УДК 577.352 + 581.17 + 632.954

MECHANISMS OF LITHIUM ACTION ON GENERATION OF MEMBRANE POTENTIAL OSCILLATIONS OF THE *NITELLA* CELL

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The results on variable mechanisms of lithium action on generation of membrane potential (MP) oscillations in the *Nitella* cell are presented. Generating of several classes of oscillations, single and local impulses of the membrane potential depend strongly on the high lithium concentration in the nutrient solution (LiCl concentration 10 mM), when the cell membrane is strongly excited. The assertion is that oscillations of the MP are caused by the total oscillatory transport processes for Li^+, K^+, Na^+ and Cl^- in cell membrane. The hypothesis on mechanisms of oscillatory transport processes of ions (Li^+, Na^+, K^+ and Cl^-) expressed over different classes of oscillations, single and local impulses of the membrane potential across the excitable membrane of the *Nitella* cell is proposed.

Key words: Nitella mucronata (A. Braun) F. Miquel, lithium, excitable membrane, membrane potential, oscillation parameters, oscillatory transport of ions.

Lithium is alkaline earth metal, which occurs in nature in the form of different minerals or ions in minerals or sea water (140—270 ppb, parts per billion) [7]. Particularly lithium in low concentrations (69—5760 ppb) found in plants, planktons and invertebrates. Almost all tissues and tissue fluids of vertebrates contain lithium (21—763 ppb). Marine organisms have tendency to accumulate lithium in greater concentrations [2]. The role of lithium in biological systems and at physiological conditions is not sufficiently studied. Recent nutritional researches on mammals show that the consumption of lithium in the rate of 1 mg per day provides health of organisms, and this fact suggests that lithium can be regarded as an essential biomicroelement. It was found that a low-dose lithium uptake promotes longevity in humans and metazoans [34]. In medicine lithium in the form of Li-carbonate or Li-citrate is used to treat bipolar disorder [3, 10, 16, 17]. This element is widely used in many industries due to its special properties [15].

We revealed lithium-oscillations of the membrane potential (MP). The method of biopotential recording by means of microelectrodes is used for study

a variable mechanism of action of lithium during generating of membrane potential oscillations (MPO), and indirectly during the inducement of the oscillatory lithium transport across the cell membrane of the *Nitella* [6, 7]. A rhythmic fluctuation of the MP recorded using the certain improvement of this method [26]. The first time, in 1976, some of the *Nitella* cell bioelectric responses (change in ψ_m, membrane oscillations and single impulses) stimulated by lithium were registered [20]. Somewhat later typical ψ_m oscillations were registered [27] and then ψ_m oscillations caused by monovalent cations among which Li^+ had also been present were registered [2].

Results obtained in scarce previous studies are not sufficient to develop a complete and complex idea of the oscillatory transport of Li^+ in the membrane of the *Nitella* cell and some new issues related to oscillatory membrane processes have been aroused. It was found that Li^+ was their inevitable inducer, but not single [1, 9, 13, 28]. New issues are primarily related to various oscillations of transport processes caused by effects of shocking levels of lithium ions [2, 25].

The aim of this study was to investigate the different mechanisms of lithium transport processes during MPO in the *Nitella* cell.

Methods

The *Nitella* and *Chara* (freshwater green algae of the family *Characeae*) have been used as an object of studies on MPO induced by lithium. The greatest number of experiments with actions of lithium was performed on the *Nitella mucronata* (A. Braun) Miquel cells.

These cells are large (diameter: 0.6—1.0 mm, length: 40—80 mm) and they are suitable for bioelectrochemical and electrophysiological studies. Today, these green algae are considered as conventional model object for studies of complex membrane-transport processes [5, 9, 21, 22, 24, 25, 30].

Growing conditions, object preparations, treatment prior and during measuring of ψ_m were described in previously published papers [2, 4, 27, 28].

The measurement of rhythmic and membrane bioelectric signals: single impulses, sequences of impulses and different forms of MPO (ψ_m, mV) were carried out by means of method of a microelectrode technique, which was also previously described in principle and details in studies carried out by Radenović, Penčić and Vuchinić [2, 4, 27, 28]. Scheme of an apparatus for measuring the membrane potential shown in Fig. 1.

