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Docking of highly selective 5-HT$_{2A/C}$ receptor peptide ligands with antipsychotic activity

©2021. A.B. Orlova[1*], A.M. Sventitskaya[1], N.G. Vengerovich[1, 2], A.S. Nikiforov[1], I.M. Ivanov[1], Y.A. Proshina[1]

[1] State Research Testing Institute of Military Medicine of the Ministry of Defense of the Russian Federation, Saint Petersburg, Russia
[2] Saint Petersburg State Chemical and Pharmaceutical University of the Ministry of Health of the Russian Federation, Saint Petersburg, Russia

* e-mail: gniiivm_15@mil.ru
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Search for new ligands selective to different subtypes of 5-HT$_2$ receptors is an important scientific and practical problem for experimental psychopharmacology and clinical medicine. The majority of existing antagonists of the 5-HT$_{2A}$ and 5-HT$_{2C}$ subtypes possess all necessary anti-anxiety and antipsychotic properties, though they are partially selective to 5-HT$_{2B}$ receptors. Their activation leads to cardiotoxic side effects, so it significantly limits clinical application of these drugs.

For the search of new highly selective ligands of 5-HT$_{2A/C}$ receptors, an in silico screening algorithm was proposed using PScore.Max and Affinity.maxPScore parameters, which included the affinity of low molecular weight compounds for each 5-HT$_2$ receptor subtype. Cyclic physiologically active substances of peptide nature have been proposed as new promising drugs with antipsychotic activity. Based on the CXXC library, a number of cyclopeptides with a high selectivity of structure to target binding sites were selected for further in vitro studies by extending of the peptide chain.

It was also found that a promising direction for increasing the selectivity of peptide ligands to 5-HT$_{2A/C}$ receptors is the introduction of non-proteinogenic amino acids during the formation of an initial docking library. The choice of these amino acids will be due to the nature of interactions between the reference ligands and amino acid residues of the binding site.

KEYWORDS: serotonin; HT$_2$ receptors; HT$_{2A}$ receptors; HT$_{2C}$ receptors; docking; peptides; neuropeptides; antipsychotics

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ABBREVIATIONS:

5-HT$_2$ – subtype 2 of serotonin receptors;
CNS – Central Nervous System;
PDB – Protein Data Bank Database;
PLIP – Protein-Ligand Interaction Profiler.

INTRODUCTION

Serotonergic neurotransmitter system plays an important role in the realization of functions of the higher nervous activity of the central nervous system (CNS). Changes in the tone of serotonergic neurotransmission are a complex process involving presynaptic autoreceptors, a serotonin transporter and 14 subtypes of postsynaptic receptors.

Postsynaptic serotonin receptors of the second subtype (5-HT_2 receptors) represent an important pharmacological target for the development of new therapeutic agents; they belong to the superfamily of metabotropic receptors associated with G-proteins and exist in three variants (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}).

Functioning of 5-HT_{2A} subtype is associated with the realization of such serotoninergic psychostimulant effects as d-lysergic acid diethylamide and psilocybin, as well as with the mediation of the effects of antipsychotics (mainly atypical ones).

Activation of the 5-HT_{2C} receptor inhibits the dopamine and norepinephrine production in certain areas of the brain (striatum, prefrontal cortex, nucleus accumbens, hippocampus, hypothalamus, amygdala). The increased activity of 5-HT_{2C} receptors can contribute to the development of depression and anxiety symptoms. 5-HT_{2C} receptor inhibitors regulate mood, anxiety, nutrition, and reproductive behavior. It has been proven that 5-HT_{2C} receptors are a target for some anti-obesity drugs, as exemplified by the selective 5-HT_{2C} agonist lorcaserin (Belviq®). Besides, this subtype is considered as a promising target for drug therapy of depression, schizophrenia, drug dependence, and other disorders [1].

5-HT_{2B} receptors are localized in the cerebellum, hypothalamus and medial amygdala. Increased expression of receptors takes place in the liver and kidneys, while a lower level is found in the cerebral cortex, pancreas and spleen. These receptors are less involved in the development of anxiety behavior than other subtypes. Activation of 5-HT_{2B} of the heart leads to proliferation of connective tissue of valves that is considered as an undesirable side effect when taking drugs tropic to the 5-HT_2 receptor family.

