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AROMATIC HYDROCARBONS OF *Arthropodae* SPECIES: MECHANISMS OF ACTION ON BIOLOGICAL MEMBRANES AND PERSPECTIVES OF BIOMEDICAL APPLICATION

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The work was aimed to summarize the results describing the mechanisms of interaction of some aromatic hydrocarbons, isolated from *Arthropodae*, with biological membranes. Neurophysiological properties of the substances obtained from spider venoms, derivatives of phenol and indole with polyamine substituents, were studied by the method of transmembrane electrical currents registration in voltage clamp mode. Their influence was revealed as a result of chemo sensitive ionic currents characteristics changes due to the action of these substances on the membranes of rat hippocampal neurons. All of the studied substances were antagonists of glutamate channel-receptor complexes. Their blocking activity characteristics were examined as follows: caused reversible and irreversible blocking effects, the effects dependence on membrane holding potential, difference of their action on activated and inactivated receptors, kinetics of blocking actions, type of antagonism. Antagonists amphiphilic properties and the role of aromatic groups and polyamine substituents during interaction with the membranes were analyzed. The results of such analysis were accepted as a basis for development of physical model of artificial memory device. Principles of its work were explained as well. The results regarding the influence mechanisms of the studied substances on biological membranes were summarized. Some characteristics and functioning peculiarities of the suggested elements of storage devices were discussed. The properties of the proposed substances-analogues meet a number of requirements for the elements of such nano-devices.

Key words: toxins, receptor antagonists, transmembrane electric currents, *Arthropodae*, artificial memory, bioinformatics.

Natural toxic substances are important tools for scientific investigations and *Arthropodae* toxins take great attention of contemporary researchers, pharmacologists, ecologists, etc. [1–29]. The results of investigations of electrophysiological stidies of some *Araneidae* venoms and toxins [30–99], namely spider species *Nephila clavata* and *Argiope lobate* are discussed. For today, the results of study of some toxins from *Arthropodae* (including *Araneidae* toxins), as well as other similar phenol and indole derivatives, were applied in agriculture [6, 8, 14, 17], in the methods of ecological monitoring of environment [76–90], etc.

The results of investigation of six types of antagonists were suggested in this article, namely integral venom JSTX-V with its main active component toxin JSTX-3 from *Nephila clavata*, integral venom AR-V with three toxins: argiopin AR (main active component), argiopinin 1 (ARN-1), argiopinin 2 (ARN-2) from *Argiope lobata*. All studied chemical substances were derivatives of phenol (JSTX-3, AR) or indole (ARN-1, ARN-2) with polyamine substituents of different length and branching (Fig. 1) [45–47]. In the Nature such substances demonstrate amphyphilic properties. Their aromatic groups (phenolic or indolic) can be dissolved in hydrophobic lipid membrane, but their polyamine chains (linear or branched)

have hydrophilic properties and stick in outside solution. Such chemical structures, their composition and geometric configuration of their molecules coupled to membranes define pequliarities of such antagonists action. These actions and our attempts to use them for artificial memory construction are described below.

Experimental studies of *Arthropodae* venoms and toxins. Electrophysiological studies of these substances influences are among the most preferable methods. There are such methods among them: microelectrode studies, patch-clamp, registration of transmembrane ionic currents, etc. The influences of glutamate receptors antagonists from *N. clavata* were studied in some institutions of the world. Numerous publications were devoted to the effects of such substances on different objects as well as to the solutions of linked scientific problems [1–4, 7, 12, 13, 19–28, 99–136]. Some aromatic hydrocarbons produced by *Araneidae* are known as antagonists of glutamate channel-receptor complexes (gCRC) [40, 41, 45–47, 49–70, 92, 91, 95–99]. Because of importance of investigation results of *Araneidae* venoms and toxins, three our previous reviews were devoted to fundamental works of the authors who studied such venoms and toxins [45–47]. The studies of some foreign colleagues were observed [1–4, 7, 12, 13, 19–28, 49–70, 92, 91, 95–99] as well as our original investigations [40, 41, 45–47, 53, 69, 71–90, 125, 128–132]. Many inventions in this and linked spheres were defended by patents [111–114, 78–90, 128–134].

Experimental materials for this work were obtained in Bogomoletz Institute of Physiology of the National Academy of Sciences of Ukraine in scientific group of Prof. Krishtal O.O., Prof. Akaike N. (Japan) and other collaborators: Drs. Tsyndrenko A., Kiskin N., Klyuchko O. These researches were carried out using voltage-clamp technique in mode of

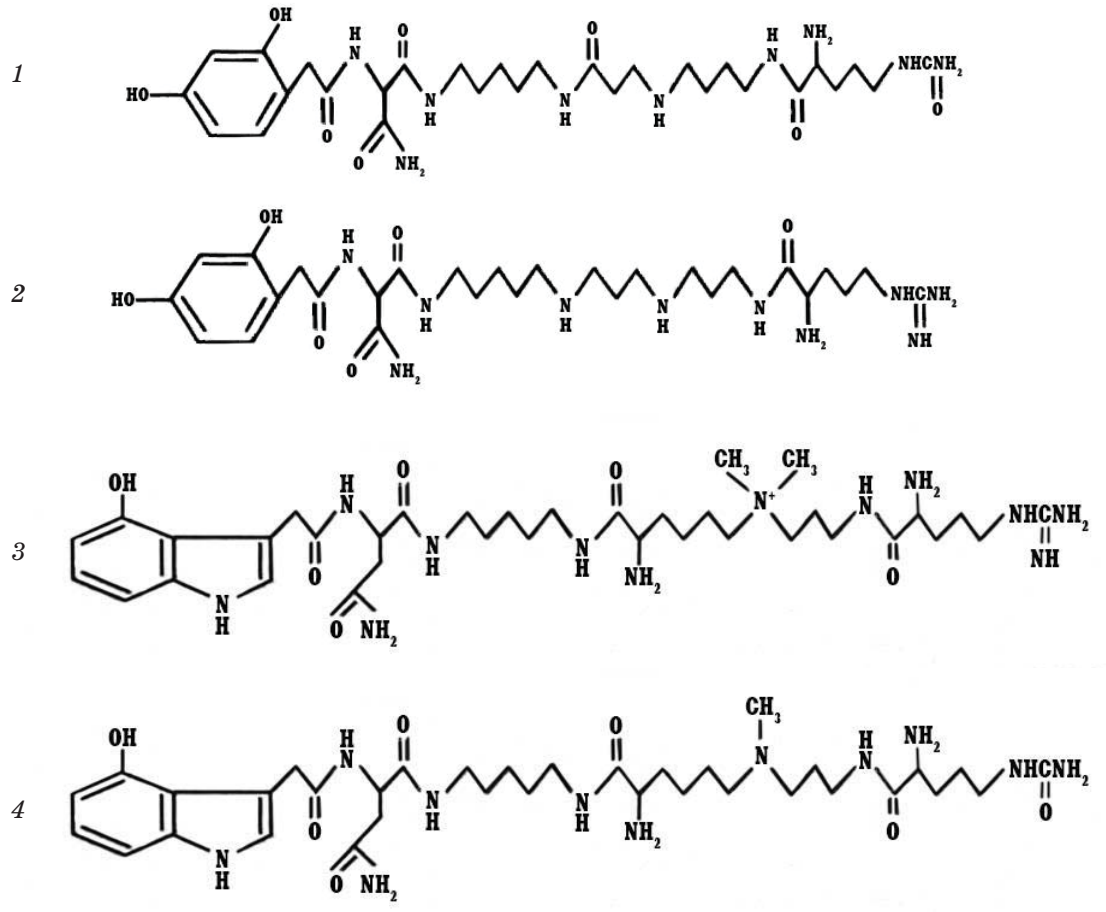


Fig. 1. **Chemical structure of studied *Araneidae* toxins** [46, 47]:
1 — JSTX-3; *2* — argiopin AR; *3* — ARN-1; *4* — ARN-2;
1 — from *Nephila clavata*; *2–4* — from *Argiope lobata*

