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Differential regulation of human cardiac β-adrenergic and muscarinic receptors by chronic β-adrenoceptor antagonist treatment

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In patients undergoing coronary artery bypass grafting chronic β_1-adrenoceptor antagonist treatment increased right atrial β_1-adrenoceptor number, did not affect β_2-adrenoceptor number and decreased muscarinic M_2-receptor number. Concomitantly, the M_2-receptor-mediated negative inotropic effect of carbachol was reduced, while the β_1-adrenoceptor-mediated positive inotropic effect of noradrenaline was not altered. The β_2- adrenoceptor mediated positive inotropic effect of procaterol, however, was markedly enhanced. We conclude that chronic β_1-adrenoceptor antagonist treatment increases β_1-adrenoceptor number, sensitizes β_2-adrenoceptor function and desensitizes M_2-receptor function in the human heart.

Keywords β_1- and β_2-adrenoceptors in the human heart muscarinic M_2-receptors in the human heart chronic β_1-adrenoceptor antagonist treatment

Introduction

β-adrenoceptor antagonists are commonly used in the therapy of hypertension and angina pectoris (McDevitt, 1979). Several groups have shown that following chronic β-adrenoceptor antagonist treatment β-adrenoceptor density is increased in rat heart, lung and lymphocytes, as well as in human heart and lymphocytes (for references see Brodde & Wang, 1988). On the other hand, nothing is known of whether and how chronic β-adrenoceptor antagonist treatment might influence parasympathetic activity of the heart. To answer this question in the present study we have investigated the effects of chronic β_1-adrenoceptor antagonist treatment (metoprolol, atenolol, bisoprolol) on density and function of right atrial β_1- and β_2-adrenergic as well as of muscarinic M_2-receptors.

Methods

The study was performed in 64 patients (42–73 years) undergoing coronary artery bypass grafting (NYHA function class I–II) after having given informed written consent. The patients were divided into two groups; group I (38 patients, mean age 58.1 ± 1.2 years) had received no β-adrenoceptor antagonist for at least 6 weeks and was taken as control; group II (26 patients, mean age 59.9 ± 1.5 years) was chronically treated with the β_1-selective antagonists metoprolol (1–4 × 50 mg day^{-1} n = 12), bisoprolol (1 × 10 mg day^{-1} n = 4), or atenolol (1–2 × 25 mg day^{-1} n = 12).

Methods for determination of right atrial β-adrenoceptor density and β-adrenoceptor subtype distribution using (–)-[^{125}I]-iodocyanopindolol (ICYP) binding, of M_2-receptor density using [N-metyl-^{3}H]-scopolamine ([^{3}H]-NMS)

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binding, and of concentration-effect curves for the positive inotropic effect of noradrenaline and procaterol as well as for the negative inotropic effect of carbachol on isolated electrically driven right atria have been described elsewhere (Brodde *et al.*, 1989; Deighton *et al.*, 1990; Michel *et al.*, 1988). The experimental data given in Table 1 are means ± s.e. mean of n experiments; the significance of differences was estimated by non-paired Student's t-test. A P-value smaller than 0.05 was considered to be significant.

Results

Chronic β_1-adrenoceptor antagonist treatment significantly increased right atrial β-adrenoceptor density by about 40%; this increase was solely due to an increase in right atrial β_1-adrenoceptor density (79.7 ± 7.7 (n = 25) *vs* 50.8 ± 5.9 (n = 21) fmol ICYP bound mg^{-1} protein, $P < 0.01$), while β_2-adrenoceptor density was not changed (26.6 ± 6.1 *vs* 22.8 ± 4.9 fmol mg^{-1} protein). On the contrary, in the patients chronically treated with β_1-adrenoceptor antagonists, right atrial muscarinic M_2-receptor number was significantly lower than in non-treated patients (173.7 ± 14.7 (n = 18) *vs* 217.7 ± 15.4 (n = 20) fmol [^{3}H]-NMS bound mg^{-1} protein, $P < 0.05$).

On isolated electrically driven right atria the concentration-effect curve for the positive inotropic effect of noradrenaline (acting in the human heart exclusively via β_1-adrenoceptors, Brodde *et al.*, 1989; Kaumann *et al.*, 1989) was not significantly different in both groups; the concentration-effect curve for the positive inotropic effect of procaterol (acting in the human heart solely via β_2-adrenoceptors, Brodde *et al.*, 1989), however, was in the patients chronically treated with β_1-adrenoceptor antagonists significantly shifted to the left (Table 1).

