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COMPARATIVE STUDY OF THE INTERACTION OF NEUROTRANSMITTERS DOPAMINE AND SEROTONIN WITH DNA

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Comparative study of the interaction of neurotransmitters dopamine and serotonin with DNA has been carried out, using the methods of ultraviolet melting, as well as absorption and fluorescence spectroscopies. The obtained results reveal that both ligands immediately bind to DNA, meanwhile serotonin stabilizes the double-stranded structure of the latter stronger, than dopamine. At the binding to DNA the similar fluorescence quenching of both neurotransmitters is observed. On the other hand, the absorption properties of the complexes dopamine–DNA and serotonin–DNA significantly differ: at the formation of dopamine complexes with DNA, hypochromic effect occurs, at the formation of serotonin – hyperchromic effect.

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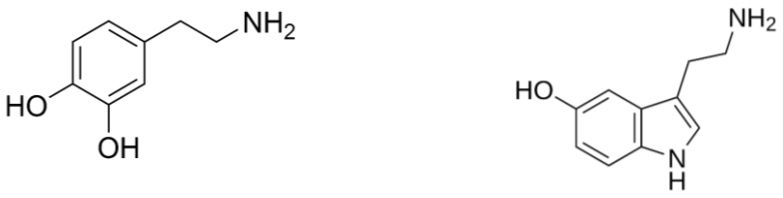
***Keywords*:** dopamine, serotonin, UV-melting, absorption spectroscopy, fluorescence spectroscopy.

Introduction. In organism functioning regulation of animals and human two macro-systems participate – neuron network and chemical compounds, particularly, hormones and neurotransmitters. From this point of view, the human organism regulation is realized due to the information transition through the nervous network that is formed between nervous fibers, which have a final length and communicate with each other via synapses – electrical and chemical. In this aspect the relevant part of neuron-neuron signaling is implemented throughout the chemical synapses, where the neurotransmitters play the crucial role. Among the important neurotransmitters in the brain, one can mention dopamine (Fig. 1) – hormone and neurotransmitter in the central nervous system, the deviation level of which may invoke different disorders, including Parkinson's disease, schizophrenia, etc. Being catecholamine derivatives, dopamine plays an important role in motivation, excitation as well as movement function control. Obviously, in the human brain, dopamine concentration should be monitored [1–5].

For dopamine level controlling, biosensor approach became one of the monitoring pathways, based on the aptamer application of nucleic acids as a matrix for dopamine [2]. Affinity of these aptamers to dopamine based on the dissociation constant was determined to be equal to 1.6 *M* [1]. Practically, the interaction of dopamine neurotransmitter with the cell chief macromolecule – DNA was revealed.

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Another important neurotransmitter in the organism is serotonin (Fig. 1) that is tryptophan derivative. This neurotransmitter affects the mood, starvation, aggressiveness, sleep and consciousness.



Dopamine Serotonin

Fig. 1. Dopamine and serotonin structure.

Serotonin toxicity results in anxiety that is called serotonin syndrome – drug-induced appearance of enhanced intra-synaptic level of serotonin. It was also revealed that serotonin possesses pro-oxidant action, revealed on the basis of deoxyribose. Literature data show that serotonin, as dopamine, can interact with DNA and control its activity [6–12]. However, despite the existing literature data, there is one gap on molecular mechanisms of the interaction of the mentioned neurotransmitters with DNA.

The goal of this work is the study of the binding mechanisms of dopamine and serotonin with DNA by the methods of ultraviolet (UV) melting, fluorescence and absorption spectroscopies.

Materials and Methods.

***Preparations*.** Dopamine hydrochloride (CAS No. 62-37-7; "Merck", Germany), serotonin (CAS Number: 50-67-9 "Sigma-Aldrich", USA), Calf Thymus DNA (73049-39-5, "Sigma-Aldrich", USA) were used in the experiments. All reagents were used without further purification. Stock solutions were prepared in standard salt-citrate (SSC) solution with an ionic strength of 0.02 *M*. Serotonin was dissolved in 0.1×SSC, at pH ~4.0.

***Equipment*.** Fluorescence studies were carried out on spectrofluorometer Agilent Cary Eclipse Fluorescence Spectrometer (USA). UV-melting and absorption studies were carried out on spectrophotometer UV-VIS Perkin Elmer Lambda 365.

