Endothelin in Hemodialysis-Resistant Hypertension

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1 -

Dear Sir,

Hypertension in patients receiving maintenance hemodialysis usually can be controlled by ultrafiltration. However, in a small number hemodialysis fails to reduce the blood pressure despite the removal of salt and water. Such patients are defined as having dialysis-resistant hypertension. In these cases, the plasma volume and cardiac output are usually lower, and the total peripheral resistance is almost always higher than in the controllable cases [1]. Therefore, dialysis-resistant hypertension is mainly the result of an increase in total peripheral resistance. An increase in PRA [2], a circulating Na/K ATPase pump inhibitor [3], and inadvertent hypercalcemia [4] have been reported to be pathogenetic factors. However, the pathogenesis of vasoconstriction in dialysis-resistant hypertension remains a question. Endothelin (ET), a newly discovered peptide hormone released from the endothelium, exhibits potent vasoconstrictive activity [5]. Recently, an increased plasma immunoreactive ET (ir-ET) concentration has been reported in patients with myocardial infarction and those with subarachnoid hemorrhage, indicating an involvement of ET in the etiology of vasospastic disorders [6,7]. To investigate the involvement of ET in hemodialysis-resistant hypertension, we measured ir-ET-1 [1-21] concentration in plasma before and after hemodialysis in 11 patients with hemodialysis-resistant hypertension and in 22 with hemodialysis-controllable hypertension. All subjects were dialyzed three times weekly for periods of 4 h each. Blood was collected from the arterio-venous shunt and plasma ir-ET-1 was extracted using Sep-Pak C-18 cartridges (Waters Associates, Milford, Mass., USA). Plasma ir-ET-1 was measured by a previously described sandwich-enzyme immunoassay for ET-1 [8]. In brief, standard ET-1 or samples

160

60

140

80 100 120

Mean blood pressure, mm Hg

Fig. 1. A positive correlation between the plasma ir-ET-1 concentration and the mean blood pressure before hemodialysis in the patients on hemodialysis.

were incubated in the plates coated with a mouse monoclonal antibody against the N-terminal peptides of ET-1. The plates were then reacted with enzyme-labeled rabbit antibody against the C-terminal peptides of ET[15–21]. The bound enzyme activity was measured with o-phenylenediamine. The detection limit was 0.2 pg/well. Both the interassay and the intraassay variations were under 10%. The cross-reactivity of this assay with ET peptides was as follows: ET-1[1–21], 100%; ET-2, 60%; ET-3 and human big ET-1[1–39], 0.2%. The plasma ir-ET-1 concentration before hemodialysis was significantly higher in the patients on hemodialysis than in the age-matched normal subjects (1.76 ± 0.10 , $n = 33$, vs. 1.38 ± 0.10 pg/ml, $n = 12$, $p < 0.05$). The plasma ir-ET-1 concentration in these patients showed a positive correlation with the mean blood pressure before hemodialysis ($r = 0.48$, $p < 0.01$, $n = 33$; fig. 1). However, there was no remarkable

688

Tsunoda/Abe/Yoshinaga
 Table 1. Mean blood pressure (MBP)
 and
 ir-ET-1 concentration before and after hemodialysis

Hemodialysis-resistant hypertension
 Hemodialysis-controllable hypertension
 Number of patients

11
 22
 Age, years

50.9 ± 4.1
 51.1 ± 2.4
 MBP before hemodialysis, mm Hg

107.8 ± 4.7
 107.5 ± 3.7
 MBP after hemodialysis, mm Hg

$113.3 \pm 5.0^*$
 $93.1 \pm 3.4^{**}$
 ir-ET-1 before hemodialysis, pg/ml

1.87 ± 0.15

1.71 ± 0.12

ir-ET-1 after hemodialysis, pg/ml

1.94 ± 0.18

1.82 ± 0.12

Values are expressed as mean ± SEM.

*p

< 0.05;

**p < 0.001 as compared with MBP before hemodialysis.

change in the plasma ir-ET-1 concentration before versus after hemodialysis either in the patients with hemodialysis-resistant hypertension or in those with dialysis-controllable hypertension (table 1). These observations suggest that circulating ET-1 may not be responsible for the hemodialysis-resistant hypertension, although a paracrine effect of this agent on adjacent vascular smooth muscle cannot be ruled out.

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