A number of drugs for the treatment of migraine (methylsergide, ergotamine), antiparkinsonian drugs (pergolide, cabergoline), drugs for the treatment of pituitary adenoma, have significant side effects (primarily, valvular disease and carcinoid syndrome) associated with 5-HT_{2B} receptor activation. It significantly limits their clinical use [2]. Currently, routine screening for 5-HT_{2B} receptor affinity is recommended for drugs planned for the clinical phase of studies [3].

Thus, the search for new ligands selective for various 5-HT_2 receptor subtypes is an important scientific and practical problem that should be solved by application of contemporary computer modeling that can significantly optimize the stage of development of active molecules which pharmacological profile would include a predominant selectivity for 5-HT_{2A} and 5-HT_{2C} subtypes.

MATERIALS AND METHODS

The study design consisted of the following constituent elements:

– analysis of theoretical data on the ligand binding site;

– determination of the localization and structure of the ligand binding pocket;

– determination of criteria for selection of compounds based on docking results;

– docking of libraries of cyclic peptides and selection of the most promising compounds.

Molecular docking was performed using open source software and information sources available in free access on the Internet. Models of 5-HT_2 receptors in combination with reference ligands placed in the Protein Data Bank (PDB) were used as targets for docking process. They were obtained by X-ray structural analysis with a resolution of 2.7 - 3.0 Å:

– model 5-HT_{2A} receptor in complex with risperide, PDB ID 6A93 (hereinafter referred to as "target A");

– 5-HT_{2B} receptor model in complex with methylergonovine, PDB ID 6DRY (hereinafter referred to as "target B");

– model 5-HT_{2C} receptor in complex with ritanserin, PDB ID 6BQH (hereinafter referred to as "target C").

Macromolecules and peptide ligands were prepared using the MGLTools 1.5.4 utility kit [4].

The generation of libraries of peptide ligands in SDF format was performed using the Bioware CycloPs software [5]. Semi-flexible docking was carried out using the AutoDock Vina 1.1.2 software [6].

The PLIP software was used to visualize the protein-ligand interaction, as well as to clarify the positions of the amino acid residues of the macromolecule involved in the interaction with the ligand [7].

The library of peptide ligands CXXC (where X is proteinogenic L-amino acids, as well as D-forms of alanine, lysine, tryptophan, and phenylalanine) was chosen as a starting set of structures for docking, while the presence of a disulfide bond in the structures was considered as a modification capable of enhance the biological activity of original peptide compounds, as well as the addition of some D-amino acids. Modeling a peptide with limited conformational mobility increases its selectivity to the selected binding site; therefore, at the first stage, we determined the basic structure with the smallest cycle, followed by an increase in selectivity by extending the chain. Thus, the chosen sequence of actions was determined by the aim of simulating a number of relatively simple physiologically active substances of peptide nature, consisting of a small number of amino acids for further synthesis of selected structures, as well as studying their biological activity in vitro and in vivo.

Following docking of the starting CXXC library the best ligands were selected (to form second-level libraries of the YCXXCY type, where X and Y are proteinogenic L-amino acids and their D-forms).

Docking was performed taking into account the following Vina software settings:

– exhaustiveness = 8,

– num_modes = 20,

– other parameters – by default.

The result of one run of semi-flexible docking using AutoDock Vina 1.1.2 software is a dataset that characterizes several binding models ("poses" of docking, binding models) with the minimum values of predicted binding energies (Affinity, kcal/mol). The number of docking poses is determined by the "num_modes" parameter (maximum number) and the "energy_range" parameter, which define the binding energy range (kcal/mol) between the best and worst result falling into the result set of one run (the default parameter equals to 3).

For the reference and studied ligands the positions of the amino acid residues of the macromolecule involved in the interaction were determined. To compare the nature of their interaction with the target, the "PScore" index was calculated using the formula.

PScore = 2×100× (hits-nonhits)/(len_ref+len_lig),

where:

hits – the number of matches of the amino acid residues of the macromolecule involved in the interaction between the reference and the studied ligand;

nonhits – the number of mismatches in the amino acid residues of the macromolecule involved in the interaction between the reference and the studied ligand;

len_ref is the number of amino acid residues of the macromolecule involved in the interaction with the reference ligand;

len_lig – the number of amino acid residues of the macromolecule involved in the interaction with the ligand under study.