***UV-Melting*.** The melting of DNA and its complexes with neurotransmitters was carried out at the wavelength λ = 260 *nm* on UV-VIS spectrophotometers Perkin Elmer Lambda 365. Increment of temperature was equal to 0.5°C, registration of the absorption values was carried out automatically, throughout 2 *min*. DNA concentration was equal to $\sim 6 \cdot 10^{-5}$ *M*, concentration ratio of the complexes r = [neurotransmitter] / [DNA] changed in the interval $0.1 \le r \le 1.0$. Based on the absorptions, the value $1-\theta$ (denaturation degree of DNA and its complexes with ligand) was calculated, according to the formula:

$$1 - \theta = \frac{A - A_0}{A_{\max} - A_0},$$

where A_0 is the sample absorption, when DNA state is native; A_{max} is the absorption at totally denatured state of DNA; A is the absorption of samples at the given

temperature. The temperature was measured in quartz cuvettes; the thermosensor was inserted in hermetically closing plug. Temperature error in cuvettes was almost 0.01°C.

Spectroscopic Measurements. Spectroscopic measurements were carried out at the temperature 25°C. Purity of double-stranded DNA solutions was checked by the absorption method at 260 *nm* and 280 *nm*. Absorbance ratio A_{260}/A_{280} was equal to ~1.80, which corresponds to purity standard of DNA solutions. Preparation concentrations were determined spectrophotometrically, using the following coefficients of extinction: ε_{280}=2550 $M^{-1}\cdot cm^{-1}$ for dopamine hydrochloride [13], ε_{276} = 5500 $M^{-1}\cdot cm^{-1}$ for serotonin, ε_{260} = 6600 $M^{-1}\cdot cm^{-1}$ for DNA [14].

Fluorescence spectra of dopamine–DNA complexes were recorded in the wavelength range of 290–450 *nm* upon excitation at 280 *nm*; at fluorescence studies the fluorescence spectra of the complexes neurotransmitter–DNA were registered in the wavelength change interval 280 ≤ λ ≤ 450 *nm*, at excitation wavelength λ_{exit} = 270 *nm*. The values of fluorescence intensity changes of the complexes were registered at each ratio up to *r* = neurotransmitter/DNA, at which these changes become insignificant.

At the absorption studies, the absorption spectra of dopamine and serotonin complexes with DNA were registered in the wavelength change interval 240 ≤ λ ≤ 400 *nm*. The curves, based on absorption and fluorescence spectra, as well as dependence of melting temperature on neurotransmitter/DNA concentration ratio were elaborated, using the program Origin 8.5.

The experimental error does not exceed 5–10%.

Results and Discussion. UV-melting method, being relatively simple, at the studies on ligand interaction with nucleic acids (NA), possesses high information capacity to reveal whether the given compound binds to NA or not. Moreover, this method permits revealing the effect of this compound on the structure of the latter, if the ligand destabilizes or stabilizes the biomacromolecule native structure [15–19]. From this point of view, to study the binding possibility of different neurotransmitters with intra- and extra-cellular biomacromolecules, UV-melting method may become a good instrument.

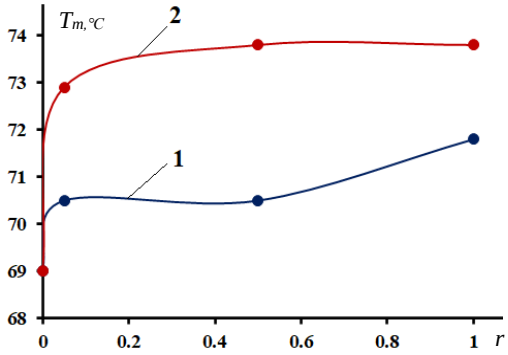


Fig. 2. Dependence curves of melting temperature (ΔT_m) on *r* for the complexes of dopamine (1) and serotonin (2) with DNA.

Using this method, the interaction of neurotransmitters dopamine and serotonin with DNA has been studied. Particularly, DNA melting curves were obtained in both presence and absence of these neurotransmitters, at different concentration ratios of the latters. It should be mentioned that the melting curves in

the presence of dopamine and serotonin were shifted toward high temperatures, which indicates that both neurotransmitters not only bind to DNA, but also stabilize its double-stranded structure. Based on these curves, the values of the melting temperatures were determined and the dependence curves of T_m on r were constructed, presented in Fig. 2. As it is obvious from the presented figure, at the same values of r, the stabilizing effect of serotonin is more pronounced, than that of dopamine. On the other hand, these curves are similar, despite the fact that these compounds differ by the structure, since dopamine is tyrosine derivative, while serotonin is tryptophan derivative [13, 14].

