DECREASED NUMBER OF ALPHA-ADRENERGIC RECEPTORS IN PLATELETS OF PATIENTS ON MAINTENANCE HAEMODIALYSIS

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Summary

In patients on maintenance haemodialysis the number of platelet α_2-adrenergic receptors, as assessed by ^{3}H-yohimbine binding, was significantly lower than that in healthy volunteers. Responses to α_1-adrenergic receptor stimulation, determined by increases in systolic blood pressure produced by intravenous injections of phenylephrine, were also diminished in chronic haemodialysis patients. Thus, reduced sympathetic activity often observed during chronic haemodialysis treatment may be due to reduced number and/or sensitivity of α_1- and α_2-adrenergic receptors.

Introduction

In human platelet membranes α_2-adrenergic receptors (α_2-R) can be identified and quantified by ^{3}H-yohimbine binding [1]. Thus, platelets are suitable tissues to study alterations in α_2-R. In the present study we have determined the number of α_2-R, as assessed by ^{3}H-yohimbine binding, in 36 healthy volunteers of different ages (14–76 years) and in 29 patients on maintenance haemodialysis (MHD) 24–69 years old. In addition, we have compared increases in systolic blood pressure produced by intravenous injections of the selective α_1-R agonist phenylephrine [2] in healthy volunteers with those in MHD patients to obtain further information on the changes of the sympathetic nervous system during MHD.

Subjects and methods

The control group consisted of 36 healthy volunteers (18 males, 18 females); they had taken no medication for at least 14 days prior to the study; they fasted and did not smoke for 12 hours before the study. The group of MHD patients, 29 subjects (10 females, 19 males) aged 24–69 years were not on any antihypertensive therapy.

Blood was always taken at 9.00 am, about 10–20 hours after the last haemodialysis. After a half-hour rest 20ml venous blood was drawn with the subjects in sitting positions and anticoagulated with 3.2 per cent sodium citrate solution. In addition 5ml of blood for plasma catecholamine (CA) determination [3] was mixed with 50μl of a solution containing 190mg ethylenebis (oxy-ethylene-nitrilo) tetra-acetic acid and 40mg dithioerythritiol per ml. Platelet membrane preparations and ^{3}H-yohimbine binding assay were performed as recently described [1].

Four healthy volunteers (mean age 34 ± 2.2 years) and four MHD patients (mean age 31.5 ± 3.2 years) participated in the phenylephrine study. The mean blood pressure of the groups averaged (RR) 115 ± 5.8/88 ± 6.6 and 111.5 ± 8.4 /86.5 ± 8.3mmHg, respectively. The subjects remained supine for at least 30 minutes. Thereafter, bolus doses of phenylephrine were injected into the cubital vein and blood pressure (RR) measured repeatedly. Progressively larger doses of phenylephrine were injected starting with 100μg, until the systolic blood pressure transiently increased by 20mmHg. Blood pressure was allowed to return to control values before each successive injection.

Results

In healthy volunteers of different ages there was a significant negative correlation between the number of platelet α_2-R determined by ^{3}H-yohimbine binding and age (Figure 1). The maximal number of binding sites for young subjects (14–30 years) amounted to 175.4 ± 14.3 fmoles ^{3}H-yohimbine bound/mg protein (n=13), whereas that for older subjects (50–76 years) was significantly lower with 103.6 ± 10.1 fmoles/mg protein (n=16, $p<0.01$). In contrast, plasma CA in the older group (0.72 ± 0.09ng/ml, n=16) was nearly twice as high as in the younger group (0.40 ± 0.07ng/ml, n=13, $p<0.01$).

In contrast, in MHD patients, such a correlation between age and platelet α_2-R did not exist (Figure 2). There was, however, a significant negative correlation between plasma CA and α_2-R (Figure 3). The mean plasma CA in MHD patients (0.93 ± 0.09ng/ml,n=29) was significantly higher than that in the control group (0.54 ± 0.07ng/ml, n=36), $p<0.01$); in contrast, the mean platelet α_2-R of MHD patients (112.4 ± 10.6fmoles/mg protein, n=29) was significantly lower than in the control group (144.9 ± 10.1fmoles/mg protein, n=36, $p<0.05$). The affinity of ^{3}H-yohimbine, to platelet α_2-R, however, was in both groups identical (K_D = 1–3nm).