holding potential at hippocampal membrane. The series of experiments were performed on cell membranes of pyramidal neurons from CA1 zone of hippocampus, isolated from the rats in age 4–7 days. The same neurons were taken from newborn rats and survived after dissociation during 4–5 days in culture conditions. The reactions of gCRC blocking by these toxins were well studied using solution sodium salt of kainic acid (KK). Sodium salt of kainic acid is the agonis of gCRC, but it causes non-inactivated transmembrane electric currents (KK-activated electric currents). That is why the kinetic characteristics of blocking (modifying) effects of antagonists could be studied well on the background of such non-desensitized KK responces as exponential dependencies. They had well registered numerical characteristics. Some results of these works were given below as well as their summarizing, analysis and comparison with the data of other authors.

***Araneidae* venoms and toxins blocking action.** Results of our experiments demonstrated that all studied substances (JSTX-V, JSTX-3, AR-V, AR, ARN-1, ARN-2) had the same properties. They suppressed significantly (sometimes to zero) the amplitudes of transmembrane ionic currents activated by glutamate (GLU), kainate (KK), and quisqualate (QL) after their application to the membranes of rat hippocampal neurons under the voltage-clamp conditions. These antagonists had not affected the kinetics of activation and desensitization (in case of GLU, QL). It can be supposed that this blocking effect was due to these antagonists blocking influence on glutamate receptor-ionophore complexes with further decrease of membrane conductivity, because GLU, KK and QL activated one (the same) type of receptors in rat hippocampal neuronal membranes [69]. This effect was described already by Ukrainian and foreign authors [47, 53, 58, 59, 63–69].

Any of the investigated substances had not blocked the excitatory transmembrane ionic currents. They also did not affect ionic currents activated in the membranes by glycine and gamma-aminobutyric acid (GABA). These results coincided with those obtained previously [54]. The results confirmed that conclusion that blocking of signal transmission in complex systems by *Araneidae* toxins (slices, neuromuscular preparations) had happen not due to the induction of GABA and glycine-activating conductivity, but under the action on glutamate receptors.

An interesting fact should be emphasized. Each of studied toxins reduced equally the amplitudes of both GLU- and KK-activated ionic currents in our experiments. This might be the evidence that GLU, KK, QL activeted one type of glutamate receptors in rat hippocampal membranes [69].

Mechanisms of the studied toxins actions. In this subchapter the mechanisms of *Araneidae* toxins influences on gCRC are represented.

A. Antagonists with reversible and irreversible effects among studied substances. The effects caused by all studied antagonists could not be called completely reversible according to the results of our experiments (Table). JSTX-V had the most expressed properties as irreversible antagonist of GLU- and KK-activating currents among other studied substances. The main active component of this venom, toxin JSTX-3 formed weakly dissociated complexes with the membrane. It looks like that JSTX-V contains not only

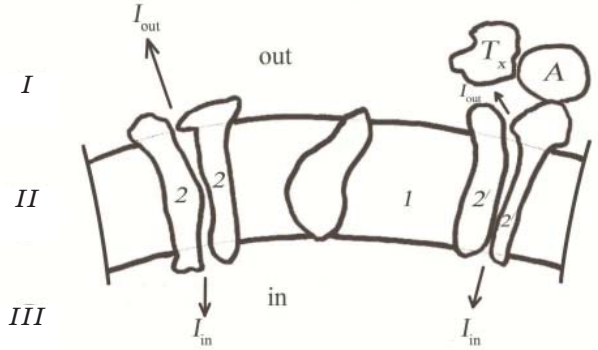


Fig. 2. **Schematic description of *Araneidae* toxin influence on gCRC:**
1 — membrane; *2* — protein — transmembrane channel; *3* — gCRC;
A — molecule of agonist (Glu, KK); T_x — toxin molecule.
Arrows indicate transmembrane electric currents (*I*): I_{out} — outside; I_{in} — inside the membrane;
I — solution outside the membrane; II — lipid membrane; III — solution inside the membrane

JSTX-3, but other toxins as well, that formed non-dissociating complexes with glutamate channel-receptor complexes (gCRC), similar to irreversible acting toxins from *A. lobata* venom.

Other studied toxins were at intermediate position between JSTX-V and AR according to the strength of binding to the membrane. The aforesaid is true for the recovery of ionic currents after the first removing of studied antagonists by "washing" in Ringer solution. Repeated applications of toxins revealed another feature of their irreversible action. During the repeated applications all toxins (including AR), caused stronger effect: the degree of blocking increased, the degree of washing decreased. After 2–3 repeating of blocking-washing procedures the cells died. Similar results were obtained on neuromuscular junctions of *Arthropods*: with repeated applications of AR, a deeper blocking effect was registered. Thus, all the toxins without exception caused substantially irreversible effect. Although for different toxins these effects were expressed in different degrees (Table).

B. Effects of toxins depended on holding transmembrane potential. According to the results of our experiments, the action of all studied substances in more or less degree depended on holding transmembrane potential. Shifting of holding potential level toward the depolarization did not caused dramatic changes in venoms and toxins properties. Thier blocking properties were the same. However, their significantly weakened action was registered due to the changes of following characteristics. 1. The degree of blocking decreased and degree of washing increased. Even in case of JSTX-V which never was washed under the holding potential equal to −100 mV, while potential level was shifted to 0 mV— a slight tendency for currents recovery was registered. 2. The velocity of blocking decreased. Such dependence of blocking properties on potential was considered to be the evidence that namely the ion channel of gCRC channel-receptor complex was blocked [92, 93]. However, it is not possible to argue that studied *Araneidae* toxins should be attributed to blockers of channel type only, since these effects were slightly expressed. Perhaps that is why this slight effect was not registered in the experiments on more complex objects, for example, on *Arthropodae* neuromuscular junctions. Basing on these results, previously it had been argued that AR was not a blocker of channel-type [54, 62, 92, 93]

C. Antagonists from Araneidae cause different effects on activated and inactivated receptor. All studied toxins from *A. lobata* — AR, ARN-1, and ARN-2 blocked chemo-activated currents by binding to the glutamate receptor of gCRC in activated state (Fig. 3, 4). Similar results were obtained in previous experiments with other toxins from venom of *A. lobata*. The data of other authors demonstrated also that the main mechanism of AR action was blocking the open ion channel [59, 62]. Binding AR to a closed channel according to these data was not a dominant mechanism. It caused allosteric initiation of the chain of processes. Such binding AR to a closed channel resulted at first the channel opening with subsequent it blocking according to the main mechanism. Blocking of closed ion channels were not registered in our experiments with the toxins AR, ARN-1, ARN-2. However, such effects could not be completely excluded (Fig. 3, 4). However, if it was, it could be demonstrated that binding of toxins to this gCRC configuration was significantly less visible.

