ACUTE ALPHA- AND BETA-ADRENOCEPTOR REGULATION IS IMPAIRED IN HYPOTENSIVE PATIENTS ON MAINTENANCE DIALYSIS

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Summary

Acute stimulation of sympathetic activity by dynamic exercise on a bicycle (80% of maximum heart rate) for 15 minutes in 10 healthy volunteers caused a 100 per cent increase in lymphocyte \( \beta_2 \)-adrenoceptor density. This effect is obviously mediated by \( \beta_2 \)-adrenoceptor stimulation, since propranolol, but not the \( \beta_1 \)-selective antagonist bisoprolol inhibits it. In contrast, platelet \( \alpha_2 \)-adrenoceptor density decreased during exercise by 15–20 per cent. In seven hypotensive haemodialysis patients exercise increased lymphocyte \( \beta_2 \)-adrenoceptor density only slightly (25%) and did not affect platelet \( \alpha_2 \)-adrenoceptors indicating that in hypotensive haemodialysis patients acute regulation of \( \alpha \)- and \( \beta \)-adrenoceptors is impaired.

Introduction

During chronic haemodialysis treatment the activity of the sympathetic nervous system seems to decline [1,2]. We have recently shown that such a decrease of the sympathetic activity is accompanied by a reduced responsiveness of \( \alpha \)- and \( \beta \)-adrenoceptors since in platelets of haemodialysis patients adrenaline-induced inhibition of adenyl cyclase activity (via \( \alpha_2 \)-adrenoceptor stimulation) was significantly reduced and in lymphocytes cyclic AMP responses to isoprenaline (via \( \beta_2 \)-adrenoceptor stimulation) were significantly diminished [3]. To gain further insight into changes of the sympathetic activity in chronic uraemia the effects of acute stimulation of sympathetic activity, induced by dynamic exercise on a bicycle ergometer, on the densities of platelet \( \alpha_2 \)-adrenoceptors (assessed by \(^3\)H-yohimbine binding) and of lymphocyte \( \beta_2 \)-adrenoceptors (assessed by \((-)^{125}\)iodocyanopindolol (ICYP) binding) were determined in haemodialysis patients with inter-dialytic hypotension and compared with those in healthy controls.
Subjects and methods

Ten male healthy volunteers (mean age: 26.5±2.4 (19–45) years; mean blood pressure: 120±6/76±5mmHg), and seven male dialysis patients with inter-dialytic hypotension (mean age: 39±3.9 (26–53) years; mean blood pressure: 88±5.3/58±2.7mmHg) participated in the study after having given informed written consent. Exercise was carried out in a quiet air-conditioned room always between 10 and 12am, i.e. 10–20 hours after the last dialysis. Subjects assumed the supine position and a cannula was inserted into an antecubital vein. After one hour of rest, exercise was performed on a bicycle ergometer (Bosch, Berlin, FRG) in a supine position starting with an initial work load of 25W in haemodialysis patients or 50W in controls. Work load was increased by 25W every two minutes until 80 per cent of the maximum heart rate (200–age) was reached. The final work load (75–125W in the haemodialysis patients, 100–150W in the controls, respectively) was kept constant until a total exercising time of 15 minutes was reached. Blood samples were obtained immediately prior to exercise, at the end of exercise and one hour after exercise. Blood pressure and heart rate were recorded automatically by a Tonomed (Speidel and Keller, FRG) and by an electrocardiogram.

ICYP binding to lymphocyte β₂-adrenoceptors and ³H-yohimbine binding to platelet α₂-adrenoceptors was performed as recently described [4,5]. Plasma catecholamines were assessed by an HPLC-method with electrochemical detection.

The experimental data given in text and figures are means ± SEM.

Results

In healthy volunteers dynamic exercise for 15 minutes on a bicycle ergometer in the supine position led to an increase of systolic blood pressure from 120 to 183mmHg; concomitantly plasma catecholamines rose from 292–718pg/ml (noradrenaline) and 51–97pg/ml (adrenaline), respectively (Figure 1). β₂-adrenoceptor density in lymphocytes increased from 1080±77 up to 2033±152 ICYP binding sites/cell (n=10), while platelet α₂-adrenoceptors decreased from 305±17 to 261±11fmol ³H-yohimbine bound/mg protein (n=10, Figure 1). One hour after exercise β₂-adrenoceptor density, systolic blood pressure and plasma catecholamines had reached pre-exercise values, while α₂-adrenoceptor density in platelets further decreased by about 10 per cent (Figure 1).

The increase of lymphocyte β₂-adrenoceptor density could be abolished by pre-treatment of the volunteers with propranolol (5mg i.v. 45 minutes prior to exercise, Figure 2). In contrast, pre-treatment with the highly selective β₁-adrenoceptor antagonist bisoprolol (2.5mg i.v. 30 minutes prior to exercise) did not influence exercise-induced increases in β₂-adrenoceptor density (Figure 2), although at this dose bisoprolol completely inhibited the isoprenaline-induced increase in plasma renin activity mediated by stimulation of intra-renal β₂-adrenoceptors [6].

