

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

Hengameh Ghazi<sup>a</sup>, Amin-Reza Khodadad<sup>a</sup>, Saeed Balalaie<sup>b</sup>, Elham Rezaiee<sup>a</sup>, Sanaz Nasoohi<sup>c\*</sup>

### Authors' Affiliations:

<sup>a</sup> School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>b</sup> Peptide Chemistry Research Center, K.N. Toosi University of Technology, Tehran, Iran

<sup>c</sup> Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

### Abstract Presenter:

Hengameh ghazi, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Email: ghazi\_hengame1991@yahoo.com

### \*Correspondence:

Sanaz Nasoohi; PhD.; Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

E-mail: sanaznasoohi@yahoo.com

### 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 (A), Phosphoramidon (P) and captopril (C). Animals were dosed with intrathecal infusion of the analogues followed by tail flick latency test for an hour. Acetyl-Met-enk-CHO and Acetyl-Met-enk did not show significant antinociceptive effects in 10 nM ( $10^{-8}$  M) concentration. However Acetyl-Met-enk-CHO described discernible effects in 100 nm ( $10^{-7}$  M) in comparison with enkephalin. To estimate resistance against peptidase, molecular modeling was performed and showed compound Acetyl-Met-enk-CHO has low affinity to active site of aminopeptidase, dipeptidylcarboxypeptidase-I and neutral endopeptidase; the degrading endogenous enkephalin opioid peptides.

**Conclusions:** According to our results, Acethyl-Met-enk-CHO may provide comparable analgesic effects with, although with 10 folds less potency. With likely resistance against endogenous peptidase, this molecule could be a valuable lead compound for further studies.

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