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ABSTRACT

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Abstracts

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S1. Molecular biophysics. Structure and dynamics of biopolymers and biomacromolecular systems

S1.1. Molecular dynamics of α-helical poly-l-glutamic acid in water solution

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α-Helix is a basic element of secondary structure from which the globular proteins are built. Since true native protein exists in water solution the structural behavior of protein is determined essentially by their dynamic properties. However, the problem is rather complicated because a majority of protein structures has been obtained in the crystal state. Here we have studied the dynamic properties of poly-L-glutamic acid model in a helical conformation in water solution. It includes 16 Glu residues placed in 4.5 turns of right-handed α-helix structure built with the data of Pauling & Corey (1951). In acidic water solution at pH about 3.5 poly-L-glutamic acid undergoes the helical conformation. Thus, our model has non-ionized side carbonyl Glu groups, as COOH, and ionized terminal groups, as NH3+ and COO-. An analysis of all the atomic groups makes no special sense. So, we have concentrated solely on dynamic study of peptide skeleton from Cα-atoms. Computational system included helical fragment, water solution molecules, and ions of sodium and chlorine. There were introduced 11 Na and 9 Cl ions which supply zero total charge of the sysytem. Numerical simulations were performed on the hybrid supercomputing system K-60 at the Keldysh Institute of Applied Mathematics, Russian Academy of Sciences. The initial part of trajectories, from 0 to 500 psec, corresponds to the refinement and relaxation of the model. A dynamic trajectory of α-helical poly-L-glutamic acid has been calculated from 0.0 to 25.0 nsec. We have inspected fluctuations of the Cα-chain at each integer numbers of time, in nanoseconds. That has been done by calculating the absolute shift values of Cα-atom positions at the next 1.0 nanosec intervals. The model has displayed several fluctuation modes along the dynamic trajectory. The most interesting modes show the distinctive shifts of Cα-atoms. These modes include two adjacent in the turns clusters of Cα-atoms which are placed approximately at one side of the helix. The observed modes are intrinsically dynamic feature of a single fragment of α-helix structure. And they suggest playing a key role in dynamics of protein molecules.

S1.2. Multiscale modelling of DNA repair by photoenzymes

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Photolyase photoenzymes, binding to damaged DNA sites, repair the main DNA photoproducts formed under the action of UV radiation. The functioning of photolyases is based on the reaction of photoinduced intermolecular electron transfer. Especially interesting from the point of view of the chemical mechanism is (6-4) photolyase, which repairs the most cytotoxic (6-4) pyrimidine-pyrimidone photoproducts of DNA. Despite the extensive study of the (6-4) photolyase mechanism using the high-end experimental and computational methods, the chemical details of the repair reaction have not been definitively established. Multiscale modeling, combining classical molecular dynamics and quantum chemical calculations of photoexcited states and reaction coordinate, is able to resolve some of the contradictions existing today in understanding the (6-4) photolyase mechanism.
The present study considers the main stages of the (6-4) photoprodroduct repair by (6-4) photolyase including photoinduced electron transfer leading to the formation of a photoprodroduct radical, breaking and formation of covalent bonds in the photoprodroduct radical and back electron transfer. Using density functional theory calculations, optimized geometries were obtained for modeling the repair reaction involving various forms of the critically important amino acid residue His365, whose role in the repair has been extensively discussed in the literature. In the case of neutral His365, the photoproduct radical rearranges by the OH-group transfer, for which the enzyme reduces the reaction energy barrier. In the presence of protonated His365, electron transfer coupled to proton transfer takes place leading to the formation of a protonated (neutral) photoproduct radical. In order for the repair reaction to proceed along this path, it is necessary to adjust electron affinity of the photoproduct. Estimates of the effect of the macromolecular environment on electronic energies were carried by computing excited electronic states for structures comprising the repair rection coordinate using the multiconfiguration quantum chemical method XMCQDPT2-CASSCF. Within the framework of these calculations, the electronic coupling matrix elements were also evaluated. The influence of the macromolecular environment on electron transfer energies was evaluated using classical molecular dynamics. To assess the electron transfer reaction rate, the results of the quantum chemical and molecular dynamics calculations were combined. The estimated electron-transfer rates indicated that the rapid recombination of the radical pair takes place in the presence of neutral His365. The presence of protonated His365, acting as a proton donor for the photoproduct radical, may substantially slow down back electron transfer. Thus, the

