Characterization of LIH383, an Analgesic Peptide Targeting the Newly Identified Opioid Receptor ACKR3.

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Opioids are currently the most prescribed analgesic compounds. Although they are effective against moderate to severe acute pain, they come with several side effects. Recently, ACKR3 (Atypical Chemokine Receptor 3) was identified as having an affinity for endogenous opioid peptides. It is speculated that ACKR3 may act as a scavenger receptor for endogenous opioids, thereby reducing their analgesic effects. Modulating this receptor could therefore increase the availability of opioid peptides and, consequently, enhance their effects.

Following this discovery, LIH383, a peptide agonist with pM-level potency, was developed. In this project, LIH383 showed significant analgesic effects in the formalin test, a model of tonic pain. Additionally, LIH383 analogs were synthesized to better understand the relevant binding interactions and crucial molecular determinants for activity. So far, our initial structure-activity relationship (SAR) studies have shown that the N-terminal part of LIH383 is particularly sensitive to chemical modifications. The proteolytic stability of LIH383 was also evaluated, revealing a half-life of less than two minutes in rat plasma. Specifically, the dibasic Arg-Arg motif at the C-terminus is rapidly targeted by proteases, making it a preferred target. An SAR study will therefore be conducted to increase stability and thus the therapeutic potential of these compounds.