Results and discussion

The initial measurement of the equilibrium resting membrane potential (ψ_m, mV) is generally accepted as a rule, for bioelectric (bioelectrochemical and electrophysiological) measurements of MP of the *Nitella* cell. If its value ranges from −80 mV to −150 mV the experiment on the membrane of the *Nitella* cell can be continued. It is known that the value of the uniform resting membrane potential (RMP) in the *Nitella* cell depends on a physiological state of the cell, growing conditions, age as well as on the season of year [4].

There is a possibility to observe different classes of MPO, single and local impulses (action potentials, AP) within numerous bioelectric studies [15]. In order to recognise easily the MPO the following features are given: 1) local impulse can occur in the initial part of the oscillation, under such conditions it is clearly seen and easily registered; 2) single AP may become more regular

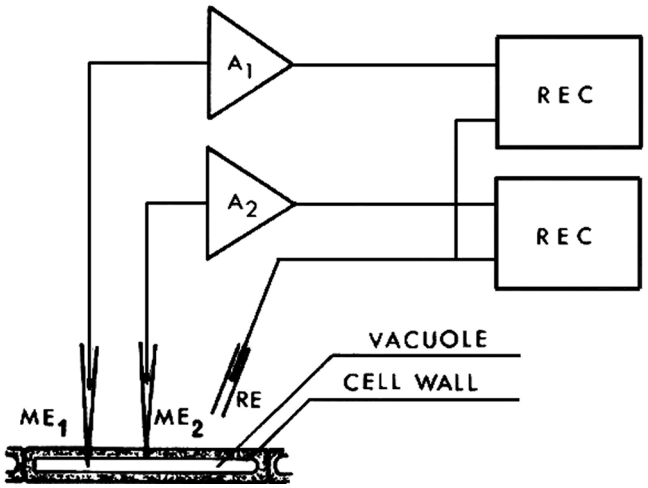

Fig. 1. Schematic diagram of the method of measurement of the membrane potential across the *Nitella* cell applying the microelectrode technique:

ME_1 — microelectrode in the vacuole; ME_2 — microelectrode in the cell wall; RE — reference electrode; A_1 and A_2 — amplifiers; REC — recorders

and it can be simply registered; 3) sequences of AP occur often and they are simply registered (in the literature, they are regarded as membrane potential oscillations); 4) it has been shown that the membranes of *Nitella* cell are capable under effect of selected stimuli to generate local and single AP as well as MPO [2, 27, 28].

Importantly, the oscillations in membrane of *Nitella* cell arise various types in the same experimental conditions under influence of high lithium concentration.

This paper presents four examples of Li-oscillations of the membrane potential.

1. Instantaneous generation of lithium-oscillations in the direction of membrane potential depolarisation. Generation of lithium-MPO at depolarisation of the membrane is manifested in the forms of six different classes (Fig. 2). The MPO generation is explained by the effects of the increased concentration of lithium (10 mM) in the presence of sodium (1 mM) and potassium (0.1 mM) in the nutrient solution. Furthermore, the electrochemical gradient and the electric potential gradient also affect the generation of lithium MPO. It stimulates the formation of an electric field that pulls out the ions (Li^+, Na^+ and K^+) and in such a way, their transport is provided. The intensity and dynamics of the Li^+, Na^+ and K^+ transport processes are significantly depend on the nature of movements of active molecules (proteins, lipids and pigments): rotational, flip-flop and lateral diffusion. When the membrane is in a strongly excited state the mentioned types of movements of active molecules and the effects of ion gradients establish the interdependence of processes that exhibit six different classes of oscillations. Therefore, the interdependence of processes of competitiveness of ions (Li^+, Na^+ and K^+) in the overall transport processes, the dominance of certain types of movements of active molecules and the very excitable membrane, determine parameters and form of six classes of membrane potential oscillations.

The stated classes of Li-oscillations of the membrane potential are characterised by non-standard parameters (Tab. 1).