Perhaps the binding of *Araneidae* toxins to the activated glutamate receptor is the most spread in the Nature. The only exception, according to our data, was JSTX-3 toxin. It was able to block both open and closed GLU- and KK-activated ion channels (Fig. 5). JSTX-V demonstrated the similar property in our experiments and, probably, this

Effect	Antagonist					
	JSTX-V	JSTX-3	AR-V	AR	ARN-1	ARN-2
Currents amplitudes suppression, %	34.0	6.0	14.4	19.0	44.0	22.0
Currents amplitudes recovery, %	34.0	39.0	34.0	77.0	56.0	47.0

Note. The degrees of changes in amplitudes of transmembrane GLU- and KK-activated currents after the studied antagonists action: averaged amplitudes suppression and recovery after the antagonist removal by "washing" in normal Ringer solution [44, 47, 86].

property was defined by JSTX-3. Indeed, this property had to be visible even when all other toxins from JSTX-V would bind to gCRC in the activated state. However, how unique are the JSTX-3 properties among other ones of studied toxins it has to be demonstrated in future experiments.

D. Kinetics of action of gCRC antagonists. The actions of all venoms and toxins were characterized in our experiments by following regularity. When the concentration of antagonist in solution was increased, the velocity of blocking was increased too. The similar results were obtained for JSTX-3

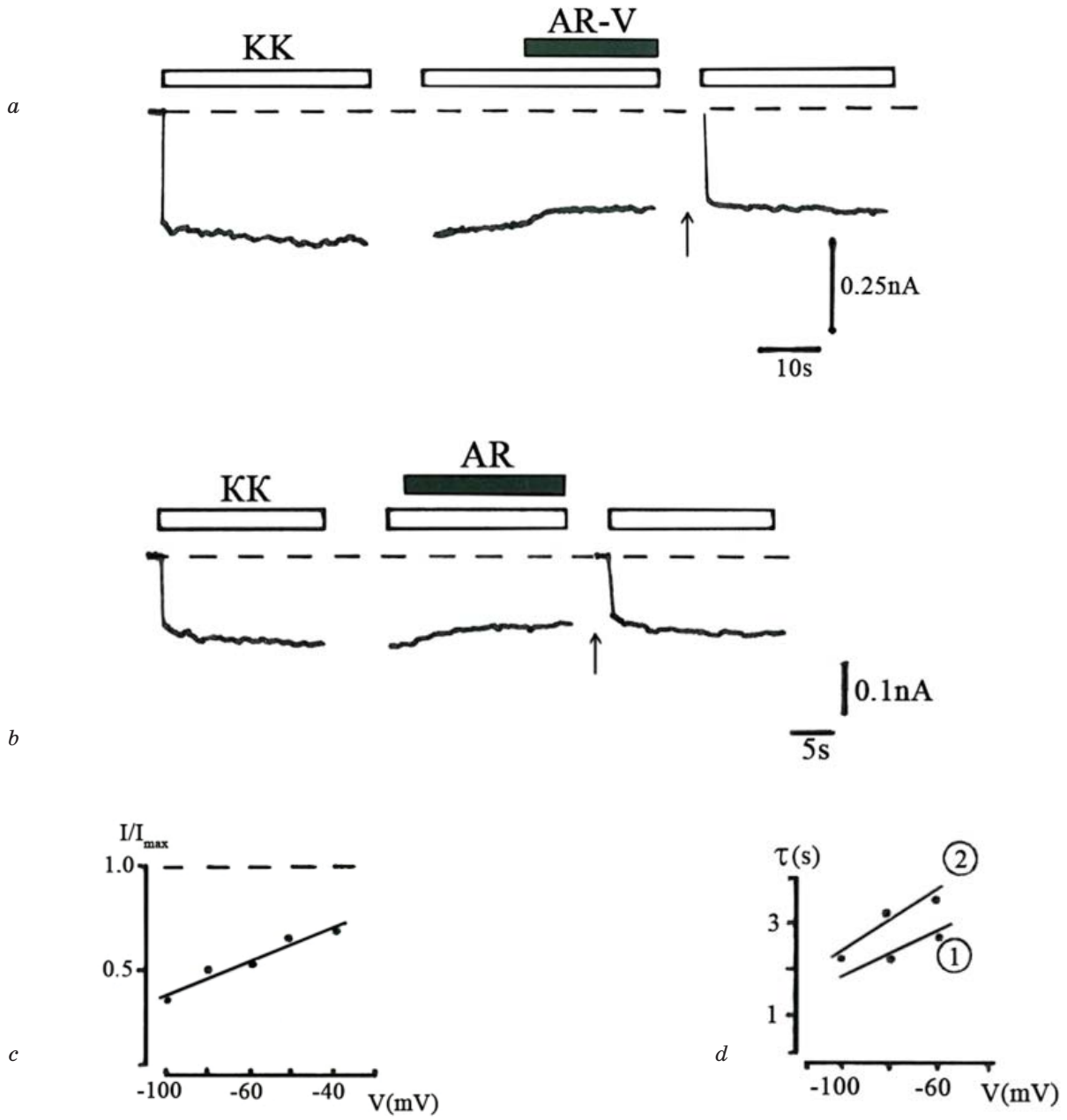


Fig. 3. **Decrease of blocking effects of AR-V (a) and AR (b) with the decrease of the levels of holding potentials [81, 83]:**
KK concentration — 1 mmol/l; AR-V — 10^{-4} g/ml; AR — $1.6 \cdot 10^{-2}$ mol/l. Durations of antagonists removal by "washing" in Ringer were 30 s (*a*), and 15 s (*b*).
Records *a*, *b* were done at two different neurons;
c — increase of amplitude of current component that was not blocked by AR with membrane depolarizing; *d* — increase of time constants of AR blocking with the decrease of holding potential; in the circles 1, 2 are slow and fast components respectively

influence on the neuromuscular junction of lobster [49] and giant squid synapse [97] as well as for AR at the neuromuscular junction of locusts [62]. However, in these works only qualitative descriptions of blocking effects of JSTX-3 depending on the concentration were done. Japanese authors were the first who started to find quantitative description of JSTX-3 concentration-effect dependence, but the interpretations of their results were ambiguous due to the complexity of experimental objects. The authors of these articles noticed that their obtained data were only approximate, since the objects were covered with a layer of connective tissues [97].

Contrary, in our experiments the object was rather simple. Registered transmembrane chemosensitive ionic currents reflected the functioning of only glutamate receptors gCRC. Therefore, the velocity of their amplitudes decrease characterized directly the velocity of glutamate receptors blocking because the toxin influenced on the steady KK-currents because KK was an agonist of gCRC too. This effect made us possible to visualize the process of toxin interaction with the receptor as well as to obtain quantitative characteristics of this process. Such kinetic characteristics were obtained for the number of substances: JSTX-V, JSTX-3, AR. Thus, a successful choice of objects and agonists enabled us to understand better the mechanisms of blocking process and toxins interaction with membrane.

