

STUDY OF CGRP-RECEPTORS IN HUMAN ISOLATED MIDDLE MENINGEAL ARTERIES USING BIBN4096BS, COMPOUND 1, AND H α CGRP(8-37)

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INTRODUCTION

Calcitonin, CGRP, adrenomedullin, and amylin require both CRLR (calcitonin-gene receptor like receptor) and receptor activity modifying proteins (RAMP1, RAMP2, and RAMP3) in different combinations for expression of selective, functional receptors[1]. We investigated whether the antagonists BIBN4096BS[2], Compound 1 (WO98/11128, [3]), and CGRP(8-37) are functionally selective for CGRP receptors in human middle meningeal arteries (HMMA).

METHODS

Isometric tension recordings were made (in presence of 10 μ M thiorphan) in isolated segments of HMMA (obtained with consent). Segments were precontracted (prostaglandin F_{2 α} , 10 μ M, as reference agonist) and relaxation responses to h α CGRP, h β CGRP, adrenomedullin, amylin, or calcitonin were obtained. The effects of BIBN4096BS (1 nM), Compound 1 (100 nM), or CGRP(8-37) (3 μ M) on h α CGRP- and of BIBN4096BS (10 nM) on adrenomedullin-evoked relaxations were tested.

RESULTS

h α CGRP, h β CGRP, adrenomedullin, and amylin showed similar vasodilator potency (-logEC₅₀: 7.7, 7.5, 7.8, and 7.5, respectively), but differed in their efficacies (i.e., maximal relaxant response, %E_{max} = 65.3, 78.3, 55.2, and 94.9, respectively). Calcitonin had no effect (E_{max} = 0%). BIBN4096BS, Compound 1, and h α CGRP(8-37) noncompetitively inhibited h α CGRP relaxations. Responses to adrenomedullin were unaltered by BIBN4096BS (10 nM).

CONCLUSION

In HMMA BIBN4096BS shows functional selectivity for CGRP receptors over adrenomedullin receptors. It is predicted that if CGRP mediated neurogenic vasodilation contributes to migraine pathophysiology then CGRP antagonists may have clinical utility.

REFERENCES

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