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PLATELET CYCLO-OXYGENASE IN HAEMODIALYSIS PATIENTS: WHAT SUPPRESSES ITS ACTIVITY?

H Tanaka, K Umimoto, N Izumi, T Maekawa, *T Kishimoto, *M Maekawa

*Tadaoka Municipal Hospital, Osaka, *Osaka City University, Osaka, Japan*

Summary

Platelet cyclo-oxygenase activity in normal platelets incubated with uraemic plasma was suppressed before but not after haemodialysis. However, in uraemic platelets before haemodialysis, no changes were observed even when incubated with normal plasma. This indicates that uraemic plasma contains a platelet cyclo-oxygenase-suppressing factor which can be removed by haemodialysis, whereas platelet cyclo-oxygenase activity in uraemic platelets remains low. Therefore, the low platelet cyclo-oxygenase activity in haemodialysis patients appears to be an intrinsic platelet defect.

Introduction

Platelet prostaglandin production is widely known to be disturbed in haemodialysis patients, and leads to many platelet abnormalities [1–3]. One cause of this is the impairment in platelet cyclo-oxygenase activity. We have reported that the platelet cyclo-oxygenase activity is impaired in haemodialysis and continuous ambulatory peritoneal dialysis (CAPD) patients [3,4], but its cause has still to be clarified.

In this study we analysed the causes of the low platelet cyclo-oxygenase activity in haemodialysis patients, separately studying the plasma and platelet. The platelet cyclo-oxygenase activity was studied in normal platelets incubated with uraemic plasma and uraemic platelets incubated with normal plasma both before and after haemodialysis.

Material and methods

Six healthy male volunteers, aged 24 to 37 years, and 10 haemodialysis patients (3 males and 7 females) aged 37 to 69 years were selected for this study. All had normal liver and splenic function, and none was diabetic. None had received

any transfusions for more than six months nor any medication affecting the platelets for at least a week.

Normal platelet rich plasma was obtained from a healthy volunteer and the platelet count measured. To obtain two platelet pellets with the same platelet count and volume distribution, platelet rich plasma was divided by volume and centrifuged at 500G for 20 minutes at room temperature after adding 1/10 volume of 77mM EDTA (pH7.4). One of the two normal platelet pellets was incubated with uraemic plasma from a haemodialysis patient for 30 minutes at 37°C and the other with normal plasma from a healthy volunteer. The malonyldialdehyde production rate of the incubated platelets was measured both before and after haemodialysis by the TBA method [5,6] as shown in Figure 1 and was expressed as nmol of malonyldialdehyde per 10^9 platelets. Uraemic platelets were also obtained from a haemodialysis patient before and after dialysis, and the malonyldialdehyde production rate of these platelets incubated with normal and uraemic plasma was measured using the same method as before.

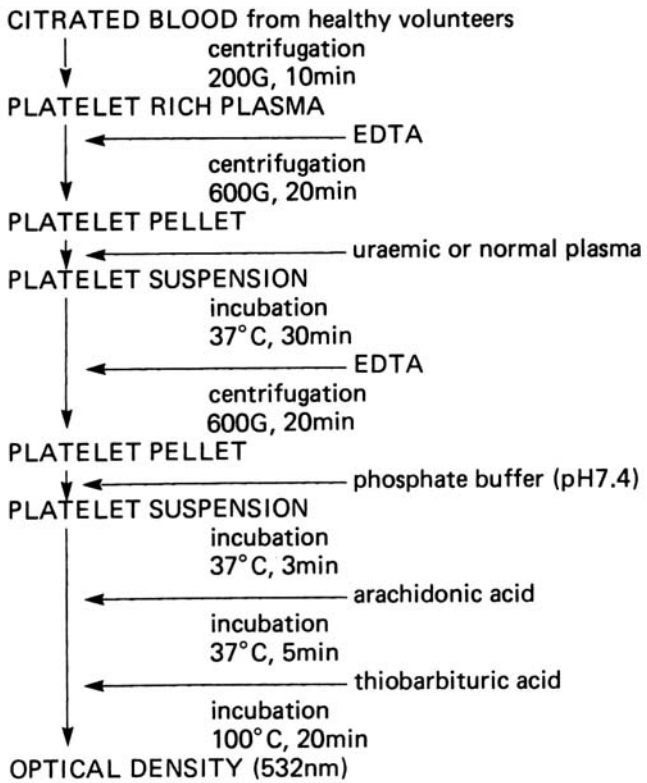

Figure 1. The method of measuring the platelet malonyldialdehyde production rate of normal platelets incubated with normal and uraemic plasma

The platelet cyclo-oxygenase activity index of the uraemic plasma (Plasma index) and uraemic platelet (Platelet index) were calculated as follows:

$$\text{Plasma Index (\%)} = \frac{\text{malonyldialdehyde production rate (uraemic plasma)}}{\text{malonyldialdehyde production rate (normal platelets)}} \times 100$$

$$\text{Platelet Index (\%)} = \frac{\text{malonyldialdehyde production rate (normal platelets)}}{\text{malonyldialdehyde production rate (uraemic plasma)}} \times 100$$

The results were expressed as mean ± SD, and statistical analysis was by the Student's 't' test.

