INSIGHTS INTO BIOACTIVE CONFORMATION OF MELANOTROPINS

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By the molecular mechanics, molecular dynamics, quantum chemical methods and modern computer programs the structure problems of hormone-receptor interactions, deals melanotropins are considered. The conformational-electronic peculiarities, which are important for the functional activity of *α*-, *β*-, *γ*-melanotropins and its active analog are revealed. On the basis received results the bioactive conformation of melanotropins were assessed. An α-spiral was revealed on the polypeptide chain of common for them fragment, pharmacophore -His-Phe-Arg-Trp-, provided specificity of melanotropin-receptor interaction.

Keywords: melanotropins, bioactive conformation, pharmacophore, structure-function relationships
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1. INTRODUCTION

α-melanotropin (H–Ser1–Tyr2–Ser3–Met4–Glu5–His6–Phe7–Arg8–Trp9–Gly10–Lys11–Pro12–Val13–H), β-melanotropin (H–Asp1–Ser2–Gly3–Pro4 –Tyr5–Lys6–Met7–Glu8– His9–Phe10–Arg11–Trp12–Gly13–Ser14–Pro15–Pro16–Lys17–Asp18-OH) and *γ*-melanotropin (H-Tyr1–Val2–Met3–Gly4–His5–Phe6–Arg7–Trp8–Asp9–Arg10–Phe11–Gly12–OH) are the cleavage products of pro-opiomelanocortic precursor (POMC), which are expressed in the pituitary gland of the cold-blooded vertebrates, bird and mammals and are found also in other cells such as neutrophils, monocytes, melanocytes, fibroblasts and keratinocytes [1,2]. The melanotropins stimulate physiological and morphological changes of skin and hair coloration [3-5]. However, the biological role of these hormones does not seem to be restricted only by a melanotropic action. A number of their other activities have been discovered, such as a lipolytic, steroidogenetic activities, sodium-uretic effects, a positive chronotropic influence on the nervous system and muscular systems. Injection of *β*-melanotropin induced a tachycardia effect and a hypersensitivity, as well as behavioural reactions. Neurotransmitting and neuromodulating activities of melanotropins were demonstrated. The effects of β-melanotropin on memory, concentration abilities were reviewed. It is shown *γ*-melanotropin decreases the effects of *β*-endorphin. It is found α-melanotropin is also a peripheral, integrative regulator of glucose and fat metabolism [6-9]. Melanotropins have also anti-inflammatory properties [10]. It is proposed -His-Phe-Arg-Trp- fragment of these peptides may be considered as the message sequence [11].

Thus above mentioned forms of melanotropins show both different and similar biological functions. The wide spectrums of diverse biological activities of melanotropins are undoubtedly connected to the conformational flexibility of these hormones that is necessary to produce structures complementary to active sites of various receptors. However, this polyfunctionality does not interfere the high sensitivity and specificity of each particular action of these hormone peptides.

The development of representations about the action mechanism of biologically active peptides, the understanding of the reasons of activity and selectivity of pharmaceutical substance binding with a biological target, is possible thanks to structure-function investigations. Many experimental works are devoted to the structure-function investigations of peptides of this family. Note that none of these methods used led to a sufficiently clear, and even more so to a reasonable quantitative representation of the structure of these molecules, but only allowed the authors to make a number of considerations about some of their probable features. In the presented work using the molecular modeling, the comparative conformational analysis of *α*-melanotropin, *β*-melanotropin and γ-melanotropin and their active analog H-His-Phe-Arg-Trp-OH, sequence of which corresponds to melanotropins pharmacophore was performed, as result the common to these molecules the optimal conformational features were found. The conformation-electronic peculiarities, which are important for the functional activity of these peptides, are revealed. On the basis received results the bioactive conformation of melanotropins was assessed.

