Disturbed Intracellular Calcium Homeostasis as a Major Reason of Vascular Contractile Dysfunction in Hypertension of Renal Origin

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Dear Sir,

Arterial hypertension and platelet dysfunction in patients on hemodialysis (HD) are common. Part of these abnormalities are ascribed to altered intracellular $[Ca^{2+}]$ concentration [1,2]. Factors influencing intracellular $[Ca^{2+}]$ homeostasis are therefore subjects of thorough investigations. Nakamura et al. [3] have reported experimental findings on the role of platelet cytosolic calcium in the regulation of blood pressure in patients on chronic HD. They found a correlation between decrease in plasma renin activity and platelet $[Ca^{2+}]$ at pre- and post-HD measurements; however, they failed to demonstrate a correlation between platelet $[Ca^{2+}]$ and C-terminal plasma PTH.

We have examined platelet-free $[Ca^{2+}]$, blood pressure, intact plasma PTH (i-PTH), plasma renin and norepinephrine (NE) in 53 HD patients (table 1) comparable in conditions of HD, age, sex and body weight and 22 age- and sex-matched normal subjects. Patients were considered to be hypertensive when hypertensive blood pressure values (RR > 140/90 mm Hg) were measurable at dry body weight after HD. None of the patients received antihypertensive medication at least 2 weeks before and during the time of investigation. Both groups of HD patients were further divided into two subgroups according to normal or elevated plasma i-PTH levels. As shown in table 1 the platelet-free $[Ca^{2+}]$, plasma renin and NE were significantly higher in HD patients than in normal subjects. When platelet-free $[Ca^{2+}]$ of normotensive and hypertensive HD patients were compared, $[Ca^{2+}]$ was in the range of normal (normal plasma i-PTH group) to only slightly elevated values (high plasma i-PTH group) in normotensive patients and strongly elevated

Table 1. Characterization of normal subjects and HD patients participating in this study in both groups of hypertensive patients (table 2). Statistical analysis of our results revealed a correlation between platelet-free $[Ca^{2+}]$ and mean arterial blood pressure when all 53 HD patients were analyzed together. This correlation was less strong, but significant in the group of hypertensive HD patients and not present in the group of normotensive HD patients. A correlation between plasma i-PTH and platelet-free $[Ca^{2+}]$ was detectable in the group of normotensive HD patients, which was also significant but less strong among hypertensive HD patients and not detectable if all 53 HD patients were analyzed together (table 3). No correlation between plasma i-PTH and mean arterial blood pressure (table 3) was found.

Correlations between NE, renin, mean arterial blood pressure and platelet cytosolic free $[Ca^{2+}]$ were detectable only when all HD patients were analyzed together and in none of any of the other subgroups of HD patients or normal subjects, plasma i-PTH did not correlate with NE or renin in any of the groups (table 4). In the group of healthy subjects who were used as normal controls, analysis of the data revealed a highly significant correlation ($r = 0.913$; $p < 0.0001$) between mean arterial blood pressure and platelet cytosolic free $[Ca^{2+}]$. No other correlation between any other of the analyzed parameters was detectable (table 4).

From these results we conclude that alteration of intracellular $[Ca^{2+}]$ homeostasis in (normotensive and hypertensive) HD patients is caused only in part by increased plasma PTH activity – other factors related to arterial blood pressure regulation appear to be of fundamental importance. However, we (and others) were unable to prove this for epinephrine [data not shown], norepinephrine and renin [4, 5]. (In this respect the results given in table 4 are inconsistent because the significant correlations between NE, renin, arterial blood pressure and platelet

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Table 2. Characterization of normotensive and hypertensive HD patients without or with secondary hyperparathyroidism

Table 3. Correlation between platelet-free $[Ca^{2+}]$, mean arterial blood pressure (BP) and plasma i-PTH levels in normal subjects and HD patients included in this study

Table 4. Correlation between platelet-free $[Ca^{2+}]$, NE, renin, mean arterial blood pressure and plasma i-PTH levels in normal subjects and HD patients included in the study

BP/
platelet Ca^{2+}
Platelet Ca^{2+} i-PTH
BP/ i-PTH
All HD patients
Hypertensive HD patients

All HD patients
Hypertensive HD patients
Normotensive HD patients
Normal subjects

$r = 0.866$ $p < 0.0001$ $r = 0.672$ $p < 0.0001$ $r = 0.568$ $p < 0.006$ $r = 0.91$ $p < 0.0001$
 $r = 0.328$ $p = 0.016$ $r = 0.662$ $p < 0.0002$ $r = 0.831$ $p < 0.0001$ $r = 0.28$

$p < 0.0001$ $p < 0.0001$ $p < 0.0001$ n.s.
n.s.
 $p < 0.0001$ $p < 0.0001$
 $p = 0.0031$

n.s.
n.s.
n.s.
n.s.
n.s. n.s.

n.s. = Not significant.

The data of normotensive patients and normal subjects are not shown because no significant correlations have been found.

[Ca²⁺] calculated for the group of all HD patients could not be demonstrated in the subgroup of hypertensive HD patients.) A connection of volume status and exchangeable sodium with platelet-free cytosolic [Ca²⁺] is likely but needs to be shown. Furthermore, we and others have reported experimental evidence for role of sodium/potassium ATPase inhibitors in increasing intra-cellular [Ca²⁺] in platelets [6]. Moreover, incubation experiments with 'normal platelets' in 'hypertensive plasma' [7] gave evidence for the presence of low molecular weight endogenous 'blood-borne' factors (ouabain/di-goxin-like factors) leading to an increase of platelet-free cytosolic [Ca²⁺].

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