SPARTIAL STRUCTURE OF HEXADECAPEPTIDE FRAGMENT OF BAM-20P`MOLECULE

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Using a method of the theoretical conformational analysis, a spatial structure of the Tyr1-Asp16 hexadecapeptide fragment of BAM-20P molecule (Tyr1-Gly2-Gly3-Phe4-Met5-Arg6-Arg7-Val8-Gly9-Arg10-Pro11-Gly12-Trp13-TRp14-Met15-Asp16-Tyr17-Gln18-Lyz19-Arg20), isolated from adrenal medulla was investigated.

The potential energy of the molecule is given as the sum of the contributions of Van der Vaals, electrostatic, torsional interactions and hydrogen bonds energy. It has been shown that the spatial structure of tyr1-asp16 fragment is represented by ten backbone forms.

The opioid peptide Tyr1Gly2-Gly3-Phe4-Met5-Arg6-Arg7-Val8-Gly9-Arg10-Pro11-Glu12-Trp13-Trp14-Met15-Asp16-Tyr17-Gln18-Lys18-Lys19-Arg20 is isolated from medulla of bovine adrenal, indicated as BAM-20P (bovine adrenal medulla 20 reside peptide). The opiate activity of the BAM-20P in several times higher, than the activity of Met-enkefalin and β-endofine. There are Met-enkefalin (Tyr1-Met5), adrenorfine (Tyr1-Val1), BAM-12P (Tyr1-Glu12), in the succession of BAM-20P, and the molecule BAM-20P itself is the part of composition of peptides *E* and *I* [1, 2]. Therefore the investigation of the spatial structure of the molecule BAM-20P is the big interest as for elucidation of structure-functional organization of the molecule itself, as all the above mentioned peptides.

The study of structure-functional organization of the hormone on the atom-molecule level requests firstly the knowledge of set of low-energy molecule states and consequently the potential physiological active conformation ones.

The spatial structure of the molecule BAM-20P is investigated fragmently. At first the conformation probabilities of fragments Val6-ValP, Arg10-Glu12,Trp13-Asp16, Asp16-Arg20 were studied on base of the low-energy states of according aminoacid residues. The spatial structures of the molecules of Met-enkefalin (Tyr1-Met5) and adrenorfine (tyr1-Val8) were investigated by us earlier, the results are presented in ref [3, 4]. On the second stage the three-dimensional structure of molecule BAM-12P (Tyr1-Glu12) was found on the base of stable conformations Tyr1-Val8, Gly19, Arg10-Glu12.

The conformation probabilities of fragment Tyr1-Asp16 (fig.1) were studied on the following stage on the base of the stable three-dimensional structures of fragments Tyr1-Glu12 and Trp13-Asp15.

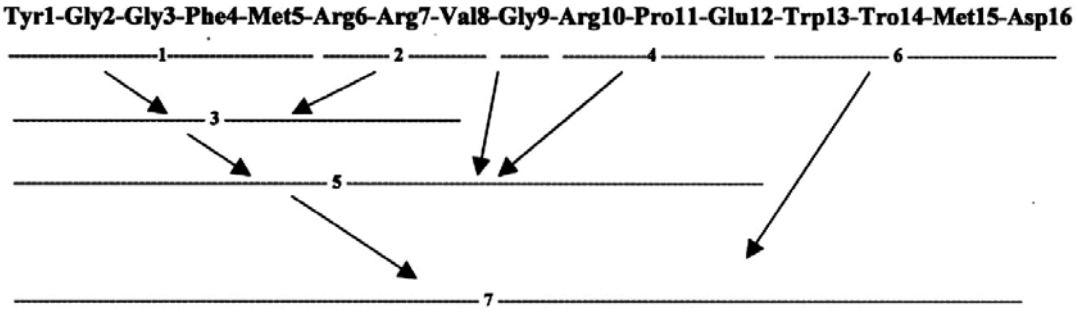

Fig.1. Circuit of the calculation of the hexadecapeptide fragment of the molecule BAM-20P.

