



Analgesic activity of novel synthesized tetrapeptides: overview

M. Vignesh and A. Jayakumar*

¹Department of pharmaceutical chemistry, pallavan pharmacy college, kolivakkam, Kanchipuram, Tamil Nadu, India-606603.

ABSTRACT



The tetrapeptide class of biased analgesics from an Australian fungus targets the μ -opioid receptor. The current study sought to investigate the analgesic and anti-inflammatory effects of Tyr-MIF-1 mimetics in rats suffering from acute pain. We report the synthesis of two new compounds which are hybrid molecules between the substituted pyrrole (Pyr) and analogues of Tyr MIF-1 peptide. The in vitro opioid activity of the analogs was tested in the guinea pig ileum (GPI) and naloxone-induced pain model. The study examined the effect of an analog to an N-terminal nociceptin fragment on the behavior of albino rats. We have also elucidated a novel G protein-biased agonist, Phe-Phe-Asp] NH₂, for the management of moderate to severe acute pain following abdominoplasty. The pharmacophore based on Phe, NH₂, was synthesized and characterized by solid phase chemistry and high-performance liquid chromatography/mass spectrometry (HPLC/MS). The results show that a series of hybrid molecules with a unique stereochemical arrangement of hydrophobic amino acids, bilaid A-C, were synthesized. The effects of a new molecule, an analog of N-Terminal Nociceptin Fragment (PK20M), on motor and exploratory activity of mature rats and in 42-day pups and 21-day rat pups were evaluated. The antinociceptive and antipyretic activities of the original molecule were evaluated in a model of post-incisional pain in rats at doses lower than 1g/kg. The present study reporting the overview of analgesic activity of some novel synthesized tetrapeptides fragments shows satisfaction effects comparing with morphine, aspirin, naloxone, etc.

Keywords: Novel tetrapeptides-opioid activity-animal model-N-terminal nociceptin.

ISSN: 2581-9143

Review Article

Corresponding Author

Name: A. Jayakumar

Email: vigneshmanohar0303@gmail.com

Article Info

Received on: 18-02-2023

Revised on: 16-03-2023

Accepted on: 29-03-2023

DOI: <https://doi.org/10.33974/ijrpst.v3i3.324>



Copyright© 2023, M. Vignesh and A. Jayakumar, Analgesic activity of novel synthesized tetrapeptides: overview, Production and hosting by Rubatosis Publications.

INTRODUCTION

Peptides (from the Greek word means "digested") are short polymers of amino acid (monomers) linked by peptide bonds, the covalent chemical bonds formed between two molecules when the carboxyl group of one molecule reacts with the amino group of the other molecule.

Amino acids are linked together by condensation reaction between carboxylic and amino groups from

two different amino acids (with elimination of water). [1]

The amide bond formed is called peptide bond. They are five types, Dipeptide it contains 2 amino acid units, Tripeptide it contains 3 amino acid units, Tetrapeptide it contains 4 amino acid units, Oligopeptide it contains not more than 10 amino acid units, Polypeptide = contains more than 10 amino acid units, up to 100 residues.

A tetrapeptide is a peptide, classified as an oligopeptide, since it only consist of four amino acids joined by peptide bonds. Many tetrapeptides are pharmacologically active, often showing affinity and specificity for a variety of receptors in protein-protein signalling. Analgesics are agents which selectively relieve pain by acting in the CNS and peripheral pain mediators without changing consciousness. Analgesics may be narcotic (or) non-narcotic. The study of pain in animals raises ethical, philosophical and technical problems.

Natural analgesics: Ginger, Garlic, Cloves, Cherries, Turmeric, Peppermint, Pineapple, Apple cider vinegar, Blueberries.

Synthetic analgesics, Morphine: intestinal motility, suppresses cough and has vasodilatory effects.

Codeine: it is a prodrug, to exert its opioid activity, it must first undergo o-demethylation by CYP2D6 to morphine, decreases pain from mild to moderate.