On the other hand, the concentration-effect curves for the negative inotropic effect of carbachol were in patients chronically treated with the β_1-adrenoceptor antagonists significantly shifted to the right independent of whether determined on atria with force for contraction enhanced with 1 μM procaterol or 100 μM noradrenaline (Table 1).

Discussion

The present results confirmed our recent observation that in patients undergoing coronary artery bypass grafting chronic treatment with β_1-adrenoceptor antagonists subtype selectively increased right atrial β_1-adrenoceptor number but did not affect β_2-adrenoceptor number (Michel *et al.*, 1988). According to the present results, in the same patients muscarinic M_2-receptor number was significantly decreased. While the decrease in muscarinic M_2-receptor number was accompanied by a similar attenuation of the negative inotropic effect of carbachol the β_1-adrenoceptor mediated positive inotropic effect of noradrenaline was not altered although β_1-adrenoceptor number was increased. On the other hand, the β_2-adrenoceptor mediated positive inotropic effect of procaterol was markedly enhanced. Similar observations have been recently reported by Kaumann *et al.* (1989) who showed that in right atria of patients chronically treated with atenolol the positive inotropic effect of adrenaline (acting in the human heart at β_1- *and* β_2-adrenoceptors), but *not* of noradrenaline, was increased.

Thus, in the human heart chronic β_1-adrenoceptor antagonist treatment increases β_1-

Table 1 Effect of chronic β_1-adrenoceptor (AR) antagonist treatment on human right atrial β-adrenergic and muscarinic receptor function

(a) pD_2 values for the positive inotropic effect of noradrenaline and procaterol

	Non-treated	*β_1-AR antagonist-treated*
Noradrenaline	6.16 ± 0.06 (16)	6.30 ± 0.13 (12)
Procaterol	7.63 ± 0.07 (15)	8.24 ± 0.13 (14)**

(b) pD_2 values for the negative inotropic effect of carbachol

Force of contraction enhanced by:		
100 μM noradrenaline	6.63 ± 0.11 (11)	6.29 ± 0.12 (11)*
1 μM procaterol	7.07 ± 0.10 (11)	6.76 ± 0.11 (11)*

Means ± s.e. mean; number of experiments in parentheses.
** $P < 0.01$, * $P < 0.05$ *vs* the corresponding values in non-treated patients.

adrenoceptor number, sensitizes β_2-adrenoceptor function and concomitantly desensitizes muscarinic M_2-receptor function. The mechanism underlying these effects is not known at present. However, it has been recently shown that long term *in vitro* treatment of rat cardiomyocytes with noradrenaline causes a shift in the G_s/G_i-ratio towards elevated G_i protein, resulting in a diminished response of the adenylate cyclase to isoprenaline or forskolin stimulation (Reithmann *et al.*, 1989). On the other hand, long term treatment of a variety of cell types with agonists inhibiting adenylate cyclase (such as muscarinic, α_2-adrenergic or adenosine) potentiates the adenylate cyclase stimulating effects of various hormones (Thomas & Hoffman, 1987). Thus it may well be that chronic β-adrenoceptor antagonist treatment reverses tonic decrease of G_s by endogenous catecholamines thus enhancing G_s-function. Since in the human heart β_2-adrenoceptors are much more efficiently coupled to the adenylate cyclase than β_1-adrenoceptors (Brodde, 1987; Kaumann *et al.*, 1989) such an increase in G_s-mediated coupling of β-adrenoceptor stimulation to adenylate cyclase might enhance β_2-adrenoceptor-mediated responses but may not significantly alter β_1-adrenoceptor-mediated responses.

In conclusion, in human heart chronic β_1-adrenoceptor antagonist treatment increases cardiac β_1-adrenoceptor number, sensitizes β_2-adrenoceptor function and desensitizes muscarinic M_2-receptor function. Such a decrease in muscarinic M_2-receptor function thus attenuating the inhibitory effect of the vagus on β-adrenergic increases in heart rate and/or contractility may considerably contribute to the symptoms of adrenergic hyperreactivity following abrupt withdrawal of β-adrenoceptor antagonists (Prichard *et al.*, 1983).

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