A NOVEL CLASS OF KAPPA OPIOID RECEPTOR (KOR) LIGANDS
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HINTERGRUND

The kappa opioid receptor (KOR) and the endogenous peptide-ligand dynorphin have received major attention in recent years due to the involvement in mediating a variety of neurophysiological and behavioral responses (Figure 1). Dysregulation of the KOR/dynorphin system contributes to the development and maintenance of neuropsychiatric conditions, with severe deleterious effects on patient's quality of life. The modulation of the KOR/dynorphin system is nowadays considered as a promising strategy for developing pharmacotherapies for the treatment of neuropsychiatric disorders. Comorbidity is a major issue in neuropsychiatry, and the KOR emerges as an important substrate for comorbidity of many conditions that belong to the family of neuropsychiatric illnesses (Figure 2). Such conditions ranging from pain to anxiety, from depression to addiction, or from cognitive dysfunction to epilepsy is triggered by severe and/or chronic stress which is a common factor for many of these disorders.

LÖSUNG

The development of KOR-targeted ligands as therapeutic agents for the treatment of neuropsychiatric disorders with a superior side effect profile led to a novel class of small molecules that modulate the KOR. Within the series of KOR ligands, molecules were discovered having distinct pharmacological activities as agonists, antagonists or partial agonists. The in vitro specificity and selectivity at the KOR was confirmed by receptor binding and functional assays. Activities ranging from full efficacy to partial activation or inhibition of the KOR were demonstrated. Efficacy and high antinociceptive potency was proven in a mouse model of visceral pain for molecules with agonism or partial agonism at the KOR. First results on the safety profile are promising, as the new KOR compounds did not induce sedation and motor dysfunction at the analgesic dose and multiples of it.

VORTEILE

- The new class of KOR ligands is synthetically readily accessible and cost
effective to prepare.

- The efficacy and high antinociceptive potency of KOR agonists and partial agonists in an animal model of visceral pain is established.
- No signs of sedation and motor impairment are detected.