LEU-GALLATOSTATINE-3 NEUROPEPTIDE SPATIAL STRUCTURE

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The space structure of *Leu*-gallatostatine-3 molecule is studied by theoretic conformational analysis method. The stability quantitative evaluation of possible molecule conformational states in dipolar medium conditions is carried out on the base of intramolecular conformational energy value.

Keywords: neuropeptides, structure, conformational analysis.
PACS: 87.80.-y

INTRODUCTION

The search and purposeful synthesis of compounds used for regulation of crop pest number is the one of actual problems in modern science. The neuropeptides synthesized by brain neurosecretory cells of insect different types, in particular, *Calliphora Vomitoria* are related to these compounds [1-3]. The neuropeptides inhibit the synthesis and extraction of juvenile hormones in ontogenesis insect process, take part in neurotransmission and regulation of nervous system functions. The study of mechanism molecular bases of their action and formation of effective analogues of these compounds with prolonged action effect is the important aspect in investigations of neuropeptides functional activity. The study of space structure and conformational properties of *Leu*-gallatostatine-3 is the aim of the present investigation. The neuropeptide chemical structure, designations of variable angles of rotation and calculation scheme of low-energy conformational states of gradually extensible tripeptide and pentapeptide fragments of molecule are given in fig.1 and fig.2.

CALCULATION RESULTS

ALA^1-ASN^2-ARG^3-TYR^4 TETRAPEPTIDE.

N-end tetrapeptide molecule sequence includes 75 atoms and 23 dihedral angles, which are varied in main and side chains of amino-acid residuals. As the fragment consists of residuals with branched side chains having integer charges (Asn^2, Arg^3) then the number of initial conformations chosen for minimization procedure of total conformational energy is 129. They belong to 8 shapes and 24 possible shapes of molecule valence chain. All permissible orientations of Asn^2, Arg^3 side chains and Tyr^4 aromatic ring in dependence on shape type are taken into consideration at variant construction. The conformation energy distribution of investigated fragments on shapes and contributions of interaction separate types into stabilization of most probable structures are given in tables 1 and 2.

From table 1 it is followed that conformations of *fff, ffe, efe, fef* four shapes with convoluted and half-convoluted shapes of fragment main chain are energetically preferable ones. They are stabilized by dispersion interactions of atoms of residual side chains Asn^2 and Arg^3 non-bonded by valence (table 2).

TYR^4-GLY^5-PHE^6-GLY^7-LEU^8-NH_2 PENTAPEPTIDE.

C-end pentapeptide fragment similar for all neuropeptides of allatostatine family includes the residuals *Tyr* and *Phe* with volume hydrophobic side chains, the interaction of which determine presuppositions for spatial organization formation of this region.

The number of permissible conformational states both the main and side chains of amino-acid residuals describing 16 fragment structural types is equal to 675. They are included in fragment potential energy minimization procedure the results of which are summarized in tables 3-4.

The conformation corresponding to energy global minimum of fragment ($E_{rel.}$=0.0 kcal/mol) is to structures with totally convoluted shape of main chain designated by *ffff* shape. The other conformations of this shape differ by *Tyr, Leu* side chain orientation and peptide frame shape of Gly^5 glycine residual.

Leu-gallatostatine-3 molecule. The investigations of spatial structure of whole *Leu*-gallatostatine-3 molecule are carried out on the base of stable conformational states of *C*-end pentapeptide and *N*-end tetrapeptide overlapping by residual Tyr^4. 530 structural variants covering all 82 permissible molecule shapes are constructed for total energy minimization procedure. The conformation distribution in *Leu*-gallatostatine-3 structure different types, the relative conformational energy of which doesn't exceed 5 kcal/mol, is given in fig.3. The results of calculated experiment including the conformational energy minimization procedure for representatives of all structure types are summarized in tables 5-6.

This allows us to classify the calculated conformations in correspondence with general elements of their spatial structures:

1) totally disordered structures (~ 20%)
2) structures with α-spiral *C*-end pentapeptide fragment and labile *N*-end tetrapeptide (~ 50%)
3) structures with two α-spiral regions connected by labile residual *Gly* in five position of linear consistency of amino-acid residuals (~30%).

The existence of a large number of disordered structures is caused by influence of surrounding water environment because of which the neuropeptides form the statistical ensembles of conformations comparable on stability divided by not high potential barriers in solution.

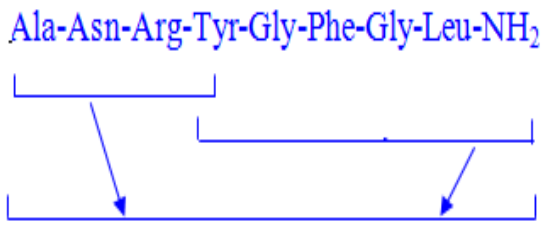

Fig.1. Calculation scheme of *Leu*-gallatostatine molecules.

