HEART FAILURE AND THE CARDIAC BETA-ADRENOCEPTOR

Otto-Erich Brodde

Introduction

In the human heart contractility and heart rate are regulated by receptor systems that act through accumulation of intracellular cAMP (G_s-protein coupled), by receptor systems that act through inhibition of cAMP formation (G_j-protein coupled) and by receptor systems that act independently of cAMP formation possibly through the phospholipase C/diacylglycerol/inositol-1,4,5-triphosphate (PLC/DAG/IP3)-pathway (Figure 1). Among all these receptors the β-adrenoceptor-G_s-protein-adenylate cyclase-cAMP system is the most powerful physiological mechanism to alter acutely contractility and heart rate. This chapter, deals with the properties of β-adrenoceptors in the human heart and their alterations in chronic heart failure.

β_1- and β_2-adrenoceptors in the nonfailing human heart

In the human heart both, β_1- and β_2-adrenoceptors coexist; this has been first demonstrated by radioligand binding studies, and was subsequently confirmed by functional experiments. The number of β-adrenoceptors is quite evenly distributed in right and left atrial and ventricular tissue; however, the proportion of β_2-adrenoceptors is somewhat higher in the atria (approximately 1/3 of the total β-adrenoceptor population) than in ventricular myocardium (about 20% of the total β-adrenoceptor population, and may be even higher (up to 50%) in the atrio-ventricular conducting system.

Both β_1- and β_2-adrenoceptors couple to adenylate cyclase and cause increases in the intracellular amount of cAMP. Interestingly, in the human heart adenylate cyclase is preferentially activated by β_2-adrenoceptor stimulation although β_1-adrenoceptors predominate: in human right atrial membranes β_2-adrenoceptor selective agonists such as fenoterol, propranolol and terbutaline caused activation of adenylate cyclase activity.
that amounted to about 50-70% of that of isoprenaline$^{8,12,13}$ although only 30% of the total β-adrenoceptor population is of the β$_2$-subtype. Similarly, in ventricular membranes of the human heart the β$_2$-adrenoceptor agonists terbutaline and zinterol caused 50% of maximal isoprenaline activation,$^{3,13}$ and isoprenaline, adrenaline, and noradrenaline evoked their stimulatory effects on adenylate cyclase activity predominantly via β$_2$-adrenoceptor stimulation$^{5,10}$ although only 20% of the whole

---

**Figure 1.** Receptor systems and their signal-transduction mechanisms in the non-failing human heart. For details see text.

**Abbreviations:** $\beta_1$, $\beta_2$, $\alpha_1$ = $\beta_1$, $\beta_2$, and $\alpha_1$-adrenoceptors; $H_2$ = histamine H2-receptors; 5-HT$_4$ = 5-HT$_4$-receptors; VIP = vasoactive intestinal peptide receptors; PGE$_1$ = prostaglandin E$_1$-receptors; Glu = glucagon receptors; $A_1$ = adenosine A$_1$-receptors; $M_2$ = muscarinic M$_2$-receptors; $SS$ = somatostatin-receptors; $AII$ = angiotensin II-receptors; $ET$ = endothelin-receptors; $G_s$ = stimulatory guanine nucleotide binding protein; $G_i$ = inhibitory guanine nucleotide binding protein; C = catalytic unit of adenylate cyclase; PLC = phospholipase C; PIP$_2$ = phosphatidylinositol 4,5-bisphosphate; DAG = 1,2-diacylglycerol; IP$_3$ = inositol-1,4,5-trisphosphate; ISO = isoprenaline; $\Theta$ = activation; $\Theta$ = inhibition.

Right atrium = positive inotropic effects were determined on isolated electrically driven right atria from patients without apparent heart failure undergoing coronary artery bypass grafting. Ventricular myocardium = positive inotropic effects were determined on isolated electrically driven right and left ventricular preparations obtained from would-be cardiac transplant donors.

From Brodde et al.$^1$