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Spatial structure of the exorphin B4 molecule

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Abstract

The conformational possibilities of the exorphin B4 molecule were studied by the method of theoretical conformational analysis. The potential function of the system is chosen as the sum of non-valence, electrostatic and torsion interactions and the energy of hydrogen bonds. The spatial structure of the exorphin B4 molecule was calculated based on the low-energy conformations of the corresponding amino acid residues. It has been shown that the spatial structure of the exorphin B4 molecule can be represented by thirteen low-energy conformations. The low-energy conformations of the molecule, the values of the dihedral angles of the main and side chains of amino acid residues were found, the energy of intra- and inter-residual interactions was estimated.

Keywords: exorphin, opioid, structure, conformation;

1. Introduction

Regulatory peptides, first discovered in the second half of the 20th century, are actively studied by both physiologists and pharmacologists, since the area of biological activity of peptides is extremely wide. They are one of the main links that unite the three regulatory systems of the body - the nervous one. endocrine and immune into a single whole. At present, more than 9000 physiologically active peptides have been characterized in various animal species and in humans. These

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are short chains of amino acids (2-70 residues) that act as signal molecules. Most of these peptides cannot be confidently attributed to either neuromodulators or hormones, since they are synthesized both by neurons (transmitting a signal at the synapse level) and by cells of peripheral tissues (transmitting a signal over longer distances, like hormones). Regulatory peptides are characterized by the impact on many systems of the body at once. Opioid peptides are currently considered the most studied group of peptides signaling substances. Opium causes pain relief, sedation and falling asleep, as well as a euphoric state and a number of vegetative reactions. Opioid peptides are of animal and plant origin. A number of exogenous peptides obtained from food have opioid-like properties. Such peptides were called exorphins [1–3].

We have studied the structural and functional organizations of a number of opioid peptides, and this work is a continuation of our previous studies [4-10].

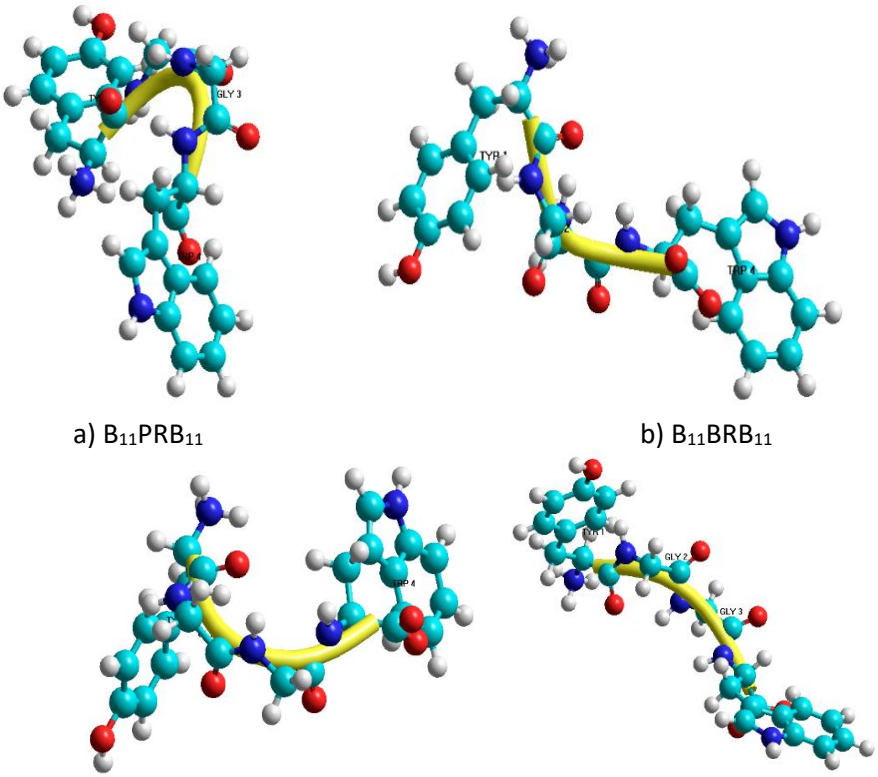
2. Research method

The calculation of the molecule was performed using the method of theoretical conformational analysis. The potential function of the system is chosen as the sum of non-valence, electrostatic and torsion interactions and the energy of hydrogen bonds. Non-valent interactions were evaluated using the Lennard-Jones potential. Electrostatic interactions were calculated in the monopole approximation according to the Coulomb law using partial charges on atoms. The conformational capabilities of the exorphin molecule were studied under conditions of an aqueous environment, in connection with which the value of the dielectric constant was taken equal to 10. The energy of hydrogen bonds was estimated using the Morse potential.

