Pharmacological characterization of calcitonin gene-related peptide receptors and BIBN4096BS -- a novel CRPG receptor antagonist

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CHAPTER 3

Characterization of CGRP receptors in rat left atrium and vas deferens

---Pharmacological evidence for a third CGRP receptor subtype---

Introduction
Calcitonin gene-related peptide (CGRP) is a 37 amino acid peptide first described in 1982 by Amara et al (1). CGRP is expressed in α- and β- forms that vary by one and three amino acids in rats and humans, respectively (2-7). CGRP exhibits several effects on the cardiovascular, gastrointestinal, bronchotraheal, endocrine systems and on the central nervous system (8). The lack of selective agonists and antagonists implies that the classification of CGRP receptors is in a relatively early stage. The existence of two CGRP receptor subtypes has been proposed on the basis of differential antagonist affinities and agonist potencies in peripheral preparations (9-10). Thus, human α-CGRP(8-37) is considered to be selective for CGRP1 receptors found in the guinea pig atrium (10), whereas the agonist [Cys(Acm)2,7]hCGRPα (9-10) is considered to be selective for the CGRP2 receptor described originally in the rat vas deferens (9). Recently, a new linear CGRP analogue, [Cys(Et)2,7]hCGRPα was proposed as a potent CGRP2 receptor selective analogue (11), since [Cys(Et)2,7]hCGRPα has a high potency to inhibit the rat vas deferens twitch response, whereas in the guinea pig atrium, this analogue induced only a slight inotropic effect at very high concentrations (11).

Adrenomedullin (ADM) is a 52 amino acid peptide and a member of a family of related neuropeptides comprising CGRP, amylin, calcitonin and adrenomedullin. Adrenomedullin and CGRP both have been shown to exhibit similar hypotensive activities (12-14) and both stimulate adenylate cyclase activity (15-16). It has been reported that h-ADM was as potent as h-αCGRP in causing concentration-dependent relaxation in rat aorta and rat pulmonary artery, h-αCGRP(8-37) antagonized the relaxant effects of h-αCGRP but not those of h-ADM, indicated that specific ADM receptors exist in rat aorta and pulmonary artery (17-18). However, in the porcine coronary artery, the relaxant effect of h-ADM was antagonized by h-αCGRP(8-37), suggesting that some of the ADM actions are mediated through CGRP receptors (17).
The aim of this study was to pharmacologically characterize the CGRP receptor subtypes in rat atrium and vas deferens by using several CGRP-related peptide agonists and three CGRP antagonists, including BIBN4096BS, a novel CGRP receptor antagonist (19).

Materials and methods

Male Wistar rats (Chbb: Thom, about 300g) were exsanguinated under sodium pentobarbitone anaesthesia. The hearts and vas deferens were dissected and immediately placed in oxygenated Krebs buffer. The left atrium and vas deferens were carefully prepared and subsequently mounted in 25ml organ baths containing Krebs solution of the following composition (mmol/L): NaCl 118; KCl 4.7; MgSO4 1.2; NaHCO3 25; KH2PO4 1.2; glucose 10; CaCl2 2.5. The Krebs solution was gassed with 95% O2 + 5% CO2 and maintained at 37°C. A resting tension of 1g was applied. Following a 60 min equilibration period, the atria were electrically driven at a frequency of 3Hz (duration: 0.5ms; voltage: initial value + 20%) and the vas deferens were stimulated at a frequency of 0.2 Hz (duration: 0.5ms; voltage: 60v). Responses were recorded on a polygraph. Following a 30 min period of electrical stimulation, concentration-effect curves to CGRP agonists were obtained in a cumulative fashion, the next concentration being added when the effect of the preceding one had reached a steady state. For experiments using the antagonists, the tissues were incubated for 15 min with antagonist prior to the construction of the concentration-effect curve to CGRP agonists. Only one concentration-effect curve was made in each preparation. To investigate the interference of metabolism by neutral endopeptidase, experiments in rat left atrium and vas deferens were performed in the absence and presence of thiorphan. Thiorphan was added to the tissue baths for 15 min prior to the addition of BIBN4096BS.

