Tackling the opioid crisis - development of kappa-opioid receptor peptide agonists for safer analgesic therapy

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Abstract

The kappa opioid receptor (KOPr) has exceptional potential as an analgesic target, seemingly devoid of the many peripheral side-effects of Mu receptors. Kappa-selective, small molecule pharmaceutical agents have been developed, but centrally mediated side effects have the limited their clinical translation. Here, we modify an active endogenous Dynorphin peptide with the aim of improving drug-likeness and developing safer KOPr agonists for clinical use. Using rational, iterative design and modern peptide chemistry, we developed a series of potent, selective and metabolically stable peptides from Dynorphin 1-7. Peptides were assessed for cAMP-modulation against Kappa, Mu and Delta opioid receptors, metabolic stability, KOPr specificity and binding, and interrogated for in vitro desensitisation and pERK signalling capability. Finally, lead peptides were evaluated for efficacy in Freund's complete adjuvant rat model of inflammatory nociception. A library of 70 peptides was synthesised and assessed for pharmacological and metabolic stability factors. At least 10 peptide candidates showed low nanomolar activity (¡50 nM) in a cAMP assay, specificity for KORr, and plasma half-life >60 min, with 6 candidates also stable in trypsin. None of the selected peptides showed pERK activity, with a bias towards cAMP signalling. In vivo, KA305 and KA311 showed anti-nociception opioid receptor-specific activity comparable to morphine and U50 844. These highly potent and metabolically stable peptides are promising opioid analgesic leads for clinical translation. Since they are biased peptide KOPr agonists, it is plausible they lack many of the most significant side effects, such as tolerance, addiction, sedation and euphoria/dysphoria, common to opioid analgesics.

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