In order to evaluate the sensitivity of α_1-R in MHD patients the effect of the selective α_1-R agonist phenylephrine [2] on systolic blood pressure was investigated. The dose of phenylephrine required to produce increases in systolic blood pressure of 20mmHg was significantly lower in the control group (233 ± 46μg, n=4) than in MHD patients (435 ± 53μg, n=4, $p<0.05$, Figure 4).

Discussion

By the use of radio ligand binding studies it has been shown that tissues exposed for a period of time to CA become less responsive to further stimulation by the

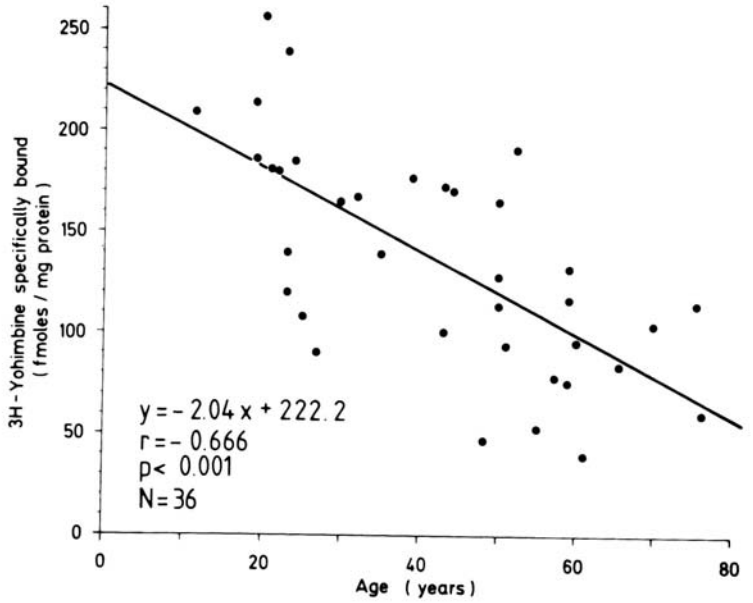

Figure 1. Number of α_2-adrenergic receptors in platelets of healthy volunteers aged 14–76 years

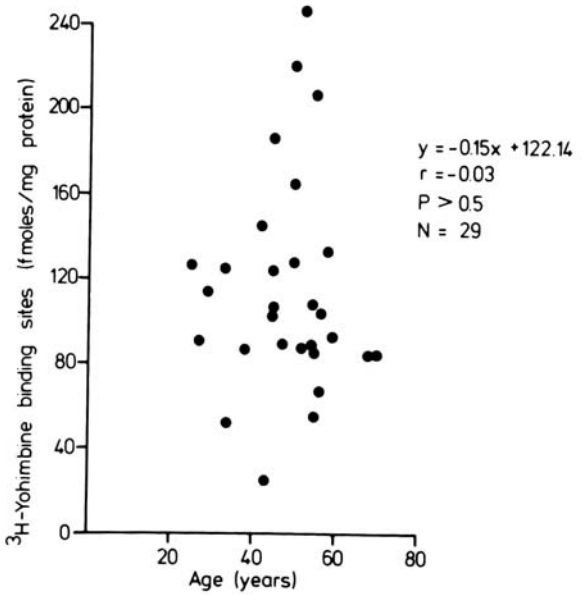

Figure 2. Number of α_2-adrenergic receptors in platelets of patients on maintenance haemodialysis aged 24–69 years

