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NEW CGRP ANTAGONISTS

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The presentation will focus on BIBN 4096 BS, since this compound is still the only potent calcitonin gene-related peptide (CGRP)-antagonist described so far[1].

Studies employing ^{3}H-BIBN 4096 revealed that this compound possesses a Kd value (nM) of 0.028, 0.077, and 2.97 for CGRP receptors on SK-N-MC cells, in marmoset cortex, and rat spleen, indicating that BIBN 4096 BS exhibits species selectivity. BIBN 4096 BS is highly selective towards CGRP receptors since very low affinities (> μM) were observed for amylin, adrenomedullin, or calcitonin binding sites. BIBN 4096 BS discriminates between putative CGRP-1 receptors in the atrium (pKb = 8.5) and CGRP-2 receptor in the vas deferens (pKb = 7.1). Moreover, BIBN 4096 BS seems to discriminate between α and β CGRP mediated effects in vascular tissue. BIBN 4096 BS has been investigated in a variety of animal models. Of special interest is that the compound is extremely potent to inhibit neurogenic vasodilation evoked by stimulation of the trigeminal ganglion in rats and marmoset monkeys. The increase of facial blood flow induced by trigeminal ganglion stimulation was inhibited with an ID_{50} of 63 and 2.8 μg/kg i.v. in rats and marmosets, respectively. BIBN 4096 BS had no effect on myocardial ischaemia and CBF autoregulation in rats in concentrations effective in the trigeminal model.

The pharmacology of BIBN 4096 BS, its role in detecting receptor heterogeneity and its potential as an anti-migraine drug will be discussed.

REFERENCE

1. Doods, H. et al. (2000) Br. J. Pharmacol. 129, 420–423.