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—Original Article—

ROLE OF PLASMA HISTAMINE IN LIVER INJURY —CLINICAL AND EXPERIMENTAL INVESTIGATIONS—

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Summary

Plasma histamine level (PHL) was evaluated by a modified fluorometric assay (Suzuki) in the patients with various forms of liver disease as well as rabbits with liver injury. And the data obtained were compared with liver function tests in assessing the stage and prognosis of hepatic dysfunction.

In acute hepatitis, if its prognosis was "good", as was also shown in the animal group with single dose administration of CCl_4, the level of plasma histamine attained a peak before that of serum transaminases, and returned to normal prior to that of the latter. In persistent and chronic hepatitis, although correlation between PHL and other liver function tests was poor and variable, PHL remained high. And the estimation of PHL during the course of this state showed that it was elevated prior to that of serum transaminases, indicating high level of plasma histamine in this state, even in apparent "steady state", worsening of the disease. In liver cirrhosis PHL correlated with the degree of serum transaminases as well as serum gammaglobulin. In "poor prognosis" group (patients with hepatic coma and rabbits treated with consecutive administration of CCl_4) PHL increased extremely high, which was contrasted with the lowered levels of transaminases.

These results strikingly suggest that histamine is involved in liver injury and estimation of PHL in the course of hepatic disorder is useful for a prediction of prognosis.

Key Words: *plasma histamine, acute hepatitis, subacute hepatitis, liver cirrhosis, carbon tetrachloride.*

Attempts to clarify the mechanism of chronicity of liver disease have met with only limited success. However, microcirculatory derangement[1] has been implicated in the pathologic process accounting for chronic liver injury. In the light of the common observation that vasoactive substances, particularly histamine, are almost invariably elevated in these disorders[2], it is postulated that these substances may be responsible for the progression and aggravation of hepatic injury[3,4].

Although the device of fluorometric assay by Shore et al.[5] has provided a surprising progress for the determination of tissue and/or blood histamine, there still remains a room for improvements. The authors comprehensively investigated Shore's method and found some points to be improved[6]. In the present study plasma histamine level (PHL) was determined

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by this method in the patients with liver disease along with in animals with hepatic injury, in an attempt to elucidate the relationship between hepatic disorder and plasma histamine, together with the likelihood involving this vasoactive amine in the chronicity of liver disease.

Part I. Clinical Study

Patients and Methods

The patients consisted of the following types: 14 cases of acute hepatitis, 62 cases of chronic hepatitis, 31 cases of liver cirrhosis, and 6 cases of hepatic coma. The diagnosis of liver disease was based upon the clinical picture, liver function tests, and the histological grounds from biopsy and autopsy material. The controls were laboratory staff and outpatients matched sex and age, with no demonstrable liver disease.

Results

Levels of plasma histamine in the control group were the following: 6.6±0.7 μg/L with a range of 5.2 to 7.4 μ/L in males and 7.7±1.2 μg/L with a range of 6.0 to 9.3 μg/L in females and the average value in all of these subjects was 7.1±1.1 μg/L with mean recovery rate of 95.2%.

1) Acute hepatitis

This group consisted of 9 cases of type B, 4 cases of type A hepatitis and 1 case of drug induced hepatitis.

"Liver function tests" together with the measurement of PHL were carried out in all cases once a week during the course of this disease. The respective maximum levels of SGOT and SGPT were 553.7±496.7U and 517.3±468.3U, and mean PHL, obtained at the height of the illness, showed 18.9±6.7 μg/L with a range of 12.1 to 35.0 μg/L. PHL and enzymatic values in a typical case with acute hepatitis (type B) are shown in **Fig. 1**.

2) Chronic hepatitis

Wide variations were observed in the levels of plasma histamine depending upon the stage of disease, i.e., 6.3 to 21 μg/L (13.7±3.7, m±SI), and 8 of 63 cases (12.7%) remained within normal range and 25 cases (40%) showed more than 15 μg/L. There was a poor and variable correlation between PHL and other liver function tests. The typical case with chronic active hepatitis is demonstrated in **Fig. 2**.