Statistical analysis

Drug-induced effects on rat left atria and vas deferens were calculated as percentage changes from resting levels, measured prior to the first concentration of agonists. Agonist relative potencies were determined by comparing EC100 values for atria and EC40 values for vas deferens. (i.e. the concentration required to produce a 100% positive inotropic effect in rat left atrium, and the concentration required to produce a 40% inhibition of electrically-evoked...
twitches in rat vas deferens). Antagonist relative potencies were determined by comparing pKß values. In the presence of an antagonist with a single concentration used, apparent pKß values were calculated from dose-ratios produced by the stated concentration of CGRP antagonists tested from the equation: pKß = log(DR-1) - log[antagonist]. Where multiple concentrations of antagonist were used, a Schild plot was constructed. Since the slopes of the Arunlakshana-Schild plots were not significantly different from unity, mean pKß values were calculated (20). All values were expressed as means ± S.E.M..

Drugs used

The following drugs were used: human adrenomedullin (h-ADM) and [Cys(ACM)²⁷]hCGRPα were purchased from Polypeptide, Wolfenbüttel, Germany; r-ßCGRP and h-ßCGRP(8-37) were purchased from Neosystem, Strasbourg, France; h-αCGRP(8-37), h-αCGRP, h-ßCGRP and r-αCGRP were purchased from Saxon Biochemicals GmbH, Hannover, Germany; [Cys(Et)²⁷]hCGRPα was purchased from Wherl GmbH, Wolfenbüttel, Germany; BIBN4096BS was synthesized by Boehringer Ingelheim Pharma KG, Biberach/Riss, Germany. All peptides were dissolved in distilled water. BIBN4096BS was dissolved with small volume (20μl) 1N HCl, further diluted with saline, then adjusted to pH 6.5-7.0 by 1N NaOH. Stock solutions (2x10⁻³ M) of each compound were stored in aliquots at -20°C until needed. Solutions were diluted to the final concentration with Krebs buffer.

Results

Effect of CGRP-related peptide agonists

CGRP related peptide agonists produced concentration-related positive inotropic effects in rat left atrium and inhibited the electrically-evoked twitch responses in vas deferens (fig 1.1-1.2). The order of potency was r-αCGRP > r-ßCGRP > h-αCGRP > h-ßCGRP > [Cys(Et)²⁷]hCGRPα > h-ADM > [Cys(ACM)²⁷]hCGRPα in rat left atrium and r-αCGRP > h-αCGRP > r-ßCGRP > h-ßCGRP > [Cys(Et)²⁷]hCGRPα > h-ADM > [Cys(ACM)²⁷]hCGRPα in vas deferens, respectively (table 1). [Cys(Et)²⁷]hCGRPα showed potent enhancing activity on producing positive inotropic effects in rat left atrium as well as on the inhibition of electrically-evoked twitch response in vas deferens. Compared to
Table 1. Influence of CGRP receptor agonists on rat isolated atria and vas deferens preparation. In rat atria a positive inotropic effect was induced, quantified by means of EC100 values. The CGRP receptor agonists inhibited electrically-evoked twitch responses in the vas deferens. The inhibitory effects were quantified by means of EC40 values.

<table>
<thead>
<tr>
<th>compound</th>
<th>Rat atria EC100: (nM)</th>
<th>Rat vas deferens EC40: (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>h-aCGRP</td>
<td>2.00</td>
<td>1.91</td>
</tr>
<tr>
<td>h-ßCGRP</td>
<td>3.02</td>
<td>5.62</td>
</tr>
<tr>
<td>r-aCGRP</td>
<td>0.25</td>
<td>0.78</td>
</tr>
<tr>
<td>r-ßCGRP</td>
<td>0.44</td>
<td>2.04</td>
</tr>
<tr>
<td>Et-hCGRPa</td>
<td>5.50</td>
<td>8.32</td>
</tr>
<tr>
<td>ACM-hCGRPa</td>
<td>274</td>
<td>234</td>
</tr>
<tr>
<td>h-ADM</td>
<td>263.00</td>
<td>93.30</td>
</tr>
</tbody>
</table>

Table 2. Influence of the CGRP receptor antagonists h-αCGRP(8-37), h-ßCGRP(8-37) and BIBN4096BS on CGRP agonist-induced responses in rat left atrium and vas deferens preparations. The pK_B values indicate the inhibitory properties of the antagonists.