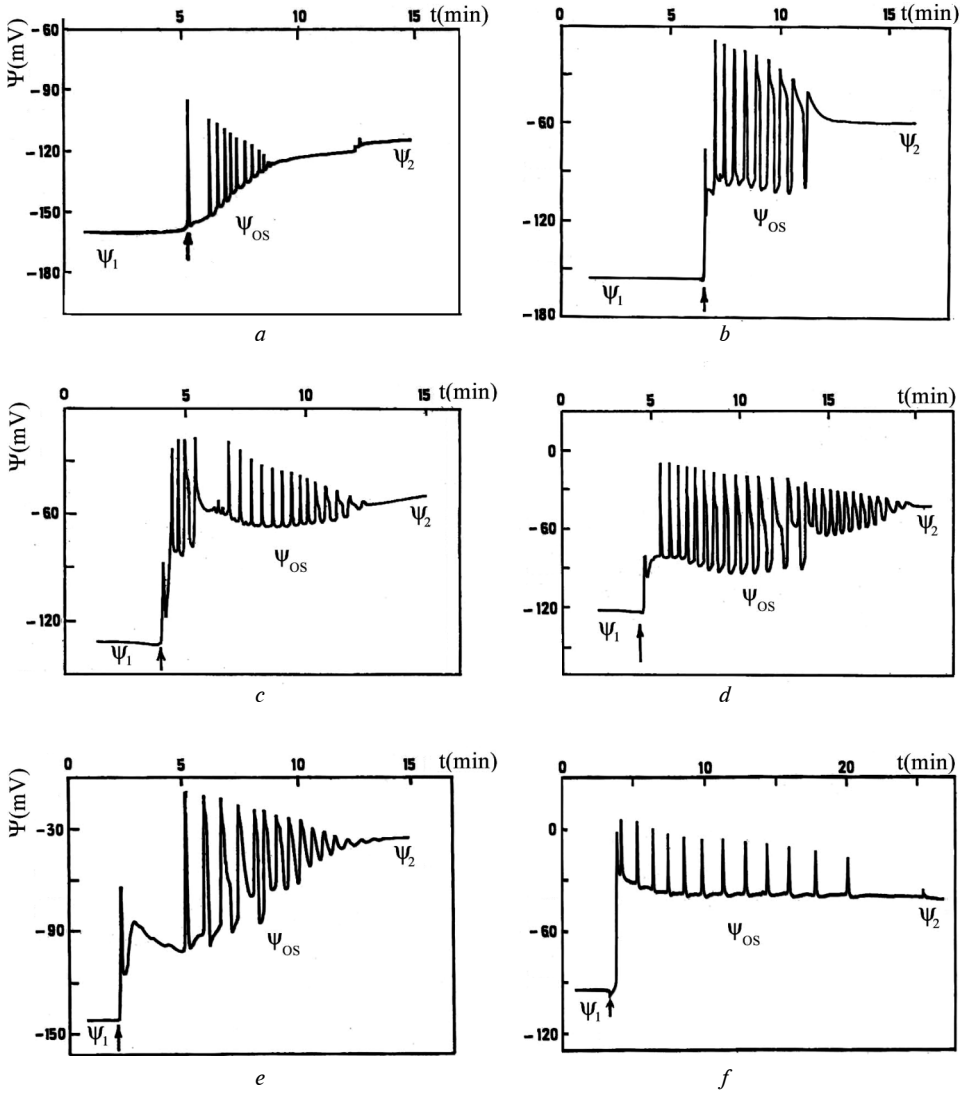

Fig. 2. Six different classes of membrane potential oscillations. Instantaneous generation of lithium-oscillations in the direction of membrane potential depolarisation triggered off by the exchange of the standard solution for the LiCl solution of the shocking concentration of 10 mM

Symbols: standard solution (SR: 0.1 mM KCl + 1.0 mM NaCl), ψ_1 — equilibrium membrane potential prior to oscillating, ψ_2 — equilibrium membrane potential generated by effects of Li after oscillating, ψ_{os} — class of membrane potential oscillations established by effects of shocking LiCl concentration, arrows — indicate the moment when SR was replaced with LiCl solution of the shocking concentration

2. Delayed generation of lithium-oscillations in the direction of membrane potential depolarisation. Delayed generation of lithium-MPO at membrane depolarisation is presented in the form of three different classes (Fig. 3). They are depended on the concentration gradients of competitive ions (Li^+, Na^+ and K^+) in transport processes. The certain classes of membrane potential oscillations (ψ_m, mV) appear when dominance of particular types of movements of active molecules (protein, lipids and pigments) are occurred. A gradual generation of the equilibrium membrane potential (ψ_1) in the direction of its repolarisation (Fig. 3, c) preceedes the occurrence of membrane potential oscillations. It is

TABLE 1. Non-standard parameters of lithium-MPO in the direction of membrane potential depolarisation

Figures designations	ψ_1	ψ_2	Non-standard parameters ψ_{os}		
			Number of impulses	Duration of oscillation	Type of oscillation
Fig. 2, a	−155	−110	10	shorter than standard	symmetric damped
Fig. 2, b	−160	−60	10	shorter than standard	asymmetric damped
Fig. 2, c	−135	−55	18	within limits of standard	symmetric / asymmetric damped
Fig. 2, d	−120	−40	28	longer than standard	asymmetric damped
Fig. 2, e	−150	−30	16	somewhat shorter than standard	irregularly - symmetric dumped
Fig. 2, f	−90	−30	14	somewhat longer than standard	differently damped

believed that Na^+ causes such generation of ψ_1. However ψ_{os} oscillations differ from all three classes of membrane potential oscillations (ψ_m, mV).