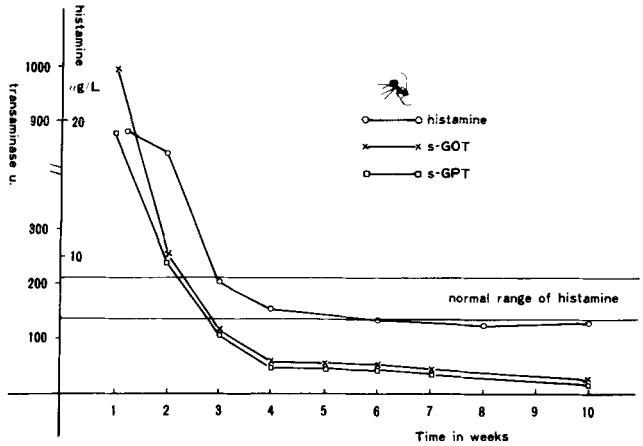

Fig. 1. Relationship between plasma histamine level and serum transsaminases in the patient with acute hepatitis (42-year-old female).

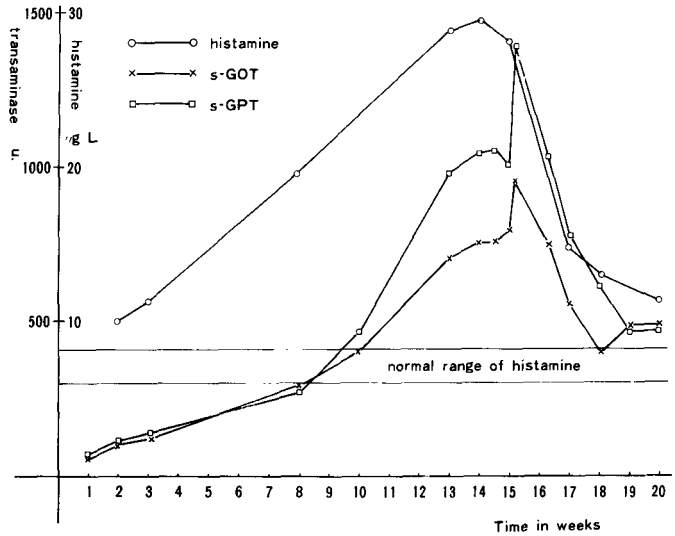

Fig. 2. Relationship between the level of plasma histamine and serum transaminases in the patient with chronic active hepatitis (28-year-old male).

3) Liver cirrhosis

PHL was elevated in all patients found to have cirrhosis of the liver, i.e., mean PHL was 15.9±3.5 μg/L with a range of 10.8 to 29.2 μg/L and the degree of hyperhistaminemia showed a close correlation with the degree of morphologic liver change. Furthermore, the mean levels of SGOT, SGPT and serum gammaglobulin showed 91.5±64.0U, 65.1±37.7U and 1.8±0.4 g/dl and these results were correlated with the degree of PHL with the correlation coefficients 0.619 (γ>0.325, α=0.05), 0.349 and 0.379, respectively.

4) Hepatic coma

The mean levels of PHL, prothrombin time, SGOT and SGPT at 3 days before coma, the 3rd and 7th day in coma, were as follows; PHL 16.2±3.1 μg/L, 16.9±3.6, 20.1±4.1, prothrombin time 15.8±3.2 sec, 18.3±2.3, 19.3±4.0, SGOT 125.7±84.9U, 72.9±26.8, 60.0±4.2 and SGPT 77.5±36.3U, 60.0±10.2, 44.5±10.6. These data showed that elevated PHL was well contrasted with the lowered levels of transaminases. **Fig. 3** and 4 depict the cases with hepatic coma.

The levels of plasma histamine in liver disease are summarized in **Table 1**.