In hypotensive haemodialysis patients platelet α₂-adrenoceptor and lymphocyte β₂-adrenoceptor densities were significantly lower than in controls (Figure 3),
Figure 1. Dynamic exercise (15 minutes on a bicycle at 80% of maximum heart rate) induced changes in lymphocyte β₂-adrenoceptor density, platelet α₂-adrenoceptor density, plasma catecholamine concentrations and systolic blood pressure in 10 healthy volunteers. 

Ordinates (from top to bottom): β₂-adrenoceptor density in specific ICYP binding sites/cell; α₂-adrenoceptor density in fmol ³H-yohimbine specifically bound/mg protein; plasma catecholamine concentrations in pg/ml and systolic blood pressure in mmHg. 

Abscissa: time in minutes.

Given data are means ± SEM. Solid horizontal lines and broken lines: pre-exercise values ± SEM, determined after one hour of rest in supine position.
Figure 2. Effects of propranolol (5mg i.v. 45 minutes before exercise, •—•) and bisoprolol (2.5mg i.v. 30 minutes before exercise, ○—○) on dynamic exercise (15 minutes on a bicycle at 80% of maximum heart rate) induced changes in lymphocyte \(\beta_2\)-adrenoceptor density, plasma catecholamine concentrations and systolic blood pressure in 10 healthy volunteers. For details see legend to Figure 1. For comparison control responses in the absence of the \(\beta\)-blockers from Figure 1 are given in broken lines. Given data are means ± SEM.
Figure 3. Dynamic exercise (15 minutes on a bicycle at 80% of maximum heart rate) induced changes in lymphocyte $\beta_2$-adrenoceptor density, platelet $\alpha_2$-adrenoceptor density, plasma catecholamine concentrations and systolic blood pressure in seven hypotensive dialysis patients. For details see legend to Figure 1 for comparison control responses in healthy volunteers from Figure 1 are given in broken lines. Given data are means ± SEM.
whereas plasma catecholamine concentrations were significantly higher (noradrenaline: 409±55pg/ml; adrenaline: 83±21pg/ml). During dynamic exercise systolic blood pressure rose from 88 to 145mmHg, accompanied by increases in plasma noradrenaline (up to 608±112pg/ml) and adrenaline (up to 118±23pg/ml) concentrations slightly less than in controls. In addition, dynamic exercise caused only a small increase in $\beta_2$-adrenoceptor density by approximately 25 per cent (Figure 3), although blood lactate was higher (8.2±0.9mEq/L) than in the control group (6.8±0.6mEq/L). In contrast to healthy controls dynamic exercise did not affect platelet $\alpha_2$-adrenoceptor density in hypotensive dialysis patients (Figure 3).

Discussion

Diminished responses to adrenergic stimulation [1] and arterial hypotension [2] have often been observed in patients on maintenance haemodialysis. We have recently shown that in these patients the density and/or responsiveness of $\alpha$- and $\beta$-adrenoceptors is reduced [3] indicating an impaired regulation of the sympathetic nervous system. The present results confirm and extend these observations. They show that not only long-term, but also acute regulation of the adrenergic system is impaired in hypotensive haemodialysis patients.

In healthy volunteers acute stimulation of sympathetic activity by dynamic exercise caused approximately a 100 per cent increase in $\beta_2$-adrenoceptor density in lymphocytes, in accordance with recently published data from several groups [4,7,8]. In contrast, the platelet $\alpha_2$-adrenoceptor density was reduced by about 15–20 per cent, presumably due to endogenous ‘down regulation’ by increased plasma noradrenaline levels [9]. The mechanism of the acute ‘up regulation’ of lymphocyte $\beta_2$-adrenoceptor density is not known at present. However, stimulation of $\beta_2$-adrenoceptors seems to be involved, since pretreatment of the volunteers with propranolol, but not with the highly selective $\beta_1$-antagonist bisoprolol completely abolished exercise-induced increases in lymphocyte $\beta_2$-adrenoceptor density.

On the contrary, in hypotensive haemodialysis patients, dynamic exercise induced only a small increase in lymphocyte $\beta_2$-adrenoceptor density, whereas platelet $\alpha_2$-adrenoceptor density was not affected. In addition, in spite of similar heart rate increases systolic blood pressure responses to exercise were significantly attenuated in haemodialysis patients, although work intensity — as evaluated by blood lactate concentrations — was even higher than in controls. These findings are in accordance with recently reported data by Kettner et al [10], who also found in haemodialysis patients a diminished cardiovascular response to submaximal acute exercise as manifested by a blunted systolic blood pressure and heart rate increase. These results, therefore, favour the idea that in hypotensive dialysis patients not only long-term, but also acute regulation of $\alpha$- and $\beta$-adrenoceptors is impaired. Such an impaired regulation of adrenergic receptors — the targets of catecholamines — might contribute to the disturbances of the sympathetic nervous system seen in hypotensive haemodialysis patients.

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References

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