Heparin, Low Molecular Weight Heparins and Analogs as Pharmaceutical Agents

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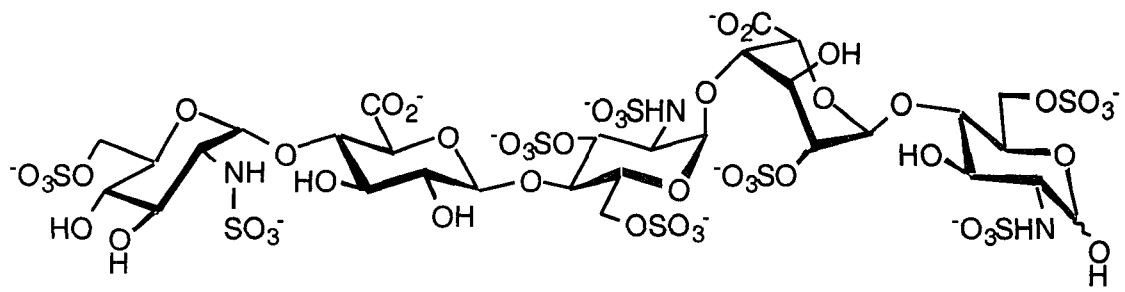
Heparin is widely used as a clinical anticoagulant, which acts on the coagulation cascade through binding and activation of the serine protease inhibitor antithrombin III.[1] Heparin is one of the oldest biopolymeric drugs and among a very few carbohydrate-based therapeutics. Despite its widespread use for 70 years and the recent successful introduction of low molecular weight heparins, the precise chemical structure of heparin remains unknown. Heparin's chemical structure and its structure-activity relationship are currently under extensive investigation.[2] Heparin, and the related heparan sulfate, are sulfated linear polymers with repeating units of glucosamine and uronic acid residues and are members of a class of polysaccharides called glycosaminoglycans (GAGs). Heparin and heparan sulfate exert their biological activities through the localization, stabilization, activation or inactivation of interacting proteins. These interactions play important roles in normal physiology and are also involved in pathological processes.



Structure of the pentasaccharide sequence in heparin responsible for its interaction with antithrombin III.

Although these interactions are of great biological importance, structural requirements for protein-GAG binding have not been well characterized.[3] Both the presence of specifically positioned sulfo groups on the GAG and consensus sequences clustering of basic residues in the protein have been proposed to be important in GAG-protein interactions. The interaction of heparin and heparan

sulfate with various proteins including, growth factors,[4] virus envelope proteins,[5] chemokines,[6] and serine protease inhibitors[1] will be presented. The structures, of the various protein-binding sites for their GAG ligand, the specificity, binding affinity are of physiological and pharmacological relevance. Finally, the glycomics of GAG structure across tissues and organs and its impact on developmental biology,[7] normal physiology and pathophysiology[8] will be discussed.

The introduction of a new class of heparin-based agents, low molecular weight heparins (LMWHs) represent a major success in the application of our basic scientific knowledge of heparin to clinical medicine.[9] These drugs have enhanced bioavailability and improved pharmacodynamics. The LMWH, Lovenox, has, to a great extent, replaced heparin as the anticoagulant drug of choice in the U.S. and Europe. The introduction of generic LMWHs are now on the horizon. Thus, the interest of the pharmaceutical industry in this area has never been greater. New directions in the development of heparin-based anticoagulants will be discussed.

Studies are underway in our laboratory on the chemoenzymatic synthesis of new heparin and heparin analogs as well as their analysis. Improved heparin analogs might solve some current problems associated with the clinical application of these agents as anticoagulants. Furthermore, our improved understanding of the proteins within the body that interact with heparin and the precise nature and specificity of these interactions is being used to design novel heparin-based therapeutics. These agents might exhibit other biological and pharmacological activities resulting in the development of new classes of heparin-based drugs.

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