Part II. Experimantal Study
Materials and Methods

Animals: Male albino rabbits weighing approximately 3 kg were used in all experiments. They were divided into 4 groups and each group consisted of 10 cases.

Antigen: Homologous liver antigen was prepared from normal rabbits, i.e., liver without lesion was extirpated immediately after sacrifice and then homogenized with 6 volume of physiological solution. The particulate fraction was removed by submitting the homogenates at 5,000 g for 10 min and the supernatant was used for antigen.

Hepatotoxic substance: CCl_4 was mixed with 3 volumes of olive oil.

Adjuvant: Freund's complete adjuvant was commercially obtained from Sigma Company (St. Louis. Missouri, U.S.A.).

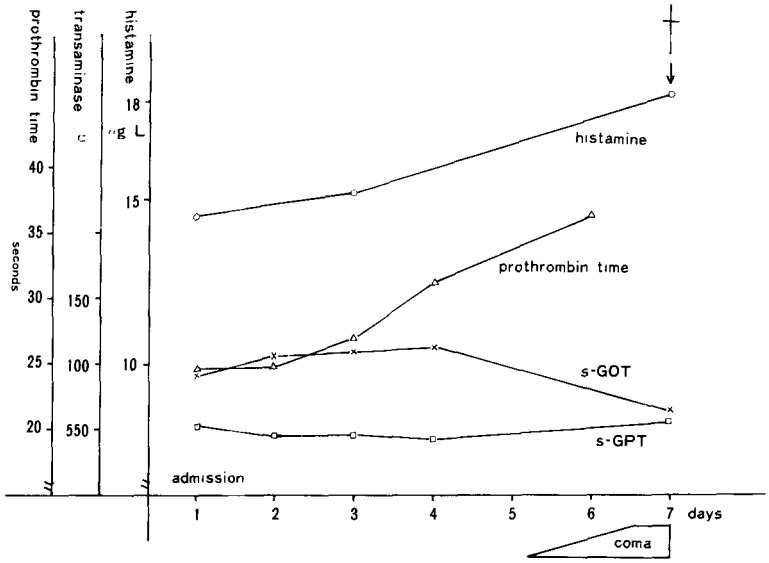

Fig. 3. Biochemical events in the patient with hepatic coma (subacute hepatitis, 45-year-old male).

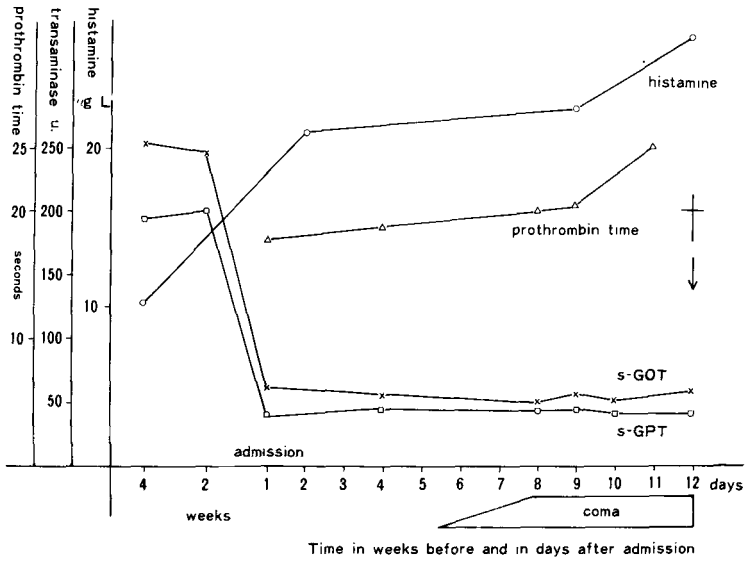

Fig. 4. Biochemical changes in the patient with hepatic coma (liver cirrhosis, 61-year-old female).

a) Group 1

Rabbits were injected intramuscularly with a single dose of hepatotoxic substance at 0.5 ml of weight.

b) Group 2

CCl_4 oil solution was administered intramuscularly at 0.3 ml/kg bw for consecutive 8 days.

c) Group 3

In this group 5 ml of homologous antigen

solution, mixed with an equal amount of Freund's adjuvant, was administered 15 to 20 sites hypodermically. After two weeks of the initial sensitization, antigen without adjuvant was injected into ear vein twice a week. Sensitization period lasted for 8 weeks.

d) Group 4

Eight weeks after a single dose administration of hepatotoxic substance, 0.5 ml/kg bw, antigen plus adjuvant was injected in the same way as group 3. After that only antigen solution was injected into ear vein once a week for consecutive 8 weeks.