These classes of cell lithium-MPO (Fig. 3) can be analysed through non-standard parameters (Tab. 2).

3. Instantaneous generation of lithium-oscillations in the direction of membrane potential repolarisation. Generation of lithium-MPO in the direction of membrane potential repolarisation rarely occurs (Fig. 4). Therefore, the explanation of this class of lithium-MPO is identical to those shown in Fig. 2 and Fig. 3. Different physical and chemical conditions occurring in strongly excitable membrane lead not so infrequently to interdependence of various processes that move in the opposite direction. Such a state of interdependent processes refers to both transport processes of ions (Li^+, Na^+ and K^+) and frequent changes in types of movements of active molecules first of all proteins. Bearing in mind herein stated, it is possible to understand «anomalies» occurring during generation of ψ_2, and in the case of specific ψ_{os} oscillation presented in Fig. 4.

Lithium-MPO at the membrane potential repolarisation (Fig. 4) has the following non-standard parameters: ψ_1 = —20 mV, ψ_2 = —130 mV, number of impulses is five, duration of lithium-oscillations is 7 min and the type of lithium-oscillation is irregular, asymmetric and undamped.

4. Instantaneous generation of lithium with the unaltered level of membrane potential prior to and after oscillating. Generation of lithium-MPO with the unaltered level of membrane potential prior to and after oscillating extremely rarely occurs and it is depicted in Fig. 5. It was triggered off by the exchange

TABLE 2. Non-standard parameters of delayed generation of lithium-MPO

Figures designations	ψ_1	ψ_2	Non-standard parameters ψ_{os}		
			Number of impulses	Duration of oscillation, min	Type of oscillation
Fig. 3, a	−95	−60	16	8	irregularly - asymmetric dumped
Fig. 3, b	−120	−55	20	15	asymmetric dumped
Fig. 3, c	−100	−60	8	10	irregularly - asymmetric dumped

