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INVESTIGATION OF INTERACTIONS BETWEEN DERMORPHIN ANALOGS AND μ-OPIOID RECEPTOR

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Abstract: Opioid receptors play the pain control function in the body. Most of the research is carried out to find the most effective analgesic. The earliest analgesic is morphine, however, unfortunately it has many side effects [Mizoguchi H *et al.* 2003 J. Pharmacol Sci. **93** 423]. At a later time dermorphin was discovered as another potent analgesic [Montecucchi P C *et al.* 1981 Int. J. Pept. Protein Res. **17** 275]. Unfortunately, this peptide is not resistant to enzymatic metabolism [Kisara K *et al.* 1986 Br. J. Pharmacol. **87** 183; Sasaki Y *et al.* 1985 Neuropeptides **5** 391].

The objective of this study is to search for new opioid analgesics by investigation of interactions between dermorphin analogs and the μ-opioid receptor using molecular modeling methods. MOPR (μ-Opioid Peptide Receptor) complexes with several ligands (with known biological activity) were modeled to explain how the structure of the complex was related to the biological activity. The investigated dermorphin analogs containing [DMT[1], *D*-Arg[2]] (especially tetrapeptides) may become a good alternative for the currently used analgesics.

Keywords: molecular modeling, opioid receptors, defmorphin, molecular docking, drug design

1. Introduction

The MOPR belongs to class A G-protein-coupled receptors (GPCRs) [5]. In the search for an effective analgesic, [Tyr-*D*-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2] dermorphin (Figure 1) has been discovered in amphibian skin with high potency and selectivity to the MOPR [2]. Unfortunately, the peptide is not resistant to enzymatic metabolism.

The recent studies of the dermorphin analogs show that modifications of the dermorphin molecule have led to better pharmacological profiles, *e.g.* the replacement of *D*-Ala with *D*-Arg has made the peptide resistant to enzymes and increased its selectivity [3, 4]. Studies have shown that the creation of a salt bridge

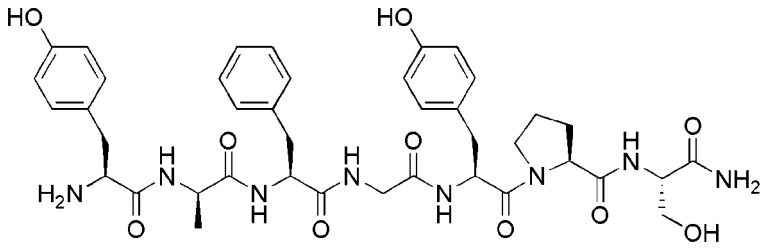

Figure 1. Structural formula of dermorphin

between the amine group of Tyr^{1}* (tyramine) of the ligand and the carboxyl group derived from Asp147* of the receptor is required for activation of the MOPR [6]. It is also known that the Tyr^{1} residue derived from the MOPR agonists willingly interacts hydrophobically with Trp293 of the receptor, and frequently forms a hydrogen bond with His297 by the hydroxyl group [7–9]. Earlier studies on dermorphin analogs have shown that some of their derivatives have interesting analgesic properties (Table 1, odd-numbered) [10].

Table 1. Built and researched ligands

1	demorphin	Tyr-*D*-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2
2	[DMT^{1}]demorphin	DMT-*D*-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2
3	[*D*-Arg^{2}]demorphin	Tyr-*D*-Arg-Phe-Gly-Tyr-Pro-Ser-NH_2
4	[DMT^{1}, *D*-Arg^{2}]demorphin	DMT-*D*-Arg-Phe-Gly-Tyr-Pro-Ser-NH_2
5	[*D*-Arg^{2}]demorphin(1–4)	Tyr-*D*-Arg-Phe-Gly-NH_2
6	[DMT^{1}-*D*-Arg^{2}]demorphin(1–4)	DMT-*D*-Arg-Phe-Gly-NH_2
7	[*D*-Arg^{2}]demorphin(1–4)OH	Tyr-*D*-Arg-Phe-Gly-OH
8	[DMT^{1}-*D*-Arg^{2}]demorphin(1–4)OH	DMT-*D*-Arg-Phe-Gly-OH
9	TAPA-NH_2	Tyr-*D*-Arg-Phe-*β*-Ala-NH_2
10	[DMT^{1}]TAPA-NH_2	DMT-*D*-Arg-Phe-*β*-Ala-NH_2
11	TAPA	Tyr-*D*-Arg-Phe-*β*-Ala-OH
12	[DMT^{1}]TAPA	DMT-*D*-Arg-Phe-*β*-Ala-OH

One of the tetrapeptide derivatives of the dermorphin, DALDA (Tyr-*D*-Arg-Phe-Lys), is characterized by a longer lasting effect [11, 12]. The substitution of Tyr^{1} by the DMT (2', 6'dimetylotyrosine – DMT) in the DALDA causes an increase in the affinity for the μ-opioid receptor and a significant increase in the potency [13].

The improvement of the therapeutic properties of the analogue [DMT^{1}] DALDA suggests that swapping Tyr^{1} on DMT^{1} in the previously discussed dermorphin analogs may affect their properties in a similar manner.

* The residue numbers of ligands are written in superscript, and the residue number of the receptor has no index.

2. Methods

Twelve different dermorphin analogs were built in the LEAP program (Table 1). The biological properties of the odd-numbered ligands (1, 3, 5, 7, 9 and 11) were previously determined experimentally [10], and the even numbered ligands were analogs of ligands $(n-1)$ preceding them, with one modification – substitution of residue Tyr^1 by residue DMT^1.