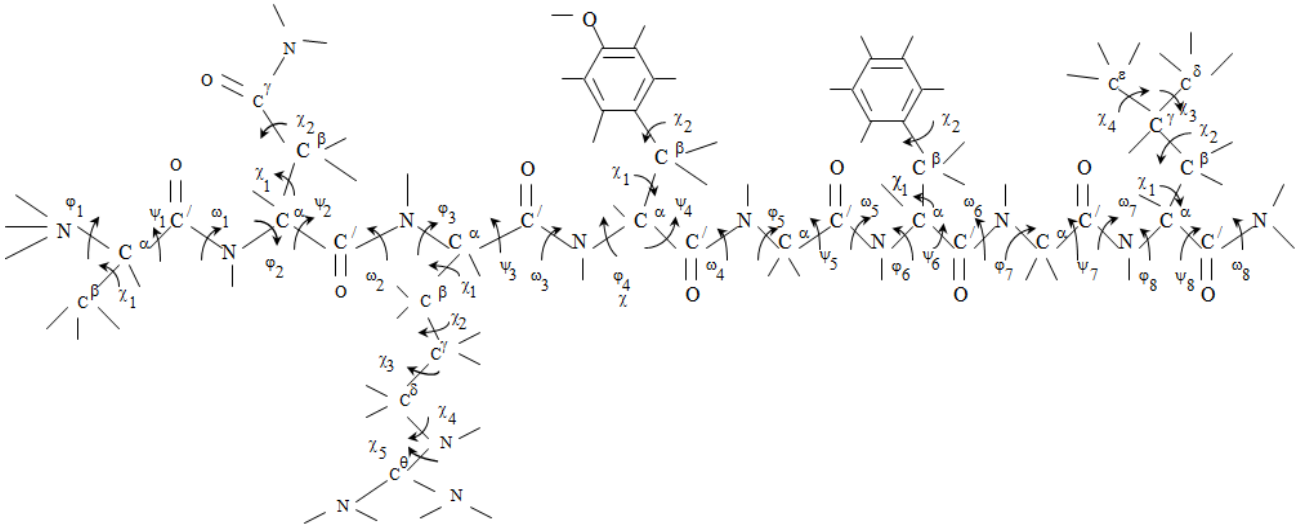

Fig.2. Calculated model of *Leu*-gallatostatine-3 molecule.

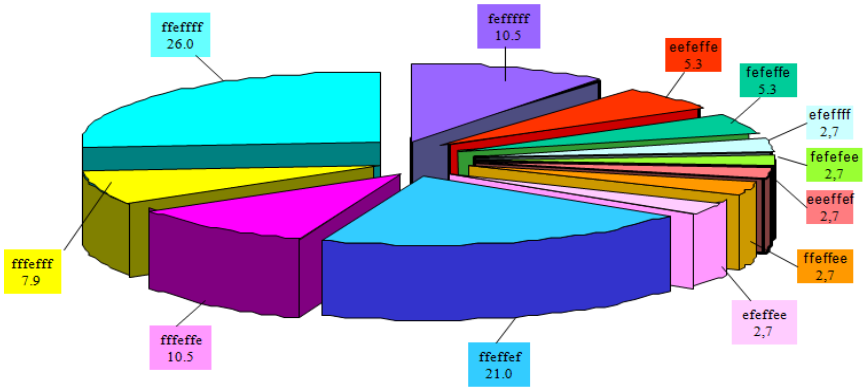

Fig.3. The percentage content of *Leu*-gallatostatine-3 molecule shape conformations ($E_{rel.}$= 0÷5 kcal/mol)

Table 1. Conformation energy distribution (kcal/mol) on *N*-end tetrapeptide fragment of *Leu*-gallatostatine-3.

№	shape	Energy interval $E_{rel.}$ (kcal/mol)					
		0 ÷ 1	1÷2	2÷3	3÷4	4÷5	>5
1.	*fff*	-	1	6	1	1	1
2.	*ffe*	3	1	1	1	-	1
3.	*fee*	-	1	3	2	-	-
4.	*eee*	-	-	1	5	5	1
5.	*eef*	-	4	12	15	7	-
6.	*eff*	-	-	9	11	2	-
7.	*efe*	1	3	3	4	5	-
8.	*fef*	1	7	5	3	-	-