<table>
<thead>
<tr>
<th></th>
<th>pK_B</th>
<th>h-αCGRP 8-37</th>
<th>h-ßCGRP 8-37</th>
<th>BIBN4096BS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>atrium</td>
<td>atrium</td>
<td></td>
</tr>
<tr>
<td>h-αCGRP</td>
<td>7.2</td>
<td>7.1</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>h-ßCGRP</td>
<td>7.0</td>
<td>7.0</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>r-αCGRP</td>
<td>7.4</td>
<td>7.2</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>r-ßCGRP</td>
<td>6.8</td>
<td>7.2</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Et-hCGRPaα</td>
<td>7.4</td>
<td>7.3</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>h-ADM</td>
<td>7.3</td>
<td>nd</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>vas deferens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>h-αCGRP</td>
<td>6.2</td>
<td>6.3</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>h-ßCGRP</td>
<td>&lt; 6 a</td>
<td>&lt; 6 a</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>r-αCGRP</td>
<td>6.3</td>
<td>&lt; 6 a</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>r-ßCGRP</td>
<td>&lt; 6 a</td>
<td>&lt; 6 a</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Et-hCGRPaα</td>
<td>7.2</td>
<td>7.3</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>h-ADM</td>
<td>7.0</td>
<td>nd</td>
<td>8.1</td>
<td></td>
</tr>
</tbody>
</table>

nd—not determined; ( a )—DR less than two fold
h-αCGRP, h-ADM was 100 times less potent in rat left atrium and 50 fold less potent in vas deferens, and [Cys(ACM)2,7]hCGRPa was 100 times less potent both in rat left atrium and vas deferens.

Table 3. Competitive antagonistic effects of BIBN4096BS to h-αCGRP and [Cys(Et)2,7]hCGRPa induced responses in rat left atria and vas deferens preparations.

<table>
<thead>
<tr>
<th></th>
<th>agonist</th>
<th>pKₐ +/- S.E.M.</th>
<th>(n)⁵</th>
<th>slope⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrium</td>
<td>h-αCGRP</td>
<td>8.48 +/- 0.03</td>
<td>16</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Et-hCGRPa</td>
<td>8.97 +/- 0.07</td>
<td>20</td>
<td>1.00</td>
</tr>
<tr>
<td>vas deferen</td>
<td>h-α-CGRP</td>
<td>7.23 +/- 0.04</td>
<td>16</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>Et-hCGRPa</td>
<td>8.37 +/- 0.05</td>
<td>20</td>
<td>0.95</td>
</tr>
</tbody>
</table>

⁵(n)= (total number of data points).
⁶slopes of the Schild regression were not significantly different from unity (p<0.01).

Effect of CGRP antagonists

The effects of h-αCGRP (8-37), h-ßCGRP (8-37) and BIBN4096BS with respect to the blockade of CGRP agonist-induced responses in rat left atrium and vas deferens are shown in Fig (2.1-2.12). Antagonist related potencies were determined by comparing pKₐ values (table 2). BIBN4096BS was in general approximately 10 times more potent in blocking the of CGRP-related peptide agonist-induced responses in rat left atrium and in vas deferens than h-αCGRP (8-37) and h-ßCGRP (8-37). In the rat atrium BIBN4096BS as well as h-αCGRP (8-37) and h-ßCGRP (8-37) were unable to discriminate between the receptors stimulated by the different agonists. The pKₐ values for BIBN4096BS were between 8.1-8.8, and for h-αCGRP (8-37) and h-ßCGRP (8-37) were 6.6-7.4, respectively.

