Platelet taurine concentration and uptake in gestosis patients with edema, proteinuria and hypertension.

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Abstract

The taurine concentration and uptake in platelets obtained from normal pregnant women and gestosis patients with edema, proteinuria and hypertension (EPH gestosis) were investigated. The taurine concentration in platelets showed a marked increase in severe EPH gestosis compared with normal pregnancy or mild and moderate EPH gestosis, while the plasma taurine concentration did not change significantly. Taurine uptake in platelets paralleled the severity of EPH gestosis. The Vmax of the uptake in severe EPH gestosis was about 2.4 times higher than that in normal pregnancy or mild and moderate EPH gestosis, but no significant difference was seen in the Km value among these groups.

KEYWORDS: platelet, taurine concentration, taurine uptake, EPH gestosis

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Platelet Taurine Concentration and Uptake in Gestosis Patients with Edema, Proteinuria and Hypertension

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The taurine concentration and uptake in platelets obtained from normal pregnant women and gestosis patients with edema, proteinuria and hypertension (EPH gestosis) were investigated. The taurine concentration in platelets showed a marked increase in severe EPH gestosis compared with normal pregnancy or mild and moderate EPH gestosis, while the plasma taurine concentration did not change significantly. Taurine uptake in platelets paralleled the severity of EPH gestosis. The Vmax of the uptake in severe EPH gestosis was about 2.4 times higher than that in normal pregnancy or mild and moderate EPH gestosis, but no significant difference was seen in the Km value among these groups.

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Although many attempts have been made to elucidate the cause of gestosis with edema, proteinuria and hypertension (EPH gestosis), its etiology is still unknown. Recently, several studies have indicated that EPH gestosis is associated with chronic hyper-coagulation of the coagulo-fibrinolytic system (1, 2). Such a hyper-coagulative state can cause thrombosis which induces various adverse reactions. On the other hand, the extent of platelet aggregation, which plays a pivotal role in the coagulation scheme, is reported to decrease in severe EPH gestosis patients (3–5).

Taurine, a sulfur-containing free amino acid, is distributed widely in mammalian organs, and its concentration is especially high in the brain, heart, muscle and platelets (6). Although the physiological role of taurine is not fully understood, there is some evidence that the promotion of platelet aggregation in essential hypertension and myocardial infarction is associated with a low platelet taurine concentration, and some of these effects are reversed by administration of taurine (7–10). These findings suggest that taurine plays an important role as a platelet anti-aggregative agent in such cases. To clarify the relationship between taurine and platelet aggregation in EPH gestosis, we compared the taurine concentration in platelets and the taurine uptake by platelets in normal pregnancy and EPH gestosis.

Subjects and Methods

Subjects. Three groups of pregnant women were studied: 18 normal pregnant women (range 28–40
weeks); 9 mild and moderate EPH gestosis cases (range 30–39 weeks); and 6 severe EPH gestosis cases (range 30–37 weeks). The severity of EPH gestosis was categorized according to the gestosis index (GI) proposed by the Organization Gestosis (11); mild and moderate, GI = 1–6; and severe, GI = 7–11.

Methods

Amino acid analysis. Venous blood was withdrawn by clean antecubital venipuncture into a plastic syringe containing 0.1 volume of acid-citrate-dextrose solution (pH 4.5–5.5) (ACD, Terumo Co., Tokyo, Japan) containing sodium citrate (2.20 w/v %), citric acid (0.80 w/v %) and glucose (2.20 w/v %). Platelet rich plasma (PRP) was prepared by centrifugation of the blood at 70 x g for 15 min at room temperature. Then, PRP was centrifuged after addition of 0.1 volume of 0.1 M EDTA (pH 7.4) at 750 x g for 15 min at room temperature to obtain platelet pellet. A portion of the pellet resuspended in physiological saline of the original volume of supernatant was subjected to freezing and thawing 3 times and centrifuged at 2200 x g for 10 min. Free amino acids in the plasma and the supernatant obtained above were determined with an amino acid analyzer (model A-5500E, IRICA, Kyoto, Japan).

Results were expressed as pmoles/10^6 cells and μ mole/ml. The values were expressed as the mean ± SD of separate determinations. The significance of the differences was calculated using Student’s t test.

Results

Concentration of taurine in platelets and plasma. The taurine concentration in platelets of severe EPH gestosis cases was significantly higher than that of normal pregnant or mild and moderate EPH gestosis cases as shown in Fig. 1A. However, no significant difference in plasma taurine concentration was detected between normal pregnant and EPH gestosis cases (Fig. 1B).

Taurine uptake by platelets. As shown in Fig. 2A, taurine uptake into platelets showed a saturating tendency. Taurine uptake was much higher in severe EPH gestosis than that in normal pregnant subjects. The result was analyzed with the Hanes-plot (Fig. 2B). As shown in Table 1, the Vmax in normal pregnant, mild and moderate EPH gestosis, and severe EPH gestosis cases

![Fig. 1](http://escholarship.lib.okayama-u.ac.jp/amo/vol46/iss1/4)
were 0.95, 0.89 and 2.25 fmol/min per 10^4 platelet cells, respectively. The Vmax in severe EPH gestosis cases was about 2.4 times higher than that in normal pregnant or mild and moderate EPH gestosis cases (p<0.001). No significant difference was seen in Km among these groups. As shown in Fig. 3, a high correlation between Vmax of taurine uptake and GI score was observed. Regression line was \( y = e^{0.208x - 1.03} \) and correlation coefficient was 0.91.