Results

The malonyldialdehyde production rate of normal platelets incubated with normal plasma, which was measured to obtain the Plasma Index before and after haemodialysis, was 13.1±2.5nmol/10^9 platelets and 12.2±2.2nmol/10^9 platelets, respectively. The rate of those incubated with uraemic plasma was 11.9±2.4nmol/10^9 platelets before haemodialysis and 12.4±2.4nmol/10^9 platelets afterwards. Accordingly, the Plasma Index before and after haemodialysis was 90.3±4.0 per cent (n=10) and 99.8±4.5 per cent (n=10), respectively, with a significant difference between the two ($p<0.001$) as shown in Figure 2. The malonyldialdehyde production rate of uraemic platelets incubated with uraemic plasma was 12.2±2.4nmol/10^9 platelets before and 12.4±2.9nmol/10^9 platelets after haemodialysis.

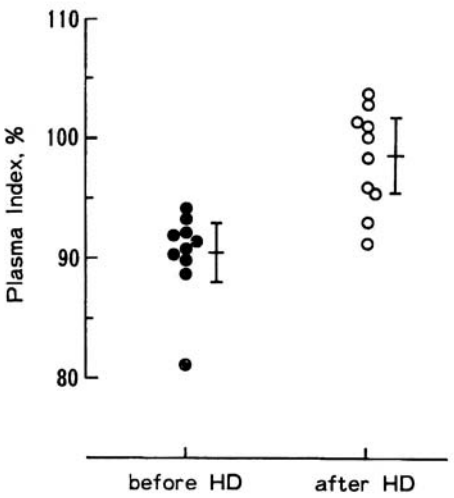

Figure 2. The platelet cyclo-oxygenase activity index of the uraemic plasma (Plasma Index). The Plasma Indexes before and after haemodialysis (HD) were significantly different ($p<0.001$)

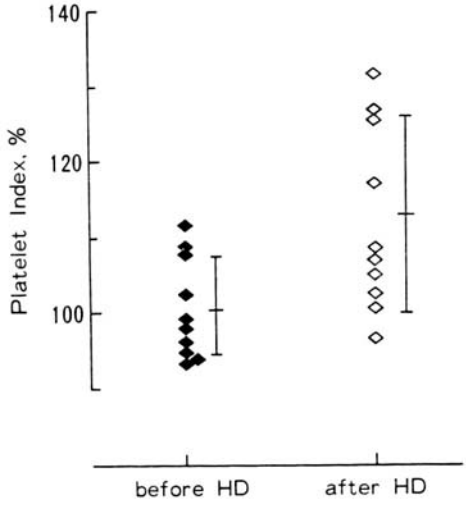

Figure 3. The platelet cyclo-oxygenase activity index of uraemic platelets (Platelet Index). The Platelet Indexes before and after haemodialysis (HD) were significantly different ($p<0.05$)

The rate of those incubated with normal plasma was 12.2±2.6nmol/10^9 platelets before haemodialysis and 14.0±3.5nmol/10^9 platelets afterwards. Accordingly, the Platelet Index before haemodialysis was 101.4±6.6 per cent (n=10) and that after was 113.7±12.9 per cent (n=10) with a significant difference between the two ($p<0.05$) as shown in Figure 3.

Discussion

Pre-dialysis uraemic plasma significantly decreased the platelet cyclo-oxygenase activity of normal platelets, indicating that a platelet cyclo-oxygenase suppressing factor was present. However, it was not suppressed after haemodialysis, which suggests that the suppressing factor was removed by haemodialysis to a level at which platelet cyclo-oxygenase was no longer suppressed. On the other hand, even though the suppressing factor was removed, its level rose again and became sufficiently high to suppress platelet cyclo-oxygenase activity by the next haemodialysis. This change in the suppressing factor was the same as that for blood urea and serum creatinine due to haemodialysis. This indicates that the platelet cyclo-oxygenase activity was not restored by a 30 minute incubation in cause of the low platelet cyclo-oxygenase activity in haemodialysis patients, but that it was only one of the factors.

The Platelet Index before haemodialysis was 101.4±6.6 per cent, and the low platelet cyclo-oxygenase activity was not restored by a 30 minute incubation as normal plasma. This indicates that the platelet cyclo-oxygenase activity in the haemodialysis patients remained irreversibly low, even though their conditions were normalized by incubation. However, the Platelet Index after haemodialysis significantly improved. It is difficult to determine the significance of this

improvement because the conditions for the calculation, in which the uraemic platelets and plasma were changed by haemodialysis, was different from that of the other three indexes. Furthermore, this change in the Platelet Index conflicted with our previous report that the platelet cyclo-oxygenase activity was not changed by haemodialysis [4]. The difference between this study and our previous report was the plasma itself, normal or uraemic, and the presence of incubation. Although this difference may have brought about the discrepancy in the values, the platelet cyclo-oxygenase activity is thought to be improved in the platelet. In fact, when uraemic platelets were incubated with normal plasma, a slight improvement in the platelet cyclo-oxygenase activity by haemodialysis could be detected. However, apart from these special conditions, uraemic platelet function was not improved by haemodialysis, as the Platelet Index before haemodialysis was 101.0 per cent and the malonyldialdehyde production rate before and after haemodialysis was comparable.

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