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Cardiac primitive cells in the adult human heart are influenced by Angiotensin II in chronic heart failure

Daria Nurzynska[1], Franca Di Meglio[1], Clotilde Castaldo[1], Rita Miraglia[1], Veronica Romano[1], Anna Maria Sacco[1], Valeria Barbato[1], Giuseppina Granato[1], Immacolata Belviso[1], Ciro Bancone[2], Alessandro Della Corte[2], Stefania Montagnani[1]

[1] Department of Public Health, University of Naples "Federico II, 80131 Naples, Italy
[2] Department of Cardiothoracic Sciences, Second University of Naples, 80131 Naples, Italy

Angiotensin II (AngII) levels are often increased in patients with cardiovascular disease and different AngII receptor (ATR) blockers are commonly used in heart failure therapy. An increase in number of cardiac primitive cells (CPCs) has been found in adult human pathological heart and these cells express AT1 and AT2 receptors (ATR). Hence, it is conceivable that AngII and ATR blockers influence CPC properties. In this study we investigated the effects of AngII and AT1R, AT2R blocking on human CPCs *in vitro*.

CPCs were isolated from adult human hearts with ischemic cardiomyopathy (n=11) by tissue digestion and adherent CD117(+) cells immunomagnetic separation. Cells were cultured in the presence of AngII 0,1 and 1μM for 24 hr with and without pretreatment with 1μM valsartan - AT1R blocker (AT1RB), 1μM PD 123319 - AT2R blocker (AT2RB), 10μM telmisartan - AT1RB with PPAR activity, 1μM GW9662 - PPARγ blocker (PPARB). The expression of PPARγ was evaluated by electrophoresis and immunoblotting, while the proliferation of cells was evaluated by MTT assay.

Administration of AngII stimulated proliferation of CPCs. The expression of PPAR γ increased 8,5 and 11,8-fold ($p<0,05$, n=3) in the presence of 0,1 and 1uM AngII, respectively. In the presence of AT1RB, proliferation of cells did not change significantly but it increased 1,5 and 2,1-fold ($p<0,05$, n=3) after addition of 0,1 and 1uM AngII, respectively, suggesting that this effect was modulated by stimulation of AT2R. In the presence of AT2RB, both basal and AngII-stimulated proliferation increased, particularly at lower AngII concentration. Interestingly, PPARγ antagonist reduced cell survival, but this effect was inversed by addition of AngII, probably due to the AngII-mediated increase of PPAR expression. Pretreatment of CPCs with AT1RB with PPAR activity increased basal cell proliferation, but was not beneficial in the presence of AngII when compared to pure AT1RB.

The results indicate that AT1RB increases CPC proliferation mostly at higher AngII concentrations, while AT2RB has similar effect in the presence of low AngII levels. Hence, complex interactions between AngII and both AT1 and AT2 receptors take place in heart failure patients and influence the survival of CPCs in concentration dependant manner.

Keywords

Cardiac primitive cells, angiotensin II, angiotensin II receptors, cell proliferation.