Cyclic opioid peptides

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Peptide based drug candidates are being discovered at an increasingly rapid pace as therapeutics for many diseases and pain management. . For decades the opioid receptors have been an attractive therapeutic target for pain management and many endogenous opioid peptides have been known to produce opioid activity and analgesia. However, their therapeutic potential has been limited due to a major drawback regarding their use as CNS drugs, mainly due to a lack of biodistribution to the brain caused by poor metabolic stability and an inability to penetrate the blood brain barrier.

Cyclic opioid peptides with more constrained topographical structure possess high potential to overcome these drawbacks compared to their linear parent peptides. The benefits that come with employing cyclization can be further enhanced through the generation of polycyclic peptides by implementing additional cycles. The increased rigidity/topological geometry of polycyclic peptides further attenuates the dynamic nature of the compound, promoting greater affinities and selectivities at target receptors as well as increased in vivo stability. Opioid ligands generally have a short peptide chain and thus the realm of polycyclic peptides has yet to be explored, but should be considered for future designs in opioid receptor ligands.

In this review, a brief history of designing ligands for the opioid receptors, including classic linear and cyclic ligands, is discussed along with recent approaches and successes of cyclic peptide ligands for the receptors. Various scaffolds and approaches have been successfully used that highlight the benefit of cyclization and have provided many

promising leads for novel therapeutics. The future of providing relief from disease states at the opioid receptors is encouraging as recent developments in our understanding about cyclic opioid peptide ligands are augmenting our capabilities of using biologically derived molecules as strong therapeutic agents.

More information: Michael Remesic et al, Cyclic Opioid Peptides, *Current Medicinal Chemistry* (2016). DOI: 10.2174/0929867323666160427123005

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