In this paper the results of theoretical conformation analysis of the *N*-ended hexapeptide fragment, Tyr1-Gly2-Gly3-Phe4-Met5-Arg6-Arg7-Val8-Gly9-Arg10-Pro11-Glu12=Trp13-Trp14-Met15-Asp16 of the molecule BAM-20P are given. The potential function of the system is taken in the sum form of the nonvalence, electrostatical and torque interactions and the energy of the hydrogene bonds. The calculation of the fragments is made on the base of the theory and method, which are presented in ref [5-8]. The classification of the peptide structure on conformations, forms of the fundamental chain and the shapes of the peptide scelet, proposed in ref [5-8] was used at the presentation of calculation results.

The optimal conformations of the molecule (Tyr1-Glu12) BAM-12P, established as a result of calculation, the energy of which isn't more, than 10kcal/mol are given in the table 1. The four conformations of Met-enkefalin (Tyr1-Met15) and the eleven conformations of adrenorfine (Tyr1-Val8) were between the lowenergy conformations BAM-12P and are presented in the table 1. In geometrical interpretation of adrenorfine fragment, given in this table, the conformations of molecule BAM-12P, which are preferred on the energy, disintegrate on the four groups (*A*-*D*). These 23 conformations are chosen as the initial approximations for the calculation of the *N*-ended hexapeptide fragment Tyr1-Asp16 of the molecule BAM-20P.

Table 1

The relative energy and energy contributions of nonvalence ($U_{nv.}$), electrostatic ($U_{el.}$), torsional interactions of optimum conformations of the molecule BAM-12P.

Gr.	№	Conformation	$U_{nv.}$	$U_{el.}$	$U_{tor.}$	$U_{rel.}$
	1	$B_{211}PRR_{21}B_{332}R_{2222}R_{3222}R_2BL_{22}RR_{32}$	-41.4	8.5	6.4	0
	2	$B_{211}PRR_{21}B_{332}R_{2222}R_{3222}B_2RB_{21}RR_{32}$	-39.6	14.7	8.0	9.7
A	3	$B_{211}PRR_{21}B_{332}R_{2222}R_{3222}R_2PB_{21}RR_{32}$	-44.2	18.0	7.7	8.0
	4	$B_{211}PRR_{21}B_{332}R_{2222}R_{3222}R_2PL_{22}RR_{32}$	-42.7	18.7	5.9	8.5
	5	$B_{211}PRR_{21}B_{332}R_{2222}R_{3222}R_2LL_{22}RR_{32}$	-42.2	18.2	6.4	9.1
	6	$B_{131}BPB_{21}B_{212}B_{1222}B_{2222}R_2BL_{22}RR_{32}$	-41.1	10.3	6.0	1.8
	7	$B_{131}BPB_{21}B_{212}B_{1222}B_{2222}R_2PB_{21}RR_{32}$	-37.4	13.4	7.1	9.7
	8	$B_{131}BPB_{21}B_{212}B_{1222}B_{2222}B_2RB_{21}RR_{32}$	-39.8	11.2	8.0	6.1
	9	$B_{131}BPB_{21}B_{212}B_{1222}B_{2222}B_2BL_{22}RR_{32}$	-39.7	10.9	8.8	6.5
B	10	$B_{131}BPB_{21}B_{212}B_{1222}R_{2222}B_2BL_{22}RR_{32}$	-42.7	15.9	7.0	6.8
	11	$B_{131}BPB_{21}B_{212}B_{1222}R_{2222}B_2RB_{21}RR_{32}$	-41.4	15.3	6.7	7.2
	12	$B_{131}BPB_{21}B_{212}B_{1222}R_{2222}B_2BB_{21}RR_{32}$	-42.2	15.2	7.8	7.4
	13	$B_{131}BPB_{21}B_{212}B_{1222}R_{2222}B_2RL_{22}RR_{32}$	-39.9	16.3	5.3	8.3
	14	$B_{132}RPB_{33}B_{222}B_{1222}B_{2222}R_2BL_{22}RR_{32}$	-40.2	10.1	5.8	2.2
	15	$B_{132}RPB_{33}B_{222}B_{1222}B_{2222}B_2RB_{21}RR_{32}$	-40.0	9.1	9.6	5.3
	16	$B_{132}RPB_{33}B_{222}B_{1222}B_{2222}B_2BL_{22}RR_{32}$	-38.4	11.7	8.4	8.4
	17	$B_{132}RPB_{33}B_{222}B_{1222}R_{2222}B_2BB_{21}RR_{32}$	-41.6	14.8	7.2	7.0
C	18	$B_{132}RPB_{33}B_{222}B_{1222}R_{2222}B_2BL_{22}RR_{32}$	-41.7	15.7	7.3	8.0
	19	$B_{132}RPB_{33}B_{222}B_{1222}R_{2222}B_2RB_{21}RR_{32}$	-40.2	15.8	6.6	8.7
	20	$B_{132}RPB_{33}R_{222}B_{1222}R_{3222}B_2BL_{22}RR_{32}$	-42.8	14.8	9.5	8.1
	21	$B_{132}RPB_{33}R_{222}B_{1222}R_{3222}B_2BB_{21}RR_{32}$	-40.9	15.5	8.2	9.3
	22	$B_{212}BPR_{21}R_{212}B_{1222}B_{2222}R_2BL_{22}RR_{32}$	-43.3	11.8	9.1	4.1
D	23	$B_{212}BPR_{21}R_{212}B_{1222}B_{2222}B_2RB_{21}RR_{32}$	-43.3	11.8	12.9	7.9