Our analysis of kinetics of KK-activated ion currents blocking effects revealed that the currents decrease under the action of *Araneidae* gCRC antagonists to the new stationary levels were exponential. The blocking process was described for the first time in the works of Saito [97]. In our experiments in the case of AR, ARN-1, ARN-2, the decrease of KK-activated currents were approximated satisfactory by two exponents. IIt is an interesting coincidence, but the decline of EPSP in locusts neuromuscular junction under the action of AR was two phase [62]. With the increase of antagonists concentrations in our experiments, the value of constant rates for downtime decreased, so, this process had gone faster. As it can be seen from the figures, this dependence is linear within the studied concentrations (Fig. 3).

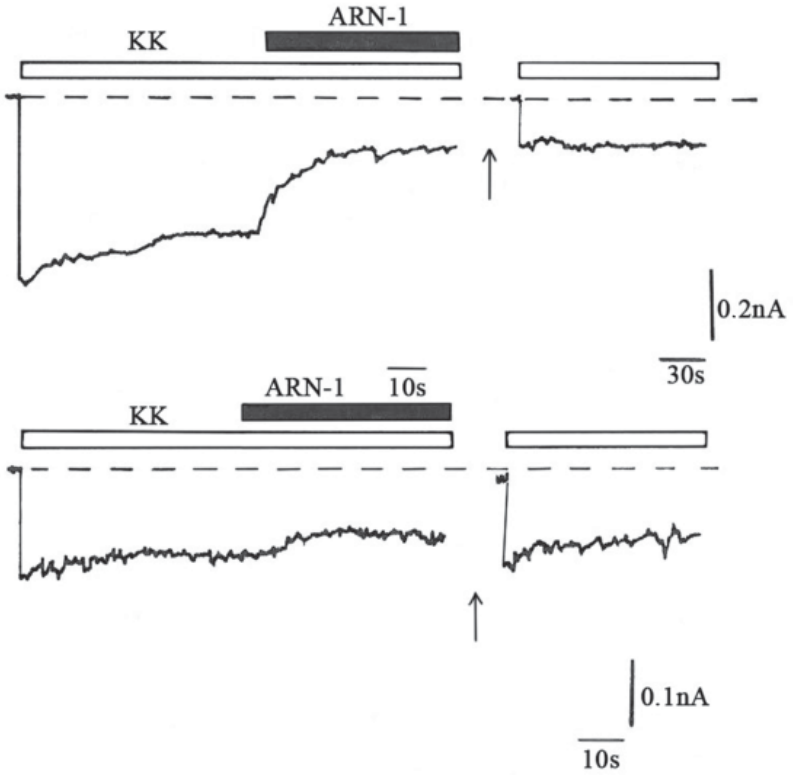


Fig. 4. **Irreversible ARN-1 block of KK-activated currents [82, 86, 87]**
During ARN-1 removal by "washing" in Ringer the response amplitudes were not restored.
In the result of repeated ARN-1 applying on the same cell the additional block was not registered.
KK concentration was 1 mmol/l; ARN-1 — $3.0 \cdot 10^{-6}$ mol/l; holding potential −100 mV;
recordings were done at one neuron both records were done at one neuron

The amplitudes of KK-activated ion currents recovery during the removal by "washing" of both JSTX-3 and AR could be described by single exponent. However, in some our experiments during "washing" of few argiopinins it was possible to distinguish two inverse rate constants for currents recovery. Perhaps the accuracy of the method did not allow us to distinguish other components of kinetics of responses recovery and obtained $1/\tau$ values reflected only approximately the true dissociation rates of antagonists. The numerical values of parameters of the kinetics of toxins blocking and washing we had already published in [44, 46, 47]. It is possible to see that toxin JSTX-3 had the lowest dissociation rate, which corresponded to its low reversibility of action. Toxin AR was characterized by the highest reversibility of action. It had also the highest dissociation rate with the receptor.

Supposed mechanism of toxins action. The studied *Araneidae* toxins influences on the glutamate- and kainate-activated currents were so similar, that the supposed mechanisms of their action were the most likely the same, or even one mechanism was realized in all cases. Basing on our obtained data, we could assume the following blocking process.

The molecule of the toxin, being near the surface of the membrane, reacted with molecular complex gCRC. In our experiments with AR, only one AR ligand was necessary for blocking of each glutamate receptor: calculated value of Hill coefficient was 0.86 in our experiments (Fig. 6).

Since studied toxins were chemically similar and they formed homologous families, we could assume that other ones might act by a single-molecular mechanism too (apparently, the same chemical reaction was going in all cases). Basing on our results, we supposed that phenol-/indole-acetatasparagine fragments of toxin molecules entered this reaction. Which groups of gCRC binded toxins? Since phenol-/indole-acetatasparagines are qualitative reagents for Fe-S protein groups [98, 99] it was natural to assume that in our case the toxins binding to the membrane were carried out through the formation of complex phenol-/indole-acetatasparagine with Fe^{3+} ion. This means that gCRC of the rat hippocampal neurons were proteids that contained the Fe-S group, similar to the gCRCs of neuromuscular invertebrate compounds [94–96]. Previously, it was shown that SH-groups were present in rat hippocampal gCRC neurons [69], but it was unclear whether these two types of groups

