

MICHAL LEBL

Peptides

BUILDING BRIDGES: THE PROCEEDINGS OF THE
TWENTY-SECOND AMERICAN PEPTIDE SYMPOSIUM



Peptides:

Building Bridges

Proceedings of the Twenty-Second
American Peptide Symposium

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Proceedings of the
Twenty-Second American Peptide Symposium
June 25 - 30, 2011, San Diego, CA, U.S.A.

Edited by
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Prompt Scientific Publishing
San Diego, CA
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American Peptide Society
San Diego

Sold and distributed by www.lulu.com

ISBN 978-0-9839741-0-9

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Produced by Prompt Scientific Publishing,
www.promptpublishing.com, San Diego, U.S.A.

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Comparative Study of Computer Modeling and Biological Testing of New Kyotorphin Analogues

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Introduction

The most important thing is to know with which receptor kyotorphin, respectively its analogues, interacts. Kyotorphin (KTP) was isolated from bovine brain by Takagi and co-workers [1,2]. This endogenous dipeptide (L-Tyr-L-Arg) belongs to the neuropeptide family due to its opiate-like activity. The Tyr-Arg motif exists widely through-out the brain, not only as KTP, but also as the N-terminal part of several endogenous analgesic peptides [3,4]. This peptide is very rapidly degraded by aminopeptidases [5]. Many of these properties are typical for neurotransmitters, and it is not surprising that KTP has also nonopioid action independent of enkephalin release [6]. There is evidence suggesting that KTP does not bind the opiate receptors (μ , δ , κ), but that it exerts Met-enkephalin-release force [7]. These results led to the suggestion that the dipeptide bind to a specific receptor (KTP receptor, KTPr) [8], triggering a cascade of events that leads to strong analgesia in the brain [9,10]. Despite the fact that several studies [7,11,12] confirm the existence of a KTPr, it has not yet been identified. There is still the question of whether the KTPr is specific [11], or the result of mixed oligomerization of μ - and δ -opioid receptors [13]. The L-Tyr residue at first position of the peptide presented in most of the opioid peptides. It is believed to be crucial for receptor recognition [14,15] due to both π -stacking [16] and hydrogen-bonding

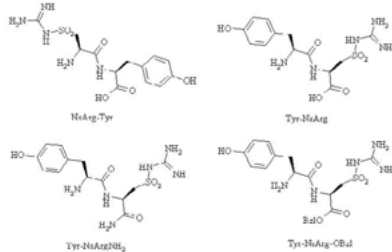


Fig. 1. New KTP analogues.

cis/trans conformation in the set; and 2) the predominance of the extended conformations (both cis and trans) results in the Arg side chain not invading the vicinities of the phenol group of the Tyr. That allowed it to be presented to the receptor without any hindering effects. These results suggest that, despite the fact that KTP does not bind to the opioid receptors, there is no indication for the KTPr pocket to be very different from those of the opioid receptors. Using all this data we can consider that the receptor pocket is the same as in μ -receptor, and to try to explain biological effect of analogues using computational methods.

Results and Discussion

Synthesis. The synthesis of the four new analogues of KTP was realized by synthetical approaches based on methods of peptide synthesis in solution – mixed anhydride and activated esters method. For N α -protection Z- and Tos-groups were used, and for carboxyl protection benzyl and methyl ester, respectively. Strategy for minimal side chain protection was applied – phenol hydroxyl group in Tyr and sulfo-guanidino group in NsArg were unprotected during the coupling reaction. Synthetic schemes were presented previously [19].

Biological activity. Male Wistar rats (180-200 g) and male albino mice (25-28 g) were used. Two methods were applied – Paw-pressure and Hot plate test. Norsulfoarginine (1 mg/kg, i.p.), NsArg-Tyr, Tyr-NsArg, Tyr-NsArgNH₂ and Tyr-NsAr-OBzl (all at a dose of 5 mg/kg, i.p.) applied alone exerted well-pronounced antinociceptive effect in PP test and they significantly

increased HP latency. Obtained results showed that only Tyr-NsArg-OBzl increase significantly the pain threshold vs. native peptide KTP on 15th minute. On the 30th minute only Tyr-NsArg had analgesic effect compared to the control and KTP [19].

Computer modeling. With a help of computer modeling we tried to explain the activity of the

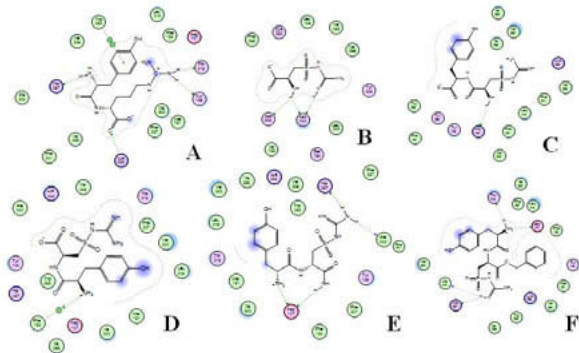


Fig. 2. Interactions in receptor surface.

kytorphin analogues synthesized by us. As a model of μ -receptor we used published in PDB (2iqo). Docking studies were performed by using GOLD 4.1 (Genetic Optimization for Ligand Docking) [17], run on Linux operating system. Energy minimization, Molecular Dynamics, and visualizations were made on MOE (Molecular Operating Environment).

The amino acid residue Asp 147 was predicted to be a key binding site of the cationic amino group in the μ selective ligands. Aromatic ring in ligand interact with Tyr 299 and hydrogen bonding interaction between the phenolic hydroxyl group of ligand, and both the amino group of Lys303, and hydroxyl group of Tyr 148 were proposed to be major forces for binding. In the case of KTP (A) interaction of guanidino group with Asp 147, and Thr 218 and Tyr 148 occurs. Free carboxyl group binds Lys 233 residue, and His 297 forms H-bond with free amino group of Tyr residue. Additional stabilization of this complex is ensured by aromatic interaction between aromatic rings of Trp 293 and Tyr. Interaction between receptor and NsArg (B) is very weak – there is no conformational fitting. Replacement of Arg with NsArg in KTP (C) makes molecule very different. Protonation of sulfoguanidino-group does not occur under physiological conditions, and all interactions due to this effect are not possible. In the case of reversed KTP (D) analogue situation is completely different. Interactions occur between different residues in the receptor. Better ligand-receptor interaction appears in the case of Tyr-NsArg-OBzl (E). Binding of the free amino group with Asp 147 and Thr 218, interaction between Tyr 148, and aromatic ring of benzyl ester, donor-acceptor interactions as well as H-bond formation – all this shows that the binding is very strong. Tyr-NsArgNH₂ (F) interacts with a receptor by forming H-bond (His 297 and sulfoguanidino group), side chain interactions, and acidic-basic interaction (Asp 147 and protonated amino group).

Acknowledgments

This work was supported by NFSR of Bulgaria (Contract MY-FS-13-07) and project DVU 01/197.

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