If the set of amino acid residues involved in the interaction with the reference and the studied ligand is fully consistent, the PScore index is 100%, and if it is incomplete, it is proportionally less than the former one.

Each docking launch was characterized by the following primary and target parameters:

– PScore.Max – the maximum value of the PScore parameter among all the "poses" of the docking for this launch;

– Affinity.maxPScore – Affinity score for the docking pose with the highest PScore.

For indirect assessment of selectivity of the studied ligands between targets "A" and "C" and target "B", PScore.Max (A+C-B) was calculated as the sum of PScore. Max (A) and PScore.Max (C) minus PScore.Max (B).

Evaluation of the selectivity of the studied ligands using the Affinity.maxPScore index was carried out by calculating the parameter "Sel" according to the formula (taking into account the minimum possible Affinity value that equals to -13.0):

Sel =100× (Affinity.maxPScore (A)/-13.0) + 100× (Affinity.maxPScore (C) / -13.0) -2×100× (Affinity. maxPScore (B) /-13.0),

where Affinity.maxPScore (A), Affinity.maxPScore (B) and Affinity.maxPScore (C) is the parameter Affinity. maxPScore score for targets "A", "B" and "C", respectively.

Taking into account the Sel index made it possible to exclude ligands with non-selective binding to all targets, which is typical, for example, for peptides, the structure of which contains several bulky lipophilic substituents.

Following docking of initial CXXC library, the best ligands were selected (for the formation of second-level libraries of YCXXCY type), corresponding to the following criteria:

– the value of the PScore.Max (A+C-B) parameter is not less than 60;

– the value of the parameter Affinity.maxPScore (A) and Affinity.maxPScore (C) no more than –6.0 (for the starting library);

– Sel value is not less than 30.

When selecting peptides in second-level libraries, additional criteria were:

– the value of the parameter Affinity.maxPScore (A) and Affinity.maxPScore (C) no more than -8.0;

– higher PScore.Max (A+C-B) and Sel values than the original compound from the first level library.

RESULTS AND DISCUSSION

Determination of localization and structure of the ligand binding pocket

Currently, a number of crystallographic structures of 5-HT_2 receptor subtypes in combination with ligands are available in free access. Analysis of these complexes makes it possible to clarify the region of drug binding in the structure of the receptor and to identify amino acid residues responsible for interactions with ligands and the development of a biological effect. Taking into account the purpose of the study, which involved the search for ligands that antagonize the A and C subtypes of the 5-HT_2 receptor and lack an agonist effect on the B subtype, the following targets were selected:

– the structure of the 5-HT_{2A} receptor in combination with the antagonist risperidone [8];

– the structure of the 5-HT_{2B} receptor in complex with the agonist methylergonovine [9];

– the structure of the 5-HT_{2C} receptor in combination with the antagonist ritanserin [10].

Based on the analysis of corresponding models from the PDB database using PLIP software and on the basis of theoretical data, the localization of the binding pocket on the receptor and the amino acid composition of protein residues involved in the interaction, as well as the nature of these interactions, were assessed. The results of the analysis of interaction of reference ligands with amino acid residues of 5-HT_2 receptors are presented in Figures 1–3.

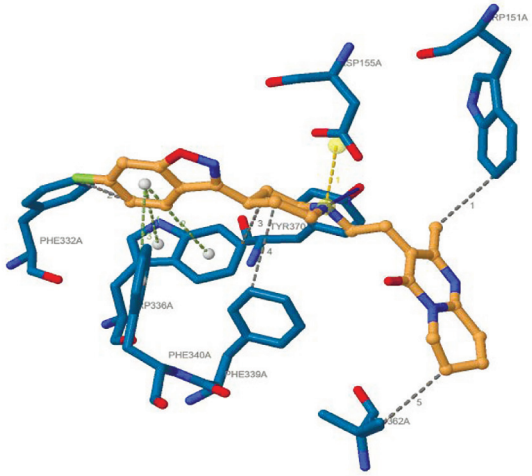

Fig. 1. Three-dimensional visualization of the interaction of risperidone with amino acid residues of the 5HT_{2A} receptor in B-chain (model 6A93)

Рис. 1. Трехмерная визуализация взаимодействия рисперидона с аминокислотными остатками 5HT_{2A}-рецептора в цепи B (модель 6A93)

For model 6A93 the following features were noted:

– the presence of hydrophobic interactions with residues in positions 139B (tyrosine), 151B (tryptophan), 156B (valine), 336B (tryptophan), 339B (phenylalanine), 362B (leucine), 370B (tyrosine);

– the formation of a salt bridge with 155B residue (aspartic acid);

– pi-stacking aromatic interactions with 336B residues (tryptophan), 340B (phenylalanine).

