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ANALGESIA

Screening for cleaner pain relief

Activation of the μ-opioid receptor by morphine and related opioids provides valuable analgesia but can also lead to addiction and potentially lethal side effects such as respiratory depression. Now, an article in *Nature* reports a structure-based approach to the discovery of novel 'biased' ligands of the μ-opioid receptor that can selectively activate beneficial signalling by this receptor.

The μ-opioid receptor is a G protein-coupled receptor (GPCR) that signals through the G protein G_i and through β-arrestin. The relative extent to which the two pathways are activated depends on the conformation adopted by the receptor upon binding of a ligand.

In the current study, Manglik *et al.* sought to identify new biased ligands of the μ-opioid receptor that preferentially activate downstream G_i signalling, as this pathway is thought to mediate the analgesic effects of the receptor. They used the resolved crystal structure of the μ-opioid receptor for computational docking of over 3 million commercially available lead-like compounds from a free public resource called ZINC. They prioritized compounds with known affinity-determining residues and putative specificity-determining residues for the μ-opioid receptor subtype, and then manually examined the top 2,500 docked molecules for features such as novelty.

Twenty-three high-scoring molecules with structural novelty were selected for further testing. The hits were found to have only low-micromolar receptor affinity in a radioligand-binding assay, so 500 analogues of the compounds — such as those that extended further into the more variable region of opioid receptors — were examined in the docking algorithm. Of the 15 top-scoring analogues tested *in vitro*, the most potent hit strongly activated $G_{i/o}$ with low levels of β-arrestin recruitment.

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To further optimize this hit, Manglik *et al.* synthesized stereochemically pure isomers. *In vitro*, the (*S*,*S*) stereoisomer, which they termed PZM21, showed a nanomolar-range affinity and potency at the μ-opioid receptor. Further docking and molecular dynamics simulations using PZM21 derivatives illuminated key ionic and hydrogen-bonding interactions underlying receptor binding by PZM21.

Next, the team tested the compound in two mouse models of pain. In the hotplate assay, PZM21 conferred substantial analgesia (87% of the maximal possible effect), which peaked at 15 minutes after administration and lasted for up to 180 minutes. Surprisingly, the drug had no effect in the tail-flick assay, a pain model that reflects predominantly spinal reflex responses. The authors suggest that PZM21 might preferentially target centrally mediated pain pathways.

Importantly, respiratory depression induced by PZM21, as measured by whole-body plethysmography, was minimal and the constipating effect of the drug was considerably lower than for morphine. PZM21 also did not seem to induce an acute hyperlocomotive response or conditioned place preference — behaviours that indicate reinforcement and addiction.

A biased ligand of the μ-opioid receptor, TRV130, is currently in phase III testing for analgesia. The authors of the current study note that the bias profile of PZM21 is indistinguishable from that of TRV130, despite apparently engaging the μ-opioid receptor in distinct ways.

The structure-based approach highlighted in this study could provide a path to GPCR-targeted drugs with more favourable clinical profiles, and high-resolution GPCR crystal structures that could support such approaches are increasingly becoming available.

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ORIGINAL ARTICLE Manglik, A. *et al.* Structure-based discovery of opioid analgesics with reduced side effects. *Nature* **537**, 185–190 (2016)
FURTHER READING Kingwell, K. Pioneering biased ligand offers efficacy with reduced on-target toxicity. *Nat. Rev. Drug Discov.* **14**, 809–810 (2015)