However, h-αCGRP (8-37) and h-ßCGRP (8-37) were very poor antagonists in blocking the r/h α-ß CGRP receptors in vas deferens. At a concentration of 1μM, the dose-ratio of the rightward shift was less than 3-fold (with pKₐ values < 6.3). BIBN4096BS antagonized r/h α-ß CGRP mediated responses with pKₐ values between 6.7-7.1. However, BIBN4096BS
**Fig. 1.** Concentration-effect curves of CGRP agonist-induced positive inotropic effects in rat left atrium and inhibition of electrically-evoked twitch response in the vas deferens. Data are presented as mean values ± S.E.M. (n=4).

**Fig. 5.** Concentration-effect curves to h-aCGRP with 300nM BIBN4096BS in the absence and presence of 10μM thiorphan. Data are presented as mean values ± S.E.M. (n=4).
Fig. 2. Concentration-effect curves of CGRP agonists in the absence and presence of CGRP antagonists (h-aCGRP(8-37), h-ßCGRP(8-37) and BIBN4096BS) in rat left atrium and vas deferens. Data are presented as mean values ± S.E.M. (n=4).
Fig. 3. Concentration-effect curves of h-aCGRP and [Cys(Et)2,7]hCGRPα in the absence and presence of different concentrations BIBN4096BS in rat left atrium and vas deferens. Data are presented as mean values ± S.E.M. (n=4).
was approximately 10 fold more effective in blocking \([\text{Cys(Et)}^{2,7}]\text{hCGRP}\alpha\) and h-ADM induced responses in the same preparations, with pKₐ values of 8.4 and 8.1, respectively.

In order to investigate the antagonism of BIBN4096BS to h-\(\alpha\)CGRP and \([\text{Cys(Et)}^{2,7}]\text{hCGRP}\alpha\) induced responses in rat left atrium and vas deferens, the Arunlakshana-Schild plot analysis was performed. BIBN4096BS induced a concentration-dependent rightward shift of the dose-response curves of h-\(\alpha\)CGRP and \([\text{Cys(Et)}^{2,7}]\text{hCGRP}\alpha\) in rat left atrium and vas deferens (fig 3.1-3.4). The slopes of the Schild plots were not significantly different from unity (fig 4.1-4.2), and for this reason mean pKₐ values were calculated (table 3). There was a significant difference in the estimated pKₐ values between h-\(\alpha\)CGRP and \([\text{Cys(Et)}^{2,7}]\text{hCGRP}\alpha\) in vas deferens; pKₐ = 7.23 +/- 0.04 (n=16) and 8.37 +/- 0.05 (n=20) for h-\(\alpha\)CGRP and \([\text{Cys(Et)}^{2,7}]\text{hCGRP}\alpha\), respectively.

**Effect of thiorphan**

The effects of BIBI4096BS to h-\(\alpha\)CGRP induced responses in the absence and presence of thiorphan in rat left atrium and vas deferens are shown in fig (5.1-5.2). The dose-response curves were superimposable.
Discussion

CGRP-related peptide agonists produced concentration-dependent positive inotropic effects in the rat left atrium, and an inhibition of electrically-evoked twitch responses in the vas deferens. It has been proposed that two different receptors (CGRP₁ and CGRP₂) are present in rat left atrium and vas deferens, respectively. \([\text{Cys(\text{Et})}^{2,7}]\text{hCGRP}\alpha\) has been proposed to be a potent CGRP₂ receptor selective analogue since it had a high potency in inhibiting the rat vas deferens twitch responses, whereas in the guinea pig atrium, this analogue induced only a slight inotropic effect at very high concentrations. In the present study, we found that \([\text{Cys(\text{Et})}^{2,7}]\text{hCGRP}\alpha\) had no selectivity between rat left atrium and vas deferens, it showed potent enhancement of the positive inotropic effects in rat left atrium as well as on inhibitions of electrically-evoked twitch responses in the vas deferens. \([\text{Cys(ACM})^{2,7}]\text{hCGRP}\alpha\) displayed weak agonist effect, and similar to \([\text{Cys(\text{Et})}^{2,7}]\text{hCGRP}\alpha\) that it had no selectivity between rat left atrium and vas deferens. To investigate whether a species difference is involved, we also tested \([\text{Cys(\text{Et})}^{2,7}]\text{hCGRP}\alpha\) on the guinea pig atrium. \([\text{Cys}(\text{Et})^{2,7}]\text{hCGRP}\alpha\) evoked concentration-dependent positive inotropic effect in guinea pig left atrium (pD₂=22nM). The results obtained suggest that \([\text{Cys(ACM})^{2,7}]\text{hCGRP}\alpha\) and \([\text{Cys(\text{Et})}^{2,7}]\text{hCGRP}\alpha\) are not CGRP₂ receptor selective, in contrast to the observation reported by Dumont et al.(11). This may be due to different strains of animals used or different experimental conditions.