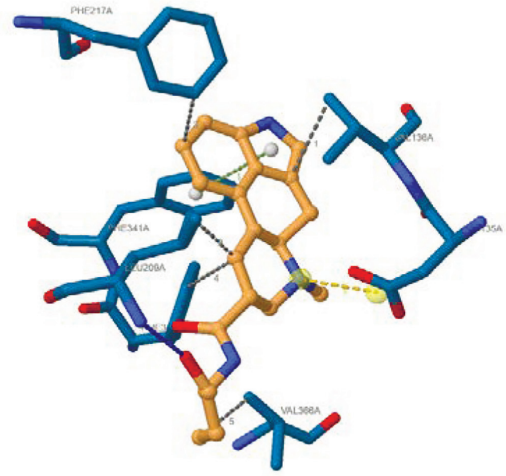

Fig. 2. Three-dimensional visualization of the interaction of methylergonovine with amino acid residues of the $5HT_{2B}$ receptor (model 6DRY)
Рис. 2. Трехмерная визуализация взаимодействия метилэргоновина с аминокислотными остатками $5HT_{2B}$-рецептора (модель 6DRY)

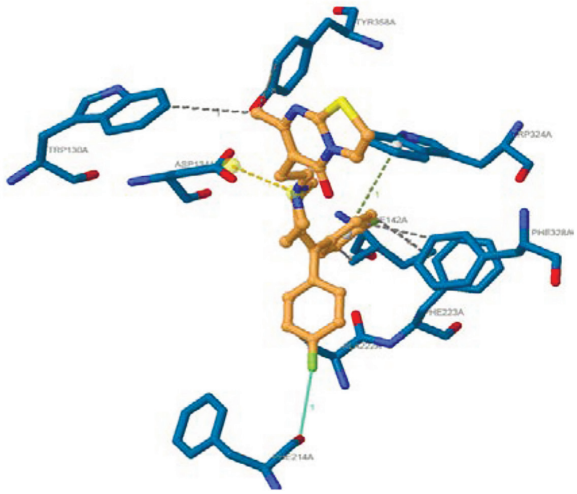

Fig. 3. Three-dimensional visualization of the interaction of ritanserin with amino acid residues of the 5-HT_{2C} receptor (model 6BQH)
Рис. 3. Трехмерная визуализация взаимодействия ритансерина с аминокислотными остатками 5-HT_{2C}-рецептора (модель 6BQH)

For model 6DRY the following features were noted:

– the presence of hydrophobic interactions with residues at positions 136A (valine), 209A (leucine), 217A (phenylalanine), 340A (phenylalanine), 366A (valine);

– a hydrogen bond with the residue 209A (leucine);

– the formation of a salt bridge with 135A (aspartic acid), aromatic pi-stacking interactions with residue 341A (phenylalanine).

For model 6BQH the following features were noted:

– the presence of hydrophobic interactions with residues in positions 130A (tryptophan), 142A (isoleucine), 222A (alanine), 340A (phenylalanine), 223A (phenylalanine), 328A (phenylalanine), 358A (tyrosine);

– the formation of a salt bridge with 134A (aspartic acid);

– aromatic π-stacking interactions with residue 324A (tryptophan), halogen bonds with residue 214A (phenylalanine).

Thus, for three subtypes of the 5-HT_2 receptor, the amino acid residues involved into interaction with the reference ligands were determined. Based on the data obtained, the search area was determined in the composition of the macromolecular target, which is described by the coordinates of the center and the dimensions of a rectangular cell. Narrowing of the region to an active center or ligand binding site provides a reduction in computing power costs, and also reduces the likelihood of obtaining false positive results (i.e., high affinity of ligands when they bind in those regions of the macromolecule that are not involved in mediating the biological effect).

