Pharmacological characterization of endomorphin-2-based cyclic pentapeptides with methylated phenylalanine residues.

Autorzy

Renata Perlikowska

Davide Malfacini

Maria Camilla Cerlesi

Girolamo Calò

Justyna Piekielna

Léonore Floriot

Tiphaine Henry

Jean Claude do-Rego

Csaba Tömböly

Alicja Kluczyk

Anna Janecka

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Kolekcja

Naukowa

Streszczenie

As part of our continuing studies on the structure–activity relationships of cyclic pentapeptides based on the structure of endomorphin-2, we report here the synthesis and biological activities of a new series of analogs incorporating 2′, 3′ or 4′-methylphenylalanine (MePhe) residues into positions 3 or 4 of the parent cyclopeptide, Dmt-c[d-Lys-Phe-Phe-Asp]NH_2 (Dmt = 2′,6′-dimethyltyrosine). Analogs with MePhe in position 4 showed a row of magnitude increased μ-opioid receptor (MOP receptor) affinity as compared with a parent compound. The in vitro potencies of the new analogs were determined in calcium mobilization assay performed in Chinese Hamster Ovary (CHO) cells expressing human recombinant opioid receptors and chimeric G proteins. All analogs were strong μ/κ (MOP/KOP) receptor agonists and weak δ (DOP) receptor agonists. In the in vivo hot-plate test in mice, the $MePhe^4$-modified peptides showed remarkable antinociceptive activity after intracerebroventricular (i.c.v.) administration which was most likely due to the concomitant activation of more than one opioid receptor type.

Słowa kluczowe

Solid phase peptide synthesis, Cyclic peptides, Opioid receptors, Receptor binding, Calcium mobilization, Hot-plate test

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