Effect of Dietary Sodium on Platelet $\alpha_2$-Adrenergic Receptors in Essential Hypertension

TERUNAO ASHIDA, TOSHIYUKI TANAKA, MASATOSHI YOKOUCHI, MORIO KURAMOCHI, FUJIO DEGUCHI, GENJIRO KIMURA, SHUNICHI KOJIMA, KEIICHI ITO, AND MASAO IKEDA

SUMMARY To study the aggregation, adhesion, and specific binding of an $\alpha_2$-antagonist, $[3H]$rauwolscine, to the platelet membrane fractions, platelets were obtained from 30 patients with essential hypertension and nine normotensive subjects fed a high sodium diet (NaCl, 16-18 g/day) for 7 days and thereafter a low sodium diet (NaCl, 1-3 g/day) for 7 days. The patients with essential hypertension were classified as either salt responders (all those who had > 7% decrease in mean arterial pressure from the high to low sodium period) or salt nonresponders (all others). In salt responders, the number of $\alpha_2$-adrenergic receptors on platelet membrane fraction was increased from 523.4 ± 55.4 fmol/mg of protein in the high sodium period to 669.4 ± 84.0 fmol/mg of protein in the low sodium period ($p < 0.01$), whereas it did not change in salt nonresponders. In contrast, the epinephrine-induced platelet aggregation through $\alpha_2$-adrenergic receptors was decreased in nonresponders, from 47.3 ± 7.4% in the high sodium period to 24.5 ± 9.3% in the low sodium period ($p < 0.05$), while it did not change in responders. No significant change in the number of $\alpha_2$-adrenergic receptors or epinephrine-induced platelet aggregation was observed in the normotensive subjects.

KEY WORDS  • blood pressure  • $[3H]$rauwolscine binding  • platelet aggregation

THE activity of the adrenergic neurons is transmitted to the effector cells by the neurotransmitter norepinephrine (NE) through adrenergic receptors. Recent biochemical and pharmacological developments enable these adrenergic receptors to be classified into $\alpha_1$ and $\alpha_2$ subclasses. In relation to the control of circulation, stimulation of the $\alpha_2$-adrenergic receptors in the brain stem attenuates the sympathetic nerve activity and stimulation of the presynaptic $\alpha_2$-adrenergic receptors in the nerve terminals inhibits NE release, which should cause a decrease in blood pressure. Stimulation of the postsynaptic $\alpha_2$-adrenergic receptors on the vascular smooth muscle cells contracts the vessels, and stimulation of the $\alpha_2$-adrenergic receptors in the renal tubular cells enhances the reabsorption of sodium in the kidney, thus, activation of these receptors should result in an increase in blood pressure. Therefore, it is important to study the characteristics of the $\alpha_2$-adrenergic receptors in essential hypertension (EH).

It has been shown that platelets are endowed with $\alpha_2$-adrenergic receptors and that these platelet $\alpha_2$-adrenergic receptors may be a suitable model of the $\alpha_2$-adrenergic receptors in other organs. Moreover, it has also been shown that the characteristics of platelet $\alpha_2$-adrenergic receptors are modified by sodium ions. These findings prompted us to study the characteristics of the platelet adrenergic receptors with a radioligand binding assay as well as aggregation and adhesion of platelets from patients with EH in sodium-loaded and sodium-deprived states.

In the present study patients with EH were given high sodium diets and thereafter low sodium diets. They were classified as either salt responders (those with a > 7% decrease in mean arterial pressure [MAP] from the high to low sodium period) or salt nonresponders (all others). The specific binding of an $\alpha_2$-antagonist, $[3H]$rauwolscine, to the membrane fractions and the aggregation and adhesion of the platelets were compared among these two groups with EH and a group of normotensive subjects.

Subjects and Methods

Thirty hospitalized patients with EH (mean age ± SEM, 50.4 ± 2.3 yr; 14 men, 16 women) and nine age-matched hospitalized normotensive subjects with no
family history of EH (aged 48.7 ± 6.0 yr; 7 men, 2 women) were first given a high sodium diet (NaCl, 16-18 g/day; K, 40-50 mEq/day) for 7 days and thereafter received a low sodium diet (NaCl, 1-3 g/day, K, 40-50 mEq/day) for 7 days. No patient had taken antihypertensive drugs, acetylsalicylic acid, or any other drugs in the 2 weeks preceding the study. All patients with EH had systolic pressure more than 160 mm Hg or diastolic pressure more than 95 mm Hg (or both) in outpatient clinics and were in World Health Organization stage I or II. All normotensive subjects had systolic pressure less than 140 mm Hg and diastolic pressure less than 90 mm Hg in outpatient clinics. Heart rate and blood pressure, measured with a sphygmomanometer, were recorded at rest at 1000 hours. Twenty-four hour urine samples were collected for determination of urinary sodium, potassium, and catecholamine excretion during last 3 days of each dietary period. The 3-day means were calculated. All blood samples were collected after an overnight fast (12 hr) on the seventh day of each dietary period. An indwelling cannula was inserted in the subject’s antecubital vein and kept patent with 5% glucose. After the subject had been quietly supine for at least 30 minutes, a blood sample was obtained for determination of serum creatinine, plasma catecholamine, plasma renin activity (PRA), platelet aggregation and adhesion, and binding characteristics of platelet α2-adrenergic receptors.

