

## Antinociceptive effects of acetyl Leu-enkephalin derivatives following intrathecal administration in rat

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### Abstract

**Introduction:** Intrathecal infusion of some enkephalin derivatives has been shown to restore analgesia in morphine tolerant patients with less adverse effects such as respiratory depression and constipation compared to morphine. Therefore developing new enkephalin derivatives is of central interest in pain management. In this study, antinociceptive effects of intrathecal administration of two novel acetyl met-enkephalin analogues were evaluated compared to met-enkephalin.

**Methods and Results:** To permit the intrathecal administration of drugs into the lumbar subarachnoid space in adult wistar rats, polyethylene (PE10) catheters were implanted in the L2 and L3 spinal segments in anesthetized animals. After a recovery time of 4-5 days, to protect the drugs from biodegradation, all rats were pretreated with peptidase inhibitors (APC) including Amastatin, Phosphoramidon and captopril. Animals were dosed with intrathecal infusion of the analogues followed by tail flick latency test for an hour. Acetyl-Leu-enk-CHO and Acetyl-Leu-enk did not show any significant antinociceptive effects in 10 nM ( $10^{-8}$  M) concentration. However Acetyl-Leu-enk demonstrated considerable effects in 100 nm ( $10^{-7}$  M) compared to Leu-enkephalin. Surprisingly, Acetyl-Met-Leu-enk-CHO antinociception did not improve but decreased with increasing intrathecal dosage to 100 nm, probably working as a partial agonist on opioid receptors.

**Conclusions:** According to our results, Acetyl-Leu-enk may provide better analgesic effects, compared to Acetyl-Leu-enk-CHO. With likely reverse dose-response effects on tail flick test, Acetyl-Leu-enk-CHO might be considered as a particular ligand for opioid receptors without full agonistic effect for further studies.

**Key words:** Enkephalin, Nociceptive, Tail flick test, Docking