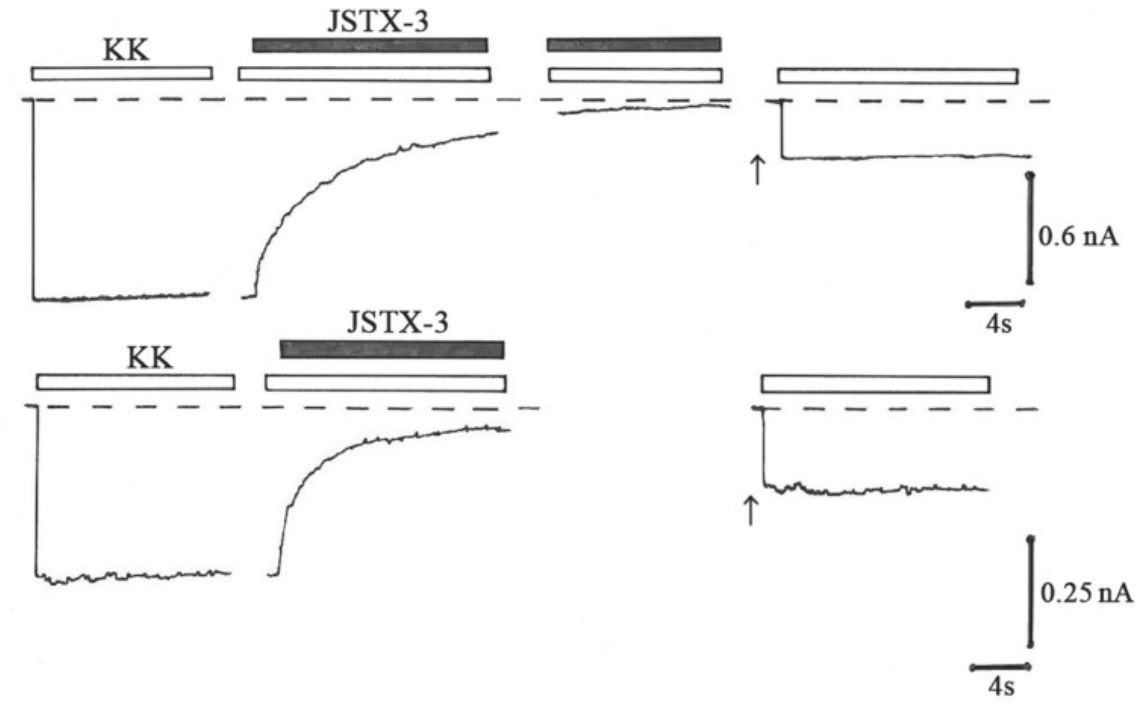


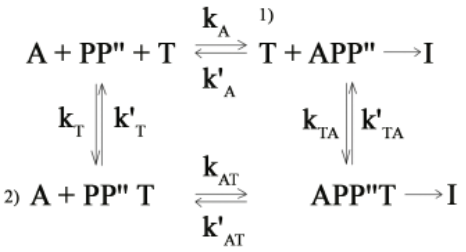
Fig. 5. **Partial reversibility of JSTX-3 effects [78, 80, 81]**
Amplitudes of KK-activated currents were possible to restore partially with JSTX-3 removal in Ringer solution (above); and it was possible to suppress these responses repeatedly (below). Concentration of KK was 1 mmol/l;
JSTX-3 — 10^{-4} mol/l; holding potential −100 mV

formed a functional "nucleus" that interacted with both *Araneidae* toxins and reagents for SH-groups.

What can other other parts of toxin molecule bind to membrane groups? Some information about this can be obtained from the fact that the decay of ion currents under the JSTX-3 influence can be approximated satisfactory by one exponent and in the cases of other toxins — only by superposition of two exponents. This may indicate that at least 2 chemical reactions occured during the binding of each toxin molecule from *A. lobata*. One of such reactions could be the reaction of complexation described above. The second one might be the reaction related to proximal oxy- and amino- groups of terminal arginine, which were found in all *A. lobata* toxins, but they were absent in JSTX-3. These groups could also react with membranes, for example, forming coordination links with ion Fe^{3+}. The values of dissociation constants of formed toxin-receptor complexes were close for JSTX-3 and AR and, according to our calculations they were $6.2 \cdot 10^{-6}$ mol/l and $2.5 \cdot 10^{-6}$ mol/l, respectively.

An interesting question is what type of competition was realized during toxins binding. According to previous studies, the interaction of toxins with agonist binding site of receptor was predicted to be both uncompetitive [54, 55] and noncompetitive [54, 55, 62, 68]. According to other point of view, the type of competition depended on the type of object [55]. In our experiments, under the toxins influence the amplitudes of maximal ion currents decreased, the types of the dose-effect curves of agonists did not change, the imaginary values of dissociation constants declined slightly. Thus, under the influence of JSTX-3 for glutamate $K_d = 2.35 \cdot 10^{-4}$ mol/l, and in control $K_d = 1.1 \cdot 10^{-3}$ mol/l. Under the influence of AR for kainate $K_d = 2.4 \cdot 10^{-4}$ mol/l, and in control $K_d = 3.5 \cdot 10^{-4}$ mol/l. According to some concepts, this effect corresponds to metafinoid type of non-competitive antagonism, and it is described by the Ariens model [57]. According to this model the interaction of agonist and antagonist with the receptor, the antagonism in this case is realized similarly to allosteric effects in enzymatic catalysis. The agonist and antagonist react with different sites of receptor molecule, these sites are functionally tightly linked. When antagonist interacts with its site, the changes are transmitted to the agonist binding site, causing a decrease of imaginary binding constant value of agonist. Basing on these ideas, *Araneidae* toxins must react with their site on the gCRC molecule, which is associated tightly with the locus of agonists action (GLU, KK). Under the action of toxins, the allosteric changes are transferred to this agonist binding site.

Ligand-receptor interactions in this model we described according to the cyclic scheme:



where I — is chemo-activating current, A — is agonist, P — is gCRC agonist binding site, T — is toxin, P″ — is gCRC toxin binding site, PP″ — forms a system of coupled receptors.

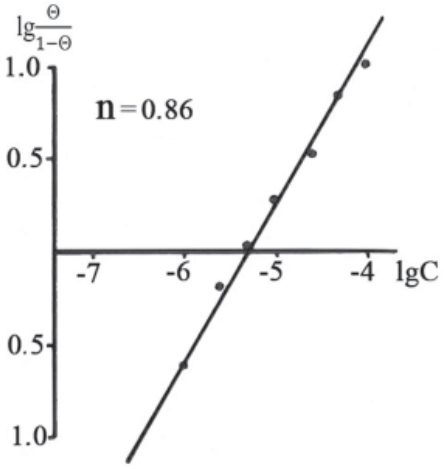


Fig. 6. **Hill graph for AR suppression of the amplitudes of KK-activated ionic currents [83]**

This scheme differs from other one that was proposed by some other authors [91], first of all because it takes into account the existence of linked PP″ receptors in gCRC molecule. The scheme takes into account that toxins block both open (1) and closed channels (2). In our experiments, the pathway of reaction 1) is realized for all agonists, and pathway 2) is only for JSTX-3 (it can be realized for AR with low probability according to [91]).

The fact that toxins from *A. lobata* block only the open channel and JSTX-3 does both open and closed channel that may be due to the fact that the toxin binding group of activated receptor is more accessible to the toxins. When the receptor conformation is not activated, this group can be accessible only for the simplest and shortest JSTX-3 molecule.

During the formation of toxin-receptor complex, the changes are transmitted also to the ion channel, complicating the movement of ions through it. Potential-dependence of blocking process evidences about this. However, the low manifestation of this phenomenon, as well as the data of other authors [54, 92, 93] did not allow us to attribute *Araneidae* toxins to the blockers of exclusively channel type.

During gCRC interaction with toxins, the properties of at least part of ion channels remained unchanged. For example, their potential dependence and ion permeability were not changed. The facts that evidenced about this were the following: the current-voltage characteristics of GLU- and KK-activated ion currents obtained after the modification of receptors by JSTX-3 and AR did not differ from corresponding characteristics in control. They remained linear in all ranges of studied concentrations. Their reversion potentials were close to the control ones. Other researchers also had done the same conclusions [92, 93].

Regularities in investigated toxins effects. During our investigations and analysis, the following regularities of investigated toxins actions were determined.

1. The presence of phenol- or indole acetate-fragments in the toxin molecules was the "key" phenomena of toxins interaction with gCRC and the reaction of interaction of aromatic groups with the membrane groups should be "at the heart" of the blocking mechanism. These fragments define the basic and similar effect for all properties of these antagonists (potential-dependence of blocking, and others).

2. The length and structure of polyamine cause individual differences in blocking properties of aromatic hydrocarbons — antagonists of gCRC as well as differences in their physiological effects. In toxins molecules, the length and structure of polyamine determined the individual properties of their toxic action. So, 1) with complication of polyamine structure, the selectivity of toxins increases and they lose their ability to bind to the inactivated Glu receptor; 2) the shorter the toxin molecule, the faster the reaction of the toxin-receptor complex formation. At the same time, with the reduction of polyamine chain, the degree of blocking increases. And finally, the longer and branched the molecule of the toxin, the faster the reaction of formation toxin-receptor complex is going, and this complex dissociates more quickly.