Table 2. Energy parameters of more optimal conformations of eight structural types of *N*-end tetrapeptide fragment of *Leu*-gallatostatine-3 neuropeptide

shape	Conformation	Energy contributions (kcal/mol)				
		E_{nv}	E_{el}	E_{tors}	E_{tot}	E_{rel}
fff	$RR_{31}R_2B_3$	-16.14	2.79	0.75	-12.60	1.99
	$RR_{32}R_3B_1$	-15.81	2.46	1.20	-12.15	2.44
ffe	$RR_{22}B_3B_1$	-18.34	2.49	1.26	-14.59	**0.00**
	$RR_{21}B_3B_1$	-17.77	2.37	1.38	-14.02	0.57
fee	$RL_{31}B_3B_1$	-16.99	2.22	1.66	-13.10	1.49
	$RB_{22}B_3R_3$	-15.66	2.17	1.13	-12.36	2.23
eee	$BL_{31}B_3B_1$	-16.47	2.01	1.98	-12.48	2.11
eef	$BB_{11}R_2B_3$	-16.09	2.16	0.73	-13.19	1.40
	$LB_{11}R_2B_3$	-15.77	2.15	1.13	-12.49	2.10
eff	$BR_{21}R_2B_3$	-15.30	2.21	0.78	-12.31	2.28
	$BR_{11}R_2B_3$	-14.91	2.44	0.85	-11.62	2.97
efe	$BR_{21}B_3B_1$	-16.61	1.97	1.01	-13.62	0.97
	$L\ R_{21}B_3B_1$	-15.55	2.21	1.42	-11.92	2.67
fef	$RB_{11}R_2B_3$	-17.01	2.14	0.88	-13.98	0.61
	$RB_{11}RR_3$	-16.39	2.40	1.16	-12.83	1.76

Table 3. Energy distribution of optimal conformations of *N*-end tetrapeptide fragment of *Leu*-gallatostatine-3 molecule.

№	shape	Energy interval $E_{rel.}$ (kcal/mol)					
		0 ÷ 1	1 ÷ 2	2 ÷ 3	3 ÷ 4	4 ÷ 5	> 5
1.	*effe*	1	4	2	2	5	15
2.	*ffff*	6	5	5	9	5	15
3.	*eefe*	-	6	5	8	6	40
4.	*fefe*	-	-	3	7	18	21
5.	*fffe*	-	2	7	15	17	34
6.	*eeee*	-	-	1	2	5	23
7.	*feee*	-	-	-	2	4	16
8.	*ffee*	-	-	-	8	9	25
9.	*efee*	-	-	5	8	3	5
10.	*efff*	-	-	-	1	1	12
11.	*eeff*	-	-	2	4	-	32
12.	*feff*	-	-	-	1	3	26
13.	*feef*	-	-	-	-	1	16
14.	*eeef*	-	-	2	2	-	20
15.	*ffef*	-	13	3	1	7	19
16.	*efef*	-	-	1	3	8	4

Table 4. Energy parameters of more optimal conformations of different structural types of *C*-end pentapeptide fragment of *Leu*-gallatostatine-3 molecule.

shape	Conformation	Energy contributions (kcal/mol)				
		E_{nv}	E_{el}	E_{tors}	E_{tot}	$E_{rel.}$
ffff	$B_2PR_2RR_{21}$	-23.68	4.42	2.16	-17.10	**0.00**
	$R_2RB_1PB_{21}$	-23.20	3.87	2.24	-17.09	0.01
	$B_1PB_1PB_{21}$	-23.01	4.34	2.33	-16.34	0.76
effe	$B_3RB_2PR_{32}$	-22.18	2.15	3.25	-16.78	0.32
	$B_3RB_2PR_{31}$	-21.80	2.18	3.72	-15.90	1.20
	$R_3PR_2BB_{21}$	-20.91	2.53	3.10	-15.27	1.83
	$R_3PB_2PR_{21}$	-20.88	2.49	3.20	-15.19	1.91
eefe	$B_2BB_1LB_{32}$	-21.54	3.59	2.36	-15.60	1.56
	$R_2LB_3LB_{32}$	-21.40	4.09	1.96	-15.36	1.74
	$R_2LR_3BR_{32}$	-20.75	4.02	1.41	-15.32	1.78
	$B_2BB_1LR_{32}$	-21.27	3.74	2.26	-15.28	1.82
efef	$R_1PR_1PR_{32}$	-20.43	3.34	2.14	-14.94	2.16
efee	$R_2PB_3BR_{32}$	-21.46	3.62	2.14	-15.71	1.39
	$R_3PR_1LR_{21}$	-20.75	3.77	1.72	-15.26	1.84
	$R_2PR_1LB_{21}$	-20.01	3.45	2.50	-14.97	2.13
ffef	$B_1PR_1PR_{21}$	-21.26	3.15	2.04	-16.07	1.03
	$B_2PR_1PB_{21}$	-21.27	3.12	2.10	-16.05	1.05

Table 5. The low-energy conformations of *Leu*-gallatostatine-3 molecule.

