Our recent work on the development of opioid receptor ligands as pharmacological tools and as analgesic drug candidates with improved activity profiles will be presented. All classical peptide and non-peptide opioid agonists contain a positively charged nitrogen, the ionic interaction of which with the Asp residue in the third transmembrane helix of opioid receptors has been thought to be indispensable for receptor binding and activation. Here we describe novel opioid receptor ligands derived from endogenous opioid peptides or from non-peptide opiates that lack a protonatable nitrogen. The results indicate that elimination of the positively charged nitrogen in opioid agonists may have diverse effects on the intrinsic efficacy (agonism, partial agonism or antagonism), depending on the receptor binding interactions of other moieties present in the molecule. Furthermore, the inability of these compounds to engage in a salt bridge may result in the stabilization of distinct receptor conformations, leading to functional selectivity with regard to receptor signalling and internalization.

Efforts to develop improved opioid analgesics based on the dermorphin-derived tetrapeptide \([\text{Dmt1}]\text{DALDA}\) will be described. \([\text{Dmt1}]\text{DALDA}\) is a highly potent \(\mu\) opioid agonist capable of producing a long-lasting, centrally mediated antinociceptive effect in rats with systemic administration, indicating that it effectively crosses the blood-brain barrier. Furthermore, the ability of \([\text{Dmt1}]\text{DALDA}\) to act as a cell-penetrating, mitochondria-targeted antioxidant was demonstrated. Because mitochondrial reactive oxygen species (ROS) play an important role in neuropathic pain mechanisms, \([\text{Dmt1}]\text{DALDA}\) turned out to be superior to morphine in neuropathic pain models as a consequence of its combined \(\mu\) opioid agonist and mitochondria-targeted antioxidant properties. Finally, the development of compounds with a mixed opioid \(\mu\) agonist/\(\delta\) antagonist profile as analgesics with low propensity to produce analgesic tolerance and physical dependence will be presented.

References


CBC SEMINAR ANNOUNCEMENT

Professor Peter Schiller
University of Montreal

New concepts in opioid analgesic drug design

Date: 11th February 2014 (Tuesday)
Time: 2:30pm – 4:00pm
Venue: NTU SPMS CBC Building Level 2, Conference Room
Host: Assoc Professor Shunsuke Chiba