3. Among all the tested toxins, JSTX-3 had the unique characteristics. Having the simplest structure, its achieved physiological effect was maximal. This observation coincides with literary data [28]. Among all known for today glutamate receptor antagonists, JSTX-3 had an optimal structure in terms of physiological effect.

Toxin AR stands out from the rest *A. lobata* toxins of its properties (the highest degree of "washing", others). We can assume that these particular features in the process of evolution have selected the toxins JSTX-3 and AR as the main active components of the *Araneidae* venoms among the large families of other toxins were antagonists of glutamate receptors.

4. gCRC antagonists differ between each other in terms of currents amplitudes suppression and their restoring during toxins removal by "washing". This regularity may be base on novel methods of qualitative analysis of compounds [44, 47].

5. We had demonstrated that the rate of blocking increases with the increasing of toxins' concentrations. This regularity may be put in base of novel methods of quantitative analysis of compounds [44, 47].

Elements of storage devices construction using molecules — derivatives of phenol and indole with linear polyamine substituents. The author tried to develop a physical model of technical storage devices with properties of artificial memory basing on the studied mechanisms of aromatic hydrocarbons interaction with biological membranes described above. The following discovered facts may be based in such model. 1. Studied toxins (derivatives of aromatic hydrocarbons with the substituents — linear polyamines of different length and complexity) are amphyphilic substances, their aromatic groups could be

dissolved in the hydrophobic lipid phase of biological membranes, and their polyamine "tails" could stick out into surrounding space. 2. Toxins molecules could make coordination complexes with the metals, for example with Fe^{3+}. 3. Calculated Hill coefficient value was 0.86 that evidenced about the coupling of one toxin molecule to one gCRC molecule, and so on.

A. Description of physical model of technical molecular storage device. The described below physical model enables to construct and test the elements of technical devices with properties of "artificial memory". Such models of devices may be considered as artificial "memory" formed out of the elements at the level of molecules and molecular complexes. New ways for the development of such types of artificial memory can be demonstrated using the models described below. Some years ago, a few similar methods-prototypes were suggested. One of them was the method of nano-electronic memory array construction [133]. This method was based on the production of nano-electronic memory matrix. This storage device contained an array of memory cells arranged in rows and columns constructed on the substrate. Each memory cell included a first signal electrode, a second signal electrode and a nanolayer located in the region of intersection between the first and the second signal electrodes. As a result the plurality of lines was obtained, each of which was connected with the first signal electrodes of number of memory cells. There was also a plurality of bit lines. Each of them connected the electrodes of the second signal with the memory cell column. This method had the following disadvantages: there were no persuasive data whether these elements functioned as memory elements (or whether or not these elements functioned well). This nano-device [133] included elements that copied macrostructures at micro- and nano- levels without using all advantages of micro- and nanotechnologies.

Another method-prototype enabled to elaborate nano-compounds and organic memory devices [134]. According to this publication, it became possible to prepare nano-mixtures (nano-compounds) for memory devices from components — organic substances. Such nano-device was a nano-mixture (nano compound) of components that had memory properties (one example of the elements with organic molecules demonstrating memory functions is on Fig. 7, *a*; 8, *a*). The mixture of nanocomponents included a metal or its oxide and an organic compound capable of oxidizing and reducing the bond with the metal or its oxide was described in this patent. The organic compounds — quinolines were used in other prototype. Such invention also related to a storage device that contained developed organic nanocomponents. However, the derivatives of phenols and indoles with substituents, polyamine chains of different lengths and complexity, whose use allows to improve molecular memory characteristics have been used insufficiently in this method [128, 132].

We have developed a method for elaboration and testing of physical model of storage devices [128, 132] with molecules of phenol and indole derivatives in anisotropic media other than prototypes [133, 134]. For this purpose it was necessary to make flat fragment of lipid hydrophobic bilayer membrane and to cover it with the compounds, phenols and/or indole derivatives with substituents, polyamine chains of different lengths and complexity, forming an anisotropic layer with asymmetric properties: "to" and "from" the aromatic group (phenolic or indolic). Flat fragments of lipid bilayer membrane have to contact with isotropic media at both sides and may be of natural or artificial origin (Fig. 7, *a*, *b*; 8, *b*).

The problem was solved by elaboration and testing of physical molecular storage device that consisted on the matrix of elements. The last ones were formed by the layers — flat fragments of lipid hydrophobic bilayer membrane with related organic and inorganic substances. These elements were done by forming (layering) 2D and/or 3D layers that had isotropic and anisotropic properties. The layers with isotropic and anisotropic properties alternated among themselves. One or more such layers included molecules of phenol and/or indole derivatives with substituents — polyamine chains of different lengths and complexity. Such molecules may be the same or of different types, of artificial or natural origin. The sample of such fragment of artificial memory is drawn on Fig. 7, *b*, *c*; 8, *b* for phenole derivative JSTX-3. Other molecules, derivatives of indole and mixture of phenol and indol derivatives with asymmetric properties of molecules, are also possible to use for such model.

The proposed methods [128, 131, 132] allowed us to modify and to form new molecular elements of natural and artificial origin for molecular storage devices, as well as to test their functions by registering of electrical currents through the prepared sample by the methods of voltage-clamp, patch-clamp.

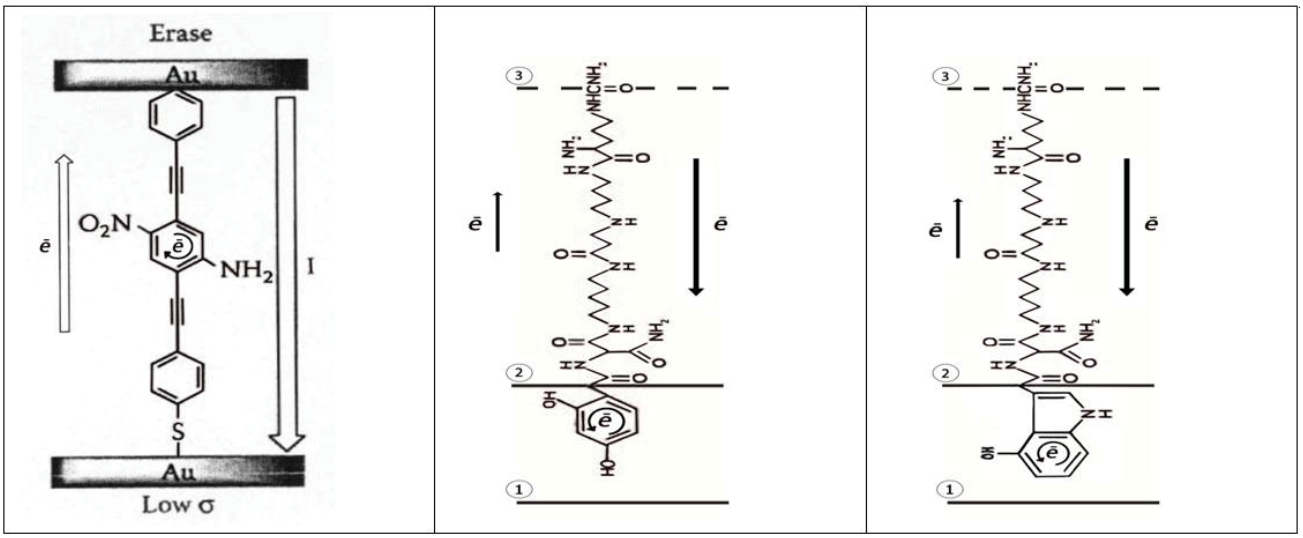


Fig. 7. **Elements of molecular artificial storage device [128, 131, 132, 134]:**
a — molecular element realized in prototype; *b* — proposed element with phenol derivative JSTX-3; *c* — proposed element with indole derivative ARN-2. Vertical asymmetric arrows indicate different values of electronic currents in both directions. The capture of electrons in a "trap" is shown schematically by the arrow in the phenol cycle

Registered transmembrane electric currents were asymmetric and demonsted properties of artificial memory.