2. METHODS

Conformational energy calculations were made on IBM computer using the version of ECEPP (Empirical Conformational Energy Program for Peptides) [12, 13]. The program was developed from the matrix method principle of Hermans and Ferro [14]. The investigations were carried out within molecular mechanics framework as described in [15, 16]. The conformational potential energy of the peptides was calculated as the sum of the independent contributions of nonvalent (E_{nv}), electrostatic (E_{el}), torsional (E_{tor}) interactions and hydrogen bonds (E_{hb}) energies. A rigid valence scheme of the molecule was assumed, namely, the searches were made only on torsional angles. The conformational state of each amino acid residue is characterized by backbone (φ, ψ, ω) and side chain (χ_1, χ_2, χ_3,...) dihedral angles. The term "conformational state" or "conformation", used in the following analysis, will always imply exact quantitative characteristics of the geometry of the residue or the fragment. The backbone was described by the "shape" symbols *e* and *f* corresponding to extended and folded configuration of virtual bonds C^{α}_{i}- C^{α}_{i+1}- C^{α}_{i+2}- C^{α}_{i+3}, respectively. The nomenclature and conventions adopted are those recommended by IUPAC-IUB [17].

The molecular dynamics of dermorphin was spent

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with use of force field AMBER in the temperature interval 293-313K with step 5K during 10 nanoseconds by means [18]. Procedure solvation with application of model of water in the set spherical volume TIP4P [19] has been used. The quantum-chemical calculations of these molecule were conducted by method CNDO [20], used the demonstration version of software package HyperChem (http:// www.hyper.com).

3. RESULTS AND DISCUSSION

The polyfunctionality of melanotropins points to the existence of a restricted number of definite spatial structures of these peptides in the conformational equilibrium. For this reason, the investigation of the structure-function relationship of these molecules at the molecular level should start from an elucidation of the complete set of low-energy states of the molecules, which may prove biological active.

We previously have considered in detail the spatial structure of investigated melanotropins [21,22,23]. In first step the conformational possibilities of active analog H-His-Phe-Arg-Trp-OH have been investigated on the basis of knowledge of low-energy states of monopeptides. It is found that low-energy conformations of this molecule have spiral form of tetrapeptide backbone or β-turn on dipeptide segment Arg-Trp. In these structures the positively charged side chain atoms of Arg and the negatively charged C-terminal carboxyl group are spatially close, that is accompanied by effective electrostatic contacts and the formation of hydrogen bonds. The nonvalent interactions of the side chains of His, Phe and Trp residues are the major contribution to the conformational energy of this molecule. These residues effectively interact both with each other and with the amino acid residue at the 3-th position.

Conformational analysis of the melanotropin molecules was carried out through a fragmental calculation, by studying of the conformational possibilities of the complicated molecular fragments. The calculations were based on the universal sets of low-energy conformation states of free amino acids. The pattern of division of a given amino acid sequence into fragments is a purely technical procedure of calculations, which was shown to have no influence on the final set of low-energy conformations.

As a result, only a very restricted set of of low-energy conformations was isolated from a great number of analysed combinations of the preferable states of the fragments, which model possible structures of investigated molecules. Conformational analysis *leads to* a unique structure of the tridecapeptide Ser1-Val13. The most probable structures of the α-melanotropin have the relative energies in a fairly wide interval 0-10.0 kcal/mol. The energy gap between the most preferred structures with a relative energy of 0.0 and 1.1 kcal / mol and subsequent conformations is approximately 8-9 kcal /mol. It is no mere chance that a steric complementarity of all parts of the molecule, are observed only for a small number of combinations of most favourable conformations of separate fragments. This fact seems to be responsible for a strictly determinative mechanism of a spontaneous and faultless folding of the amino acid sequence under native conformations and a rapid shifting of conformational equilibrium towards an actual structure of the hormone induced by a specific receptor or by other inter-molecular forces. In the optimal structures of this molecule belonging to *ffffff*-shape the fragment Met4-Gly10 has α-spiral structure, in other structures this part of molecule has *fffeee, fffeef, fffeff, fffefe*-shapes of backbone. It can be mentioned that in preferable structures of this molecule the central site, N- and C-terminal segments of molecule are close in space. The increase in energy during the transition from the optimal structures to the other is due to the loss of stabilizing contacts between the N- and C-terminal parts of the chain, i.e., the weakening of long-range interactions. In the optimal structures, the interaction of fragments Tyr2-Met4 and Pro12-Val13 is equal to 8.5kcal/mol. With respect to average interactions, all optimal conformations are approximately equivalent, so one can expect that the conformational capabilities of the molecule increase at interaction with different receptors, in which their specificity manifests itself. These structures may prove to be relevant when the sequence of this molecule will be embedded into a polypeptide chain or changing the nature of the nearest residues on either side of the Met4-Gly10 fragment. In the low-energy structures of the molecule the side chains of Glu5, Arg8 and Lys11 are oriented from the molecule to the environment and the side chain of Glu5 is closely approached to the side chain of Lys11 and is away from side chain of Glu8.

