EFECTS OF IRBESARTAN ON THE MYOCARDIAL ISCHEMIA/REPERFUSION INJURY IN ZDF RATS WITH METABOLIC SYNDROME

Di Filippo Clara[1,2], Lampa Enrico[1,2], Martella Raffaele[3] , Vargiu Giuseppe[4], Paizis Georges[4], D'Amico Michele [1,2]

[1]Department of Experimental Medicine, Section of Pharmacology L. Donatelli,[2]"Excellence Centre for Cardiovascular Disease", and [3]Department of Geriatrics and Metabolic Diseases, 2nd University of Naples, Italy. [4]Sanofi-Aventis, Milano

We investigated the potential cardio-protective effect of irbesartan against the acute myocardial infarct induced in a experimental model of metabolic syndrome. The study was performed on obese-diabetic-hypertensive (ZDF) rats and lean controls (Sprague-Dawley rats) treated or not with irbesartan, for three weeks, at the doses of 3-10-30 mg/kg/day by oral route. The treatment was done for three weeks. In vivo myocardial infarct was induced as previously described (1). At the end of the treatment period rats were subjcted to myocardial ischemia (25 min) followed by two hours of reperfusion procedure. Measurement of area at risk (AR) and infarct size (IS) were assessed by staining with Evans blue dye and by computerized planimetry using an image analysis software program. Functional parameters (mean arterial blood pressure, the heart rate, and the pressure rate index) were monitored during the I/R period. Local tissutal biochemical changes with specific ELISA methods (e.g. the myeloperoxidase activity, index of leukocytes infiltration within the infarcted tissue, the cytokines TNF-α, IL-1β and the chemokines MIP-1 α, monocyte inflammatory protein-1) and specific markers of oxidative stress released within the cardiac specimens (e.g. nitrotyrosine levels, index of peroxynitrite; malondialdehyde activity, index of lipid peroxidation) were assaied at the end of the reperfusion period. We reported the AT1 antagonist irbesartan being cardio-protective against the myocardial damage induced by the ischemia/reperfusion procedure at doses of 10 and 30 mg/kg/day following three weeks treatment of ZDF rats with metabolic. Particularly, the compound has associated a significant ($P<0.01$) reduction of the cardiac level of cytokines, chemokines, myelopreroxydase activity and markers of oxidative and nitrosative stress to a significant ($P<0.01$) effect of reduction of the necrotic area, likely be 50% smaller for the dose of 30 mg/kg/day if compared to the one in ZDF rats without irbesartan treatment. Interesting enough, the reductive effect of irbesartan in ZDF rats was stronger (almost 38%) than that observed in lean controls subject to the same infarct procedure. To our knowledge this would underline the benefit of irbesartan in reducing the extended myocardial damage as cardiac complicance of metabolic syndrome, due to its ability to block the RAS hyperactivity, and then reduce the consequent release of inflammatory mediators, oxidative stress and the insurgence of the endothelial dysfunction bad companions of the metabolic syndrome.

1) D'Amico M, Di Filippo C, et al., FASEB J, 14:1867-69, 2000.