When presenting the results of the calculation, we used the classification of peptide structures according to conformations, forms of the main chain, and shapes of the peptide skeleton. Conformational states are completely determined by the dihedral angles of the main and side chains of all amino acid residues included in a given molecule. The main chain forms of the fragment are formed by combinations of the R, B, L forms of the residues in the given sequence. The forms of the main chain of the dipeptide can be divided into two classes - folded (f) and unfolded (e) forms, which are called shapes. All conformations are grouped according to the forms of the main chain, and the forms are grouped according to the shapes. To designate the conformational states of the residues, identifiers of the Xij type were used, where X determines the low-energy regions of the conformational map and ij…=11…,12…,13…,21… determines the position of the side chain, with index 1 corresponding to an angle value ranging from 0 to 120°, 2 - from 120° to (-120°), and 3 - from (-120°) to 0°. The designations and readings of rotation angles correspond to the IUPAC-IUB nomenclature [11].

3. Results and discussion

The spatial structure of the exorphin B4 (Tyr1-Gly2-Gly3-Trp4) molecule was studied on the basis of low-energy conformations of N-acetylglycine methylamide, N-acetyl-L-tyrosine methylamide, and N-acetyl-L-tryptophan methylamide. The calculation results are shown in tables 1-3. The relative energy and energy contributions of non-valent, electrostatic, torsion interactions of these conformations of the exorphin B4 molecule are given in Table 1. The energy of intra- and interresidual interactions of the lowest energy conformation of each form is in Table 2, and the geometric parameters of these conformations are in Table 3. The spatial arrangement of amino acids in low-energy conformations $B_{11}PRB_{11}$, $B_{11}BRB_{11}$, $B_{11}BLR_{11}$ and $B_{11}PLR_{11}$ is shown in Figure 1.



a) $B_{11}PRB_{11}$ b) $B_{11}BRB_{11}$

c) $B_{11}BLR_{11}$ d) $B_{11}PLR_{11}$

Figure 1. Atomic model of spatial structure of the exorphin B4 molecule

a) $B_{11}PRB_{11}$, b) $B_{11}BRB_{11}$, c) $B_{11}BLR_{11}$ and d) $B_{11}PLR_{11}$

The results of the calculation of the exorphin B4 molecule show that energy differentiation occurs according to the conformations and forms of the main chain. Thirteen forms of the main chain of four shapes fff, eef, efe, fee fall into the energy range of 0-25 kJ/mol. In these conformations, the energy contributions of non-valent interactions change in the energy range (-68.5) - (-47.0) kJ/mol, electrostatic interactions change in the energy range 8.4–15.5 kJ/mol, torsion interactions change in the energy range 8.0-11.8 kJ/mol (Table 1). Shape fff is represented by six forms of the main chain, the energy of which varies in the range of 0–20.0 kJ/mol. The global conformation of the exorphin B4 molecule is $B_{11}PRB_{11}$ (Table 1). This conformation is simultaneously advantageous for non-valent and electrostatic interactions. In this structure, effective interactions of Tyr1 with Gly2, Gly3 and Trp4 occur, which contribute to the total energy (-52.5) kJ/mol (Table 2). The eef shape has four low-energy forms of the main chain, the relative energy of which varies in the range of 15.5–20.6 kJ/mol. The lowest energy conformation of this shape is B11BRB11 with a relative energy of 15.5 kJ/mol. According to non-valent interactions, it is 11.4 kJ/mol, according to electrostatic interactions, 3.4 kJ/mol, it loses to the global conformation (Table 1). Here, Tyr1 interactions with other amino acid residues are -37.8 kJ/mol (Table 2).