Most probable structures of the β–melanotropin have the relative energies in a sufficiently wide interval 0-12.0 kcal/mol. There are only nine such variants. Such an extremely sharp energy range of conformations of Asp1-Asp18, which is produced by joining of low-energy conformations of free fragments into a united chain, undoubtedly indicates that strong stabilizing contacts between far-ranging residues might work in unique situations, with maximum compact packing and consistency of interactions within every fragment of the natural octadecapeptide. Low-energy conformations of β -melanotropin may be divide on several groups, in which the relative structures are combined. Just so, three groups consist of conformations, which have identical shape of the peptide skeleton and stabilize, as rule, by identical interactions and have close values of dihedral angles of amino acid residues. Each group is characterized by the definite conformational state of central segment Met7-Trp12: *ffffef, fffef* and *fffff*, correspondently. The third group in which the amino acids of this fragment form spiral conformation, represent special interest. For β-melanotropin the α-spiral form of the peptide skeleton of fragment Met-Glu-His-Phe-Arg-Trp is realized in the optimal conformation with $E_{rel.}$= 4.2 kcal/mol. The values of intra- and inter-residue dispersion and electrostatic interactions, as well as of torsional energy are indicative of the alternative nature of stabilization of different low-energy structures. Thus, the global conformation of this molecule exhibits an inter-residue dispersion energy which is 5.0 kcal/mol lower than that in the next low-energy structure with $E_{rel.}$= 0.5 kcal/mol. This provides for a sensitivity of the conformational equilibrium to external factors, shifting it towards the second structure by a change from a polar medium to a more hydrophobic one. Conformation, which is inferior to the global structure by

8.7 kcal/mol, appears to have few prospects at first sight. The high energy of this structure results from a comparatively small contribution of inter-residue electrostatic interactions. However, this conformation exhibits the most favourable dispersion contacts and therefore may be expected to become the most preferred one in a strongly polar medium, when electrostatic interactions do not play a significant part. Both the nonvalent and electrostatic interactions of the side chains of Phe and Trp residues are the major contribution to the conformational energy of this molecule. These residues effectively interact both with each other and with the amino acid residues at other positions of this sequence. In the preferable conformations of this molecule the positive charged amino group of the side chains of Lys6, Arg11, Lys17 and the negatively charged atoms of the side chain of residue Glu8 and COO^- terminal group interacts by effective electrostatic interactions. Such structures are stabilized also by intensive dispersion contacts of the backbone atoms and are characterized by compactness of the spatial structure, as evidenced by the value of the distance between the heavy atoms. Besides, these structures are stabilized also by the hydrogen bonds between the backbone atoms.

The most probable structures of γ-melanotropin have relative energies in the interval of 0-10 kcal/mol. There are 14 such variants. The results of calculations shows that this peptide hasn't the clean-cut fixed threedimentional structure, yet it make be realized by restricted number of definite spatial structures in the conformational equilibrium. As it turned out the fragment Tyr1-Gly4 of this peptide is flexible. The conformational-rigid nucleation is found on the fragment His5-Arg10. The form of backbone of the central fragment Arg7-Arg10 defines the basic stabilizing forces of whole molecule. The global and four relative conformations, which belong to identical shape, contain the α-spiral on the fragment His5-Arg10 (*fffff*-shape). As for α- and β - melanotropin, in such conformations of γ-melanotropin the central site and C-terminal segments are close in space. In the low-energy structure with $E_{rel.}$= 3.6 kcal/mol and 15 relative conformations the fragments Tyr1-Gly4 and Phe 6-Phe11 have folded structure. β-turn is found on the segment His5-Phe6 of these structures. The fragment His5-Arg10 of these structures has *effff*-shape of backbone. The calculations show that in the optimal structures of this molecule the residues Phe6 and Trp8 participates in the effective interactions with charged residues Asp9 and Arg10. As can be seen from these results, the stability of spatial structure of this peptide molecule is determined by mutual position of the aromatic side chains of the residues Phe6, Trp8 and charged groups of the residues Asp9, Arg10.