Table 1: Synthetic analgesics

Chemical name	Dose (mg)	Duration of action (hrs)	Symptoms
Hydromorphone	1.5	4-5	Similar to morphine
Oxymorphone	1.0-1.5	4-5	Similar to morphine
Hydrocodone	5-10	4-8	Similar to morphine and codeine
Dihydrocodeine	60	4-5	Similar to morphine and codeine
Oxycodone	10-15	4-5	Similar to morphine and codeine

The molecular modeling (MD) simulations of -opioid ligands, (Tyr-D-Ala-Gly-Phe-NH)₂, and the active tetrapeptide hydrazide, Tyr-D, Ala, Gly, Phe, and NH₂ were performed to investigate the cause of the increased and receptor activation. The MD simulations performed in this study were carried out using a pharmacophore model established by them. The results demonstrate that the acylation of the two opioid receptors exhibits their analgesic activity via activating the opioid, or agonist receptors, resulting in significant side-effects. [2]

Sequence: Tyr-D-Ala-Gly-Phe-NH₂; Tyr-D-Ala-Gly-Phe-NH-NH₂

The series of novel endomorphin analogs with multiple agonists against opioid receptor have been synthesized and characterized. The peptides were characterized by X-ray diffraction, ¹H-NMR spectroscopy, and scanning electron microscopy (SEM). The in vitro opioid activity of the analogs was tested in the guinea pig ileum (GPI) and naloxone-induced pain model. The in vivo analgesic activity of MEL-N16 compounds was evaluated in a variety of pain models. The analogs were more active than the -arrestin-2 antagonists in the tested nociceptive models. Moreover, the compounds were able to induce cyclic AMP accumulation in the GPI model. In addition, the neoadrenergic system was used to investigate the mechanism of action of the compounds. The results showed that the MEL series of compounds showed very good antinociceptive activity and a favorable side effect profile. [3]

Sequence: Endomorphin-1: EM-1: H-Tyr¹-Pro²-Trp³-Phe⁴-NH₂; Endomorphin-2: EM-2: H-Tyr¹-Pro²-Phe³-Phe⁴-NH₂

The discovery of 3 tetrapeptides, bilaid A-C, with a unique stereochemical arrangement of hydrophobic amino acids from an Australian estuarine isolate. Bilorphan, a potent and selective partial opioid

agonist of G proteins in AtT20 cells, was able to induce C-terminal phosphorylation, -arrestin recruitment, and G-protein pathway selective (-GPS) modulation in vivo, consistent with predicted G protein efficacy. We have also elucidated an analgesic pharmacophore based on Phe-Phe-Asp] NH₂, a novel G protein-biased agonist, for the management of moderate to severe acute pain following abdominoplasty. [4]

Enkephalin-D-Ala, N-MePhe⁴, Gly⁵-ol

The effect of an analog to N-terminal nociceptin fragment AcOH-Phe-Gly-Gly-Phe-NH₂ on motor and exploratory activity of mature rats and in 42-day pups and 21-day rat pups. The experiments revealed activation effect of the examined peptide on the open-field behavior of the mature rats. The experimental group received tetrapeptide 5 mg/kg intraperitoneally. The experiment revealed that the examined analog significantly enhanced the open field behavior in mature rats under dim red conditions and produced opposite effects in 21-day pups, which attests to the complex dynamics of maturation of nervous structures involved in the realization of nociceptin action. [5]

Sequence: AcOH x Phe-Gly-Gly-Phe-NH₂

The antinociceptive and antipyretic activities of a novel tetrapeptide were evaluated in a model of post-incisional pain in rats at doses lower than 1 lg/kg due to morphine, aspirin, and naloxone. Treatment 1 was intraperitoneally administered 2 h 40 min postincision, and treatment 2 was subdermally administered 3 h post-incidence (15 min). Treatment 1 did not induce any analgesic activity in the Brennan model of pain. Treatment 2 did not. Treatment 3 did not inhibit the antipyrexia induced by naloxone, but at 5.4 mg/kg it inhibited the anti-nociception activity in rats. At a dose of 30 IM, a reduction of 70% in the antidiabetic activity was observed. In the first set of experiments, treatment 1 was administered 2 hours after incision and was administered 3 hours later. The results of the screening assay suggest that the peptide does not affect known therapeutic targets for pain and temperature control. [6]

A novel endomorphin-2-like opioid peptide was introduced as a highly active analgesic because it elicited a strong dose- and time-dependent antinociceptive response when administered centrally and peripherally. The N-terminal tetrapeptide fragment of Dmt-D-Lys-Phe-Phen-OH (PK20M) was synthesized and characterized by solid phase chemistry and HPLC/MS. The metabolite was pharmacologically characterized in in vitro MOP and DOP receptor binding and [35S] GTPS receptor binding assays. Peptides were evaluated in vivo in C57Bl6 mice after intravenous or intrathecal applications. PK20 showed high potency in a wide range of doses and a time- and dose-dependent nociception response. During a 2h postinjection period, the antinociceptive profile was preserved for

every examined dose. This novel analogue is a promising compound for future studies in pain management.^[7]