The lack of availability of selective agonists and antagonists implies that the classification of CGRP receptors is in a relatively early stage. CGRP receptors were classified into two subtypes, the h-\(\alpha\text{CGRP}(8-37)^{-}\)sensitive CGRP₁ receptor and h-\(\alpha\text{CGRP}(8-37)^{-}\)insensitive CGRP₂ receptor, respectively (9-11). In the present study, we provided further experimental evidence for a CGRP receptor subclassification by using BIBN4096BS, a novel CGRP receptor antagonist (19).

BIBN4096BS proved about 10 fold more potent in antagonizing r/h \(\alpha\-\beta\text{CGRP}\) mediated responses in rat left atria than in the vas deferens. The same observation was found for both h-\(\alpha\text{CGRP}(8-37)\) and h-\(\beta\text{CGRP}(8-37)\). However, BIBN4096BS was about 10 fold more potent in
blocking r/h α-β CGRP mediated responses in both rat left atrium and vas deferens than h-αCGRP(8-37)and h-βCGRP(8-37), respectively. These findings clearly indicated that r/h α-β CGRP act through different receptors in rat atrium and vas deferens.

It seems of interest that BIBN4096BS did not discriminate between the effects of [Cys(Et)²⁷]hCGRPα / h-ADM and r/h α-β CGRP in rat atrium, whereas it displayed an approximately 10-fold difference in potency between antagonizing agonist responses of the peptides in the vas deferens. This findings suggest that rat vas deferens contains two CGRP receptor subtypes.

To investigate the antagonism of BIBN4096BS towards h-αCGRP and [Cys(Et)²⁷]hCGRPα induced responses in rat left atrium and vas deferens, we performed experiments in the absence and presence of different concentrations of BIBN4096BS. BIBN4096BS induced a concentration-dependent rightward shift of the dose-response curves of h-αCGRP and [Cys(Et)²⁷]hCGRPα in rat left atrium and vas deferens. The slopes of the Schild plots were not significantly different from unity, this indicated that BIBN4096BS is a competitive antagonist for the receptors of the two agonists in both tissues. This also ruled out the possibility that h-αCGRP and [Cys(Et)²⁷]hCGRPα interact with two different receptors, named low/high affinity for BIBN4096BS in vas deferens. It has been suggested that differences in enzyme distribution may reflect differential responses of CGRP analogues in functional assays (21). In the present study, thiorphan, an inhibitor of the enzyme neutral endopeptidase (NEP), did not interfere with the effects of BIBN4096 to h-αCGRP-induced responses in rat left atrium and vas deferens. This suggests that degradation by neutral endopeptidase does not play a major role in the inactivation of CGRP in these tissues.

In accordance with the suggestion by Quirion et al.(22), that h-αCGRP acts through CGRP₁ receptors in rat left atrium and via CGRP₂ receptors in vas deferens, we propose that [Cys(Et)²⁷]hCGRPα acts through CGRP₃ receptors in the vas deferens. The pKₐ values for BIBN4096BS in antagonizing h-αCGRP and [Cys(Et)²⁷]hCGRPα induced response in rat left atrium were similar (8.5 and 8.8), and the pKₐ values for BIBN4096BS in antagonizing [Cys(Et)²⁷]hCGRPα induced response in rat left atrium and vas deferens were also similar.
Therefore, we have no evidence to assume that \([\text{Cys(Et)}^{2,7}]\text{hCGRP}\alpha\) can discriminate between \text{CGRP}₁ and \text{CGRP}₃ receptors in rat left atrium. Accordingly, \([\text{Cys(Et)}^{2,7}]\text{hCGRP}\alpha\) may act through \text{CGRP}₁ or \text{CGRP}₃ receptors in the rat left atrium.

