. In the case of the Cgrp receptor, RAMP1 also contains a large extracellular domain. A recent report demonstrated that CRLR and RAMP1 form a 1:1 heterodimer that is internalized as a stable receptor complex (16). Furthermore, the peptides Cgrp and adrenomedullin could be cross-linked to both CRLR and RAMP1 or RAMP2, respectively (18), suggesting that either the accessory proteins are in close proximity to the agonist binding sites or the peptide agonists interact directly with both CRLR and RAMP. The present study has demonstrated that the Kd of the radioligand 125I-T-Cgrp was unaffected by the species of RAMP1 that was co-expressed with CRLR, suggesting that any potential interaction with the RAMP likely occurs through residues that are conserved between these species. The fact that the affinity of small molecule antagonists can be affected by a single amino acid change suggests that these compounds may interact directly with RAMP1. From a mechanistic standpoint, both Compound 1 and BIBN4096BS have been shown to be competitive antagonists of the Cgrp receptor (2, 3). Taken together, these observations strongly suggest that the receptor binding sites of both Cgrp and these small molecule antagonists include RAMP1. The observation that the affinity of the peptide antagonist Cgrp 8–37 is similar for both human and rat receptors may suggest that this antagonist does not interact with RAMP1. It is tempting, therefore, to speculate that the amino-terminal disulfide-linked ring structure of Cgrp, which is lacking in the truncated antagonist Cgrp 8–37, makes unique contacts with RAMP1 that trigger or facilitate signal transduction by Cgrp. However, the possibility that Cgrp 8–37 interacts with a conserved region of RAMP1 cannot be ruled out.

Several potential mechanisms could account for the ability of Trp-74 of RAMP1 to confer high affinity binding to non-peptide antagonists of the human Cgrp receptor. An indirect mechanism could involve modulation of the conformation of CRLR by residues in the extracellular domain of RAMP1. An alternative scenario could be envisioned whereby these antagonists interact, at least in part, with RAMP1 directly. Favorable hydrophobic interactions between Trp-74 and the antagonists could potentially account for the additional binding energy relative to that seen with Lys-74 of the rat receptor. Conversely, repulsive interactions with the charged lysine in rat RAMP1 could result in decreased antagonist affinity. An alternative model could involve the formation of a binding pocket that includes Trp-74 and other amino acids found within either CRLR or RAMP1. Identification of additional residues within the CRLR-RAMP1 heterodimer involved in binding of these small molecule antagonists remains to be determined. It should be pointed out that a tryptophan residue (Trp-33) was recently shown to confer high affinity binding to a small molecule antagonist of the class B human glucagon-like peptide 1 (GLP-1) receptor (24).

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