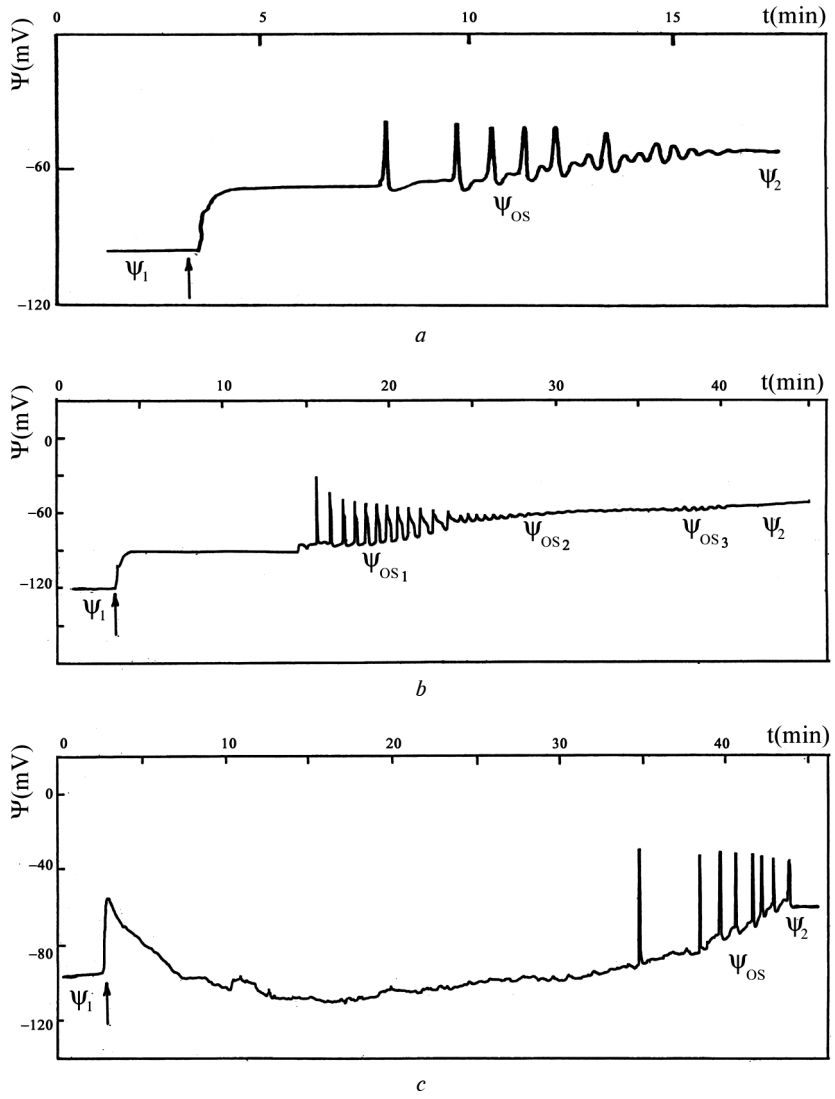

Fig. 3. Three different classes of membrane potential oscillations.

Delayed generation of lithium-oscillations in the direction of membrane potential depolarisation triggered off by the exchange of SR for the LiCl solution of shocking concentration (10 mM). Symbols are the same as in Fig. 2

of SR for the LiCl solution of a shocking concentration and has the following non-standard parameters: ψ_1 = —100 mV, ψ_2 = —100 mV, number of impulses is 8, duration of lithium-oscillation is 4 min and the type of lithium-oscillation is less regular, asymmetric and damped.

Molecular mechanisms of effects of lithium are still insufficiently clarified [14]. According to its ionic radius Li^+ is the most similar to Mg^{2+} ion, which suggests its possible competition with the activities of Mg^{2+} ion. It is believed that Li^+ ion can affect inactivation of enzyme GSK3β that can cause resetting of the brain «circadian clock» [33]. Recently it has been suggested that lithium could interact with NO regulatory pathway, which has a key role in the nervous system [16]. It was also shown that lithium could interfere with inositol phosphatases, i.e. could inhibit inositol monophosphatase [14]. Further consider that the Li^+ ions interact with the transmembrane transport of univa-

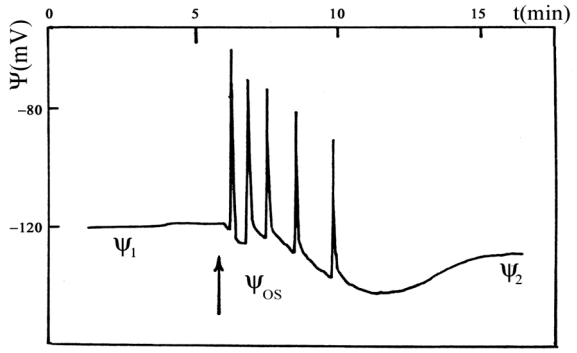

Fig. 4. Instantaneous generation of lithium-oscillations in the direction of membrane potential repolarisation triggered off by the exchange of SR for the LiCl solution of the shocking concentration of 10 mM. Symbols are the same as in Fig. 2.

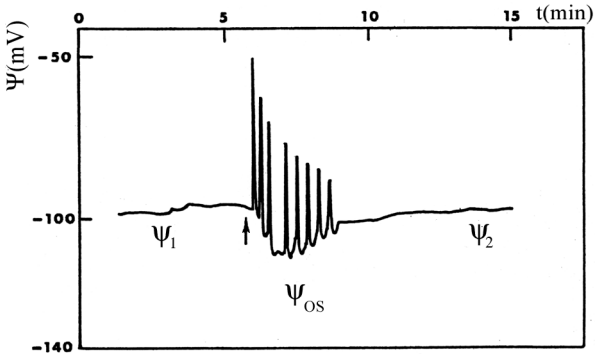

Fig. 5. Instantaneous generation of lithium oscillations with the unaltered level of the equilibrium membrane potential prior to and after oscillating triggered off by the exchange of SR for the LiCl solution of the shocking concentration of 10 mM. Symbols are the same as in Fig. 2.

lent and bivalent cations in nerve cells due to its similarity with Na^+, K^+ and Mg^{2+} (Tab. 3) [19].