Table 2.

Energy distribution of conformations of the fragment Trp-13-Asp16 of the molecule BAM-20P

The fundamental chain form	The number of energy conformations, kcal/mol.					
	0-1	1-2	2-3	3-4	4-5	>5
BBBB	-	-	2	1	7	7
RRRR	3	5	7	2	-	25
RRBR	-	-	-	-	2	7
BRRR	-	-	-	-	1	2
RBBB	-	-	-	2	1	3
BBRR	-	1	1	-	-	4
BRBB	-	-	-	-	1	8
RBRR	-	-	-	-	-	6

The spatial structure of the tetrapeptide fragment Trp13-Trp14-Met15-Asp16 of the molecule BAM-20P is investigated on the base of the lowenergy conformations according aminoacid residues of triptofane, methionine and the calculation was made on the forms of the fundamental chain. Firstly the conformations of the total unwrapped form BBBB and the total curtailed form RRRR. The considered interactions between the aminoacid residues in these forms are taken into consideration in another forms of the fundamental chain too. Therefore the number of the considered conformations for them is less, than in curtailed and unwrapped forms. The energy distribution of the conformations of the fragment Trp13–Asp16 of the molecule BAM 20P is shown in the table 2. At the energy 0-4kcal/mol there are 24 conformations of the four forms of the fundamental chain, but in the energy interval 0-6kcal/mol. there are conformations of the eight forms of the fundamental chain. The relative energy of the lowenergy conformations of each form of the fragment Trp13-Asp16 of the molecule BAM-20P is shown in the table 3. These conformations are chosen for the calculation of the fragment Tyr1–Asp16 of the molecule BAM-20P. Thus, the lowenergy states of the fragments Tyr1–Glu12 and Trp13–Asp16 became the base of the consisting of the zero approximations for the calculation of the three-dimensional structure of the *N*-ended hexapeptide fragment Tyr1–Asp16 of the molecule BAM-20P, the number of which is 184. The results of the calculations are shown, that the sharp energy differentiation appears between the forms of the fundamental chain and between conformations.

