The Synthetic Pentasaccharide Fondaparinux Attenuates Myocardial Ischemia-Reperfusion Injury in Rats Via STAT-3

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Résumé en anglais	Acute myocardial infarction is a leading cause of mortality and morbidity worldwide. Although essential for successful recovery, myocardium reperfusion is associated with reperfusion injury. Two major cell survival signaling cascades are known to be protective against ischemia-reperfusion (I/R) injury: the reperfusion injury salvage kinase, including Akt, extracellular signal–regulated kinase 1/2, and the downstream target GSK-3β, and the survivor activating factor enhancement, which involves STAT-3. Pharmacologic inhibition of factor Xa has been shown to attenuate I/R injury, but the cellular mechanism is poorly understood. Our aim was to determine the role of whole blood in fondaparinux (FDX)-induced cardioprotection and the involvement of reperfusion injury salvage kinase and survivor activating factor enhancement pathways. We investigated FDX ability to prevent in vivo I/R injury using a transient coronary ligation rat model and ex vivo using a model of crystalloid-perfused isolated rat heart. In both models, infarct size was assessed after 120 min of reperfusion. Myocardial tissues were collected after 15 and 30 min of reperfusion for Western blot analysis. In vivo, FDX decreased infarct size by 29% and induced significant STAT-3 and GSK-3β phosphorylation in comparison to controls. Adding AG490, an inhibitor of JAK/STAT pathway, before I/R, prevented STAT-3 phosphorylation and abolished FDX-induced cardioprotection. On the contrary, FDX did not have an effect on infarct size or hemodynamic parameters in the isolated-heart model. Fondaparinux decreased I/R injury in vivo, but not in a crystalloid-perfused isolated heart. Under our experimental conditions, FDX required whole blood to be protective, and this beneficial effect was mediated through STAT-3 phosphorylation.

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