Isolation of Platelet Membranes and Radioligand Binding Assay

The radioligand binding studies were performed according to the method previously described by Garcia-Sevilla et al.10 with some modification. Blood was dispensed into plastic centrifuge tubes containing (8:1 vol/vol) acid citrate dextrose solution as an anticoagulant. The blood was centrifuged at 190 g for 10 minutes (25 °C), and the resulting platelet-rich plasma was recentrifuged at 5100 g for 15 minutes. The pellet was washed twice with 5 ml of Tyrode’s solution and recentrifuged at 5100 g for 15 minutes. The pellet was homogenized in 4 ml of ice-cold hypotonic buffer (Tris-ethylenediaminetetraacetic acid, 5 mM; pH 7.5) for 20 strokes with a motor-driven Teflon-tipped pestle (B. Braun, West Germany) at a setting of 1000. After centrifugation at 39,000 g for 10 minutes at 4 °C, the platelet membranes were resuspended in Tris incubation buffer containing the fresh platelet membranes (1.0-1.5 mg protein/ml) and 5 × 10^-10 M to 1.6 × 10^-8 M [3H]rauwolscine with or without a competitive agent. Duplicate samples were incubated for 30 minutes at 25 °C. Incubation was terminated by filtration through a Whatman GF/B filter (Clifton, NJ, USA) under vacuum. The filters were washed three times with 5 ml of cold Tris incubation buffer. The filters were then air dried, placed in glass scintillation vials, and counted by scintillation spectrometry with an efficiency of 45.6%. Specific binding of [3H]rauwolscine was defined as the portion of total binding displaced by 10^-5 M phentolamine. Maximum binding (Bmax) and the dissociation constant (Kd) for the rauwolscine binding were calculated from Scatchard plots of specific binding data.

Preliminary experiments showed that the binding characteristics of [3H]rauwolscine to human platelet membranes satisfied criteria required for the identification of a physiological α2-adrenergic receptor; that is, the binding of the radioligand was specific, rapid, saturable, reversible, and of high affinity. Scatchard analysis of [3H]rauwolscine binding suggested that only a single population of binding sites was present on the platelet membranes.

Assay Methods

Plasma and urinary catecholamines were analyzed by the trihydroxyindole method after high-performance liquid chromatography separation. The PRA was measured by radioimmunoassay. Urinary sodium and potassium were measured with a flame photometer (Beckman Instruments, Inc., Fullerton, CA, USA). Platelet aggregation was determined with an aggregometer (Model PAT-4A, NKK Hema tracer 1, Japan) within 30 minutes after blood drawing. The aggregating agents used in the present study were 1 µg/ml epinephrine, 2 µM adenosine 5’-diphosphate (ADP), and 1 µM collagen. In epinephrine-induced aggregation, the percent aggregation was determined 3 minutes after the addition of the aggregating agents (Figure 1A). In ADP- and collagen-induced aggregation, the percent aggregation was determined as a maximal aggregation (Figure 1B). The percent aggregation was standardized by assuming that platelet-rich plasma represented 0% aggregation and platelet-poor plasma represented 100% aggregation. All the drugs used in the aggregation were dissolved in veronal-saline buffer (pH 7.4). Platelet adhesion was measured following the Salzman14 method with modification.

Drugs

The [3H]rauwolscine (specific activity, 84.4 Ci/mmol) was purchased from New England Nuclear (Boston, MA, USA) and stored at -20 °C. Phentolamine HCl was a gift from Japan Ciba Geigy Co. Drugs for buffer solution were purchased from Sigma Co. (Japan).

Statistics

Paired or unpaired Student’s t test was used for the statistical evaluations. Correlation coefficients were calculated by the method of least squares. The level of significance was chosen as a p value less than 0.05.