In the work [14] it was shown that having present the phenol OH-group and azote atoms in indole ring, serotonin participates in formation of hydrogen bonds with atoms O and N of DNA azotic bases in minor groove that is more hydrophobic (groove binding). However, it should not be excluded that serotonin, being aromatic compound, can interact with DNA nucleotide pairs through π-π contacts as well, as intercalating compounds. Analogous binding mechanisms were revealed for dopamine as well [13]. However, we assume that different curves of T_m dependencies on r are due to the affinity degree of the mentioned neurotransmitters toward DNA, which is higher for serotonin, compared to dopamine [13, 14].

In the Fig. 3, the curves of maxima of fluorescence spectra of the complexes of dopamine (curve 1) and serotonin (curve 2) with DNA were presented, depending on concentration of the mentioned neurotransmitters. From the presented figure, it is obvious that these curves decrease, depending on the increasing concentrations of dopamine and serotonin, which indicates that the binding with DNA results in fluorescence quenching of both neurotransmitters. From the other hand, despite the difference of their chemical structures, the fluorescence properties, while binding to DNA, are similar, which indicates that both neurotransmitters perform the same interaction mechanism. It should be mentioned that dopamine and serotonin contain aromatic ring with π-electronic system and are in protonated (cationic) form.

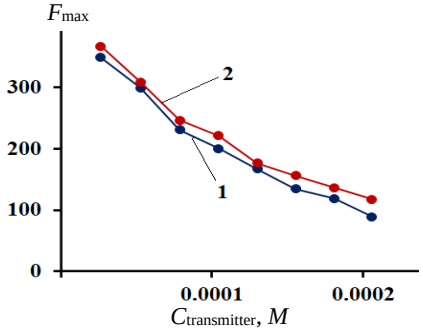


Fig. 3. Curves of maxima dependencies of dopamine (1) and serotonin (2) fluorescence on the neurotransmitter concentration.

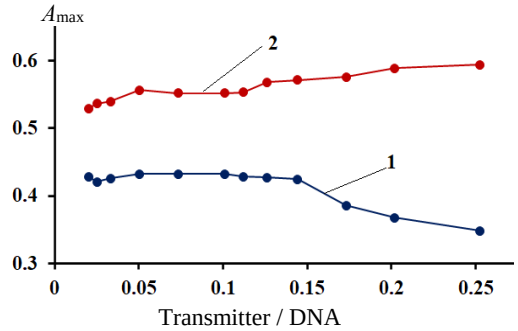


Fig. 4. Dependence curves of absorption maxima of dopamine (1) and serotonin (2) on the concentration ratio transmitter/DNA.

In the work [13] it was shown that dopamine fluorescence quenching, at the binding to DNA, is dynamic. It indicates that the quenching occurs at collision of excited molecules of neurotransmitter with DNA. We assume that analogous phenomenon takes place for serotonin. In this process, the electrostatic interaction

between molecules of neurotransmitter and DNA plays an important role, which enhances the probability of collision of excited fluorophores with nucleic acid, in consequence of which molecules of the mentioned neurotransmitters are absorbed from the external side of sugar-phosphate backbone of NA, with the further translocation toward more hydrophobic intramolecular regions of the latter. It is obvious that the polarity changes of the immediate surrounding of dopamine and serotonin molecules should affect the intensity of their fluorescence. On this basis, we conclude that both neurotransmitters perform similar interaction mechanisms with DNA and, as it was shown in [13–15], bind to it mainly by intercalation and groove binding modes.

At intercalation mode, π-electronic system of molecules of these ligands plays an important role, which at the excitation is able to transit additional energy to π-electronic system of nucleotide pairs of DNA by non-participatory mechanism, due to which the fluorescence intensity decreases. By non-participatory mechanism, the excitation energy is transited by the groove binding mode as well, which decreases the intensity, due to which the fluorescence quenching is practically similar at dopamine and serotonin binding.

In the Fig. 4, the curves of maxima of the absorption spectra of the complexes of these neurotransmitters with DNA, depending on the concentration ratio transmitter/DNA (r) are presented. From the presented Fig. 4, it is obvious that this dependence for dopamine (curve 1) changes less at low concentrations of the transmitter, but at relatively high values r decreases.

Taking into account that dopamine (as serotonin) absorbs practically in the same interval of wavelength change as DNA (in the interval 200–300 *nm*, with maximum at ~270 *nm*), the absorption decreasing effect is surprising at dopamine increasing concentrations. Meanwhile, the absorption of dopamine–DNA systems is not the sum of absorption of separate components, which indicates the formation of the complexes because of which, the additive increase of dopamine and DNA absorptions are compensated by high hypochromic effect. For serotonin, a little increase of this curve is observed. Despite this fact, for serotonin the value of the absorption system serotonin–DNA is much less from the sum of their separate absorptions. In contrast to fluorescence properties, it is obvious that the optic ones of these neurotransmitters differ. We assume that the localization of these neurotransmitter molecules on DNA binding sites differently affect the oscillation force due to the chromophore electronic state changes of these ligands. Most apparently, the revealed spectral characteristics are resulted from the similar modes in relation of dopamine and serotonin binding process to DNA, which variously affects the electronic state of their chromophores.