To substantiate the search area for each target using the VinaConfigBuilder utility [11], conditional geometric centers of amino acid residues involved in the interaction with the reference ligands were calculated (Table 1). The dimensions of the search area were chosen so that all amino acid residues involved in the interaction with the ligand were completely inside it, with a margin of 20 angstroms in each dimension (x;y;z) for the possibility of unimpeded rotation of the ligand. Subsequently, the obtained results were used as settings for docking with Vina software.

Thus, based on the results of analysis of literature data and using visualization tools, the centers and sizes of the search area were determined for molecular docking with receptor models. In addition, positions of amino acid residues that form binding pockets were determined for ligands that are reference for these targets. These data were used in the next stage of the study to set up docking launches and interpret its results.

Table 1.

Search area and positions of target amino acid residues involved in the interaction with the reference ligand

Табл. 1.

Область поиска и позиции аминокислотных остатков мишени, участвующих во взаимодействии с референтными лигандом

PDB ID	Receptor	Reference ligand	Coordinates (x;y;z) and size of the search area, Å	Positions of target amino acid residues involved in the interaction with the reference ligand
6A93	5-HT_{2A}	risperidone (inverse agonist)	(16.18;-0.39;18.56) 44*38,7*41	139B, 151B, 156B, 336B, 339B, 362B, 370B, 340B, 155B
6DRY	5-HT_{2B}	methylergonovine (agonist)	(-25,17;-16,55;8,78) 36,6*36,8*37,7	136A, 209A, 217A, 340A, 366A, 341A, 135A
6BQH	5-HT_{2C}	ritanserin (antagonist)	(38,8;30,40;53,84) 43,6*41,3*41,4	130A, 142A, 222A, 223A, 328A, 358A, 324A, 214A, 134A

Docking of cyclic peptide libraries and selection of the most perspective compounds

The initial library of cyclic peptides CXXC was docked. The number of ligands was 462 small molecules. The PScore parameter for each "posture" of docking within one run indirectly indicated the localization of the ligand-target binding site and its remoteness from the binding region of the reference ligand, thus making it possible to estimate the biological value of the Affinity indicator for this "pose". It is obvious that binding with high affinity in the physiologically insignificant region of the receptor (outside the ligand binding pocket) is nonspecific and cannot be considered as a criterion for the selection of promising compounds.

This feature is typical for peptides with a large number of "heavy" lipophilic amino acids (phenylalanine, tyrosine, tryptophan). Their presence in the structure provides high values of scoring function for Affinity, though, the predicted sites of localization of binding to the receptor are determined in physiologically insignificant regions. This may be due to the Vina software's default scoring feature, where hydrophobic interactions have higher weighting coefficients.

Based on the docking results, 7 compounds were selected. Their indicators closely correspond to the specified criteria. The results are shown in Table 2.

It was noted that in terms of PScore.Max (A+C-B), which indirectly characterizes the selectivity between targets "A" and "C" and target "B", the best results were obtained for the peptides CRMC, CWSC and CVVC, CKTC. An important indicator for the selection of promising peptides for the formation of second-level libraries is the Affinity indicator and the ratio of the values of this indicator between targets (Sel).

Based on the selected peptides, 7 second-level libraries of the YCXXCY type were generated and docked with the previously selected targets. The selection strategy assumed an increase in selectivity in level 2 libraries. The research results are presented in Table 3.

It was found that modifications to the CRMC, CWSC and CVVC libraries did not allow the identification of compounds that fully met the selection criteria. When analyzing the results of docking of other libraries, a number of derivatives were noted that met the selection criteria and exceeded the parent compounds in terms of selectivity between targets and the calculated binding energy. The peptide structures FCKTCa, wCfWCY, VCffCG, WCWACA were selected as the most promising.

Table 2.

Results of docking of the starting library of cyclic peptides CXXC with targets A, B and C, selected according to the specified criteria

Табл. 2.

