Sulfated Galactan as an Anticoagulant and Antithrombotic Agent

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Cardiovascular diseases are the leading causes of death, and thrombosis appears as a primary complication of these diseases. Heparin is the initial choice of anticoagulant for the treatment and prevention of most thromboembolic conditions, although it presents several side effects. This explains the current efforts to develop new antithrombotic agents. Recently, we isolated a sulfated galactan (SG) from the red algae *Botryocladia occidentalis,* a potent anticoagulant due the ability to enhance thrombin and factor Xa inhibition by antithrombin (AT) and/or heparin cofactor II, as heparin does. Assays using specific ligands for thrombin exosites I and II had demonstrated that the SG binds to thrombin exosite II, the same site of heparin binding. However, experiments carried out using affinity columns showed that the SG possesses higher affinity for thrombin and lower for AT, when compared to heparin. These results indicate that the SG and heparin differ in the assembly mechanism to achieve the thrombin inhibitory complex. Initially, SG associates with thrombin and only then interacts with AT and induces the formation of a covalent complex between the protease and the coagulation inhibitor. SG is also a potent antithrombotic agent when tested in animal experimental models of venous and arterial thrombosis. However, SG has also an unexpected action inducing platelet aggregation, which prevents its antithrombotic effect at higher doses. In order to overcome this undesirable effect we prepared low-molecular-weight (LMW) derivatives of the SG using mild acid hydrolysis. The decrease of the molecular weight of the sulfated galactan reduces its anticoagulant activity, abolishes the undesirable effect on platelet but does not modify its antithrombotic action in venous and arterial models. Finally, native and LWM derivatives of the SG show no bleeding effect. Overall, ours results indicate that SG achieves similar anticoagulant activity as unfractionated heparin but thought a different mechanism. The reaction starts by the binding of the polysaccharide to thrombin instead of AT. Finally, native and LMW derivatives of SG are potent antithrombotic agents in animal models of thrombosis.

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