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 α2-adrenergic receptors, as assessed by 3H-yohimbine binding, was significantly lower than that in healthy volunteers. Responses to α1-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 α1- and α2-adrenergic receptors.

Introduction

In human platelet membranes α2-adrenergic receptors (α2-R) can be identified and quantified by 3H-yohimbine binding [1]. Thus, platelets are suitable tissues to study alterations in α2-R. In the present study we have determined the number of α2-R, as assessed by 3H-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 α1-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 ethyleneglycol (oxy-ethylene-nitriolo) tetra-acetic acid and 40mg dithioerythritol per ml. Platelet membrane preparations and 3H-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 α2- R determined by 3H-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 3H-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 α2- R did not exist (Figure 2). There was, however, a significant negative correlation between plasma CA and α2- 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 α2- 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 3H-yohimbine, to platelet α2- R, however, was in both groups identical (K_D = 1–3nm).

In order to evaluate the sensitivity of α1- R in MHD patients the effect of the selective α1- 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 $\alpha_2$-adrenergic receptors in platelets of healthy volunteers aged 14–76 years

$$y = -2.04x + 222.2$$
$$r = -0.666$$
$$p < 0.001$$
$$N = 36$$

Figure 2. Number of $\alpha_2$-adrenergic receptors in platelets of patients on maintenance haemodialysis aged 24–69 years

$$y = -0.15x + 122.14$$
$$r = -0.03$$
$$P > 0.5$$
$$N = 29$$
Figure 3. Correlation between number of $\alpha_2$-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 $\mu$g
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 $\alpha_2$-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 $\alpha_2$-R number with age is due to the elevated plasma CA.

In MHD patients there was no correlation between age and $\alpha_2$-R number. MHD patients are known to have elevated plasma CA [6]. Thus, the lack of correlation between age and $\alpha_2$-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 $\alpha_2$-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 $\alpha_1$-R are also insensitive in MHD patients. Since no easily obtainable human tissue bearing an $\alpha_1$-R is available for binding studies, the sensitivity of $\alpha_1$-R has been measured indirectly by blood pressure responses to the selective $\alpha_1$-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 $\alpha_1$-R became 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 $\alpha_1$- and $\alpha_2$-R perhaps due to endogenous ‘desensitisation’ by elevated plasma CA may be responsible for this reduced sympathetic activity.

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References

1 Brodde O-E, Hardung A, Ebel H et al. Arch Int Pharmacodyn Ther 1982; in press
5 Ziegler MG, Lake CR, Kopin IJ. Nature 1976; 261: 333
6 Brecht HM, Ernst W, Koch KM. Proc EDTA 1975; 12: 281

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