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Calcium uptake in red blood cells of sickle cell disease patients as a new potential pharmacological target

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Abstract

Calcium is a master regulator of multiple processes in red blood cells and its intracellular concentration in red blood cells (RBCs) is precisely controlled. Up-regulation of Ca^{2+} uptake into the RBCs of sickle cell disease (SCD) patients is suggested to contribute to their resistance to malaria infection. The price to pay for this protective measure is high. Calcium overload facilitates dehydration promoting thereby hemoglobin S polymerization, activates calpain, causes alteration in cellular metabolism, and stimulates NADPH oxidase and NO synthase. Molecular identity of ion channels involved in pathologically high Ca^{2+} uptake in SCD-RBCs remained unknown. We have recently identified N-methyl D-aspartate receptors (NMDARs) as channels mediating Ca^{2+} influx into healthy human RBCs. Abnormal expression pattern for NMDAR subunits is characteristic for erythroid precursor cells of SCD patients. The number of receptor copies and activity of the NMDAR is up-regulated in RBCs of SCD patients during asymptomatic periods compared to that in healthy human RBCs. Hemolytic crises were associated with further increase in the number of active NMDAR units per cell. Activation of the NMDARs in SCD-RBCs and consequent Ca^{2+} accumulation induced oxidative stress. Dehydration caused by Ca2+ accumulation in the presence of NMDAR agonists was particularly pronounced in deoxygenated cells in sickle cell transformation was facilitated. Treatment of RBCs of patients with the NMDAR antagonist memantine reversed these effects causing re-hydration and largely preventing sickle cell transformation under hypoxic conditions. Taken together these findings make NMDARs in RBCs of SCD patients into an attractive target for pharmacological intervention.

Biography

Dr. Habil. Anna Bogdanova has graduated as a chemist from the Leningrad State University, completed her Ph.D in experimental biophysics from Humboldt University in Berlin and postdoctoral studies in animal and human physiology from the Laboratory of Animal Physiology, University of Turku, Finland and the Medical Faculty, University of Zurich. She is a Lecturer (Privatdozent) at the Institute of Veterinary Physiology and a member of steering committee of the European Red Cell Research Society (ERCS). Her work on various aspects of red cell function has been summarized in more than 20 papers in reputed journals and a patent.