Dual-activity GPCR: ACKR3 at the crossroads between chemokine and opioid peptide regulation

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Endogenous opioid peptides and prescription opioid drugs modulate pain, anxiety and stress. They activate opioid receptors, which are currently classified into four subtypes (mu, delta kappa and nociceptin receptors). Here we demonstrate that ACKR3/CXCR7, hitherto known as an atypical receptor for chemokines, is a broad-spectrum scavenger of opioid peptides. Phylogenetically, ACKR3 is intermediate between chemokine and opioid receptors and is present in various brain regions together with classical opioid receptors. Functionally, ACKR3 is a scavenger receptor for a wide variety of opioid peptides, especially enkephalins and dynorphins, reducing their availability for the classical opioid receptors. ACKR3 is not modulated by prescription opioids such as morphine, fentanyl or naloxone, but we show that a new ACKR3-selective subnanomolar competitor peptide, LIH383, and conolidine, a natural analgesic used in traditional Chinese medicine, can restrain ACKR3's negative regulatory function on opioid peptides *in vitro* and in rat brain and potentiate their activity towards classical receptors. Altogether, our results reveal that ACKR3 is an atypical opioid receptor with cross-family ligand selectivity, which may open alternative therapeutic avenues for opioid-related disorders.

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Szpakowska M., Decker A., Meyrath M., Palmer C., Blough B., Namjoshi O.* and Chevigné A.* (2021). The natural analgesic conolidine targets the newly identified opioid scavenger ACKR3/CXCR7. *Signal Transduct Target Ther* **6**(1):209.