Результаты докинга стартовой библиотеки циклических пептидов CXXC с мишенями A, B и C, отобранные по соответствию заданным критериям

Peptide ligand	Minimal among all "poses" (PScore.Max)				Affinity for docking pose with PScore.Max (Affinity.maxPScore)			
	A+C-B	A	B	C	Sel	A	B	C
CRMC	100,6	58,8	18,2	60,0	33,1	-7,4	-5,0	-6,9
CWSC	99,5	58,8	18,2	58,8	44,6	-7,8	-5,6	-9,2
CVVC	94,0	58,8	18,2	53,3	46,9	-6,4	-4,7	-9,1
CKTC	74,4	40,0	18,2	52,6	48,5	-7,5	-4,4	-7,6
CfWC	66,3	30,8	20,0	55,6	40,8	-7,6	-6,4	-10,5
CffC	65,1	47,6	20,0	37,5	34,6	-10,1	-6,6	-7,6
CWAC	62,0	52,6	22,2	31,6	38,5	-7,5	-5,6	-8,7

– *Sel is an indicator reflecting the ratio of Affinity values between targets*

Table 3.

Results of docking of second-level libraries with targets A, B and C, selected according to the specified criteria

Табл. 3.

Результаты докинга библиотек второго уровня с мишенями A, B и C, отобранные по соответствию заданным критериям

Peptide ligand	Minimal among all "poses" (PScore.Max)				Affinity for docking pose with PScore.Max (Affinity.maxPScore)			
	A+C-B	A	B	C	Sel	A	B	C
CRMC library - no matching connections found								
CWSC library - no matching connections found								
CVVC library - no connections found								
CKTC library								
CKTC (initial)	74,4	40,0	18,2	52,6	48,5	-7,5	-4,4	-7,6
FCKTCa	77,1	57,1	23,5	43,5	48,5	-9,2	-6,3	-9,7
CfWC library								
CfWC (initial)	66,3	30,8	20,0	55,6	40,8	-7,6	-6,4	-10,5
wCfWCY	80,4	47,1	16,7	50,0	49,2	-9,1	-5,7	-8,7

				CffC library				
CffC (initial)	65,1	47,6	20,0	37,5	34,6	-10,1	-6,6	-7,6
VCffCG	83,3	50,0	16,7	50,0	40,8	-8,7	-6,4	-9,4
RCffCk	77,6	52,2	16,7	42,1	58,5	-8,3	-5,4	-10,1
VCffCW	75,3	37,5	18,2	56,0	42,3	-8,5	-7,7	-12,4
wCffCR	71,2	33,3	18,2	56,0	43,8	-8,2	-5,4	-8,3
FCffCW	69,4	40,0	18,2	47,6	34,6	-8,9	-7,9	-11,4
kCffCY	65,8	36,4	18,2	47,6	36,2	-8,6	-6,9	-9,9
				CWAC library				
CWAC(initial)	62,0	52,6	22,2	31,6	38,5	-7,5	-5,6	-8,7
WCWACA	94,8	58,8	16,7	52,6	40,8	-8,3	-7,2	-11,4
SCWACV	69,5	63,2	22,2	28,6	47,7	-7,4	-5,1	-9
FCWACw	66,3	30,8	16,7	52,2	48,5	-8,7	-7	-11,6
PCWACG	65,2	50,0	18,2	33,3	39,2	-8,7	-6,7	-9,8
NCWACR	64,3	52,6	13,3	25,0	38,5	-7,4	-5,8	-9,2

SUMMARY

Thus, based on the results of theoretical data research and carrying out computer modeling, the binding sites of risperidone, methylegonovine, and ritanserin with the corresponding 5-HT_2 receptor subtypes were determined. A two-stage scheme of virtual screening of cyclic peptide libraries was carried out as well. The PScore.Max and Affinity.maxPScore parameters were used to select peptide ligands for their further synthesis and study of their biological activity in vitro and in vivo.

The selected structures FCKTCa, wCfWCY, VCffCG, and WCWACA are characterized by higher selectivity for subtypes A and C of 5-HT_2 receptors compared to subtype B, which was the main selection criterion for modeling active compounds with antipsychotic activity without manifestation of possible cardiotoxic side effects.

The introduction of non-proteinogenic amino acids during the formation of an initial docking library should be considered as a promising direction for increasing the selectivity of peptide ligands to 5-$HT_{2A/C}$ receptors. This choice should be determined by the nature of interactions between the reference ligands and amino acid residues of the binding site.

It is advisable to carry out studies to confirm the obtained results in silico using the MM-GBSA, MM-PBSA and in vitro methods by measuring the characteristics of affinity (Kd or Ki).