In order to prepare such samples of artificial storage devices, the work of several stages was fulfilled. This work processes were described in our previous publications and they were protected by the patents of Ukraine [128, 131, 132].

B. "Electronic trap" in organic molecular artificial memory. Physical model of such artificial"molecular memory" similar to prototype with quinoline molecules [134] was prepared as a result of this work. On Fig. 7, *a*; 8, *a* the fragment of nano-memory from molecules derived from nitro aniline oligo (phenylene ethylene) was presented. We proposed to use another phenol derivative, the natural JSTX-3 toxin, or molecules of other toxins described above — phenol or indole derivatives (Fig. 7, *b, c*). The mechanism of memory due to the "electronic trap" effect is shown here. Electrons of electric nano-currens were captured in a cycle "trap" of phenole (or indole). Their living times in such "traps" were different in directions "to" and "from" due to the system asymmetry. So, the resistances in both directions were veried too, realizing "1" or "0" in this elementary information storage device.

C. *Asymmetry in the model of storage device — the system with organic molecular elements.* In the model system we prepared the monolayer with anisotropic properties (lipid bilayer membrane with applied JSTX-3) that separated two isotropic media. Schematic representation of a fragment of the prepared model using JSTX-3 is on Fig. 8, it may be seen as one with functions of "memory". The necessary condition for its functioning is the separation of system compartments with a layer with anisotropic properties (layer II) between two isotropic media (layers I and III). Respectively, the molecular structures of this anisotropic media have anisotropic properties by themselves. Anisotropic structures must have also the property of existance in several states, and to be able to stay in one state longer than the opposite for memory functions realization. Some organic molecules demonstrate such properties. From the other side, the same property demonstrated our studied experimental objects — complex of molecular structures of neuronal membranes: molecules CRC — A — Tx (channel–receptor complex — agonist — toxin). This complex provides asymmetry of electric currents flows inside and outside the membranes. Such structures can stay longer in one of the states as compared to another.

It is possible to suppose that in mammalian brain, neuronal membranes molecular memory at the level of protein complexes CRC could be realized in similar manner (Fig. 2). It is possible to see the separation by the layer with anisotropic properties (layer II) of two isotropic media (layers I and III). Molecular system with the simplest memory functions

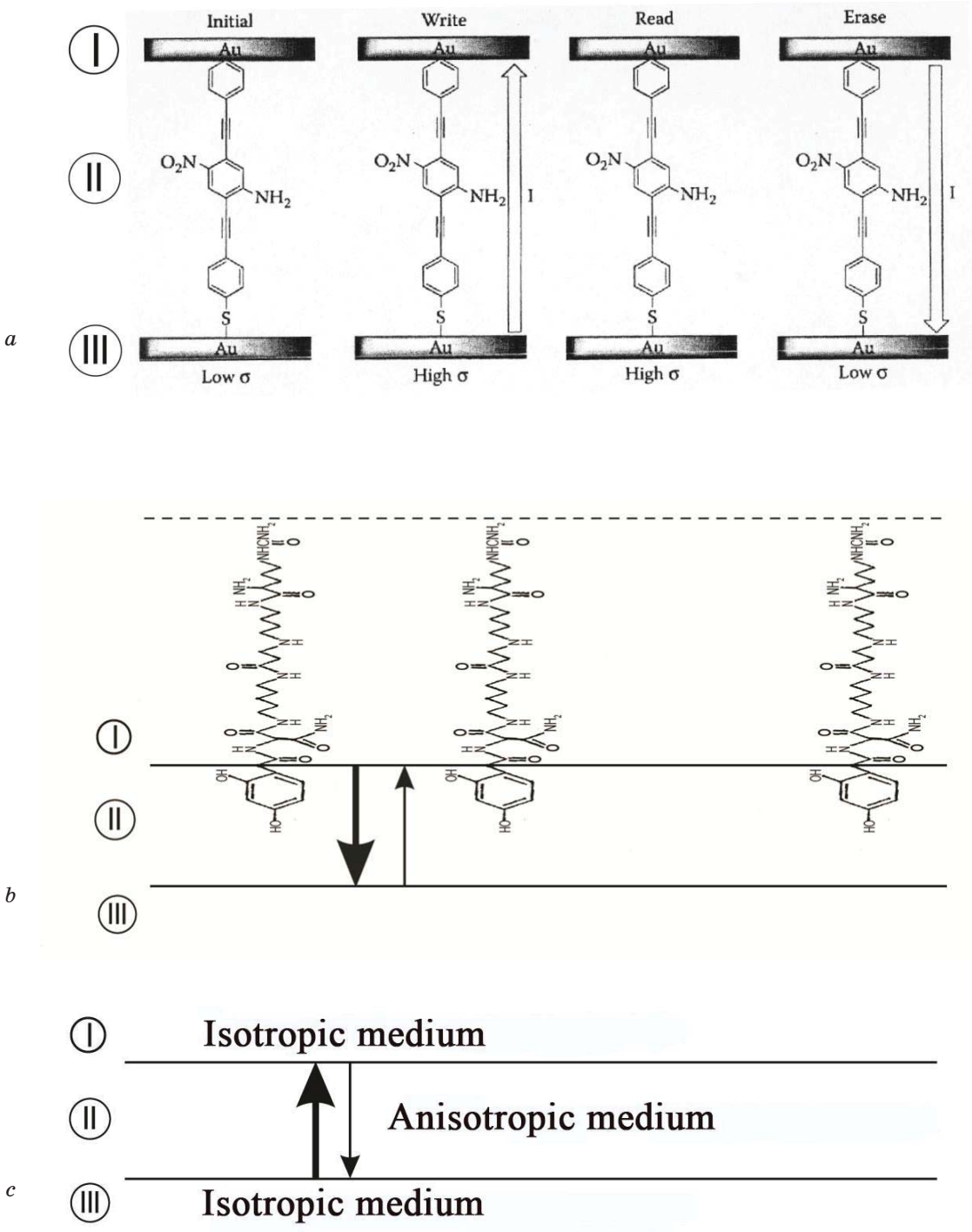


Fig. 8. **Assembling of elementary storage devices from organic nano-compaunds [128, 132, 134]:** *a* — prototype; *b* — fragment of proposed storage device with organic molecules — derivatives of phenol with linear substituent — polyamine; in this case was used JSTX-3 but other molecules with the same properties are possible as well; *c* — elementary system with "artificial memory" have to be assembled from the set of isotropic and anisotropic layers which alternate among themselves. I, III — isotropic media, II — anisotropic medium

could be organized in the same way in living organism and derivatives of phenol and indole could play the key role in such system.