Results obtained in the studies of oscillatory bioelectric signals (local impulses, isolated single AP, sequence of local and single impulses and typical oscillation of the membrane potential) are presented in this paper. These results are only a smaller part of our long-term studies on total membrane potential oscillations, and indirectly on oscillatory transport of ions (K^+, Na^+, Ca^{2+}, Li^+ and Cl^-) across excitable cell membrane [9, 21, 29, 31, 32]. This is especially true for lithium-MPO of the membrane potential which is very specific and as such gives the possibility to analyze a number questions to which answers are not yet known in details.

TABLE 3. Physical and chemical characteristics of Li, K, Na and Mg [19]

Characteristics	Li	K	Na	Mg
Atomic radius (Å)	1.33	2.03	1.57	1.36
Ionic radius (Å)	0.60	1.33	0.95	0.65
Hydrated radius (Å)	3.40	2.32	2.76	4.67
Polarizing power (z/r^2)	2.80	0.56	1.12	2.05
Electronegativity	1.0	0.80	0.9	1.0

TABLE 4. Standard parameters of membrane potential oscillations induced by effects of standard concentrations of Li, Na and K on the membrane of the Nitella cell [2]

Ions	Oscillation duration (min)	Number of impulses	Impulse amplitude (mV)	Frequency (imp/min)	Damping factor
Li^+	11.7	13	39±14	1.44±0.6	1.195
K^+	1.9	6	39±19	3.62±1.4	2.153
Na^+	24.1	24	54±16	1.04±0.5	1.081

Some parameters of lithium-MPO have already been studied [2, 9, 21, 22] and the following note that their use provides an opportunity to establish some correlation between oscillations in physical and biological systems [8, 30]. These parameters are: basic level of the membrane potential oscillations, impulse AP (the level up to which a membrane is depolarised during generation single or successive AP and the oscillation), amplitude of single or successive impulses generated during the membrane potential oscillation. The relationship of the amplitude of one AP with the amplitude of the following or previous AP in the selected MPO, impulse interval (the duration between two successive impulses) and other standard parameters are given in Tab. 4 [2].

Special attention should be paid to the kinetics of single AP and the kinetics of the oscillation of the membrane potential. The important issues are not only a character of occurrence and behaviour of rhythms of bioelectric signals [13, 28, 29] but also effects of selected ions on generating membrane potential oscillations [31, 32]. Above mentioned issues and parameters of MPO are directly dependent on transport processes occurring across the very excitable cell membrane [23].

Furthermore different types of movements of lipids, proteins, pigments and other complex-bound structures contribute to the mechanisms of the transport processes across the cell membrane [23]. These types of movements within the membrane can be as follows: lateral movement (typical for lipids and proteins), rotational movement (typical for proteins specialised for the ion transport) and so-called flip-flop movement (typical for lipids and proteins that regulate the ion transport from one side of excitable cell membrane to other). When the degree of sensitivity to excitability of the cell membrane is high then the variable types of movements of active molecules (lipids, proteins and other molecules) are more significant in their intensity, dynamics and diversity, which affects the total ion transport processes [8, 23] especially lithium transport processes [1, 2, 5, 25].

As it is known transport of ions (including lithium) across the strongly excitable cell membrane is characterised by passive and active ion transport processes. Diffusion is considered as a dominant bearer of passive transport processes in the very excitable membrane. It is expressed as a simple, limited and facilitated diffusion. It is clear that there are at least three promoters of the passive ion transport: concentration gradient, electrochemical potential gradient and electric potential gradient (electrochemical potential includes electric potential and concentration potential)

Results presented in this paper indicate that lithium-oscillations in the direction of membrane potential depolarisation occur under particular conditions (Fig. 2, Tab. 1). Moreover delayed generation of lithium-oscillations in

the direction of membrane potential depolarisation occurs (Fig. 3, Tab. 2). Generation of lithium-oscillations in the direction of membrane potential repolarisation also occurs (Fig. 4). It is interesting to mention that generation of lithium oscillations with the unaltered level of the membrane potential before and after oscillating also occurs (Fig. 5).

Based on the gained results and the discussion as well as on our overall information on oscillatory processes induced by Li^+, K^+, Na^+, NH_4^+ and Ca^{2+}, we present the following hypothesis:

1). Lithium-oscillations (local and single impulses and other classes of oscillations) in the membrane potential occur when the cell membrane is strongly excited. Such membrane state as a rule is accompanied by the activities of ions K^+, Na^+, Li^+ and Cl^- that are not constant under such conditions in subcellular components (vacuole, cytoplasm and cell wall).