REFERENCES

1. Palacios JM, Pazos A, Hoyer D. A short history of the 5-HT2C receptor: from the choroid plexus to depression, obesity and addiction treatment. Psychopharmacology. 2017; 234 (9–10): 1395–1418. DOI: 10.1007/s00213-017-4545-5.

2. Roth BL. Drugs and valvular heart disease. N Engl J Med. 2007; 356 (1): 6–9. DOI: 10.1056/NEJMp068265.

3. Papoian T, Jagadeesh G, Saulnier M, et al. Regulatory Forum Review*: Utility of in Vitro Secondary Pharmacology Data to Assess Risk of Drug-induced Valvular Heart Disease in Humans: Regulatory Considerations. Toxicol Pathol. 2017; 45 (3): 381–8. DOI: 10.1177/0192623317690609.

4. Morris GM, Huey R, Lindstrom W, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem. 2009; 30 (16): 2785–91. DOI: 10.1002/jcc.21256.

5. Duffy FJ, Verniere M, Devocelle M, et al. CycloPs: generating virtual libraries of cyclized and constrained peptides including nonnatural amino acids. J Chem Inf Model. 2011; 51 (4): 829–36. DOI: 10.1021/ci100431r.

6. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. Journal of Computational Chemistry. 2010; 31 (2): 455–61. DOI: 10.1002/jcc.21334.

7. Salentin S, Schreiber S, Haupt VJ. PLIP: fully automated protein-ligand interaction profiler. Nucleic Acids Res. 2015; 43 (W1): W443–W447. DOI: 10.1093/nar/gkv315.

8. Kimura KT, Asada H, Inoue A, et al. Structures of the 5-HT_{2A} receptor in complex with the antipsychotics risperidone and zotepine. Nat Struct Mol Biol. 2019; 26 (2): 121–8. DOI: 10.1038/s41594-018-0180-z.

9. McCorvy JD, Wacker D, Wang S, et al. Structural determinants of 5-HT_{2B} receptor activation and biased agonism. Nat Struct Mol Biol. 2018; 25 (9): 787–96. DOI: 10.1038/s41594-018-0116-7.

10. Peng Y, McCorvy JD, Harpsoe K, et al. 5-HT_{2C} Receptor Structures Reveal the Structural Basis of GPCR Polypharmacology. Cell. 2018; 172 (4): 719–30.e14. DOI: 10.1016/j.cell.2018.01.001.

11. VinaConfigBuilder. GitHub [Internet]. 2021. Available from: https://github.com/DeBob-git/VinaConfigBuilder.

ADDITIONAL INFORMATION ABOUT AUTHORS

Anastasia B. Orlova, Junior Research Fellow, State Scientific Research Testing Institute of Military Medicine of the Ministry of Defense of the Russian Federation, Saint Petersburg, Russia; e-mail: gniiivm_15@mil.ru

Alevtina M. Sventitskaya, Junior Research Fellow, State Scientific Research Testing Institute of Military Medicine of the Ministry of Defense of the Russian Federation, Saint Petersburg, Russia; e-mail: gniiivm_15@mil.ru

Nikolay G. Vengerovich, Doctor of Medicine (MD), Deputy Head of the Scientific Department, State Scientific Research Testing Institute of Military Medicine of the Ministry of Defense of the Russian Federation, Saint Petersburg, Russia; Professor at the Industrial Ecology Department, Saint Petersburg State Chemical and Pharmaceutical University, Saint Petersburg, Russia; e-mail: nikolai.vengerovich@pharminnotech.com

Aleksandr S. Nikiforov, D.Sc. in Biology, Senior Researcher, State Scientific Research Testing Institute of Military Medicine of the Ministry of Defense of the Russian Federation, Saint Petersburg, Russia; e-mail: gniiivm_15@mil.ru

Igor M. Ivanov, Ph.D in Medicine, Head of the Scientific Department, State Scientific Research Testing Institute of Military Medicine of the Ministry of Defense of the Russian Federation, Saint Petersburg, Russia; e-mail: gniiivm_15@mil.ru

Ylia A. Proshina, Research Fellow of the Scientific Department, State Scientific Research Testing Institute of Military Medicine of the Ministry of Defense of the Russian Federation, Saint Petersburg, Russia; e-mail: gniiivm_15@mil.ru

