Overcoming opioid side effects with combination peptide therapy

Review Article

Opioids are the analgesics most prescribed to treat moderate to severe pain but their use leads to a number of debilitating side effects, diminishing efficacy, and also the risk of abuse and misuse. A research team at Université de Sherbrooke in Canada has investigated combining the prototypical opioid morphine and an analgesic neurotensin brain-penetrant peptide analog to treat pain. They discovered that co-administration resulted in an additive analgesic response that permitted the dosing of morphine to be reduced and also decreased the level of a typical adverse side effect, constipation.

Unrelieved pain is a major global healthcare problem

There are two types of pain: acute pain, which is typical after surgery and trauma and chronic or recurring pain, which is common in individuals suffering from osteo- and rheumatoid arthritis, those with spine problems, and can be developed after operations and injuries (1). The problem is so great that chronic and recurrent pain is regarded as a disease in its own right (European Pain Federation, https://europeanpainfederation.eu/history/about-pain/). Apart from the burden of suffering, chronic pain results in a considerable cost to society that is on a par with cancer or cardiovascular disease by affecting one in five adults (1).

The downsides of pain relief – side effects and the opioid crisis

The search for pain relief has resulted in a wide range of painkillers, from ibuprofen to morphine, but opioids are still considered to be the most powerful for relieving moderate-to-severe short-term pain due to, for example, injury or surgery, or for prolonged pain caused by cancer. Opioid use has, however, two major drawbacks. Firstly, there are a number of side effects, including drowsiness, constipation, nausea, respiratory depression, and the development of tolerance that requires increased dosing to achieve the same effect.

Secondly, there are massive problems with the use, and misuse, of opioids particularly in the US where there is an ongoing 'opioid crisis'. This is thought to have begun with over-prescription, and up to 30% of patients prescribed opioids for chronic pain misuse them, with 8–12 % developing an opioid use disorder – that's an estimated 1.7 million people in the United States in 2017 alone. And there are signs that the problem is spreading to other countries, with opioid dosing increasing three-fold over a ten-year period in Europe (2,3).

Combination therapy – more benefits with fewer side effects?

One approach to avoiding these issues is combination treatment involving opioids and other analgesic drugs. One promising non-opioid candidate is neurotensin (NT), a 13-amino acid peptide that can deliver significant pain relief in animal models through the activation of G protein-coupled receptors in a manner that is independent of the opioid pathway, which involves the Mu opioid receptor. The researchers at the Department of Pharmacology and Physiology, Université de Sherbrooke in Canada, therefore explored the effect of treating an animal model with a combination of morphine and a NT brain-penetrant analog, An2-NT(8–13), studying both the analgesic effect and the level of constipation, which is a typical side effect of opioid treatment (4).

Peptide synthesis

Angiopep-2-NT(8-13) (An2-NT(8-13)) was synthesized by conjugating the NT(8-13) (RRPYIL-OH) peptide fragment to the Angiopep-2-Cys (TFFYGGSRGKRNNFKTEEYC-NH2), which were both prepared by solid-phase peptide synthesis on a Symphony® peptide synthesizer using standard Fmoc chemistry with commercially available Fmoc amino acids. Purity was analyzed by ultra-performance liquid chromatography (UPLC) and peptide identity was determined by ESI-TOF mass spectrometry. The An2-NT(8-13) conjugate was subsequently ligated in phosphate buffered saline by a two-step ligation method at room temperature, monitored by RP-UPLC. In the first step, a sulfo-EMCS was used to incorporate a maleimidyl linker site specifically at arginine 8 of NT(8-13), resulting in [Arg(MHA)8]NT. The second step involved conjugation with the C-terminal Cys-modified An2 peptide. Both reactions were stopped with acetic acid, and the final conjugate was purified by HPLC.

NT peptide analog has potent pain-relieving effect

The initial evaluation of the antinociceptive effects of the peptide analog gave promising results. For example, dose-response curves showed that while morphine had an effective dose for 50% relief (ED50) in an animal model of 1.39 mg/kg, the peptide analog had an ED50 of only 0.014 mg/kg.

NT peptide and morphine complement each other

The next step was to evaluate if morphine and An2-NT(8-13) interacted in an inhibitory, additive or synergistic manner to relieve pain. To do this, the researchers first generated isobolograms[1] from the doses required to produce 30%, 50%, 70% and 90% pain relief using the ED30, ED50, ED70 and ED90 values obtained for morphine and An2-NT(8-13) alone, as determined from the dose-response curves. One example is shown in Figure 1. A subsequent experiment determined if the pain relief was the result of an interaction between morphine and the NT peptide analog. This involved measuring the effect of increasing doses of morphine with a constant sub-analgesic dose of the peptide, and these dose-response curves revealed an additive analgesic effect of morphine and An2-NT(8–13).

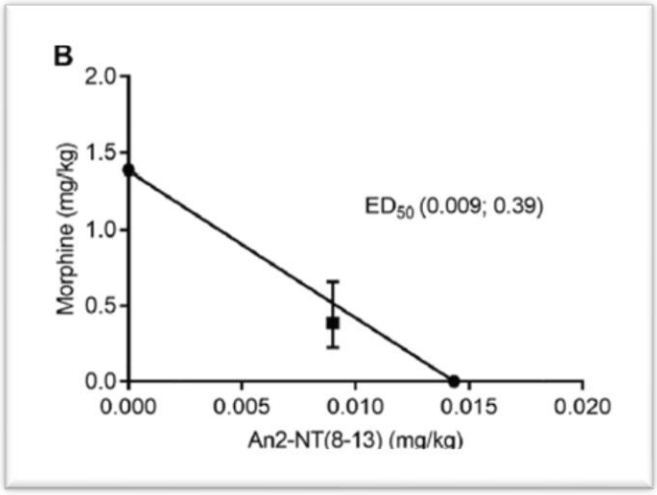

Figure 1. *An isobologram showing the concentrations of morphine or the peptide analog An2-NT(8-13) required to achieve 50% pain relief (ED_{50}). The line connecting each ED of single administration represents the theoretical line of additivity. The black square in the middle represents the ED_{50} for the co-administration of An2-NT(8–13) and morphine, showing the additive effect. From Figure 2B, Eiselt et al, 2019.*

[1] An isobologram is a diagram that shows the varying levels of agents that give a constant effect.

Combination treatment reduces side effects

Constipation is a typical debilitating side effect of morphine treatment, so the researchers tested whether combining morphine and An2-NT(8–13) would give sufficient pain relief without constipation. Their model showed that treatment with the peptide did not result in constipation. They could also show that combining morphine with the peptide at doses required to achieve ED90 overall resulted in lower levels of constipation than caused by the higher level of morphine required alone to achieve the same level of pain relief.

The promise of lowered dose in combination therapy

Morphine and An2-NT(8–13) do not mask or increase the efficacy of each other, but combining them clearly enables lower dosages of, for example, morphine that help avoid debilitating side effects such as constipation. This work clearly illustrates the potential of combination drug therapies for pain patients that exploit complementary analgesic actions to provide superior pain relief with reduced adverse effects. The anticonvulsant gabapentin is another example of a non-opioid analgesic that can be used in combination with morphine to give effective pain relief at lower doses, thus lowering the risk for adverse effects (5, 6).

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