Direct Rivaroxaban-Induced Factor Xa Inhibition Proves to be Cardioprotective in Rats

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Résumé en anglais	BACKGROUND: Acute myocardial infarction is a leading cause of death worldwide. Though highly beneficial, reperfusion of myocardium is associated with reperfusion injury. While indirect inhibition of Factor Xa has been shown to attenuate myocardial ischemia-reperfusion (I/R) injury, the underlying mechanism remains unclear. Our study sought to evaluate the effect of rivaroxaban (RIV), a direct inhibitor of Factor Xa, on myocardial I/R injury and determine its cellular targets. EXPERIMENTAL APPROACH: We used a rat model of 40-minutes coronary ligation followed by reperfusion. RIV (3 mg/Kg) was given per os 1 hour before reperfusion. Infarct size and myocardial proteic expression of survival pathways were assessed at 120 and 30 minutes of reperfusion, respectively. Plasmatic levels of P-selectin and von Willebrand factor were measured at 60 minutes of reperfusion. Cellular RIV effects were assessed using hypoxia-reoxygenation (H/R) models on human umbilical vein endothelial cells and on rat cardiomyoblasts (H9c2 cell line). KEY RESULTS: RIV decreased infarct size by 21% (42.9% vs. 54.2% in RIV-treated rats and controls respectively, $p < 0.05$) at blood concentrations similar to human therapeutic (387.7 ± 152.3 ng/mL) levels. RIV had no effect on H/R-induced modulation of endothelial phenotype, nor did it alter myocardial activation of RISK and SAFE pathways at 30 min after reperfusion. However, RIV exerted a cytoprotective effect on H9c2 cells submitted to H/R. CONCLUSION: RIV decreased myocardial I/R injury in rats at concentrations similar to human therapeutic ones. This protection was not associated with endothelial phenotype modulation but rather with potential direct cytoprotection on cardiomyocytes.
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