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NOVEL ORALLY-ACTIVE NPFF RECEPTOR ANTAGONISTS PREVENTING OPIOID-INDUCED HYPERALGESIA DURING THE TREATMENT OF ACUTE OR CHRONIC PAINS

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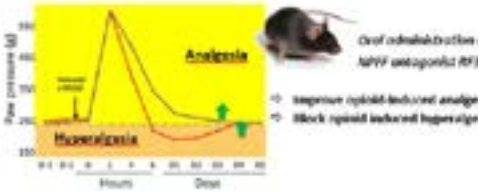
The development of drugs that can more effectively and safely treat both acute and chronic pain remains a major unmet challenge in pharmaceutical industry. Opiate analgesics, such as morphine or fentanyl, continue to be the cornerstone medication for treating moderate to severe pain, but their use upon chronic administration suffers from important side-effects such as tolerance, addiction and hyperalgesia. Several anti-opioid systems have been reported as valuable targets for blocking opioid-induced hyperalgesia (OIH). Among them, the NPFF receptors belonging to the GPCR family were recently identified as one of the keystone of the opioid-induced hyperalgesia. We developed the first NPFF-receptor antagonist (RF9), and its co-administration with opioid analgesics (fentanyl) led to block the delayed and long lasting paradoxical opioid induced-hyperalgesia and prevent the development of associated tolerance. However, the dipeptide nature of RF9 limited its application to sc or iv administration. Based on an extensive SAR study, we developed a peptidomimetic of RF9 containing novel unnatural amino-acids. These basic amino acids were obtained through a specific Ru-catalyzed reduction of tertiary amides to afford in very high yields novel families of chiral α or β Y amino acids exhibiting a large diversity of basic side chains. Obtained at a gram-scale, these unnatural amino acids are directly suitable for peptide synthesis in liquid or solid phase. When applied to the development of new ligand of NPFF receptors, we were able to design and synthesize RF313 as the first orally-active NPFF receptor antagonist able to reverse opioid-induced hyperalgesia in several pain models (post-operative pain, neuropathic pain, inflammatory pain). Active at low dose (1 mg/kg p.o. in rat), RF313 is also able to extend the duration of the analgesic effect induced by the opiates, opening the way to a promising therapeutic pathway to treat acute or chronic pain.



Biography

F Bihel has completed his PhD from University of Marseille (France) and Postdoctoral studies from Harvard Medical School and BWH (Boston, MA, USA). He is currently Senior Researcher and Group Leader at the French National Center for Scientific Research (CNRS), within the Laboratoire d'Innovation Thérapeutique (UMR7200 – CNRS/University of Strasbourg). He is a member of several academic societies and has published more than 60 papers in reputed journals, and 6 patents. He is an expert in Medicinal Chemistry, with research programs dedicated to design and functionalization of innovative molecular scaffolds targeting proteins involved in CNS pathologies or cancers.

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