Table3

The relative energy of lowenergy conformations of the fragment Trp13-Asp16 of the molecule BAM-20P

The fundamental chain form	$E_{rel.}$
$B_2B_2B_{21}B_1$	2.1
$R_1R_1R_{32}R_1$	0
$R_1R_1B_{21}R_1$	4.9
$B_3R_1R_{32}R_1$	4.6
$R_2B_2B_{21}B_1$	4.0
$B_2B_1R_{21}R_1$	1.4
$B_1R_2B_{21}B_1$	5.0
$R_2R_2R_{32}R_1$	5.7

In the wide energy interval 0-10kcal/mol there are only ten conformations. The forms of the fundamental chain, the energies of nonvalence, electrostatical and torsional interactions, and also the relative energy of these conformations are presented in the table 4. The addition of

the tetrapeptide fragment Trp13-Asp16 leads to the sharp decrease of the number of their lowenergy conformations, entering to the preferred structures Tyr1-Asp16. The group *A* of the molecule Tyr1-Glu12 has the 5 conformations, but the fragment Tyr1-Asp16 has the remaining 3 conformations, the group *B* is presented by *P* conformations, and the remain is 5 conformations, the group *C* is presented by 8 conformations and the remain is 2 ones. Among the lowenergy conformations of the fragment Tyr1-Asp16 the 3 forms of the fundamental chain from the 8 chosen of the *C*-ended tetrapeptide region Trp13-Trp14-Met15-Asp16 are realized. The form of the fundamental chain BRRR is realized in the 5 conformations, RBRR is in the 4, and RBBB is in the only one. The triptofane and methionine have the big and the labile side chain, therefore only in the especial cases they can arrange energetically by propit to the formed structures.

In the stable conformations of the fragment Tyr1-Asp16 the energy of nonvalence interactions changes in the interval 71.3-62.4kcal/mol, the energy of electrostatical interactions changes in the interval 5.9-13.6kcal/mol, the energy of torque interactions changes in the interval 8.1-13.6kcal/mol. As it is seen, the difference between the energies of nonvalence, electrostatical and torsional interactions is equal to 8.9, 7.7 and 5.2kcal/mol among the optimal conformations of the fragment Tyr1-Asp16 BAM-20P correspondingly. It means, that the each from these three forms of interactions playes the important role at the formation of the spatial structure of the fragment Tyr1-Asp16. The global conformation is the most benefit on the nonvalence (-71.3kcal/mol) and electrostatical (5.9kcal/mol) interactions, but the less benefit on the torsional interactions (13.3kcal/mol). This conformation of Met-enkefalin has the relative energy 3.5kcal/mol, of adrenofine one is 4.3kcal/mol, of BAM-12P one is 6.5kcal/mol. This means, that the far-away interactions, playing the essential role in the stabilization of the spatial structure of the investigated fragment with the lengthening of the peptide chain. The pentapeptide region in the structure with relative energy 5.2kcal/mol has the conformation, according to the clobal conformation of the Met-enkefalin. It loses 1.6kcal/mol on the nonvalence, 6.3kcal/mol on the electrostatical, but benefits the 3.7kcal/mol on the torsional interactions in comparison of the global conformation. The relative energy of the rest of three conformations of the group B changes in the interval 9.2-9.8kcal/mol. The group *A* is presented by the three conformations, the relative energy of which changes in the interval 6.4-9.0kcal/mol, but the group *C* is presented by the two conformations with the relative energies 6.7 and 9.2kcal/mol (table 4). The conformations, given in table 4, are the base for the finishing of the investigation of the spatial structure of the whole molecule BAM-20P.

Table 4.

