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Stratification of surface lysine residues of bovine testicular hyaluronidase on the basis of its 3D structure model: Design of chondroitin sulphate modified enzyme derivative

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Deficiency of structural information hampers the mammalian hyaluronidase study. We used archetype of the obtained earlier crystal structure of human hyaluronidase-1. Superposition of 3D BTH model with 3D structure of human hyaluronidase-1 was quite satisfactory, while with 3D structure of bee venom hyaluronidase had some discrepancies (including the presence of epidermal growth factor-like domain in BTH). The active site of 3D BTH model was indicate as well as sorption complex between BTH and minimal substrate (hyaluronan hexamer) and positions of charged amino acid residues (mainly Lys, Asp, Glu). The surface Lys residues were stratificated according to their access for chemical modification (Lys of first, second, third access level and unproductive residues for Lys modification) due to analysis of Lys microenvironment. The destination of BTH modification is the production of stabilized enzyme forms of targeted action for medical application. The glycosidases (as hyaluronidases) determine the catabolism of glycosaminoglycan part of glycocalyx. The injury of vascular wall begins with endothelial glycocalyx degradation. The regulator of glycocalyx state is glycosidase enzymes particularly. According to experimental results, the covalent complex between BTH and chondroitin sulphate (CHS) is more preferable as compared to complexes with other glycosaminoglycans. CHS modified BTH covalent complexes (BTH-CHS) were constructed *in silico* with different degree of Lys modification (on the base of 3D BTH model). Moreover, the 3D model of BTH-CHS was constructed with practically full modified/blocked Lys residues. According to experimental data, the BTH-CHS conjugate had molecular mass 180 kDa and more and it was perspective for medical use. From *in silico* point of view, 140 kDa molecular mass of this conjugate was enough already for fully blockade of Lys residues. The 3D position of CHS chains around BTH globule can be multiform. The fully blockade of surface Lys residues can gain *in silico* with two CHS chains (m.m. 35-50 kDa) or with one CHS chain (m.m. 120-140 kDa). In latter case, BTH globule is located in CHS coat except two sites only without Lys residues. One of these sites is the area around active site of BTH. Such *in silico* results are agreed with appreciable remain endoglycosidase activity of BTH (68-78%) after its deep modification by CHS with different molecular mass. The topography of Lys residues stipulates the preservation of substrate access to active site of modified BTH that determines the Lys residue selection for development of modified enzyme derivatives.

Biography

Alexander V Maksimenko is an enzyme engineer of medical preparations and began his work in chemistry at Moscow State University, Chemistry Department where he received a Master of Science degree in 1975 and then Ph.D. in chemistry in 1978. He completed a Doctor of Science in biochemistry and cardiology in 1989 at USSR Cardiology Research Center. He has a long history of work at the Cardiology Center, Moscow beginning in 1978 to present. He is currently the Director of biochemical engineering laboratory, Professor in the Institute of Experimental Cardiology at Russian Cardiology Research-and-Production Complex, Moscow, Russia. He has published more than 200 papers and is the holder of over ten Russian and foreign patents. He is the recipient of medals of exhibition for national economy achievements, the prize winner for research scholarship, laureate of different national and international prizes and decrees of merit. He received membership in the International Commission on Pharmaceutical Enzymes (F.I.P.) in Ghent, Belgium and other International Scientific Societies. His research interests are focused on therapeutic enzymes, polymeric drugs, dosage regimen, courses of enzyme therapy, drug targeting and therapeutic compositions.

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