**Summary**

In patients with chronic heart failure, cardiac β-adrenoceptor function is decreased, and this decrease is related to the degree of heart failure. Under these conditions, treatment with β-adrenoceptor agonists seems to be of limited value as it might further down-regulate cardiac β-adrenoceptors, resulting, finally, in a loss of therapeutic efficacy. However, β-adrenoceptor antagonists might have beneficial effects, because they can protect the myocardium from the deleterious effects of elevated endogenous catecholamines and can, simultaneously, restore the previously down-regulated β-adrenoceptor function. Stimulation of cardiac α-adrenoceptors, however, seems not to be of any therapeutic value in patients with chronic heart failure, because a) the number of α-adrenoceptors in the human heart is very low and its function is not completely understood, and b) no α-adrenoceptor agonist is presently available that selectively stimulates cardiac α-adrenoceptors without concomitantly activating vascular α-adrenoceptors. In acute myocardial ischemia, cardiac β-adrenoceptors increase; this increase is – at least in early acute myocardial ischemia – accompanied by an increased β-adrenoceptor functional responsiveness; thus, under these conditions, β-adrenoceptor agonists again might not be of clinical value, while β-adrenoceptor antagonists may exert beneficial effects, because they can block (over)activation of the sensitized β-adrenoceptors by elevated endogenous catecholamines.

**Introduction**

Adrenoceptors were originally subdivided into the subtypes α and β based on the findings that catecholamines evoked their effects on different organs with different orders of potency [3]. α-Adrenoceptors mediate catecholamine-induced vasoconstriction; at these receptors noradrenaline and adrenaline are much more potent than isoprenaline. β-Adrenoceptors mediate the myocardial effects of the catecholamines; at these receptors isoprenaline is more potent than noradrenaline and adrenaline. It later became clear that both α- and β-adrenoceptors can be subdivided into at least two major subtypes: α₁ - and α₂ - and β₁ - and β₂-adrenoceptors (for reviews see [10, 27, 61, 64]).

**Cardiac β-adrenoceptors**

Beta-adrenoceptors were originally subclassified [40] into cardiac β₁-(noradrenaline and adrenaline equipotent) and vascular and bronchial smooth muscle β₂-adrenoceptors (adrenaline about 10–30 times more potent than noradrenaline). However, it rapidly became apparent that this organ-specific subclassification was an oversimplification; it is now generally accepted that, in a variety of tissues including the heart of various species, β-adrenoceptors are...
not a homogeneous population but that $\beta_1$- and $\beta_2$-adrenoceptors coexist [10, 11, 49, 62]. This holds true also for the human heart, where several groups have convincingly demonstrated the coexistence of $\beta_1$- and $\beta_2$-adrenoceptors, first by radioligand binding studies, and subsequently, by functional experiments [10, 11, 37, 62]. Both $\beta_1$- and $\beta_2$-adrenoceptors are coupled to adenylate cyclase [6, 20, 38] and can mediate positive inotropic effects of $\beta$-adrenoceptor agonists. Among the classical catecholamines isoprenaline and adrenaline cause their positive inotropic effects on the human heart via stimulation of $\beta_1$- and $\beta_2$-adrenoceptors, while noradrenaline, the main transmitter of the sympathetic nervous system, evokes its positive inotropic effect predominantly, if not exclusively, via $\beta_1$-adrenoceptor stimulation [33, 38, 50, 73].

In the last few years evidence has accumulated that in patients with chronic heart failure cardiac $\beta$-adrenoceptor density and functional responsiveness are markedly reduced, and the amount of this reduction is related to the degree of heart failure (as judged clinically by NYHA functional class) [5, 7, 9, 13, 19]. Such a decrease might be very likely caused by “endogenous” down-regulation through elevated catecholamines, since it is well known that in chronic heart failure plasma noradrenaline levels are elevated in response to the depressed cardiac function [31, 32]. Interestingly, the etiology of heart failure and/or some other (presently unknown) factors seem to differentially regulate cardiac $\beta_1$- and $\beta_2$-adrenoceptors in heart failure; while in all kinds of heart failure $\beta_1$-adrenoceptors are decreased in number and function, $\beta_2$-adrenoceptors are not altered in end-stage idiopathic dilated cardiomyopathy [5, 9, 19] and in patients with aortic valve disease [46], but are down-regulated to a very similar extent as $\beta_1$-adrenoceptors in end-stage ischemic cardiomyopathy [13], mitral valve disease [14], and tetralogy of Fallot [13].

We were interested in studying whether such a down-regulation of $\beta_1$- and $\beta_2$-adrenoceptors may also occur during long-term treatment with $\beta$-adrenoceptor agonists. Therefore, we have determined the effects of chronic treatment of healthy volunteers with the selective $\beta_1$-adrenoceptor agonist xamoterol [25, 55] and the selective $\beta_2$-adrenoceptor agonist procaterol [71, 72] on the number of $\beta$-adrenoceptors in circulating lymphocytes (containing exclusively $\beta_2$-adrenoceptors, see [18]) and on $\beta_1$- and $\beta_2$-adrenoceptor-mediated in vivo physiological effects [12]. As $\beta_1$-adrenoceptor-mediated in vivo physiological effects, we determined isoprenaline infusion-induced increases in systolic blood pressure and exercise-induced tachycardia; as $\beta_2$-adrenoceptor-mediated effect isoprenaline infusion-induced decreases in diastolic blood pressure; in addition, isoprenaline infusion-induced tachycardia was assessed as a mixed (cardiac) $\beta_1$- and $\beta_2$-adrenoceptor mediated effect [12].

After 14 days oral treatment of healthy volunteers with the selective $\beta_1$-adrenoceptor agonist xamoterol, the lymphocyte $\beta_2$-adrenoceptor density was not changed (Fig. 1); however, the isoprenaline-induced increase in systolic blood pressure and the exercise-induced tachycardia were significantly decreased (Figs. 2 and 3), while the isoprenaline-induced decrease in diastolic blood pressure was not affected (Fig. 2), indicating that under these conditions $\beta_1$-adrenoceptor-mediated effects are attenuated while $\beta_2$-adrenoceptor-mediated effects are not. The isoprenaline-induced increase in heart rate (the mixed $\beta_1$- and $\beta_2$-adrenoceptor mediated effect) was also decreased following the xamoterol treatment (Fig. 3) but to a lesser extent than the pure $\beta_1$-adrenoceptor-mediated effects [12].

In contrast to the xamoterol treatment, after 9 days treatment of healthy volunteers with the selective $\beta_2$-adrenoceptor agonist procaterol, lymphocyte $\beta_2$-adrenoceptor density was significantly reduced by about 35% (Fig. 1). Concomitantly, the isoprenaline-induced decrease in diastolic blood pressure (the $\beta_2$-adrenoceptor-mediated effect) was significantly attenuated (Fig. 2) while the isoprenaline-induced increase in systolic blood pressure and the exercise-induced tachycardia (the $\beta_1$-adrenoceptor-mediated effects) were not at all affected (Figs. 2 and 3). Isoprenaline-induced tachycardia (the mixed $\beta_1$- and $\beta_2$-adrenoceptor-mediated effect) was also attenuated (Fig. 3), but to a lesser extent than the pure $\beta_2$-adrenoceptor mediated decrease in diastolic blood pressure [12]. These results demonstrate that, obviously, in general long-term treatment of patients with $\beta$-adrenoceptor agonists (for example $\beta_2$-adrenergic bronchodilators in the therapy of asthma or $\beta_1$-adrenergic positive inotropic drugs in the therapy of chronic...