shape	Conformation	Energy contributions (kcal/mol)				
		E_{nv}	E_{el}	E_{tors}	E_{tot}	E_{rel}
ffeffef	$RR_{22}B_3B_1PR_1PR_{32}$	-40.99	5.91	3.33	-31.75	**0.00**
	$RR_{21}B_3B_1PR_1PR_{32}$	-40.67	5.95	3.27	-31.44	0.31
	$RR_{22}B_3B_1PR_1PB_{21}$	-40.78	5.84	3.69	-31.26	0.49
	$RR_{32}B_3B_1PR_1PR_{32}$	-39.95	5.66	3.25	-31.04	0.71
ffeffff	$RR_{11}B_1B_3PR_2RR_{21}$	-39.88	5.89	2.99	-31.00	0.75
	$RR_{11}B_1B_3PR_2RR_{32}$	-40.63	6.06	3.72	-30.85	0.90
	$RR_{11}B_1B_3PB_2PB_{32}$	-39.56	5.76	2.97	-30.84	0.91
feffffff	$RB_{11}R_2B_3PB_2PB_{21}$	-39.55	5.44	2.66	-31.45	0.30
	$RB_{21}R_2B_3PR_2RR_{21}$	-39.66	5.72	2.99	-30.95	0.80
fffefff	$RR_{11}R_2R_3PB_2PB_{32}$	-42.41	6.20	5.12	-31.09	0.66
	$RR_{11}R_2R_3PB_2PB_{31}$	-42.56	6.29	5.51	-30.76	0.99
feeffef	$RL_{31}B_3B_1PR_1PR_{32}$	-39.34	5.89	4.05	-29.40	2.35
	$RL_{31}B_3B_1PR_1PB_{21}$	-37.86	5.77	3.89	-28.19	3.56
efeffef	$BR_{21}B_3B_1PR_1PB_{32}$	-37.27	5.54	3.15	-28.58	3.17
	$BR_{21}B_3B_1PR_1PR_{32}$	-36.64	5.47	3.06	-28.11	3.64

Table 6. Energy contributions (kcal/mol) of inter-and intra-residual interactions of *Leu*-gallatostatine-3 molecule.

Ala	*Asn*	*Arg*	*Tyr*	*Gly*	*Phe*	*Gly*	*Leu*	
1.06	-0.55	-0.62	-1.88	0.00	0.00	0.00	0.00	
1.07	-1.11	-0.25	-0.03	0.01	-0.04	0.00	-0.01	*Ala*
1.04	-1.18	-0.79	-0.47	-0.88	0.01	0.00	-0.07	
	-0.11	-2.51	-3.35	-0.02	-0.29	-0.38	-0.10	
	0.40	-1.63	-3.29	-0.48	-4.47	-0.19	-0.30	*Asn*
	-0.39	-1.00	-0.75	-0.23	0.00	0.00	0.01	
		0.30	-0.80	-0.22	-0.38	-2.21	-3.71	
		-0.09	-4.95	-0.20	-0.19	-0.03	-.43	*Arg*
		0.07	-5.31	-0.43	-0.10	0.02	-0.16	
			-0.71	-1.28	-2.69	-2.63	0.07	
			0.00	-0.51	-1.15	-0.07	-4.51	*Tyr*
			-0.28	-0.48	-1.30	-0.12	-4.77	
				1.28	-1.11	-0.76	-0.02	
				1.22	-1.06	-0.39	-1.85	*Gly*
				1.18	0.89	-0.35	-0.73	
					0.30	-1.05	-3.31	
					0.00	-1.17	-1.83	*Phe*
					0.19	-1.33	-1.82	
						1.26	-1.54	
						1.30	-0.91	*Gly*
						1.29	-1.60	
							-0.75	
							-1.20	*Leu*
							-0.75	

****Note*** The data for low-energy conformations of *ffeffef* ($E_{rel.}$*= 0.00 kcal/mol), fefffff* ($E_{rel.}$*= 0.30 kcal/mol)* and *fffefff* ($E_{rel.}$*= 0.66 kcal/mol)* shapes correspondingly are given in 1-3 lines.

The structures of other two types are stabilized mainly by intramolecular atomic interactions in limits di-, tri- and other types of inter-residual contacts (table 6).

Summarizing the investigation results one can conclude that there are two functionally important fragments of *Leu*-gallatostatine-3 neuropeptides. This is α-spiral pentapeptide realized in all energetically preferable neuropeptides conformations and labile *N*-end fragment playing the hinge role for supplying of ligand molecule steric correspondence to its receptor.

The obtained results agree with data of numerous experimental investigations by the fact that glycine residual has the big flexibility and promotes to polypeptide chain swerving in compact structure.

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Received: 06.02.2015