The physical dependence liability of biphalin, a dimeric enkephalin analogue that possesses high antinociceptive activity, with that of morphine in equipotent intravenous doses. Male Wistar rats were injected every hour for five days according to the schedule presented in the literature. The animals were subjected to naloxone challenge for 5 days. The group of rats treated with morphines showed classical withdrawal signs, but only minor withdrawal signs after a 5-day infusion of a bivalent opioid peptide. We also found that pentazocine showed a moderate ability to suppress weight loss after pentazocine withdrawal, but successfully suppressed body weight loss. We found the less liability of physical dependence after chronic biphalin infusion in rats, which is different from that of the drug. Biphalin is able to reverse symptoms of pentocine withdrawal. The present findings support consideration of biphases as a new analgesic with a minimum dependence liability.^[8]

Sequence: N-terminal tetrapeptide: Dmt-D-Lys-Phe-Phe-OH(PK20M)

CONCLUSION

The opioid system plays an important role in the regulation of the inflammatory response. In this study, we report the synthesis and analgesic activity of a tetrapeptide fragment of Dmt-D-Lys-Phe-Phen-OH (PK20M) synthesized and characterized by solid phase chemistry and HPLC/MS. The synthesized analogues of Tyr-MIF-1 peptide were used to investigate the pharmacological effects of the analogs in the central nervous system (CNS) of rats. The results showed that some of the new compounds had manifested antinociceptive activity, with the opioid system playing a role. Moreover, a novel endomorphin-2-like opioid pharmacophore, PK20, was introduced as a highly active analgesic agent in a model of post-incisional pain in rats at doses lower than 1 g/kg due to morphine, aspirin, and naloxone. This study is an attempt to give an overview about some of the novel synthesized tetrapeptide fragments. The forthcoming researches can evaluate some more important tetrapeptide fragments showing better analgesic activity.

REFERENCES

1. Satyanarayana, U. (2013). *Biochemistry*. Elsevier Health Sciences.
2. Hsieh, J. Y., Chiang, T. Y., Chen, J. L., Chen, Y. W., Lin, H. C., & Hwang, C. C. (2011). A molecular dynamics study on opioid activities of biphalin molecule. *Journal of molecular modeling*, 17(10), 2455-2464.
3. Liu, X., Zhao, L., Wang, Y., Zhou, J., Wang, D., Zhang, Y., ... & Wang, R. (2017). MEL-N16: a series of novel endomorphin analogs with good analgesic activity and a favorable side effect profile. *ACS chemical neuroscience*, 8(10), 2180-2193.
4. Dekan, Z., Sianati, S., Yousuf, A., Sutcliffe, K. J., Gillis, A., Mallet, C., ... & Christie, M. J. (2019). A tetrapeptide class of biased analgesics from an Australian fungus targets the μ -opioid receptor. *Proceedings of the National Academy of Sciences*, 116(44), 22353-22358.
5. Ivanova, E. A., Sarycheva, N. Y., Dubynin, V. A., Malyshev, A. V., Kalikhevich, V. N., Ardemasova, Z. A., & Kamensky, A. A. (2012). Behavioral effects of original tetrapeptide, an analog of N-terminal nociceptin fragment. *Bulletin of experimental biology and medicine*, 153, 177-181.
6. Skubatz, H., & Klatt, B. (2012). Further Characterization of a Novel Tetrapeptide with an Analgesic Action in the Central and Peripheral Nervous System in Rats. *International Journal of Peptide Research and Therapeutics*, 18(1), 41-52.
7. Kleczkowska, P., Bojnik, E., Leśniak, A., Kosson, P., Van den Eynde, I., Ballet, S., ... & Lipkowski, A. W. (2013). Identification of Dmt-D-Lys-Phe-Phe-OH as a highly antinociceptive tetrapeptide metabolite of the opioid-neurotensin hybrid peptide PK20. *Pharmacological Reports*, 65(4), 836-846.
8. Yamazaki, M., Suzuki, T., Narita, M., & Lipkowski, A. W. (2001). The opioid peptide analogue biphalin induces less physical dependence than morphine. *Life Sciences*, 69(9), 1023-1028.