Then the established low-energy conformations of all melanotropins were subjected to the molecular dynamics simulations of 10 ps. As a result of simulation process, the ranges of change of dihedral angles and distances between atoms of amino acid residues are defined. The results of molecular dynamics demonstrate the conformational rigidity of the peptide backbone of tetrapeptide fragment His-Phe-Arg-Trp and the mobility of functional groups of the side chains. The quantitative estimation of the distances between the atoms shows that at modelling the mentioned part of the molecules preserves the spiral structure throughout molecular dynamics simulation; the structure of this part of molecules upon termination of modelling process practically does not differ from the initial stage. The dispersion contacts between the atoms of backbone of the amino acid residues His and Trp are invariable, the distance between C^{α}- atoms of the specified residues does not exceed 12Å during simulation. It is possible to assume the conformational stability of specified tetrapeptide fragment plays important role in functional activity of melanotropin molecules and defines the specificity of its interaction with the receptor. It is shown in the optimal structures of investigated molecules the aromatic side chains of residues Phe and Trp have conformational mobility because of localization on surface of the peptide molecules and therefore may be in the specific orientations, which are favourable for interaction with receptor. It is found that the amplitudes of the fluctuations of the atoms of these residues in the aqueous environment are decreased. You can come to the conclusion that the atoms in the side chain of these residues contact with a certain number of water molecules that limits the mobility of these residues. It can be assumed that at interaction with receptor the side chains of these residues will be free from water molecules and may be involved in the intermolecular contacts in the role of the substrate. This assumption is confirmed by the work [24], which suggests that the aromatic groups of these residues may be involved as a donor or acceptor at the formation of hydrogen bond with the less acidic hydroxy groups of the receptor. The topography of the pharmacophore revealed the significance of the indole ring of the Trp side chain at interactions with melanocortin MC1 receptor [25]. Note that the side chain of residue Arg of central tetrapeptide showed some dynamics in simulation process, which enables, apparently, them to participate in the receptor selectivity of these molecules. This assumption is confirmed by the work of [26], which suggests that this positive charched residue may be involved in electrostatic interactions with the negative charched residues Asp or Glu (at mutation) of MC2 receptor.

The bioactive conformation of α-, β- and γ-melanotropins was assessed by a comparative conformational analysis by pairwise cross comparisons of the low energy conformations found for melanotropins and their active analog H-His-Phe-Arg-Trp-OH, corresponding to their pharmacophore. Subsets of conformations common to these peptides were pairwisely compared for similarity. Comparisons were carried out superimposing residues of pharmacophore -His-Phe-Arg-Trp- of melanotropins with their active analog, respectively. Thus, an *rmsd* (root-mean-square deviation) values of the putative bioactive conformation of melanotropins with all conformations of the subset of low-energy conformations of the active analog were computed. In the structures of α-melanotropin residues 6–9 exhibit *rmsd* of 0.75 Å, of β- melanotropin residues 9-12 exhibit *rmsd* of 0.82 Å, of γ-melanotropin residues 5-8 exhibit *rmsd* 0.79 Å when these residues are compared with mentioned active analog. It was found the spiral conformation of the molecule H-His-Phe-Arg-Trp-

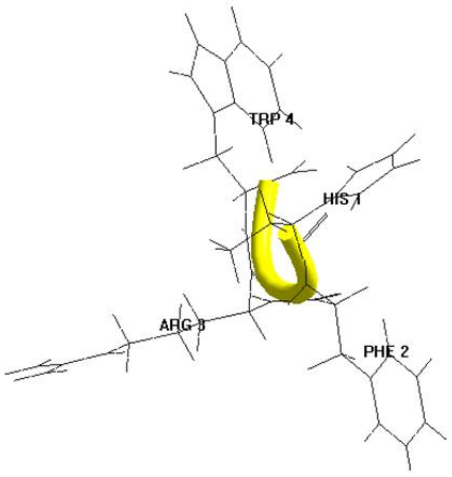
OH, is realized in the optimal conformations of melanotropin molecules. Such conformations of melanotropins showed a common properties. Indeed, the selected structures among all the common to the investigated active peptides are stabilized by a hydrogen bond between the hydroxyl group of the side chain of residue His and the carbonyl oxygen of the residue Trp, the positive and negative charged side chain atoms take part in the effective electrostatic contacts. The dihedral angles of most similar structures to the putative bioactive conformation found in the set of low-energy structures of the active analog H-His-Phe-Arg-Trp-OH of melanotropins and α-, β- and γ-melanotropins are listed in Table 1 and Table 2 These structures are shown in Fig.1. The superimposition of the putative bioactive conformation of α-melanotropin, that exhibits the smaller *rmsd* with the spiral structure of the active analog H-His-Phe-Arg-Trp-OH of melanotropins, is shown in Fig.2. The superimposition of the putative bioactive conformations of *α*- and *β*-melanotropins, that exhibits the smaller *rmsd* with the spiral structure of the active analog H-His-Phe-Arg-Trp-OH of melanotropins is shown in Fig.3. The superimposition of the putative bioactive conformations of *β*- and *γ*-melanotropins, that exhibits the smaller *rmsd* with the spiral structure of the molecule H-His-Phe-Arg-Trp-OH is shown in Fig4.

