Dual enkephalinase inhibitor (DENKI) PL265: a novel topical treatment for ocular pain?

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INTRODUCTION

The peripheral endogenous opioid system is critically involved in neuropathic and inflammatory pain (1). Enkephalins, the main endogenous opioids, play a key role at all levels of pain control and exhibit an analgesic efficacy comparable to morphine without the adverse effects.

DUAL ENKEPHALINASE INHIBITORS (DENKIS) are specific and selective inhibitors of aminopeptidase N (APN) and neprilysin (NEP), protecting enkephalins from enzyme degradation. DENKIS thereby potentiate physiological functions of enkephalins (e.g., pain control).

The DENKI PL265 – Mechanism of action and pharmacology

• PL265 is a small non-peptide molecule (MW: 576 Da).
• PL265 is active orally in all rodent models of neuropathic pain tested with a strictly peripheral effect (2).
• PL265 has been given orally to rats (up to 1200 mg/kg) and dogs up to 800 mg/kg with no toxic effects.
• Oral PL265 has safely completed Phase 1 single ascending dose (100-800 mg) and is now in Phase 1 multiple ascending dose (up to 300 mg b.i.d.) for 4 days, before entering Phase 2 in 2018 in painful diabetic neuropathy.

METHODS

Adult male C57BL/6 mice (8-week-old) were used. Animal procedures were carried out by authorized investigators in accordance with institutional guidelines for the care and use of experimental animals approved by the European Communities Council Directive 2010/63/UE.

RESULTS

• All elements of the enkephalinergic system (opioid receptors, enkephalins and their degrading enzymes) are also expressed in ocular surface tissues. Topical morphine has actually been shown to relieve pain associated with corneal lesions in rat and dog pain models (3,4).
• To date, no topical ocular analgesics are available for the treatment of acute or chronic pain, only anesthetics which have many shortcomings.
• Here, we display the antinociceptive and anti-inflammatory effects of a highly effective DENKI produg, PL265, using experimental murine models of ocular nociception and inflammation.

CONCLUSIONS

• This study provides the first evidence that PL265, a prodrug from a new therapeutic class, DENKI, is highly effective in decreasing corneal nociception after various experimental corneal lesions.
• PL265 also significantly reduces corneal inflammation in a model of LPS-induced inflammatory pain.
• The antinociceptive effects of PL265 are mediated by opioid receptors on ocular surface nerve endings, without involvement of the central nervous system.
• PL265 appears as a promising topical medicine for safely and effectively alleviating ocular pain and inflammation.