Table 1. Levels of plasma histamine in liver disease

Normal Control	7.1±1.1 μg/L
Acute Hepatitis	
at onset	18.9±6.7
convalescence	10.1±2.4
Chronic Hepatitis	
aggressive	15.1±2.0
persistent	7.2±0.8
Liver Cirrhosis	
compensated	15.9±3.5
decompensated	16.2±3.1

Venous blood samples were obtained from each rabbits before the experiment and applied to the control study of SGOT, SGPT, serum protein fraction and PHL.

Results

The mean values of PHL, SGOT, SGPT and serum gammaglobulin in normal rabbits revealed 36.8±2.8 μg/L, 59.8±4.0U, 56.3±3.4U and 0.36±0.08 g/dl, respectively. The levels of histamine in the portal vein showed 40.9±1.7 μg/L, indicating significantly higher than that in the plasma ($t=2.51>2.45$, $\alpha=0.05$).

a) Group 1

Although the morphological finding is different from that of acute hepatitis in man, CCl_4 was administered in an attempt to induce parenchymal change. Blood was taken from ear vein at 6, 12, 24, 36 and 48 hr for the estimation of blood histamine as well as transaminase levels. PHL reached its maximum by 36 hr (**Fig. 5**). The peak of transaminase levels lagged behind the rise in histamine activity approximately 12 hr. PHL in

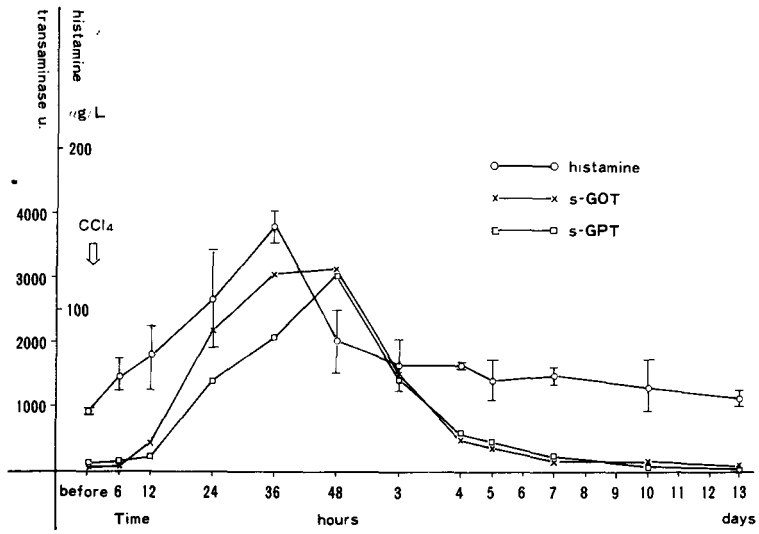

Fig. 5. Sequential biochemical events following the injection of a single dose of CCl_4 (rabbits).

