Nature Reviews Drug Discovery | Published online 18 Apr 2017; doi:10.1038/nrd.2017.68

ANALGESIA

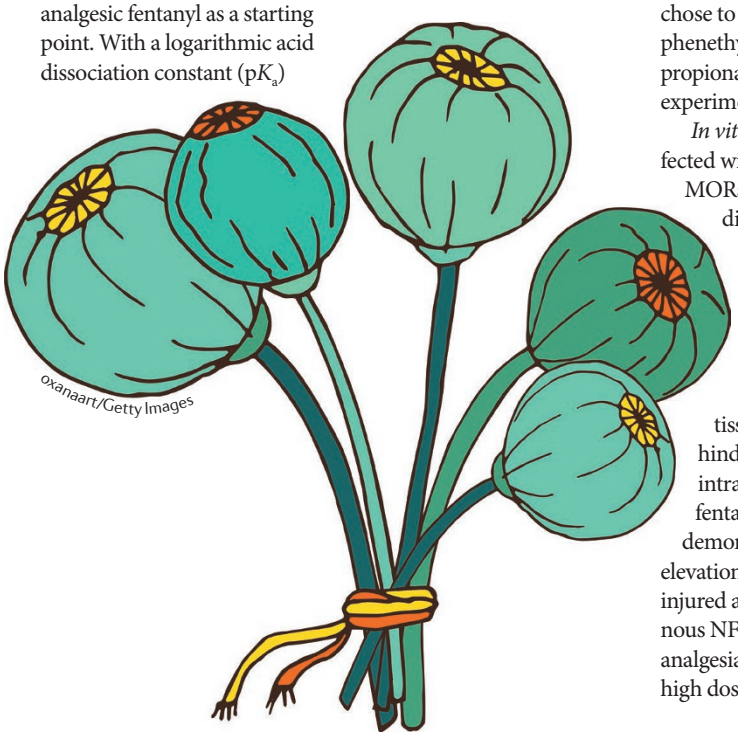
Designing out opioid side effects

Although opioids are very effective in treating pain that is associated with tissue damage and inflammation, they have important adverse effects, such as drowsiness, constipation, potential respiratory arrest and addiction. By analysing drug–opioid receptor interactions in damaged tissues, as opposed to healthy tissues, Stein and colleagues have designed an opioid receptor agonist that provides strong pain relief without the side effects of standard opioids.

> Stein and colleagues have designed an opioid receptor agonist that provides strong pain relief without the side effects of standard opioids

Inflammation in painful processes — such as arthritis, neuropathy or surgery — is accompanied by tissue acidosis, so the authors wondered whether an agonist designed to selectively activate μ-opioid receptors (MORs) at low pH might not activate MORs in physiological conditions.

To design this selective agonist, Stein and colleagues used the opioid analgesic fentanyl as a starting point. With a logarithmic acid dissociation constant (pK_a) value >8, fentanyl is protonated and an active MOR agonist in both normal (pH 7.4) and inflamed (pH 5–7) tissues. A ligand with a lower pK_a, which would be protonated only at low pH, could activate MORs exclusively in acidic inflamed tissues, assuming that protonation of the ligand has an important role in its interaction with MORs. Indeed, computer simulation revealed that replacement of various hydrogens in the fentanyl structure with fluorines could decrease the predicted pK_a of the ligand, and computational binding studies indicated that deprotonation of such a ligand would result in the loss of a key interaction between the ligand and an aspartate residue in the MOR. After evaluating different fluoro-substituted candidates according to their estimated pK_a values and MOR binding energies, the authors chose to synthesize (±)-*N*-(3-fluoro-1-phenethylpiperidin-4-yl)-*N*-phenylpropionamide (NFEPP), which had an experimentally determined pK_a of 6.8.



oxanaart/Getty Images

In vitro, in HEK293cells transfected with MORs, NFEPP activated MORs (measured by G protein dissociation) at low pH but not at physiological pH. The analgesic effect of NFEPP was also assessed *in vivo,* in rat models of chronic and acute inflammatory pain with a low pH in injured tissues, such as unilateral hindpaw inflammation. Whereas intravenous administration of fentanyl resulted in analgesia — as demonstrated by dose-dependent elevation of pain thresholds — in both injured and non-injured paws, intravenous NFEPP caused dose-dependent analgesia only in inflamed paws. At high doses, of up to 150 μg per kg, NFEPP administration did not result in overt sedation or respiratory depression, but fentanyl was lethal at a dose of 32 μg per kg because of respiratory depression. The analgesic effects of fentanyl were only partially reversed by naloxone methiodide (NLXM), an opioid antagonist that does not cross the blood–brain barrier. By contrast, the analgesic effects of NFEPP were completely blocked by NLXM, which confirms that NFEPP selectively activates peripheral opioid receptors.

Finally, the authors assessed the common side effects mediated by central opioid receptors (reward, sedation, motor impairment and respiratory depression) as well as those mediated by intestinal opioid receptors (constipation). Whereas fentanyl produced reward, and reduced locomotion and defecation, NFEPP had no effect on these parameters, even at the highest doses.

Overall, Stein and colleagues provide a new strategy to develop MOR agonists that lack the addictive potential of current drugs, and the results highlight the potential of exploiting pH differences between normal and diseased tissue to achieve a therapeutic effect in a tissue-specific manner. Other novel MOR ligands for treatment of post-operative pain have been developed, such as the biased ligand oliceridine, which showed dose-related trends of improvements on respiratory safety and gastrointestinal tolerability compared with morphine in two phase III trials, although reduced potential for addiction has not been evaluated yet.

M. Teresa Villanueva

ORIGINAL ARTICLE Spahn, V. *et al.* A nontoxic pain killer designed by modeling of pathological receptor conformations. *Science* **355**, 966–969 (2017)