Results

Normotensive Subjects

Blood pressure, heart rate, body weight, and laboratory data for normotensive subjects are summarized in Table 1. Urinary sodium excretion was greater in the high sodium period than in the low sodium period,
which reflected the difference in the sodium intake, but urinary potassium excretion was comparable in the two periods. The MAP was not different between the high and low sodium periods. The results of \(^3\)H]rauwolscine binding to platelet membranes and platelet aggregation and adhesion are summarized in Table 2. There was no difference in number or affinity of platelet \(\alpha_2\)-adrenergic receptors or platelet aggregation between the high and low sodium periods.

Patients with Essential Hypertension

In patients with EH, MAP was significantly higher in the high sodium period than in the low sodium period (Table 1). Heart rate was significantly greater in the low sodium period than in the high sodium period. Plasma and urinary NE and PRA were significantly higher in the low sodium period than in the high sodium period.

The number of platelet \(\alpha_2\)-adrenergic receptors

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**TABLE 1. Clinical and Laboratory Data in the High and Low Sodium Periods in Hypertensive and Normotensive Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive</th>
<th>Normotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Na</td>
<td>Low Na</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50.4±2.3</td>
<td>50.4±2.3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58.1±1.5</td>
<td>56.6±1.4*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>113.7±2.5</td>
<td>106.9±2.7*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65.7±1.2</td>
<td>68.2±1.1†</td>
</tr>
<tr>
<td>UNaV (mEq/day)</td>
<td>247.9±10.2</td>
<td>317.5±4.5</td>
</tr>
<tr>
<td>UKV (mEq/day)</td>
<td>41.1±1.8</td>
<td>43.6±2.5</td>
</tr>
<tr>
<td>SCr (mg/dl)</td>
<td>0.94±0.04</td>
<td>1.00±0.06</td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>235.0±28.0</td>
<td>475.8±67.0*</td>
</tr>
<tr>
<td>PE (pg/ml)</td>
<td>28.2±7.3</td>
<td>25.1±3.8</td>
</tr>
<tr>
<td>UNE (µg/day)</td>
<td>66.1±4.5</td>
<td>117.9±10.0*</td>
</tr>
<tr>
<td>UE (µg/day)</td>
<td>11.8±1.4</td>
<td>11.5±1.1</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>0.7±0.1</td>
<td>5.6±1.2*</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

MAP = mean arterial pressure; UNaV = urinary sodium excretion; UKV = urinary potassium excretion; SCr = serum creatinine; PNE = plasma norepinephrine concentration; PE = plasma epinephrine concentration; UNE = urinary norepinephrine excretion; UE = urinary epinephrine excretion; PRA = plasma renin activity.

*\(p < 0.01\), †\(p < 0.05\) (differences between groups) compared with the values in the high sodium period (by paired \(t\) tests).
Table 2. Binding Characteristics of Platelet \( \alpha_2 \)-Adrenergic Receptors and Platelet Aggregation and Adhesion in the High and Low Sodium Periods in Hypertensive and Normotensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive</th>
<th>Normotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Na</td>
<td>Low Na</td>
</tr>
<tr>
<td>Binding study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( K_d ) (nM)</td>
<td>6.49 ±0.59</td>
<td>7.08±0.62</td>
</tr>
<tr>
<td>( B_{max} ) (fmol/mg protein)</td>
<td>504.8±36.7</td>
<td>564.2±43.7*</td>
</tr>
<tr>
<td>Aggregation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (%)</td>
<td>48.4±4.6</td>
<td>32.9±7.3*</td>
</tr>
<tr>
<td>ADP (%)</td>
<td>59.5±4.1</td>
<td>46.6±6.31</td>
</tr>
<tr>
<td>Collagen (%)</td>
<td>88.9±2.0</td>
<td>88.2±2.3</td>
</tr>
<tr>
<td>Adhesion (%)</td>
<td>38.6±3.7</td>
<td>42.5±4.8</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

\( K_d \) = dissociation constant of platelet \( \alpha_2 \)-adrenergic receptors; \( B_{max} \) = number of platelet \( \alpha_2 \)-adrenergic receptors.

*\( p < 0.05 \), †\( p < 0.01 \) (differences between groups) compared with the values in the high sodium period (by paired \( t \) tests).

(B\( _{max} \)) was significantly greater in the low sodium period than in the high sodium period (Table 2). On the other hand, \( K_d \), the reciprocal of which indicates affinity, was not significantly different between the high and low sodium periods. Epinephrine-induced platelet aggregation and ADP-induced platelet aggregation were significantly greater in the high sodium period than in the low sodium period, while collagen-induced platelet aggregation and platelet adhesion were not.