Table 1. Energy contributions of non-valent (U_{nv}), electrostatic (U_{el}), torsional (U_{tors}) interactions and the relative energy (U_{rel}) of the optimal conformations of the exorphin B4 molecule

№	Shape	Conformation	$U_{nv.}$	$U_{el.}$	$U_{tors.}$	$U_{tot.}$	$U_{rel.}$
1	f f f	B_{11}P R B_{11}	-68.5	8.4	10.1	-50.0	0
2		B_{11}P R R_{11}	-55.0	15.5	10.1	-29.8	20.2
3		B_{11}L P B_{11}	-59.2	9.2	8.0	-42.4	7.6
4		B_{11}L P R_{11}	-51.7	11.3	9.7	-30.7	19.3
5		L_{11}L P R_{11}	-55.4	12.6	11.3	-31.9	18.1
6		L_{11}L P B_{11}	-52.5	12.6	9.2	-30.2	19.7
7	e e f	B_{11}B R B_{11}	-57.1	11.8	10.9	-34.4	15.5
8		B_{11}B R R_{11}	-56.3	13.0	10.1	-33.6	16.4
9		B_{11}R P R_{11}	-51.2	12.2	8.8	-30.7	19.3
10	e f e	B_{11}R P B_{11}	-50.0	11.3	9.2	-29.4	20.6
11		B_{11}B L R_{11}	-51.2	11.8	11.8	-28.1	21.8
12	f e e	B_{11}P L R_{11}	-47.5	12.6	8.6	-26.5	23.5
13		B_{11}P L B_{11}	-47.0	11.8	9.2	-26.5	23.5

The efe and fee shapes are represented by only three forms of the main chain, the relative energy of which varies in the energy range of 21.8–23.5 kJ/mol. In all low-energy structures of the exorphin B4 molecule, the Tyr1 and Trp4 side chains are in the same positions, the Tyr1 side chain is directed to the C-terminus of the molecule, and the Trp4 side chain is directed to the N-terminus of the molecule. In

such positions, they effectively interact with each other and with the atoms of the main chain of the molecule.

Conformational maps were constructed around the dihedral angles of the Tyr1 and Trp4 side chains. The conformational maps show that almost complete conformational freedom is possible around the dihedral angles χ1 of the Tyr1 and Trp4 residues. The positions of the Tyr1 and Trp4 side chains found by us are energetically the most favorable. The side chains of tyrosine and tryptophan freely rotate from (-180°) to 180° and, therefore, can easily interact with other molecules and receptors.

Table 2.Energy inside and between residual interactions in the conformations of the molecule exorphin B4: $B_{11}PRB_{11}$ (Urel=0 kJ/mol, first line), $B_{11}BRB11$ (U_{rel}= 15.5 kJ/mol, second line), $B_{11}BLR_{11}$ (Urel= 21.8 kJ/mol, third line), $B_{11}PLR_{11}$ (Urel=23.5 kJ/mol, fourth line)

Tyr1	Gly2	Gly3	Trp4	
7.1 8.0 9.7 7.1	-5.9 -6.7 -9.2 -5.9	-4.2 -11.8 -7.6 -5.0	-42.4 -19.3 -18.1 -13.4	Tyr1
	5.0 5.5 5.5 5.5	0.4 -0.4 2.1 0	-4.6 -5.0 -4.6 6.3	Gly2
		5.5 5.0 5.5 5.5	-8.0 -7.6 -9.2 -9.2	Gly3
			-13.4 -13.4 -19.9 -13.0	Trp4

Table 3. Geometrical parameters (degrees) of the optimal conformations of the exorphin B4 molecule.

Residue	Conformations			
	$B_{11}PRB_{11}$	$B_{11}BRB_{11}$	$B_{11}BLR_{11}$	$B_{11}PLR_{11}$
Tyr1	-63 156 176 61 88 0	-69 167 -176 66 94 0	-78 157 -175 68 100 0	-64 159 177 65 87 0
Gly2	75 -91	-82 63 172	-72 126 -179	78 -81 179

	180			
Gly3	-83 -50 -175	-87 -40 -172	82 61 -174	87 58 178
Trp4	-100 150 180 64 93	-116 154 180 57 99	-97 -43 180 67 93	-100 -57 180 58 91
$U_{rel.}$	0	15.5	21.8	23.5

Note: the values of the dihedral angles are given in the sequence φ, ψ, ω, χ1, χ2,…

4. Conlusions

Thus, the theoretical conformational analysis of the exorphin B4 molecule showed that the spatial structure of the molecule can be represented by four structural types, leading to such structural organizations of the molecule that do not exclude the implementation by the molecule of a number of very diverse functions that require strictly specific interactions with various receptors.

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