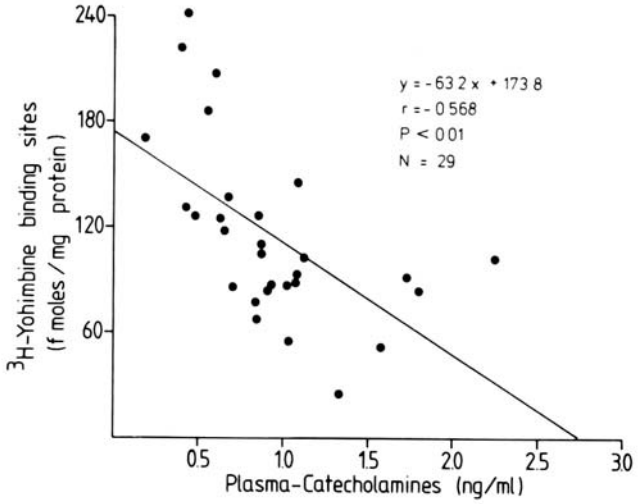

Figure 3. Correlation between number of α_2-adrenergic receptors in platelets and plasma catecholamine concentrations in patients on maintenance haemodialysis

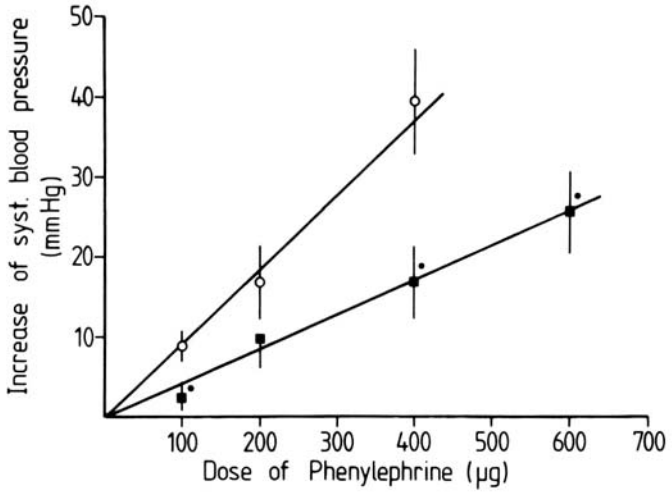

Figure 4. Dose-response curve for blood pressure increasing effects of phenylephrine in healthy volunteers (○–○) and in patients on maintenance haemodialysis (■–■).
Ordinate: Increase in systolic blood pressure in mmHg
Abscissa: Dose of phenylephrine in µg
Given are means ± SEM of four experiments
*$p<0.05$ vs control group

same agents. This 'desensitisation' to the stimulatory effects of CA was associated with a decrease in the number of functional adrenergic receptors [4]. In the present study a significant negative correlation between α_2-R number on platelets and age was found in healthy volunteers. In contrast, in accordance with previously reported data [5], plasma CA increased in the elderly. It may be possible, therefore, that the decrease in α_2-R number with age is due to the elevated plasma CA.

In MHD patients there was no correlation between age and α_2-R number. MHD patients are known to have elevated plasma CA [6]. Thus, the lack of correlation between age and α_2-R number may be due to the fact that even in young MHD patients plasma CA are rather high. The significant negative correlation between plasma CA and α_2-R number supports this assumption. It may be concluded, therefore, that endogenous CA may play an important role in regulating the number and accordingly the responsiveness of adrenergic receptors to adrenergic stimuli.

This conclusion is further supported by the fact that α_1-R are also insensitive in MHD patients. Since no easily obtainable human tissue bearing an α_1-R is available for binding studies, the sensitivity of α_1-R has been measured indirectly by blood pressure responses to the selective α_1-R agonist phenylephrine. In MHD patients, the dose-response curve for blood pressure response to phenylephrine was shifted to the right to higher concentrations when compared with the control group indicating that during chronic haemodialysis treatment α_1-R become insensitive to adrenergic stimulation.

During chronic haemodialysis treatment patients often become hypotensive and insensitive to adrenergic stimulation [7]. As demonstrated in the present study, a reduced number and/or sensitivity of α_1- and α_2-R perhaps due to endogenous 'desensitisation' by elevated plasma CA may be responsible for this reduced sympathetic activity.

Acknowledgments

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