In the hypertensive subjects as a whole, the changes in the number of platelet adrenergic receptors from the high to low sodium period showed a significant negative correlation with the change in MAP (\( r = -0.459 \); Figure 2) and with the change in plasma NE concentration (\( r = -0.521 \); Figure 3) and a significant positive correlation with the change in epinephrine-induced platelet aggregation (\( r = 0.525 \); Figure 4). When three outliers were excluded, the correlation coefficients \( (r) \) for Figures 2 and 3 were \(-0.413 \) (\( p < 0.05 \)) and \(-0.375 \) (\( p > 0.05 \)) respectively.

Except for MAP in both high and low sodium periods, none of the parameter values were significantly different between the hypertensive and the normotensive subjects in either the high or the low sodium period.

Salt Responders and Nonresponders with Essential Hypertension

There were 13 salt responders and 17 nonresponders; their data are summarized in Table 3. Ages were not significantly different between the two groups. In responders, MAP was significantly lower in the low sodium period than in the high sodium period,
Figure 4. Correlation between changes in epinephrine-induced platelet aggregation (ΔE-Agg; abscissa) and in the number of platelet α2-adrenergic receptors (ΔB_max; ordinate) from the high to low sodium period in essential hypertension. Linear regression was used, and the correlation coefficient (r) is shown. Closed circles = salt responders; open circles = salt nonresponders. The means ± SEM of ΔE-Agg and ΔB_max are shown.

whereas it was not different between the two periods in nonresponders. In nonresponders, heart rate was significantly greater in the low sodium period than in the high sodium period, whereas it was not different between the two periods in responders.

Table 4 summarizes the comparison of the results of the binding study and platelet aggregation and adhesion. In responders, the number of platelet α2-adrenergic receptors (B_max) was significantly higher in the low sodium period than in the high sodium period, but there was no difference in nonresponders. The affinity of the antagonist was not different between the high and low sodium periods. Epinephrine- and ADP-induced platelet aggregation in nonresponders was significantly lower in the low sodium period than in the high sodium period, but there was no difference in responders.

Plasma NE concentration and urinary NE excretion were significantly higher in the low sodium period than in the high sodium period in both responders and nonresponders; however, plasma NE concentration tended to increase more in nonresponders than in responders from the high to low sodium period. Changes in plasma NE concentration from the high to low sodium period for responders and nonresponders were 131.3 ± 39.0 pg/ml and 305.0 ± 107.5 pg/ml respectively. In addition, PRA was significantly higher in the low sodium period than in the high sodium period in nonresponders and also tended to be higher in the low sodium period in responders.

When responders and nonresponders were compared, only MAP and the number of platelet α2-adrenergic receptors in the low sodium period were significantly different. Other parameters were not significantly different between the two groups during either the high or the low sodium period (Tables 3 and 4).

Discussion
Excessive intake of salt13-14 and hyperactivity of the sympathetic nervous system15-16 play important roles in the development and maintenance of EH. In addition, an abnormal relationship between sodium intake

Table 3. Clinical and Laboratory Data in the High and Low Sodium Periods in Salt Responders and Nonresponders with Essential Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responders (n = 13)</th>
<th>Nonresponders (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Na</td>
<td>Low Na</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46.6 ± 3.0</td>
<td>53.3 ± 3.3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58.7 ± 2.3</td>
<td>57.0 ± 2.1*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>115.7 ± 2.5</td>
<td>100.5 ± 2.4*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65.3 ± 1.9</td>
<td>66.2 ± 2.0</td>
</tr>
<tr>
<td>UNaV (mEq/day)</td>
<td>257.6 ± 11.8</td>
<td>32.0 ± 7.4*</td>
</tr>
<tr>
<td>UKV (mEq/day)</td>
<td>42.2 ± 1.8</td>
<td>45.9 ± 2.6</td>
</tr>
<tr>
<td>Scr (mg/dl)</td>
<td>0.94 ± 0.06</td>
<td>1.01 ± 0.07</td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>221.6 ± 39.3</td>
<td>354.9 ± 41.7‡</td>
</tr>
<tr>
<td>PE (pg/ml)</td>
<td>21.9 ± 3.6</td>
<td>24.1 ± 2.8</td>
</tr>
<tr>
<td>UuE (µg/day)</td>
<td>64.1 ± 6.0</td>
<td>112.5 ± 9.5*</td>
</tr>
<tr>
<td>UE (µg/day)</td>
<td>12.2 ± 1.8</td>
<td>12.1 ± 1.7</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>0.6 ± 0.2</td>
<td>3.5 ± 1.3</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
The differences between responders and nonresponders are italicized.
Abbreviations are the same as in Table 1.
Differences between the groups: *p < 0.01, †p < 0.05 compared with the values in the high sodium period (by paired t tests); ‡p < 0.05 compared with the values in responders.
and sympathetic nervous system activity has been shown in some patients with EH. To explore these relationships, we studied patients with EH and normotensive subjects fed high sodium diets for 1 week and then low sodium diets for 1 week. When the patients with EH were switched from the high to the low sodium diet, their MAP decreased significantly; concurrently, plasma and urinary NE levels increased, as did the number of platelet α2-adrenergic receptors. These changes in the entire group with EH were due mainly to those in platelets, and presumably also in the brain stem or sympathetic nerve endings, as reflected by increased platelet α2-adrenergic receptors and in plasma NE concentration in patients with EH from the high to low sodium period. Thus, an increase in sympathetic drive caused by intravascular volume contraction was then attenuated, so that the plasma NE concentration increased less than that in nonresponders and heart rate remained unchanged. As a consequence, blood pressure was decreased in this subgroup. Epinephrine-induced platelet aggregation, which should otherwise have been decreased in the sodium-deprived state, was not significantly decreased, because the number of α2-adrenergic receptors on platelet membranes increased.