The fundamental Chain forms, energy contributions of non valence ($U_{nv.}$) electrostatic ($U_{el.}$), torsional interactions (U_{tor}) and relative energy ($U_{rel.}$) of lowenergy conformations of fragment Tyr1-Asp16 of molecule BAM-20P

Gr.	№	Conformation	$U_{nv.}$	$U_{el.}$	$U_{tor.}$	$U_{rel.}$
A	1	$B_{211}PRR_{21}B_{322}R_{222}R_{322}R_2BL_{222}RR_{32}B_3R_1R_{322}R_1$	-64.3	9.4	9.2	6.4
	2	$B_{111}PRR_{21}B_{322}R_{222}R_{322}R_2BL_{222}RR_{32}B_3R_1R_{21}R_1$	-64.1	12.0	8.1	8.1
	3	$B_{211}PRR_{21}B_{332}R_{222}R_{222}R_2PL_{222}RR_{32}R_2B_2R_{33}R_1$	-65.2	13.6	8.5	9.0
B	4	$B_{131}BPB_{21}B_{212}B_{122}B_{222}R_2BL_{222}RR_{32}B_3R_1R_{32}R_1$	-64.6	12.8	8.9	9.2
	5	$B_{131}BPB_{21}B_{212}B_{122}B_{222}B_2BL_{222}RR_{32}B_3R_1R_{32}R_1$	-64.6	10.5	11.8	9.8
	6	$B_{131}BPB_{21}B_{212}B_{122}B_{222}B_2BL_{222}RR_{32}R_2B_2B_{21}B_1$	-62.4	9.0	10.8	9.4
	7	$B_{131}BPB_{21}B_{212}B_{122}B_{222}B_2BL_{222}RR_{32}R_2B_2R_{33}R_1$	-71.3	5.9	13.3	0
	8	$B_{131}PRR_{21}B_{212}B_{122}R_{222}B_2BL_{222}RR_{32}R_2B_1R_{33}R_1$	-69.7	12.2	9.6	5.2
C	9	$B_{131}PRB_{33}B_{222}B_{122}B_{322}B_2BL_{222}RR_{32}B_3R_1R_{32}R_1$	-63.6	11.9	8.7	9.2
	10	$B_{132}PRB_{33}B_{222}B_{122}B_{222}B_2BL_{222}RR_{32}R_2B_2R_{33}R_1$	-65.6	7.4	12.9	6.7

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BAM-20P MOLEKULUNUN HEKSADEKAPEPTİD FRAQMENTİNİN FƏZA QURULUŞU

Sümük iliyindən ayrılmış BAM-20P molekulunun (Tyr1-Gly2-Gly3-Phe4-Met5-Arg6-Arg7-Val8-Gly9-Arg10-Pro11-Gly12-Trp13-TRp14-Met15-Asp16-Tyr17-Gln18-Lyz19-Arg20) Tyr1-Asp16 heksadekapeptid fraqmentinin fəza quruluşu nəzəri konformasiya metodu ilə öyrənilmişdir. Molekulun potensial enerjisi Van-der Vaals elektrostatik, torsion qarşılıqlı təsir

enerjilərinin və hidrogen rabitəsi enerjisinin cəmi şəklində seçilmişdir. Göstərilmişdir ki, Tyr1-Asp16 fraqmentinin fəza quruluşu əsas zəncirin on forması ilə tərənnüm olunur.

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ПРОСТРАНСТВЕННАЯ СТРУКТУРА ГЕКСАДЕКАПЕПТИДНОГО ФРАГМЕНТА ВАМ-20Р

Методом теоретического конформационного анализа изучена пространственная структура гексадекапептидного фрагмента (Tyr1-Gly2-Gly3-Phe4-Met5-Arg6-Arg7-Val8-Gly9-Arg10-Pro11-Gly12-Trp13-TRp14-Met15-Asp16-Tyr17-Gln18-Lyz19-Arg20) молекулы ВАМ-20Р выделенной из костного мозга. Потенциальная энергия молекулы выбрана в виде суммы энергии Ван-дер Ваальсовых, электростатических, торсионных взаимодействий и энергии водородных связей. Показано, что пространственная структура фрагмента Tyr1-Asp16 представлена десятью формами основной цепи.

Received: 14.04.03