Therefore, the obtained data indicate that dopamine and serotonin can immediately bind to DNA, which is revealed based on the spectroscopic studies and results of UV-melting.

Conclusion. Summarizing the obtained data, the general model of dopamine and serotonin binding description to DNA is possible:

– electrostatic binding of these neurotransmitters to DNA;

– intramolecular translocation of their aromatic chromophore in DNA;

– similar mechanisms of binding of these ligands with DNA, which, in turn, results in similarity of fluorescence quenching;

– various mechanisms of change of their electronic state at the binding to DNA, which results in different absorption of their complexes with DNA.

In the given aspect, we assume that at the electrostatic mode, dopamine and serotonin binding with DNA is practically similar – adsorption on sugar-phosphate backbone from external side, due to which the chromophore groups of ligands still have relatively high freedom degree and behave as free molecules. At intramolecular localization in DNA, the freedom degree of their chromophores changes and the chromophores immediately contact with nucleotide pairs and transit part of excited energy of the latters by non-participatory mechanism [13–15]. It results in similarity of their fluorescence quenching. However, the specific catechol structure of dopamine turns its chromophore more sensitive to electronic interaction with DNA bases, in the result of which along with aforementioned binding mechanisms (electrostatic, intercalation and groove-binding), donor-acceptor charge-transfer may occur at the interaction with bases, which significantly decreases dopamine oscillation force in the complex with DNA in UV region of their absorption. In the case of serotonin molecule localization in DNA, the change of its electronic system differs from that of dopamine, due to which the oscillation force decrease is much less, resulting in little hyperchromic effect.

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ԴՆԹ-Ի ՀԵՏ ՄԻՋՆՈՐԴԱՆՅՈՒԹԵՐ ԴՈՖԱՄԻՆԻ ԵՎ ՍԵՐՈՏՈՆԻՆԻ ՓՈԽԱԶԴԵՑՈՒԹՅԱՆ ՀԱՄԵՄԱՏԱԿԱՆ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆԸ

Իրականացվել է ԴՆԹ-ի հետ միջնորդանյութեր դոֆամինի և սերոտոնինի փոխազդեցության համեմատական ուսումնասիրություն ուլտրամանուշակագույն հալման, ինչպես նաև կլանման և ֆլուորեսցենտային սպեկտրալուսաչափական եղանակներով: Ստացված արդյունքները բացահայտում են, որ երկու լիգանդներն էլ անմիջականորեն կապվում են ԴՆԹ-ի հետ, սակայն

սերոտոնինը ավելի ուժեղ է կայունացնում վերջինիս երկշղթա կառուցվածքը, քան դոֆամինը: ԴՆԹ-ի հետ կապման դեպքում դիտվում է երկու միջնորդանյութերի ֆլուորեսցենցիայի նման մարում: Մյուս կողմից, դոֆամին-ԴՆԹ և սերոտոնին-ԴՆԹ կոմպլեքսների կլանման հատկությունները էականորեն տարբերվում են. ԴՆԹ-ի հետ դոֆամինի կոմպլեքսագոյացման դեպքում տեղի ունի հիպոքրոմային, իսկ սերոտոնինի դեպքում՝ հիպերքրոմային էֆեկտ:

А. В. ВАРДАНЯН

СРАВНИТЕЛЬНОЕ ИССЛЕДОВАНИЕ ВЗАИМОДЕЙСТВИЯ НЕЙРОТРАНСМИТТЕРОВ ДОФАМИНА И СЕРОТОНИНА С ДНК

Проведено сравнительное исследование взаимодействия нейротрансмиттеров дофамина и серотонина с ДНК методами ультрафиолетового плавления, а также флуоресцентной и абсорбционной спектроскопии. Полученные результаты выявили, что оба лиганда непосредственно связываются с ДНК, однако серотонин намного сильнее, чем дофамин стабилизирует двухцепочечную структуру последней. При связывании с ДНК наблюдается схожее тушение флуоресцнеции обоих нейромедиаторов. С другой стороны, абсорбционные свойства комплексов дофамин–ДНК и серотонин–ДНК существенно различаются: при образовании комплексов дофамина с ДНК имеет место гипохромный, а в случае серотонина – гиперхромный эффекты.