CHANGES OF A_{2A} RECEPTORS IN CHRONIC HEART FAILURE: A BIOCHEMICAL STUDY BEFORE AND AFTER HEART TRANSPLANTATION

Camurri A., 3° anno di corso del Dottorato in Farmacologia Clinica. Sede di servizio: Dip. Medicina Clinica e Scienze Immunologiche, Univ. Siena; Dip. Scienze Farmacologiche, Univ. Milano.

Neurohumoral factors and some proinflammatory cytokines (including TNFa and IL-6) play a pathogenic role in Chronic Heart Failure (CHF) and are involved in the immunologic response, myocardial damage and myocyte apoptotic death during acute allograft rejection of transplanted heart. Cytokines production from peripheral blood mononuclear cells (PBMC) seems to mirror the activation state of inflammatory cells infiltrating failing heart and cardiac allograft during acute rejection.
Adenosine plays important protective effects at the cardiovascular level through the activation of its membrane receptors; recent studies have shown that activation of the adenosine adenylyl cyclase-linked A_{2A} receptor reduces TNFa release. Therefore, pathological alterations of the adenosinergic system may contribute to the development of cardiac dysfunction.
On this basis, we have designed a study aimed at monitoring the status of the A_{2A} receptor in PBMC and (when available) in myocardial tissue from the explanted hearts of CHF patients undergoing cardiac transplantation. Various A_{2A} receptor parameters (i.e., binding, mRNA levels and adenylyl cyclase activity) have been evaluated; concomitantly, determination of adenosine and TNFa concentrations has been carried out in the blood of the same patients.
In PBMC of CHF patients we have found an increase of the number of A_{2A} receptors and of A_{2A} receptor mRNA levels; a concomitant increased response of A_{2A}-receptor stimulated adenylyl cyclase activity with respect to normal subjects was also found. The same alteration of A_{2A} receptors has been found at myocardial level, suggesting that the peripheral circulating cells of CHF patients express the same changes of A_{2A} receptors occurring in the failing heart.
Moreover, we are currently evaluating the ability of A_{2A} receptor agonists to decrease the production of inflammatory cytokines in PBMC of CHF patients and healthy subjects upon *in vitro* stimulation with LPS. With this analysis, it will be possible to correlate the detected levels of A_{2A} receptors (both mRNA and protein), with the ability of this receptor to modulate cytokine release in the peripheral cells of the same patients at various disease stages.
In a cohort of patients undergoing heart transplantation, A_{2A} receptor mRNA levels and A_{2A} receptor number in PBMC returned to normal values within 6 months after transplantation.
Globally, these data suggest an increase of A_{2A} receptor function in CHF, likely reflecting an attempt to reduce excessive cytokine release, and a progressive restoration of a normal adenosinergic system, at least in terms of A_{2A} receptor expression, after heart transplantation, in association with the improvement of cardiac performance.
These results suggest that the adenosinergic system play an important role in CHF, and that the evaluation of A_{2A} receptor parametrs in peripheral blood cells may be useful for monitoring hemodynamic changes and the efficacy of pharmacological treatments in CHF patients.