Heparin Also Interacts With Selectins and Modulates the Cell Adhesion Process

To the Editor:

We read with great interest the article by Peter and coworkers in the October 5, 1999 issue of Circulation in which the authors demonstrated the binding of heparin to integrin Mac-1 on stimulated leukocytes. Recent investigations have revealed that heparin can modulate biological processes, such as binding to adhesion receptors on endothelial cells and leukocytes. Leukocyte adhesion is a complex molecular process, and multiple adhesion receptor systems mediate the recruitment of leukocytes from the blood. The initial trafficking of circulating leukocytes to sites of inflammation is mediated by the selectin family of adhesion receptors; this is followed by the engagement of additional cellular recognition receptors, including the immunoglobulin superfamily and integrins. Heparin interacts with adhesion molecules, including integrin Mac-1 (CD11b/CD18) and selectins.1,2

Peter and colleagues speculated that the binding of heparin to Mac-1 and the consequent inhibition of Mac-1 ligand binding could directly modulate coagulation, inflammation, and cell proliferation. They failed to mention the role of other adhesion molecules, such as selectins, in this process. We would like to bring to the authors’ attention our study on the role of heparin in the cell adhesion process.3,4 This study revealed that heparin inhibits leukocyte adhesion by antagonizing the function of selectins. We evaluated the efficacy of sulfated polysaccharides (unfractionated heparin, low-molecular-weight heparin, heparan sulfate, chondroitin sulfate, and dextran sulfate) on leukocyte accumulation in the infarcted brain and found that the administration of these sulfated polysaccharides led to reduced leukocyte accumulation. The relative potency of leukocyte accumulation inhibition of the sulfated polysaccharides tested was as follows: dextran sulfate ≫ unfractionated heparin > low-molecular-weight heparin ≫ chondroitin sulfate ≫ heparan sulfate. Potency was correlated with the molecule’s degree of sulfation. We hypothesized that leukocyte recruitment was due to an interaction between leukocyte selectins and carbohydrate ligands, such as the sulfated polysaccharide side chains of proteoglycans on the endothelial cell surface. Therefore, in addition to integrin Mac-1, selectins also play an important role in the cell adhesion process, and this promiscuous binding of heparin may modulate inflammation and cell proliferation.

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Response

We thank Yanaka et al for their comments on the effects of heparin in cell adhesion processes. Indeed, because of space restrictions, we did not discuss the multiple functions of heparin in depth in our article.2 We agree that the inhibition of P- and L-selectin by heparin may participate in the modulation of cell adhesion by heparin.

Only a few reports have addressed the inhibition of cell adhesion by heparin. Most of these reports demonstrate an overall inhibitory effect of heparin on leukocyte recruitment, without defining the nature of the inhibition. For example, Yanaka et al demonstrated that heparins inhibit leukocyte accumulation, reduce infarct size, and improve outcome in cerebral ischemia in a rat model. At least 2 reports define the inhibition of selectins as a potential mechanism by which heparin modulates cell adhesion. In an original approach, Nelson et al demonstrated that heparins directly inhibit L- and P-selectin; they further demonstrated reduced neutrophil influx in an in vivo model of acute inflammation. Koenig et al3 proved that L- and P-selectin were inhibited by heparins. For unfractionated heparin, the IC50 (concentration that inhibits 50%) was ≈10-fold less than the recommended levels for anticoagulation in an in vitro binding assay that evaluated L- and P-selectin–mediated cell adhesion.

Two major adhesion steps of the cascade of leukocyte adhesion, the initial rolling that is mediated by selectins and the buildup of a firm adhesion that is mediated by integrins such as Mac-1, can be inhibited by heparin. As shown by us for the inhibition of Mac-1,7 the inhibition of L- and P-selectin is also achieved at heparin concentrations commonly used in the clinic. Thus, besides its anticoagulative properties, heparin may provide significant benefits by the blocking leukocyte adhesion and function in clinical settings such as cerebral and myocardial ischemia, restenosis after angioplasty, and thrombosis.

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