Table 1.

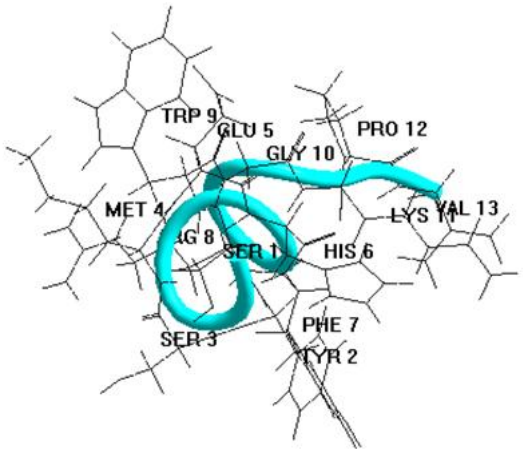
Backbone dihedral angles (in degrees) of the putative bioactive conformation of active analog H-His-Phe-Arg-Trp-OH of melanotropins

Molecule H-His-Phe-Arg-Trp-OH			
Amino acid residues	φ	ψ	ω
His5	-62	-37	176
Phe6	-75	-35	-160
Arg7	-73	-40	-177
Trp8	-90	-45	-172

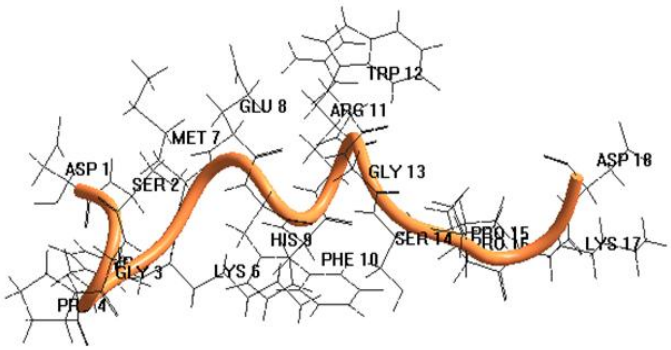
The conformational-electronic peculiarities, which are important for the functional activity of investigated peptides are revealed too. It was found that the bioactive conformations of melanotropins are characterized by specific distribution of electron density, that is reflected on the values of effective charges of atoms of the functional residues.



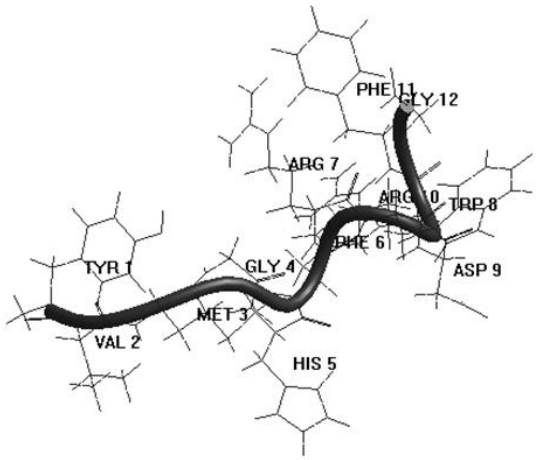
(a)



(b)



(c)



(d)

Fig.1. The putative bioactive conformation of active analog H-His-Phe-Arg-Trp-OH of melanotropins (a), *α*- melanotropin (b), *β*-melanotropin (c) and *γ*-melanotropin (d).