2). The usual ion transport processes are disturbed under effects of lithium: first of all diffusion (concentration gradient is altered), electrodiffusion (electrochemical potential gradient is changed), biocurrents (electric potential gradient is altered) and fluid flow (hydrostatic pressure gradient is modified). The mentioned dynamic states determine the degree of excitability of the strongly excitable cell membrane. Therefore when the cell membrane is strongly excited local, single and complete membrane potential oscillations inevitably occur. These oscillations occur in the form of certain classes but sometimes they can appear in the form of different irregularities (chaos). At the same time and under such conditions oscillating of active proteins starts in the cell membrane, and they rhythmically, regularly, irregularly (state of chaos) induce the transport of ions Na^+, K^+ and Li^+ across the strongly excitable membrane which takes an oscillatory regime. In such state transport processes of ions K^+, Na^+ and Li^+ adopt a co-operative character which induce conformational changes of active ion channels that stretch and contract within the oscillatory regime and thereby rhythmically modify transport ability of the excitable cell membrane for ions of K^+, Na^+ and Li^+.

3). Under such conditions, oscillatory changes occur in cell supplying and thereby in supplying the very excitable membrane with energy: electric, osmotic and chemical.

4). Moreover, the bonds between membrane transport processes and metabolism are disturbed i.e. weakened. This is particularly related to weakening of the self-regulation of the matter within each cell.

5). Rhythmic process in excitable cell depends on relation between slow depolarisation and repolarisation processes after single action potential propagation. Slow depolarisation connected with activation of Na- and Ca-membrane potential depends on Na-pump activation. In Li case, possible all this mechanisms play famous role. For example, when slow membrane depolarisation increases the frequency of rhythmic membrane potential oscillation increases, but when slow membrane repolarisation increases — frequency decreases.

Authors devote this paper to a memory and long remembrance of prematurely deceased L.N. Vorobiev, Department of Biophysics, Faculty of Biology, Lomonosov Moscow State University, Moscow, Russia.

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Received 14.07.14

МЕХАНИЗМЫ ВЛИЯНИЯ ЛИТИЯ НА ГЕНЕРАЦИЮ КОЛЕБАНИЙ МЕМБРАННОГО ПОТЕНЦИАЛА В КЛЕТКАХ НИТЕЛЛЫ

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Изложены результаты исследования воздействия лития на осцилляции мембранного потенциала (МП) в клетках нителлы. Показано, что под влиянием высокой концентрации хлорида лития (10 мМ) возникает несколько классов осцилляций МП, включая единичные и локальные импульсы в случае сильного возбуждения клетки. Предполагается, что осцилляции МП, индуцируемые литием, обусловлены колебательным характером процессов транспорта Li^+, K^+, Na^+, Cl^- через клеточную мембрану. Предложена гипотеза, объясняющая механизмы колебательных процессов транспорта ионов (Li^+, Na^+, K^+ и Cl^-) и наличие различных классов колебаний, а также возникновения единичных и локальных импульсов МП в возбудимой мембране клетки *Nitella*.

МЕХАНІЗМИ ВПЛИВУ ЛІТІЮ НА ГЕНЕРАЦІЮ ОСЦИЛЯЦІЙ МЕМБРАННОГО ПОТЕНЦІАЛУ В КЛІТИНАХ НІТЕЛИ

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Викладено результати дослідження дії літію на осциляції мембранного потенціалу (МП) в клітинах нітели. Показано, що під впливом високої концентрації хлориду літію

(10 мМ) виникає кілька класів осциляцій МП, включно з поодинокими й локальними імпульсами в разі сильного збудження клітини. Припускається, що осциляції МП, індуковані літієм, зумовлені коливальним характером процесів транспорту Li^+, K^+, Na^+ і Cl^- через клітинну мембрану. Запропоновано гіпотезу, що пояснює механізми коливальних процесів транспорту іонів (Li^+, K^+, Na^+, Cl^-) і наявність різних класів коливань, а також виникнення одиничних і локальних імпульсів МП у збудливій мембрані клітини *Nitella*.

Ключові слова: Nitella mucronata (A. Braun) F. Miquel, літій, збудлива мембрана, мембранний потенціал, параметри осциляцій, осциляційний транспорт іонів.