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Targeting protected enkephalins: Beyond morphine

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The story of endogenous opioid systems will be presented to introduce the new and recent approaches in pais treatments especially those focussed on dual enkephalinase inhibitors Enkephalins are endogenous peptide-ligands of opioid receptors with affinities for the mu (MOR) and delta (DOR) receptors in the range of morphine. They are released by stimuli such as pain are transient effects $(\leq \min)$ due to their rapid degradation by two metallopeptidases, NEP and APN. As early as 1984, we have developed inhibitors named DENKIs increasing concentration and half-life of ENKs, in the painful area, hence inducing a "physiological" analgesia. The most advanced DENKIs are PL37 and PL265 both in clinical trials which are first new concept emerging in clinical pair treatment since decades [Roques B.P. et al. Nature Rev. Drug Discovery, 2012, 11, 292-311]. DENKIs have two main indications: i) via i.v., severe acute or chronic pain; ii) p.o., severe neuropathic pain due to chemical, metabolic, infectious or mechanical lesions. Both types of pain are unsatisfactorily treated. As DENKIs are devoid of MO side effects P37 can be substituted, combined or alternated with MO. Their potencies are amplified by their stronger effects than MO on the emotional status of the suffering patient by DORs recruitment in the limbic system of reward. Current medications for neuropathic pain have been used: duloxetine, pregabalin, but are effective in less than half of patients, with total relief in only 30% of responders. Opiates are sometimes prescribed in neuropathic pain, but their use is limited: i) by an inhibitory effect on descending pathway; ii) "need of high" doses generating unacceptable side-effects (tolerance, constipation and dependence liability). None of these inconveninces were observed with DENKIs protected ENKs. Finally, a high synergy has been demonstrated when PL37 and various compounds are combined. The phase 2a trial confirms that use of PL37 for the treatment of diabetic neuropathy is safe and causes no major side effects and decreases pains intensity.

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