It was found that the distribution of charges on the atoms of pharmacophore elements (the side chains of the tyrosine, phenylalanine and tryptophan residues and charged group of arginine residue) in the bioactive conformation of the molecule H-His-Phe-Arg-Trp-OH and of the investigated molecules of melanotropins are similar.

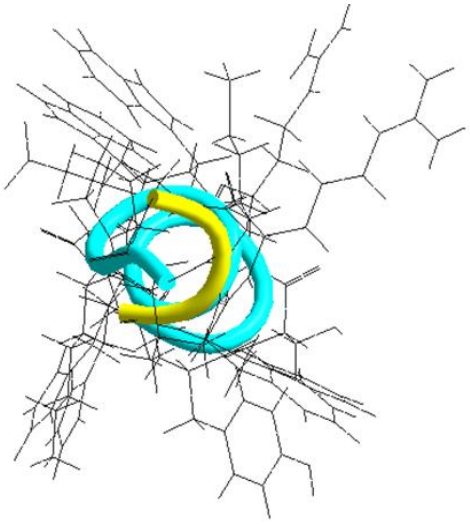


Fig.2. The superimposition of the putative bioactive conformation of α-melanotropin (in cyan), that exhibits the smaller *rmsd* with the spiral structure of active analog H-His-Phe-Arg-Trp-OH of melanotropins (in yellow).

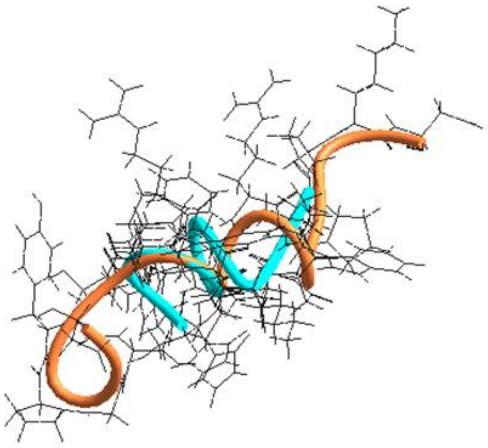


Fig.3. The superimposition of the putative bioactive conformations of α-melanotropin (in cyan) and β-melanotropin (in orange), that exhibits the smaller *rmsd* with the spiral structure of active analog H-His-Phe-Arg-Trp-OH of melanotropins.

The observed differences in the values of the charges on the certain groups of atoms as of backbone and of side chains of the residues are dictated by the specific relative position of them in each molecule. It was found that the electronic structure of the optimal conformations of these molecules is characterized by significantly lower dipole moment, than others due to the uniformity of the distribution of electron density in them. It seems that the presence of the positively charged groups of atoms in melanotropin sequences is necessary for electrostatic attraction to the negatively charged binding sites of receptors and the electrostatic repulsion from the positively charged sites of receptor. It can be assumed that the mechanism of receptor binding of melanotropins in addition to hydrophobic interactions is the formation hydrogen bonds with participation of ionizable functional groups of these molecules.

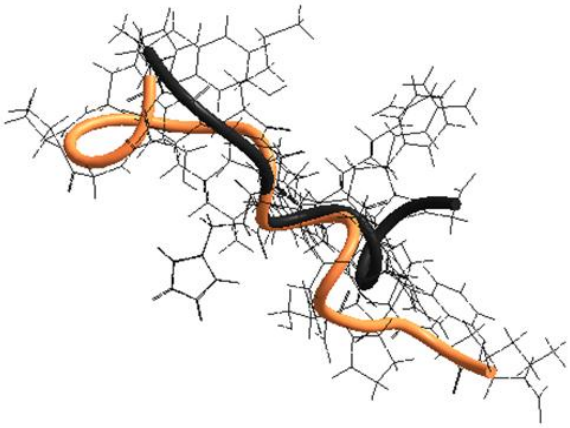


Fig.4. Superimposition of the putative bioactive conformations of β-melanotropin (in orange) and γ-melanotropin (in black), that exhibits the smaller *rmsd* with the spiral structure of active analog H-His-Phe-Arg-Trp-OH of melanotropins

