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Theoretical analysis of metabolic system of an ethanol-neutralizing erythrocyte-bioreactor

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Introduction: Erythrocytes-bioreactors (EBRs), containing an artificially built-in metabolic pathway that is absent in a normal erythrocyte, can potentially be used in the treatment of some diseases. They can regulate the concentration of certain target substances in a patient's blood by producing or consuming these substances in reactions of the embedded pathway. EBRs consuming ethanol, methanol, ammonium, asparagine, and other substances have been developed by different scientific groups worldwide. However, most of these bioreactors were ineffective in vitro and in vivo. Many factors can limit the effectiveness of a complex metabolic system like EBR. Mathematical modeling of metabolic systems can help reveal these limitations and turn the EBR development process into an engineering problem.

Methods: Systems of the first-order ordinary differential equations (ODEs) were used to model metabolic systems of various EBRs. The models included equations describing the rate of glycolysis and the pentose phosphate pathway, built-in reactions, and the transport of certain metabolites across the erythrocyte membrane. To analyze the models, numerical solutions of ODE systems, methods of the theory of dynamical systems, and methods of reduction of ODE systems (Tichonov theorem) were used.

Results: Mathematical models of ethanol-neutralizing EBRs based on alcohol dehydrogenase and acetaldehyde dehydrogenase were studied. Pyruvate influx from the external media turned out to be the main limitation of the EBR's efficiency. In the case of lack of pyruvate influx increase of activities of ethanol-consuming enzymes leads to the disappearance of the steady-state in glycolysis due to a decrease of NAD/(NAD+NADH) value. In normal RBCs this value I maintained near 1 by the NADH oxidation in the reaction catalyzed by lactate dehydrogenase. As NAD is reduced by alcohol dehydrogenase and acetaldehyde dehydrogenase, an increase in their activities leads to a decrease in NAD concentration. The steady- state disappears due to the dependence of the maximum possible rate of glyceraldehyde phosphate dehydrogenase reaction on NAD/(NAD+NADH) value, that leads to accumulation of some metabolites of glycolysis in the cell.

Conclusion: Analysis of mathematical models has shown that ethanol-neutralizing EBRs based on alcohol dehydrogenase and acetaldehyde dehydrogenase are potentially able to decrease ethanol concentration in blood. An increase in the activities of the enzymes of the embedded pathway can lead to the disappearance of the steady- state in glycolysis. Maximum permissible activity depends on the pyruvate influx from the external media.

Speaker Biography

Evgeniy Protasov was born in Stavropol, Russia in 1991. In 2015, he graduated from the Physics Department of Lomonosov Moscow State University. He is a junior researcher at the Center for Theoretical Problems of Physicochemical Pharmacology, Russian Academy of Sciences, and the Dmitriy Rogachev National Medical Research Center of Pediatric Hematology, Oncology, and Immunology, Moscow, Russia.

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