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In vitro and *in vivo* activity of opioid cyclopeptide with mu/delta agonist profile

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Centrally acting opioid agonists, such as morphine, are the most widely used analgesics for the treatment of severe pain. Among the three types of classic opioid receptors, mu, delta and kappa, the mu receptor was identified as primarily responsible for the pain-relieving effects but also responsible for a number of undesired side effects, including sedation, respiratory depression, inhibition of gastrointestinal transit, tolerance and physical dependence. In the previous decades, chemists and pharmacologists focused on obtaining analogs with high selectivity for one opioid receptor type. More recently, the development of compounds with mixed opioid profile is gaining a lot of interest eg. synergistic antinociceptive effects in response to the mu and delta receptor activation were observed in several *in vivo* studies. In this study we have shown that the replacement of the tyrosine residue in the mu-selective opioid ligand Tyr-c[D-Lys-Phe-Asp]NH_2 with 2',6'-dimethyltyrosine (Dmt) produced a cyclopeptide Dmt-c[D-Lys-Phe-Asp]NH_2 with mu-delta opioid receptor profile. This new analog showed improved antinociception in the hot-plate test as compared to the parent peptide but also significantly inhibited the gastrointestinal transit. Using the bioluminescence resonance energy transfer (BRET) assay it was shown that this analog was biased toward β-arrestin. To the best of our knowledge, it is the first reported β-arrestin biased opioid analog of a peptide structure. Our data are in accordance with earlier reports indicating that various *in vivo* activities of opioid agonists arise not only from the activation of one or more opioid receptors, but also from promoting G-protein or β-arrestin pathways.

Biography

Katarzyna Gach-Janczak has been working in the Department of Biomolecular Chemistry at Medical University of Lodz since 2006, first as a PhD student, then as an Assistant and now as an Assistant Professor. In May 2010, she defended her Doctoral thesis. She completed her Post-doctoral training in the Laboratory of Neuronal and Neuroendocrine Differentiation and Communication, University of Rouen (France). Her area of scientific interests is bidirectional. She is searching for new analgesics based on the structure of the endogenous opioid peptides and studying synthetic heterocyclic compounds as potential anticancer agents. She has published 43 research papers in international journals.

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