ADENOSINERGIC SYSTEM AND GENETIC POLYMORPHISMS: POSSIBLE CLINICAL IMPLICATIONS IN THE CARDIOVASCULAR FIELD

Capecchi Pier Leopoldo*, Andreassi Maria Grazia°, Giuntini Serena*, Foffa Ilenia°, Natale Maria Rita*, Pompella Gerarda*, Varani Katia^, Borea Pier Andrea^, Picano Eugenio°, Laghi Pasini Franco*.

* Department of Clinical Medicine and Immunological Sciences, University of Siena. ° CNR, Institute of Clinical Physiology, Pisa and Massa. ^ Department of Clinical and Experimental Medicine, University of Ferrara

Identifying specific genetic variations that influence cardiovascular disease risk provides new opportunities for diagnostic tests, and drug development. Adenosine exerts several protective effects through activation of 3 distinct receptor (AR) subtypes. Common single nucleotide polymorphisms (SNPs) of adenosine system recently described may have important clinical implication in cardiovascular disease. These include the C34T variant of adenosine monophosphate deaminase 1 (AMPD1), and two SPNs in $A_{2A}R$ (C263→T and 1976C→T). AMPD1 C34T variant gene was associated with a prolonged survival in heart failure and coronary artery disease, hypothetically linked to an enhanced adenosine production. Since adenosine administration is a promising approach for the prevention of I/R in myocardial revascularization, we investigated if the AMPD1 (34T) allele is associated with a favourable prognosis after coronary revascularization. We studied 161 patients receiving coronary revascularization (70 coronary angioplasty and 91 coronary artery bypass). Plasma adenosine was also measured by HPLC methods in a subset of patients. Our results indicate that AMPD1 (34T) allele is not associated with a more favourable outcome after revascularization. In addition, plasma adenosine levels were similar for AMPD1 (34T) and AMPD1 (C34) allele subjects (290.5±31.0 vs 303.3±28.5 nM, p=n.s.). As regards $A_{2A}R$ gene polymorphisms, the 1976C→T but not C263→T gene polymorphism was associated with individual differences in the acute anxiogenic response to caffeine and amphetamine suggesting that this genetic variability may be functionally relevant. Therefore, we assessed if $A_{2A}R$ receptor (263 C→T and 1976 C→T) polymorphism may affect coronary flow reserve (CFR) response in patients with non-ischemic dilated cardiomyopathy (DCM) undergone dipyridamole (0.84 mg/kg) stress echocardiography. We enrolled 44 DCM patients who had an ejection fraction <40% (mean 21.1±16.3) and normal coronary arteries. CFR was assessed on left anterior descending coronary artery using Doppler as the ratio of maximal peak vasodilation (dipyridamole) to rest diastolic flow velocity. No correlation was found between CFR and 263 C→T variant of $A_{2A}R$ gene. On the contrary, patients with 1976 TT genotype had significantly lower values than 1976 CC patients (2.3±0.7, 2.0±0.4 and 1.8±0.3 for CC, CT and TT, respectively; $p<0.05$). In DCM patients 1976 C→T polymorphism of the adenosine A2A receptor gene may affect CFR response. In particular, the 1976-TT variant of A2a gene blunts the coronary vasodilatory response. Thus, SNPs of the $A_{2A}R$ gene are new candidate genes for cardiovascular risk.