Potential protection from the side effects of antileukemic drug asparaginase

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Asparaginase is an essential element in the successful treatment of childhood acute lymphoblastic leukemia, the most common type of cancer affecting children. However, in about 5–10% of cases this treatment causes acute pancreatitis (AP) as a side-effect. In AP, a potentially fatal human disease, the inactive pancreatic pro-enzymes become active enzymes inside the pancreatic acinar cells, digesting the pancreas and its surroundings. Under physiological conditions intracellular calcium signalling and Mg-ATP level are the key elements needed for stimulant-evoked exocytotic enzyme secretion from pancreatic acinar cells. Physiological Ca^{2+} signals stimulate ATP production, whereas sustained global cytosolic Ca^{2+} elevations decrease ATP levels and cause necrosis leading to AP. Alcohol and gallstones are the major causes of the disease. Recently we have investigated *in vitro* the mechanism by which L-Asparaginase evokes AP. For the first time, we have shown that like other pancreatitis-inducing agents, L-Asparaginase evoked excessive intracellular Ca^{2+} release followed by Ca^{2+} entry, decreased the intracellular ATP levels and reduced Ca^{2+} extrusion. The toxic Ca^{2+} signals induced by L-Asparaginase caused extensive cell necrosis. Our data suggest that the L-Asparaginase-induced pathology depends on protease activated receptor 2. The inhibition of PAR2 receptor prevented the toxic L-Asparaginase-elicited Ca^{2+} signals and cell necrosis. Inhibition of Ca^{2+} entry with GSK-7975A markedly reduced L-Asparaginase-induced cellular pathology. We have demonstrated a decreased rate of Ca^{2+} extrusion due to the reduction in the intracellular ATP level limiting the energy supply to the Ca^{2+} ATPase in the plasma membrane. Supplementation of the medium with sodium pyruvate provided a similar degree of protection against pancreatic necrosis as PAR2 inhibition or GSK-7579A. The established mechanism of action of L-Asparaginase has been confirmed for several sources of asparaginase, including drug Elspar, PEG-asparaginase and asparaginase from both *E. Coli* and *Erwinia*. We have now developed model of asparaginase-induced AP that allows us to fully test our previous findings and develop protection from the side effects of Asparaginase. Both Ca^{2+} overload and ATP loss play key roles in Asparaginase-induced AP and therapeutic strategies must take both target points into account. We suggest that a combined pharmacological control of intracellular calcium and ATP levels will prevent or alleviate AP and improve childhood cancer treatments.

Biography

Oleg V Gerasimenko completed his PhD in 1991 at BogomoletzInst, Kiev, Ukraine before moving to Liverpool, UK in 1993 to join research group lead by Prof. Ole H Petersen. He became Lecturer in 2000 and Reader in 2005 before moving to Cardiff School of Biosciences in 2010. Since then he is a Team Leader of well-equipped MRC funded research group together with Prof. Ole H Petersen (Head of School of Biosciences) and Dr. Julia Gerasimenko.

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