Each ligand was surrounded by water molecules (TIP3PBOX) and was in this form subjected to the process of energy minimization and geometry optimization in the AMBER force field under periodic conditions. Each peptide was separately docked into the MOPR binding pocket using the Autodock program. The version used was Autodock 4.2.5.1. We docked a flexible ligand into a rigid receptor. The grid size was 3543.75 Å^3 (Grid Point Spacing = 0.375 Å; Even Number of User-specified Grid Points = 30 x-points; 70 y-points; 32 z-points). The Genetic Algorithm option was selected for the docking. The Lamarckian Genetic Algorithm was chosen as the docking search parameter. After docking 90 different structures for each ligand were generated. The selection was made on the basis of the binding energy and the ligand location criteria (required for the salt bridge interaction between Tyr^1 of the ligand and Asp147 of the receptor (Figure 2)). Five of the best receptor-ligand complexes were chosen for each analog. Subsequently, the energy of each receptor-ligand system was minimized and one arrangement with the lowest-energy was selected for each ligand. The interactions were examined by the Yasara program.

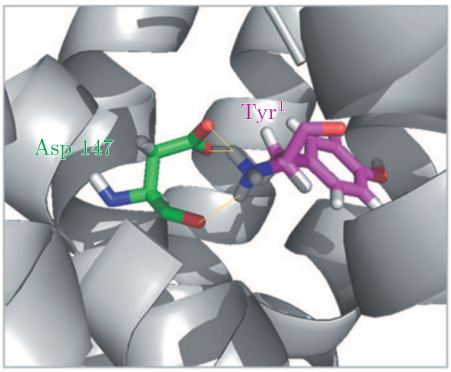

Figure 2. Required interaction between Tyr^1/DMT^1 from the ligand and Asp from the receptor

3. Results

The results are summarized in Table 2 – interactions between amino acid residues of the MOPR and the studied ligands were estimated by the Yasara program.

Almost all of the ligands, except for [DMT^1, *D*-Arg^2]dermorphin and [DMT^1, *D*-Arg^2]dermorphin(1–4)OH, form a hydrogen bond with His297 of the

Table 2. Summary of interactions between amino acid residues of MOR and studied ligands (Table 1); the first column includes amino acid residues of the receptor, and the numbers of the studied ligands are shown in the first row

	1	2	3	4	5	6	7	8	9	10	11	12
Gln124												
Ile144												
Asp147												
Tyr148												
Met151												
Val202												
Lys209												
Arg211												
Asp216												
Cys217												
Thr218												
Leu219												
Phe221												
Thr225												
Trp226												
Glu229												
Leu232												
Lys233												
Val236												
Phe241												
Trp293												
Ile296												
His297												
Val300												
Ile301												
Lys303												
Ala304												
Gln314												
Trp318												
Ile322												
Gly325												
Tyr326												
Asn328												

	very strong interaction $E > 20\,\mathrm{KJ/mol}$
	medium strong interaction $20 > E > 10\,\mathrm{KJ/mol}$
	medium weak interaction $10 > E > 1.5\,\mathrm{KJ/mol}$
	very weak interaction $E < 1.5\,\mathrm{KJ/mol}$

MOPR. All ligands interact hydrophobically with Trp293 of the receptor. These three types of interactions are essential for activation of the MOPR and are present in the receptor-ligand complexes with known biological activity (Table 2, odd-numbered), and therefore, it can be deduced that the ligands modified in this study can be agonists for the MOPR. All the ligands interact with Leu219 of the receptor, and almost all, besides [*D*-Arg^2]dermorphin(1–4) and TAPA, interact strongly with Glu229, which further stabilizes the receptor-ligand complexes. It is interesting to note that all the derivatives containing DMT^1, excluding [DMT^1]TAPA, interact with Cys217, which may be important in the stabilization of the complex with the receptor. In addition to the above-mentioned impacts, there are many weaker interactions between ligands and the receptor, which also further stabilize the receptor-ligand complexes.

4. Conclusions

The models of receptor-ligand complexes obtained in these studies indicate a high affinity of the investigated ligands to the MOPR, as confirmed by the number of similarities of the interactions between the receptor and ligands with known biological activity and with ligands substituted in position 1 by the DMT residue. Of all the ligands, the [DMT^1, *D*-Arg^2]dermorphin and [*D*-Arg^2]dermorphin present the strongest bond with the receptor. TAPA-NH_2, [DMT^1]TAPA-NH_2, [*D*-Arg^2]dermorphin(1–4)OH, [DMT^1, *D*-Arg^2]dermorphin(1–4)OH and TAPA relatively strongly interact with the MOPR. Finally dermorphin [DMT^1]dermorphin [*D*-Arg^2]dermorphin(1–4), [DMT^1, *D*-Arg^2]dermorphin(1–4) and [DMT^1]-TAPA show somewhat weaker interactions with the MOPR.

The substitution of Tyr^1 residue by DMT^1 in some cases causes strengthening or the appearance of certain interactions (often strengthens the bond with Leu219), and in other cases, weakening or disappearance of other interactions (often weakness or loss of the hydrogen bond with His297). Most often, the substitution of the DMT^1 residue reduces slightly the total energies of ligand-receptor interactions, however, due to the presence of interactions with Cys217 and the impact of dermorphin [DMT^1, *D*-Arg^2] on the Lys303 it may suggested in biological research that these analogs can cause the activation of the receptor.

Based on the analysis of interactions it may be suggested that the studied novel dermorphin derivatives containing DMT^1, namely dermorphin[DMT^1, *D*-Arg^2], dermorphin[DMT^1, *D*-Arg^2](1–4)OH and [DMT^1]TAPA-NH_2 are worth examining by experimental methods and may become an alternative to the currently used analgesics.

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