In contrast, these results indicate that, in salt nonresponders, the number of α2-adrenergic receptors on the brain stem or sympathetic nerve terminals, remained unchanged from the high to low sodium period. Thus, an increase in sympathetic nervous activity could be fully developed; hence, the plasma NE concentration rose more and heart rate increased. As a consequence, blood pressure did not decrease. Epinephrine-induced platelet aggregation was decreased in the low sodium period because the number of platelet α2-adrenergic receptors was unchanged and no compensation occurred.

It has been reported that the number of platelet α2-adrenergic receptors from hypertensive women was greater than that from normotensive women and that estrogens or progesterone or both altered the α2-adrenergic receptor density in human platelets. However, others have found no alteration in the number of α2-adrenergic receptors, brought about inhibition of NE release from sympathetic nerve endings. These results suggest an important role for dietary sodium intake in the modulation of central sympathetic function. In addition, sodium restriction decreases epinephrine-induced platelet aggregation through some unknown mechanism(s). Consistent with these data is the increase of platelet aggregation by high salt intake.

Several investigators have reported a negative correlation between plasma catecholamine levels and platelet α2-adrenergic receptor density, whereas others have observed no correlation between these parameters. In our study, Bmax increased despite an elevation in plasma NE levels from the high to low sodium period in salt responders. Our data also showed a negative correlation between the change in plasma NE levels and the change in Bmax from the high to low sodium period in subjects with EH, although there was no relationship between plasma NE level and Bmax. Therefore, we cannot entirely exclude down regulation in platelet α2-adrenergic receptor density.

Several investigators have reported that the α2-adrenergic receptors in the nervous system are related to those in platelets. Thus, changes in the properties of platelet α2-adrenergic receptors may also reflect parallel changes in such receptors in the brain stem or sympathetic nerve endings. The finding of a negative correlation between the changes in the number of platelet α2-adrenergic receptors and in plasma NE concentration in patients with EH from the high to low sodium period is compatible with the idea that an increase in α2-adrenergic receptors in the brain stem sympathetic nerve endings, as reflected by increased platelet α2-adrenergic receptors in the brain stem or sympathet
platelet $\alpha_2$-adrenergic receptors in hypertensive subjects. In our study, the number was not significantly different between the hypertensive and normotensive subjects.

Pettinger et al. reported that high dietary sodium increased renal $\alpha_2$-adrenergic receptors in Dahl salt-sensitive rats, but not in salt-resistant Dahl rats. The difference between our results and theirs might be due to the difference in the amount of salt ingested, the species difference, the tissue difference, or the difference in the type of hypertension. As to the relationship between sodium balance and adrenergic receptors other than the $\alpha_2$-subclass, the report of Fraser et al. is of interest: they showed that high dietary sodium increased the leukocyte $\beta$-adrenergic receptor density in normotensive men. Further investigation is required to clarify the basis of these differences.

In summary, in a salt-responsive group of patients with EH, in whom MAP decreased more than 7% when dietary sodium was reduced, the number of platelet $\alpha_2$-adrenergic receptors was increased after sodium deprivation. In a salt-nonresponsive group, the remainder of the patients with EH, such a change in receptor number was not observed. In contrast, epinephrine-induced platelet aggregation was decreased during sodium deprivation only in salt nonresponders. Our results indicate that dietary sodium restriction is associated with an increase in the number of platelet $\alpha_2$-adrenergic receptors in a subgroup of patients with EH.

Acknowledgments
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