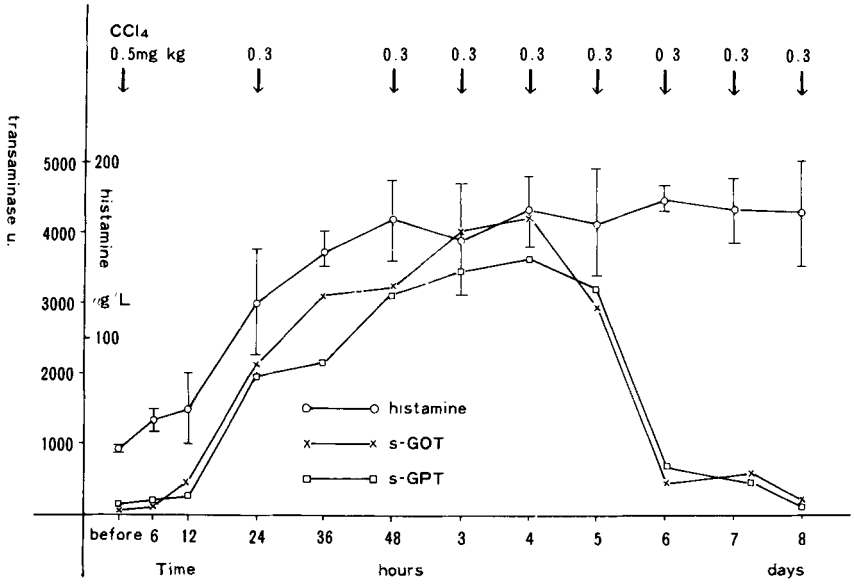

Fig. 6. Sequential biochemical changes following consecutive injection of CCl_4 (rabbits).

the portal vein, obtained from animals sacrified after 36 hr of CCl_4 administration, revealed 148.8 μg/L and differed in no way from that of venous value (144.0 μg/L).

b) Group 2

With consecutive administration of CCl_4, massive parenchymal necroses with fatty degeneration developed by the 7th day and no normal hepatocyte was seen in the liver. As is shown in **Fig. 6**, PHL increased gradually and reached extremely high (160 to 190 μg/L), whereas serum transaminases rapidly decreased at the 5th day with resultant apparent normal level at the 6th day.

c) Group 3

Sensitization yielded an increase in serum transaminases, which resulted in approximately 2 times by six weeks. PHL reached 60 μg/L at the 4th week (**Fig. 7**). Histological finding of the liver showed an increase in number and size of Kupffer cells and spotty necroses in parenchyma as well as an increase in fiber formation with small round cell infiltration in the portal tract.

d) Group 4

In the group receiving a single dose of CCl_4, serum transaminases and PHL all reversed to normal by the 8th week. The histology revealed almost normal liver. However, when homologous liver extract plus adjuvant was administered at this stage, serum gammaglobulin increased up to 1.1 g/dl by 4 weeks associated with a striking increase in PHL and serum transaminase. With consecutive administration of homologous liver extract the latter two attained their high levels (**Fig. 8**). Histology in this stage showed granulomatous change along with proliferation of plasma cells in parenchyma. In mesenchyma, fiber formation with small cell infiltration was seen in almost all animals.

Discussion

Many substances, including histamine, are metabolised almost exclusively in the liver. Therefore, impaired hepatic function due to

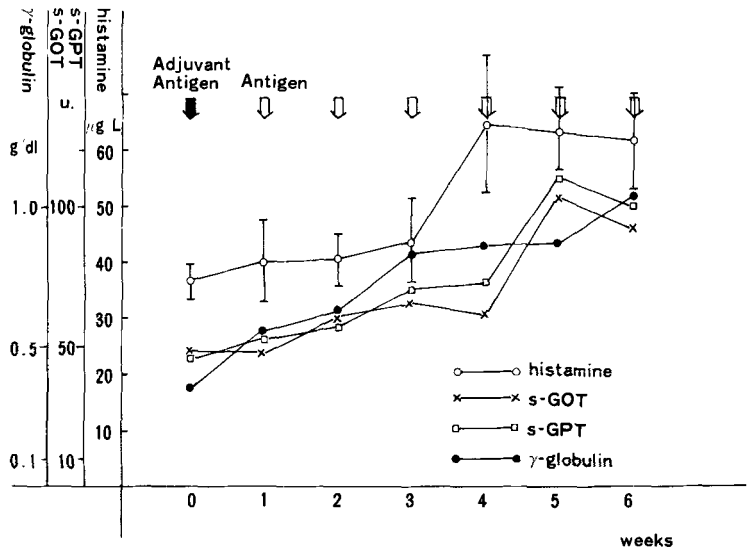

Fig. 7. Sequential biochemical events following the administration of homologous liver antigen plus Freund's complete adjuvant (rabbits).