![Table 1 Kinetic constants of taurine uptake by platelets in normal pregnancy and EPH gestosis.](image)

<table>
<thead>
<tr>
<th>Cases</th>
<th>Vmax (fmol/10^6 cells * min^-1)</th>
<th>Km (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pregnancy (n=8)</td>
<td>0.95±0.29</td>
<td>48.1±25.9</td>
</tr>
<tr>
<td>Mild and moderate EPH gestosis (n=9)</td>
<td>0.89±0.33</td>
<td>33.8±24.2</td>
</tr>
<tr>
<td>Severe EPH gestosis (n=6)</td>
<td>2.25±0.76*</td>
<td>60.3±49.4</td>
</tr>
</tbody>
</table>

\( a \): Results are expressed as the mean±SD. Numbers of patients are shown in the parentheses. The Vmax of severe EPH gestosis which differs significantly from other groups is shown by * (p<0.001).
That is, the taurine uptake into platelets increased exponentially as the EPH gestosis became more severe.

Discussion

From a hemo-coagulative point of view, EPH gestosis is a state of chronic hyper-coagulation (1, 2). Under such a condition, the coagulations in small vessels may occur which can cause intra-uterine growth retardation and fetal distress due to impaired utero-placental circulation, or renal dysfunction caused by fibrin precipitation in glomeruli with a consequent decrease in renal blood flow (12, 13).

Several hypotheses have been proposed to explain the inhibition of the platelet aggregation in EPH gestosis cases even in a hyper-coagulative state. For example, it has been suggested that fibrin degraded products that inhibit platelet aggregation (14). Another explanation is that the inhibition of platelet aggregation is due to an increased number of exhausted platelets (5). However, these hypotheses fail to completely explain the phenomenon.

Taurine is reported to inhibit the aggregation of platelets (8–10, 15). We, therefore, investigated the platelet taurine concentration and uptake in patients with EPH gestosis.

Taurine is the most abundant free amino acid in the platelets (13.5 μmoles/ml, based on calculations derived from normal pregnancy shown in Fig. 1A) and is at least 340 times greater than that in plasma, which is relatively low (40 nmoles/ml, Fig. 1B). In neuronal cells, taurine is actively transported into cells through a specific carrier system which is driven by the gradient of sodium concentration (16). We have also confirmed that the uptake of taurine by platelets is dependent on sodium concentration (17) and incubation temperature (Fig. 2A). On rat heart sarcolemma, there are specific taurine receptors and taurine is incorporated into the cells (18). However, the mechanism that accounts for the marked difference in taurine concentrations inside and outside of the platelet is still unknown.

The uptake of taurine by platelets in normal pregnant women and patients with EPH gestosis showed a saturating tendency and the curve of taurine uptake approached a plateau value, which is typical for the Michaelis-Menten type of saturation phenomenon. The Km obtained from the Hanes plot of taurine uptake was essentially the same among three groups. However, the Vmax of taurine uptake by platelets in severe EPH gestosis was higher than that in the normal pregnancy group, or in mild and moderate EPH gestosis. The Vmax of taurine uptake reflects the capacity of taurine incorporation into platelets. Therefore, when the Vmax reading becomes higher, the intraplatelet taurine concentration is expected to be augmented. However, there was no significant difference in the Km values among these groups. Km reflects the affinity or quality of the uptake system. Thus, the high concentration of taurine in the platelets of patients with EPH gestosis reflects a higher capacity rather than a change in characteristics of the taurine uptake system on the platelet membrane.

Taurine in the platelets is reported to inhibit platelet aggregation (8–10, 15). We have confirmed that addition of exogenous taurine at the concentrations of 25 or 50 mM to platelets obtained from nonpregnant women followed by incubation at 37°C for 5 min inhibits the aggregation of platelets in a dose dependent manner; 63 % or 26 % of control, respectively (17).

Several studies suggest that platelet aggregation is inhibited in cases of EPH gestosis (3–5). Our findings indicate that the taurine concentration in platelets is increased in cases of severe EPH gestosis due to the augmentation of Vmax for taurine uptake. These factors indicate that augmentation of the taurine concentration in the platelets of EPH gestosis patients is responsible for the inhibition of platelet aggregation in spite of the general hypercoagulative state in these patients. This system may help to maintain the homeostasis of coagulation mechanism.
How the increased taurine in platelets prevents the aggregation of platelets is not clear. However, in the heart, taurine antagonizes the calcium paradox and retards the development of lesion formation in calcium overload myopathy (19). There are also reports that in both central and peripheral nervous systems, taurine acts as a modulator of membrane excitability by inhibiting the release of other neurotransmitters and by decreasing mitochondrial release of calcium (20). Some reports have indicated that taurine in the platelets prevents the release of serotonin and ATP which are suggested to affect platelet aggregation (8, 21). Thus, taurine seems to be acting as a stabilizer of membrane excitability (22) and this may be the mechanism by which taurine prevents platelet aggregation.

We found that the taurine uptake by platelets sharply decreased within 7 days prior to the onset of disseminated intravascular coagulation (DIC) in severe EPH gestosis (23). This might be due to impairment of the membrane transport system of taurine by DIC. These findings appear to contribute to the understanding of how increased intraplatelet taurine concentration in severe EPH gestosis patients appears to prevent platelet aggregation. However, further studies are needed to elucidate in detail the relationship between platelet taurine and platelet aggregation.

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References


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