Thus, we presented the results of studying of mechanisms of some *Arthropodae* aromatic hydrocarbons interaction with biological membranes with further development of hypothetic physical models of artificial storage devices on the base of such molecules. Properties of the substances, derivatives of phenol and indole with polyamine substituents, were studied on the examples of substances from spiders' venoms. Their effects were registered on the transmembrame chemosensitive ionic currents using voltage clamp method. The studied substances were antagonists of glutamate channel-receptor complexes. Different characteristics of their blocking activity were examined. They were caused reversible and irreversible blocking effects, effects dependence on membrane holding potential, difference of their action on activated and inactivated receptor, kinetics of blocking actions, type of antagonism. Antagonists amphiphylic properties and the roles of aromatic groups and polyamine substituents during interaction with the membranes were analyzed. Interaction of toxins with gCRC molecule was according to "one molecule-to one molecule" scheme. In our experiments, only one AR ligand was necessary for blocking of each glutamate receptor. Calculated value of Hill coefficient was 0.86.

The values of dissociation constants of the formed toxin-receptor complexes were close for JSTX-3 and AR and, according to our calculations they were $6.2 \cdot 10^{-6}$ mol/l and $2.5 \cdot 10^{-6}$ mol/l, respectively.

According to our data, the toxins interactions with membranes corresponded to metafinoid type of non-competitive antagonism. In this case the interaction was realized similarly to allosteric effects in enzymatic catalysis. Agonist and antagonist reacted with different sites of receptor molecule which were functionally tightly linked.

Ligand-receptor interactions in our model were described according to the cyclic scheme. The scheme is considred that both toxins block were open (1) and closed channels (2), but the toxin binding group of activated receptor is more accessible to antagonists. Finally, during the formation of toxin-receptor complex, the changes were transmitted to the ion channel, complicating of ions flow through it.

The results of such analysis were based on development of physical model of artificial technical storage device. It was described the principles of its functioning as well. The advantage of the presented molecular storage device was also that the domestic chemical industry can produce all components of proposed system, and their production is inexpensive.

During the system preparation we elaborated a few-stage process of biological fragment pre-treatment and preparation of bilayer membranes fragments from the components of organic substances. We obtained a system that is a physical model of storage device by elaboration of a sequence of stages of the work. The developed physical model demonstrated properties of artificial "memory" (Fig. 7, 8). It was similar to other ones from prototypes that were prepared using quinoline molecules and/or molecules derived from nitro aniline oligo (phenylene ethylene). However, in our case, the work was done using other types of molecules, derivatives of phenol, indole and their mixtures (JSTX-3, AR, and others). Phenol and/or indole derivatives with the substituents, polyamine chains of different lengths and complexity, were applied at the surface of the membranes. The molecules of these substances can be the same or different types, artificial or natural origin. The systems were formed of layered one-on-one 2D and/or 3D layers of replaceable organic and inorganic substances.

The layers with isotropic and anisotropic properties must alternate each other. Testing the functioning of such samples was performed by recording of electric currents through them. The currents were asymmetrical according to whether they flowed "along" the polyamine chain or "away" from the phenolic cycle (or indolic cycle). The patch-clamp and voltage-clamp methods were used for the registration and testing of such elementary electric currents. Thereby our physical model demonstrated the storage properties, properties of "molecular memory". It is interesting that in all observed prototypes and in our model the ideas of technical artificial "memory" realization is close to the molecular memory effects realized in the Nature.

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АРОМАТИЧНІ ВУГЛЕВОДНІ ВИДІВ *Arthropodae*: МЕХАНІЗМИ ДІЇ НА БІОЛОГІЧНІ МЕМБРАНИ ТА ПЕРСПЕКТИВИ БІОМЕДИЧНОГО ЗАСТОСУВАННЯ

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Метою роботи було узагальнити результати досліджень механізмів взаємодії деяких похідних ароматичних вуглеводнів із *Arthropodae* з біологічними мембранами. Нейрофізіологічні властивості речовин, отриманих з отрут павуків, — похідних фенолу та індолу із поліамінновими замісниками — досліджували методом реєстрації трансмембранних електричних струмів у режимі фіксації потенціалу. Їхній вплив було виявлено як результат зміни характеристик трансмембранних хемочутливих іонних струмів унаслідок дії цих речовин на мембрани нейронів гіпокампа щурів. Усі досліджені речовини були антагоністами глутаматних канало-рецепторних комплексів, вивчено характеристики їхньої дії, а саме: зворотні та незворотні ефекти блокування, залежність ефектів від підтримуваного на мембрані потенціалу, відмінність їхньої дії на активований та інактивований рецептори, кінетику блокування, тип антагонізму. Проаналізовано амфіфільні властивості антагоністів та роль ароматичних груп і поліамінових замісників під час взаємодії з мембранами. Результати аналізу було покладено в основу розроблення фізичної моделі пристрою молекулярної пам'яті та пояснено принципи його роботи. Узагальнено результати стосовно механізмів впливу досліджуваних речовин на біологічні мембрани. Також обговорено деякі характеристики та особливості функціонування запропонованих елементів молекулярної пам'яті. Властивості запропонованих речовин-аналогів відповідають низці вимог до елементів подібних нанопристроїв.

Ключові слова: токсини, антагоністи рецепторів, трансмембранні електричні струми, *Arthropodae*, штучна пам'ять, біоінформатика.

АРОМАТИЧЕСКИЕ УГЛЕВОДОРОДЫ ВИДОВ *Arthropodae*: МЕХАНИЗМЫ ДЕЙСТВИЯ НА БИОЛОГИЧЕСКИЕ МЕМБРАНЫ И ПЕРСПЕКТИВЫ БИОМЕДИЦИНСКОГО ПРИМЕНЕНИЯ

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Целью работы было обобщить результаты исследований механизмов взаимодействия некоторых производных ароматических углеводородов из *Arthropodae* с биологическими мембранами. Нейрофизиологические свойства веществ, полученных из ядов пауков, — производных фенола и индола с полиаминовыми заместителями — исследовали методом регистрации трансмембранных электрических токов в режиме фиксации потенциала. Их влияние проявлялось, как результат изменения характеристик трансмембранных хемочувствительных ионных токов вследствие действия этих веществ на мембраны нейронов гиппокампа крыс. Все исследованные вещества были антагонистами глутаматных канало-рецепторных комплексов, изучены характеристики их действия, а именно: обратимые и необратимые эффекты блокирования, зависимость эффектов от поддерживаемого на мембране потенциала, отличие их действия на активированный и инактивированный рецепторы, кинетику блокирования, тип антагонизма. Проанализированы амфифильные свойства антагонистов и роль ароматических групп и полиаминовых заместителей при взаимодействии с мембранами. Результаты анализа были положены в основу разработки физической модели устройства молекулярной памяти и объяснены принципы его работы. Обобщены результаты относительно механизмов влияния исследуемых веществ на биологические мембраны. Также обсуждались некоторые характеристики и особенности функционирования предложенных элементов молекулярной памяти. Свойства предложенных веществ-аналогов соответствуют ряду требований к элементам подобных наноустройств.

Ключевые слова: токсины, антагонисты рецепторов, трансмембранные электрические токи, *Arthropodae*, искусственная память, биоинформатика.