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IS NLRP3 INFLAMMASOME A NEW PHARMACOLOGICAL TARGET IN MYOCARDIAL ISCHEMIA/REPERFUSION INJURY?

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Objectives: Recently it has been documented that the NLRP3 inflammasome plays a pivotal role in the inflammatory response to tissue injury. The NLRP3 inflammasome is a large multimeric danger-sensing platform that induces activation of the caspase-1 and mediates the cleavage of inactive pro-IL-1 β , among other proteins, into its active form. We have shown that the activation of the NLRP3 inflammasome exacerbates myocardial ischemia/reperfusion (I/R) injury in diabetic mice. Moreover, our group previously demonstrated that INF-4E inhibits NLRP3, ATPase and caspase-1 activities in THP-1 cells. Here we test in an ex-vivo model whether INF-4E inhibiting NLRP3 may positively affect I/R injury, post-ischemic cardiac function and molecular response in the rat hearts.

Materials and methods: Isolated hearts from male Wistar rats (body weight 450-550 g; n=7) underwent perfusion without ischemia (Sham) or I/R (30-min ischemia plus 20-min or 60 min reperfusion) with and without IFN-4E treatment (50M for 20-min before ischemia). Coronary perfusion pressure and left ventricular pressure (LVP) were monitored, and dP/dt_{max} assessed during the entire period of perfusion. Biopsies obtained at the end of reperfusion were used for Western blotting evaluations of NLRP3 and caspase-1 (apoptosis index) levels/activities and for assessment of RISK pathway involvement. At the end of 60 min reperfusion infarct size was measured with nitro-blue-tetrazolium technique by an independent observer.

Results: In this preliminary study, the 20 min IFN-4E pre-ischemic administration induced a significant reduction of infarct size and an improvement in post-ischemic LVP recovery. Western blot analysis demonstrated NLRP3 and caspase-1 activation by I/R procedure, which were strongly attenuated after IFN-4E pre-treatment. Moreover, an important modulation of RISK kinase phosphorylation was observed, though a clear-cut correlation between the reduction in infarct size and phosphorylation of RISK kinases was not observed.

Conclusions: These preliminary results demonstrate that the IFN-4E inhibits the formation of the NLRP3 inflammasome in the rat heart and ameliorates the response to myocardial I/R injury, confirming the ability of this drug to affect NLRP3 inflammasome complex activation.