ДОПОЛНИТЕЛЬНЫЕ СВЕДЕНИЯ ОБ АВТОРАХ

Анастасия Борисовна Орлова, младший научный сотрудник Государственного научно-исследовательского испытательного института военной медицины Министерства обороны Российской Федерации, Санкт-Петербург, Россия; e-mail: gniiivm_15@mil.ru

Алевтина Митрофановна Свентицкая, младший научный сотрудник Государственного научно-исследовательского испытательного института военной медицины Министерства обороны Российской Федерации, Санкт-Петербург, Россия; e-mail: gniiivm_15@mil.ru

Николай Григорьевич Венгерович, д-р мед. наук, заместитель начальника научного отдела Государственного научно-исследовательского испытательного института военной медицины Министерства обороны Российской Федерации, Санкт-Петербург, Россия; профессор кафедры промышленной экологии Санкт-Петербургского государственного химико-фармацевтического университета Министерства здравоохранения Российской Федерации, Санкт-Петербург, Россия; e-mail: nikolai.vengerovich@pharminnotech.com

Александр Сергеевич Никифоров, д-р биол. наук, ведущий научный сотрудник Государственного научно-исследовательского испытательного института военной медицины Министерства обороны Российской Федерации, Санкт-Петербург, Россия; e-mail: gniiivm_15@mil.ru

Игорь Михайлович Иванов, канд. мед. наук, начальник научного отдела Государственного научно-исследовательского испытательного института военной медицины Министерства обороны Российской Федерации, Санкт-Петербург, Россия; e-mail: gniiivm_15@mil.ru

Юлия Александровна Прошина, научный сотрудник научно-исследовательского отдела Государственного научно-исследовательского испытательного института военной медицины Министерства обороны Российской Федерации, Санкт-Петербург, Россия; e-mail: gniiivm_15@mil.ru

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Докинг высокоселективных пептидных лигандов 5-$HT_{2A/C}$-рецепторов с антипсихотической активностью

©2021. А.Б. Орлова[1*], А.М. Свентицкая[1], Н.Г. Венгерович[1, 2], А.С. Никифоров[1], И.М. Иванов[1], Ю.А. Прошина[1]

[1] Государственный научно-исследовательский испытательный институт военной медицины Министерства обороны Российской Федерации, Санкт Петербург, Россия

[2] Санкт-Петербургский государственный химико-фармацевтический университет Министерства здравоохранения Российской Федерации, Санкт Петербург, Россия

* e-mail: gniiivm_15@mil.ru
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Поиск новых лигандов, селективных для различных подтипов 5-HT_2-рецепторов, представляет собой важную научно-практическую задачу для экспериментальной психофармакологии и клинической медицины. Большинство существующих антагонистов 5-HT_{2A}- и 5-HT_{2C}-подтипов обладают необходимыми противотревожными и антипсихотическими свойствами. При этом они частично селективны к 5-HT_{2B}-рецепторам, активация которых приводит к кардиотоксичным побочным эффектам, что существенно ограничивает клиническое применение данных лекарственных средств.

Для поиска новых высокоселективных лигандов 5-$HT_{2A/C}$-рецепторов предложен алгоритм проведения скрининга in silico с использованием показателей PScore.Max и Affinity.maxPScore, учитывающих сродство низкомолекулярных соединений к каждому подтипу 5-HT_2-рецепторов. В качестве новых перспективных лекарственных средств с антипсихотической активностью рассматриваются циклические физиологически активные вещества пептидной природы. На основе библиотеки CXXC, за счет наращивания пептидной цепи, для дальнейших исследований in vitro отобран ряд циклопептидов с высокой селективностью структуры к целевым сайтам связывания.

Также установлено, что, в качестве перспективных направлений повышения селективности пептидных лигандов к 5-$HT_{2A/C}$-рецепторам, следует рассматривать при формировании стартовой библиотеки докинга введение непротеиногенных аминокислот, выбор которых будет обусловлен природой взаимодействий между референтными лигандами и аминокислотными остатками сайта связывания.

КЛЮЧЕВЫЕ СЛОВА: серотонин; HT_2-рецепторы; HT_{2A}-рецепторы; HT_{2C}-рецепторы; докинг; пептиды; нейропептиды; антипсихотики