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DO P2Y12RECEPTOR ANTAGONISM AND NLRP3INHIBITION EXERT ADDITIVE CARDIOPROTECTIVE EFFECTS AGAINST ISCHEMIA/REPERFUSION INJURY?

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Introduction: P2Y12receptor antagonists, including Ticagrelor, are routinely used in patients with acute coronary syndromes. Inhibition of the P2Y12receptor somehow triggers protective signaling of ischemic conditioning via a platelet-dependent mechanism. Recently, we have contributed to demonstrate the pivotal role of NLRP3inflammasome pathway in myocardial dysfunction. Here we investigated whether selective NLRP3inflammasome inhibition exerts additive effects on myocardial protection induced by the P2Y12receptor antagonist Ticagrelor.

Materials and Methods: Ticagrelor (150 mg kg-1) was orally administered to rats for three consecutive days. At the end of treatment, hearts were isolated and subjected to a protocol of ischemia/reperfusion (30 min ischemia/60 min reperfusion; I/R). In hearts of animals pretreated or not with Ticagrelor, the selective NLRP3inflammasome inhibitor INF4E (50 μM) was infused just before the I/R protocol. For comparative purpose, isolated hearts were treated with Ticagrelor (3.70 μM before ischemia) and subjected to I/R. At the end of reperfusion, infarct size (IS) was assessed by an independent observer with nitro-blue-tetrazolium technique and expressed as a percentage of total left ventricular mass (LVM).

Results: Pre-treatment with Ticagrelor significantly reduced IS (49±3% LVM) when compared to control I/R group (65±3% LVM). Similarly, acute administration of INF4E just before the I/R injury resulted in significant IS reduction (42±6% LVM). The formation of the NLRP3inflammasome complex was induced by myocardial IR and attenuated by INF4E acute treatment, not being affected by acute or repeated exposure to Ticagrelor. The beneficial effects induced by either P2Y12antagonism or NLRP3inhibition were associated with a marked improvement of the protective Reperfusion Injury Salvage Kinase (RISK) pathway. In contrast, no protective effects were recorded when Ticagrelor was administered acutely before ischemia. No synergist effects were recorded when Ticagrelor was co-administered with INF4E before the induction of ischemia. The acute exposure to INF4E of hearts of animals pretreated with Ticagrelor showed a slight, not statistically significant, additive cardioprotective effect.

Discussion and conclusion: The NLRP3inhibitor is protective when administered to blood-free, isolated hearts suggesting that the lethal inflammasome is mainly located in cardiac tissue rather than the blood. On the contrary, Ticagrelor induces cardioprotection when given to the whole animal only, indicating that its direct target is not in the heart. Besides, these findings indicate that Ticagrelor needs platelet (or its factors) to trigger its beneficial effects against ischemia/reperfusion. Nevertheless, the co-infusion of the two inhibitors has a little, if any, adjunctive cardioprotective effect.