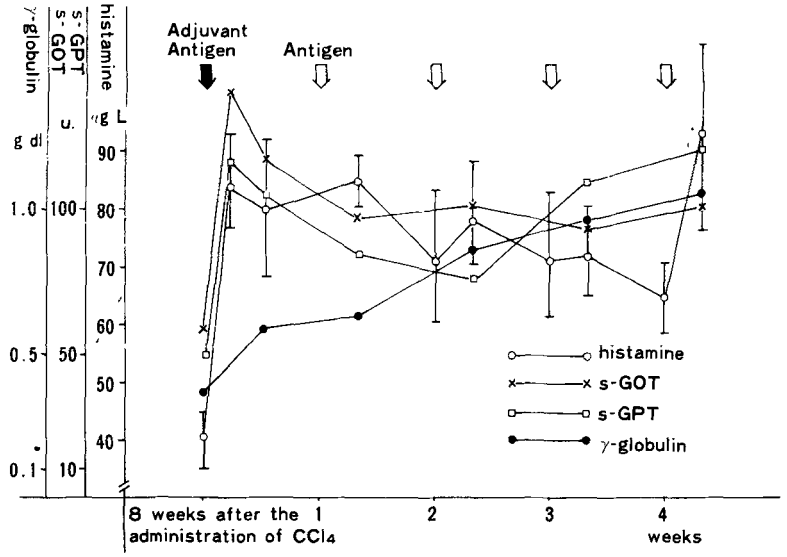

Fig. 8. Sequential biochemical changes following the injection of homologous liver antigen, administered after eight weeks of single dose of CCl_4 (rabbits).

acute or chronic hepatic disorder may be reflected in disturbed histamine metabolism[8,9].

Previous reports have shown a rise in the level of plasma histamine in patients with acute and chronic hepatitis as well as liver cirrhosis. Unfortunately, however, much of the data has been published without any experimental detail so that a cause and effect relationship

cannot be adequately compared.

In comparing experimental study with clinical data from the viewpoint of histamine metabolism, hepatic injury may be divided into several types—in "good prognosis" group (experimental group induced by a single injection of CCl_4 and clinical case given in **Fig. 1**), although hyperhistaminemia is evident in the initial stage of the disease, it is a transient event following with a rapid fall. In "poor prognosis" group (experimental group induced by the consecutive administration of CCl_4 and clinical cases with hepatic coma), PHL remains extremely high in the stage of lowered levels of transaminases. Furthermore, experimental study (group 4) represents that even a single episode of noxious agent is sufficient to set in motion of a process that readily leads to considerably aggravation of liver disease. The most typical case is demonstrated in case 2 (**Fig. 2**), in which data is obtained indicating that inflammatory change exists continuously in an apparrent normal state.

The mode of action of histamine in liver cirrhosis seems to be somewhat different from that of in acute hepatitis. The information available is insufficient to say what the difference is. However, in recent years attention has been paid on the influence of bacterial endotoxin, particularly Escherichia coli derived lipopolysaccharide, in chronic liver disease[10,11]. Many clinical and experimental data are gained raising the possibility that endotoxin, with resultant release and enhanced synthesis of histamine, is responsible for this process. Furthermore, exogenous histamine induced chronic liver injury has been documented experimentally[3,4]. From these facts it can be assumed that a vicious circle operates in which damaged liver favors impairment of histamine breakdown and hyperhistaminemia in turn accentuates liver injury.

There have been often difficulties in assessing the stage and severity of hepatic dysfunction. However, measurement of PHL during the course of hepatic disorder provides a prediction for the prognosis and several preliminary conclusion can be drawn from these data.

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