The received results are in agreement to the data of the theoretical and experimental research of the melanotropins. The available experimental studies of the spatial structure of melanotropins are limited to works on CD-, NMR- and IR-spectroscopy, and fluorescence analysis [27-30]. Based on these investigations it is assumed that the N-terminal fragment of ACTH, which sequence includes α-melanotropin, has an ordered structure close to the α-helical structure, which is stabilized upon transition to non-aqueous solutions simulating the natural environment of membrane proteins. A conclusion was also made on the significant conformational rigidity of the fragment of His-Phe-Arg-Trp, which determines the melanocyte-stimulating activity of melanotropins. It was estimated from the fluorescence spectra that the distance between the aromatic rings of the residues Tyr and Trp is 9 Å. In [31], where a secondary structure for the α-, β-melanotropins was predicted by Chow and Fasman's method, the content of the α-helix on the fragment Met-Glu-His-Phe-Arg-Trp-Gly is also indicated. The possible topographic role of the residues of the fragment His-Phe-Arg-Trp, that may be explained by similar conformational effects of the side chains are discussed in [32]. These data explain the covariant character of replacements for amino acid residues Glu in 5-th and Gly in 10-nd positions of α-melanotropin, Glu in 8-th and Gly in 13-th positions of β -melanotropin, Gly in 4-th and Asp in 9-th positions of γ-melanotropin. Apparently, the maintenance of the function of these hormones is found to be possible if above indicated residues are close in space and act on the same points of receptors by functional groups. Evidently, for the same functions of melanotropins their close central segment corresponding to mutacion-stable sequence Met-Glu(Gly)-His-Phe-Arg-Trp through its structure organization are responsible. The conformational-electronic similarity of "common fragment" His-Phe-Arg-Trp and the data of its biology activity allow think this segment provides the specificity of melanotropin-receptor interaction.

Table 2.

Backbone dihedral angles (in degrees) of the putative bioactive conformation of α -, β- and γ-melanotropins

α- melanotropin				β- melanotropin				γ- melanotropin			
Amino acid residue	φ	ψ	ω	Amino acid residue	φ	ψ	ω	Amino acid residue	φ	ψ	ω
				Asp1	-71	151	-179				
				Ser2	-57	131	-178				
				Gly3	127	-85	168				
Ser1	-99	165	-177	Pro4	-60	-43	174				
Tyr2	-58	-37	-178	Tyr5	-108	143	-173	Tyr1	-107	141	176
Ser3	-76	-31	-173	Lys6	-100	119	178	Val2	-123	-71	180
Met4	-130	-73	175	Met7	-135	-53	175	Met3	-133	168	179
Glu5	-88	-42	-170	Glu8	-86	-31	-169	Gly4	-80	61	180
His6	-73	-55	176	His9	-67	-38	-177	His5	-57	-37	174
Phe7	-90	-58	170	Phe10	-78	-50	-168	Phe6	-80	-45	-151
Arg8	-95	-45	-175	Arg11	-80	-40	-176	Arg7	-65	-40	-178
Trp9	-100	-58	-174	Trp12	-99	-48	-174	Trp8	-88	-40	-170
Gly10	-70	-49	-178	Gly13	-70	-49	-179	Asp9	-77	-49	180
Lys11	-119	98	172	Ser14	-97	136	176	Arg10	-83	-67	-164
Pro12	-60	138	176	Pro15	-60	135	177	Phe11	-77	-46	-173
Val13	-137	158	-	Pro16	-60	-57	178	Gly12	90	89	-
				Lys17	-121	-67	-179				
				Asp18	-122	158	-				

4. CONCLUSION

The stability of spatial structure of melanotropins is defined by mutual position of pharmacophore elements: the aromatic rings the side chains of the tyrosine, phenylalanine and triptophan residues and charged group of Arg and is characterized by a specific distribution of electron density, which plays an important role in the interaction with the receptor. The conformational-electronic similarity of the "common fragment" His-Phe-Arg-Trp of melanotropins suggests that the helical structure of this tetrapeptide provides the specificity of melanotropin-receptor interaction. It can be assumed that the mechanism of receptor binding molecules melanotropins is to form the hydrophob interactions of aromatic rings and electrostatic contacts with participation of ionizable functional groups of these molecules.The received structural data are of interest for the study of the mechanism of the physiological effect of the melanotropins and can be used in the design of new artificial analogues.

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