Adrenomedullin shows approximately 30% of structural homology with CGRP. \(\text{h-}\alpha\text{CGRP}_{(8,37)}\) blocked the ADM induced elevation of cyclic AMP level in rat cultured vascular smooth muscle cells (15,23) and also attenuated the vasodilator response to ADM in the perfused mesenteric artery of the rat (24). It is therefore likely that ADM acted through CGRP receptors in these preparations. It has been reported that \(\text{h-ADM}\) was as potent as \(\text{h-}\alpha\text{CGRP}\) to cause concentration-dependent relaxation in rat aorta and rat pulmonary artery. \(\text{h-}\alpha\text{CGRP}_{(8,37)}\) antagonized the relaxant effects of \(\text{h-}\alpha\text{CGRP}\) but not those of \(\text{h-ADM}\), indicating that specific ADM receptors (which cannot be blocked by CGRP antagonists) exist in both rat aorta and pulmonary artery (17-18). It has been reported recently that the calcitonin-receptor-like receptor (CRLR) can function as either a CGRP receptor or an adrenomedullin receptor, respectively, depending on which members of new family of single-transmembrane-domain proteins, called receptor-activity-modifying proteins or RAMPs are expressed. Three types of RAMPs have been found, which have been named RAMP₁, RAMP₂ and RAMP₃, respectively. RAMP₁ presents the CGRP receptor. RAMP₂-transported receptors are adrenomedullin receptors, and the receptor generated by expression of RAMP₃ and calcitonin-receptor-like receptor (CRLR ) is similar to the ADM receptor and is being investigated in detail at present (25). In our own in vivo study, BIBN4096BS as well as \(\text{h-}\alpha\text{CGRP}(8-37)\) and \(\text{h-}\beta\text{CGRP}(8-37)\) did not block the hypotensive effect of \(\text{h-ADM}\) in anesthetized rats (see chapter 5). Radioligand binding studies showed that BIBN4096BS has very low affinity for ADM receptors (see chapter 1). In the present study, \(\text{h-ADM}\) produced concentration-related positive inotropic effects in rat left atrium and inhibited electrically-evoked twitch responses in vas deferens. When compared with \(\text{h-}\alpha\text{CGRP}\), \(\text{h-ADM}\) was 100 times less potent in rat left atrium and 50 times less potent in vas deferens. BIBN4096BS blocked \(\text{h-ADM}\) induced effects in rat left atrium and vas deferens. \(\text{h-ADM}\) may act through CGRP receptors, but not via ADM receptors in the rat left atrium and vas deferens. The \(pK_B\) values for BIBN4096BS in antagonizing \(\text{h-ADM}\) induced responses in rat left atrium and vas
deferens were 8.6 and 8.1, respectively, corresponding to the pKₐ values of BIBN4096BS in antagonizing \([\text{Cys(Et)}^{2,7}]\text{hCGRPα}\) induced responses in the same tissues. h-ADM may act through the same receptors as \([\text{Cys(Et)}^{2,7}]\text{hCGRPα}\) in rat left atrium and vas deferens.

In conclusion, the present study has demonstrated that BIBN4096BS is a potent competitive CGRP antagonist. Rat vas deferens is equipped with two CGRP receptor subtypes, CGRP₂ and CGRP₃ receptors; and rat left atrium contains CGRP₁ and/or CGRP₃ receptors. R/h α-β CGRP acts through CGRP₁ receptors in the rat left atrium and via CGRP₂ receptors in the vas deferens. \([\text{Cys(ACM)}^{2,7}]\text{hCGRPα}\) and \([\text{Cys(Et)}^{2,7}]\text{hCGRPα}\) are not a CGRP₂ receptor selective analogues. \([\text{Cys(Et)}^{2,7}]\text{hCGRPα}\) acts through CGRP₃ receptors in the rat vas deferens and via CGRP₁ or CGRP₃ receptors in rat left atrium. h-ADM may act through the same receptors as \([\text{Cys(Et)}^{2,7}]\text{hCGRPα}\) in the rat left atrium and vas deferens.

References