chambers either without maintaining 5% CO2, or with its maintenance. One camera was located in the Earth's magnetic field (control), the second was placed in a Helmholtz coil pair (in which a combined magnetic field was generated or not generated).
Field parameters: Ca2+-CMF: BDC = 48.7 mcT, BAC = 89.6 mcT, f = 37.2 Hz; K+-CMF: BDC = 48.7 mcT, BAC = 89.6 mcT, f = 57.2 Hz; Mg2+-CMF: BDC = 48.7 mcT, BAC = 89.6 mcT, f = 61.2 Hz. The growth dynamics, morphology and viability of cells were evaluated every day by fluorescent staining and further microscopy.
The results of the first series of experiments, according to the assessment of cell culture conditions, showed that short-term exposure (2 hours) cultivation, without exposure to CMF, can be carried out without maintaining 5% CO2. Under such conditions, the dynamics of cell growth coincided in both chambers and showed no significant changes in comparison with the control group, which was cultured under standard conditions of a CO2 incubator. Similar results were shown by prolonged exposure (3 days) cultivation without exposure to CMF and with the maintenance of 5% CO2. DMEM/F-12 was determined to be the optimal culture medium for cell culture under such conditions. The results obtained allow the further use of the described setup to assess the effect of CMF on various "physical" targets of substrate-dependent cells. It has been shown that prolonged exposure to Ca2+-CMF does not change the normal morphology and good viability, and a change in the growth rate of NCTC clone L929 cells, in comparison with the control cameras located in the Earth field and the control group in a CO2 incubator.
Prolonged exposure to K+-CMF showed a slowdown in growth, preservation of normal morphology and good viability of NCTC clone L929 cells, in comparison with the control cameras located in the Earth field and the control group in a CO2 incubator.
With prolonged exposure to Mg2+-CMF, the preservation of normal morphology, good viability is observed, and a change in the growth rate of cells of the NCTC clone L929 line, in comparison with the control cameras located in the Earth field and the control group in the CO2 incubator. But the effect was lower than when exposed to a CMF tuned to parametric resonance for Ca2+ or K+ ions.
The results obtained by us show the possibility of the influence of the described fields on human cells, which will be used for further development of magnetotherapy methods.

S2.204. The effect of methoxamine on the action potential of newborn rats cardiomyocytes

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Background: α1-Adrenoceptors are seven transmembrane domain GPCRs involved in numerous physiological functions controlled by endogenous catecholamines, noradrenaline and adrenaline, and targeted by drugs useful in therapeutics. Three separate genes, whose products are named α1A-, α1B-, and α1D- adrenoceptors, encode these receptors. Although the existence of multiple α1-adrenoceptors has been acknowledged for almost 25 years, the specific functions regulated by each subtype are still largely unknown. This work aimed to study the role of methoxamine in the regulation of electrical activity of the myocardium of the right atrium of rats in early postnatal ontogenesis.
Materials and Methods: The study was carried out on white rats (n =7). Membrane potential (MP) and action potential (AP) of the imposed rhythm were recorded using glass microelectrodes. The stimulus duration of the imposed (1ms) and repetition rate (3Hz). The phases of AP were analyzed: the duration of depolarization, the duration of repolarization at the level of 20%, 50%, 90% (APD 20, APD 50, APD 90). Statistical significance was assessed using Student's t-test.
Results: Methoxamine at a concentration of 10-8 M lengthened the repolarization phase of the action potential of working atrial cardiomyocytes, while there was no change in the duration of the depolarization phase. Methoxamine increased APD20 by 57% APD50 by 54% APD 90 by 41% ($P < 0.05$). Methoxamine did not cause significant changes in membrane potential (MP). In addition, the values of the amplitude of the action potential, and overshoot did not change.
Conclusions: Methoxamine causes changes in the pattern of the electrical activity of the myocardium of the atria in newborn rats by increasing the repolarization phase of the action potential. This paper has been supported by the Kazan Federal University Strategic Academic Leadership Program (PRIORITY-2030).

S2.205. The effect of a1-adrenoreceptors stimulation on AP frequency of cardiomyocytes in different ages rats

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Background: α1-Adrenergic receptors (ARs) are catecholamine-activated G protein-coupled receptors (GPCRs) that are expressed in rat and human myocardium and vasculature,and play essential roles in the regulation of cardiovascular physiology. Though α1-ARs are less abundant in the heart than β1-ARs, activation of cardiac α1-ARs results in important biological processes such as hypertrophy, positive inotropy, ischemic preconditioning, and protection from cell death. This work aimed to study the role of α1-adrenergic receptor agonist methoxamine (10-8 M) on the frequency of generation of the action potential in the heart of rats at different ages of postnatal ontogenesis.
Materials and Methods: The study was carried out on newborn, 3- and 20- week-old white rats using the microelectrode technique. A preparation of atrial myocardium with preserved sinus node and spontaneous activity was prepared. Methoxamine was immersed in a special tank, where a thermostatically controlled working solution "Tyrode" was supplied (which contains 7.54 g/l NaCl; 0.3 g/l KCl; 0.134 g/l; CaCl12; 0.06 g/l MgSO4; 0.14g/l NaH2PO4; 1.68 g/l NaHCO3; 0.9 g/l of glucose), which was concentrated by a gas mixture consisting of 95% oxygen and 5% carbon dioxide (37±1°C). The results were processed by the Elph 3.0 program. The samples were tested for normal distribution. Statistical processing was carried out using paired Student's t-test. The effect of the α1-adrenergic receptor agonist methoxamine was studied at a concentration of 10-8M.
Results: Methoxamine at a concentration of 10-8M in newborn animals caused an increase in the frequency of occurrence of the action potential by 42% ($p < 0.05$), and in 3-week-old animals caused an increase in the frequency of spontaneous activity by 24% ($p < 0.05$). In 20-week-old animals caused an increase in the frequency of spontaneous activity by 10% ($p < 0.05$).
Conclusions: the results revealed that the stimulation of α1-adrenoreceptors in newborn, 3- and 20- week-old rats led to an increase in the frequency of action potential generation. However, the maximum effect was expressed in newborn rats, and the minimum effect was observed in adult animals. This paper has been supported by the Kazan Federal University Strategic Academic Leadership Program (PRIORITY-2030).

S2.206. The penetration of low-melting agarose molecules in the liquid state through cellular and nuclear membranes is the reason for the variability in the results of Comet assay

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