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Effect of Selenium on “Low T₃ Syndrome” in Hepatic Failure

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Abstract: Triiodothyronine occurs especially in 5'-monodeiodination of thyroxin in peripheral tissues. Deiodination of thyroxin mainly occurs in the liver. The enzyme which catalyzes this reaction is a seleno-enzyme. Deiodinase enzyme activity and the triiodothyronine level decrease in selenium deficiency.

After the occurrence of chronic hepatic failure by carbon tetrachloride in rats, we gave sodium selenite to these rats. Then, we tried to evaluate the changes in thyroid hormone levels.

Liver function tests, thyroxin and triiodothyronine levels, and hepatic 5'-deiodinase and glutathione peroxidase enzyme activities were measured.

Triiodothyronine levels in the carbon tetrachloride group and carbon tetrachloride + selenium group were significantly lower than in the control group ($P<0.01$, $P<0.05$, respectively). In the carbon tetrachloride + selenium group, the level of triiodothyronine was higher than in the carbon tetrachloride group ($P<0.05$).

Deiodination of thyroxin was impaired in hepatic failure. Selenium couldn't prevent the inhibition of hepatic deiodination of thyroxin completely.

Key Words: Hepatic failure, Selenium, Thyroid hormones.

Introduction

Selenium (Se) deficiency has important pathological sequelae in both animals and in man and may cause poor growth, impaired neutrophil function, and increased susceptibility to infections (1–3). In man, lowered Se status has been associated with cardiomyopathy and an increased risk of developing certain cancers (4, 5).

Hepatic enzyme expression changes with Se deficiency, but the mechanism is unclear (6). Thyroid hormones have many effects on hepatic enzyme expression. The relationships between thyroid hormones and Se had been documented by many studies (7–10). All thyroxine (T₄) is obtained from thyroidal synthesis, but over 85% of circulating T₃ is derived from 5'-monodeiodination of T₄ in peripheral tissues. 5'-monodeiodination of T₄ mainly occurs in the liver (11).

Changes in enzyme expression in Se deficiency may also affect the peripheral thyroid hormone metabolism. Deiodination of T₄ to T₃ is especially caused in the liver by Type I 5'-deiodinase enzyme, which is a seleno-enzyme.

Therefore, Se deficiency may decrease the biologically active T₃ level. In non-thyroidal tissues, two types of enzyme are responsible for 5'-monodeiodination of thyroxine. The type I enzyme is present mainly in the liver and kidney and it is inhibited by low concentrations of propylthiouracil. The type II enzyme is found mainly in the pituitary and in the brain (11).

The Se level is very high in the liver, the pituitary, the renal cortex, and the pancreas tissues. The Se level decreases in hepatic failure and in cardiovascular diseases (11).

Decreased T₃ level in hepatic failure has been attributed to various causes (12). Because Se affects deiodination of T₄ to T₃, it is possible that thyroid hormone composition may change in hepatic failure due to Se deficiency. After experimental hepatic failure occurred in rats, we tried to investigate the effect of Se injections on the T₄ metabolism.

Materials and Methods

Forty male Wistar rats were used in this study. The rats were divided into 4 groups.

Group 1 (n=10): Carbon tetrachloride (CCl₄) was diluted in refined olive oil at a ratio of 3:2. Diluted CCl₄, at a dose of 0.15 ml/100 g, was administered subcutaneously 3 times a week for 6 weeks. By administering CCl₄, cirrhosis was induced in these rats (CCl₄ group). Diagnosis of cirrhosis confirmed by biopsy.

Group 2 (n=10): By administering CCl₄, cirrhosis was induced in this group. Then sodium selenite, at a dose of 0.1 mg/kg, was administered intraperitoneally once a day for one week (CCl₄+Se group).

Group 3 (n=10): Only refined olive oil, at a dose of 0.15 ml/100 g, was administered subcutaneously 3 times a week for 6 weeks (Control group).

Group 4 (n=10): Refined olive oil, at a dose of 0.15 ml/100 g, was administered subcutaneously 3 times a week for 6 weeks. Then sodium selenite, at a dose of 0.1 mg/kg, was administered intraperitoneally once a day for one week (Se group).

All rats were fed standard rat food and distilled water. 24 hours after the last feeding, all the animals were decapitated. Blood samples were taken and centrifuged at 3000 g for 10 minutes. Then, serum was extracted and stored at -20°C. Liver function tests (Serum total bilirubin-T. bilirubin, conjugated bilirubin-C. bilirubin, aspartate aminotransferase-AST, alanine aminotransferase-ALT, lactic dehydrogenase-LDH, alkaline phosphatase-ALP, and gamma-glutamyltranspeptidase-GGT) were evaluated with a Tecnicon RA, XT model autoanalyzer. Serum T₄ and T₃ levels were measured using radioimmunoassay methods. We used DPC test kits-Diagnostic Product Corporation, Los Angeles, California and LKB 1261 Multigamma gamma counter.

Preparation of tissue homogenates

Liver tissues were homogenized in 3 volumes of buffer [0.25 M sucrose/0.05 M-Tris/HCl (pH 7.4)/mM-DDT] using a Teflon-pestle/glass-body homogenizer (6).

Measurement of T₃ production

Homogenates (2 ml) were placed into glass tubes and incubated at 37°C for 5 min before the addition of 10 µg of T₄ dissolved in 20 µl of phosphate buffer (0.5 M; pH 7.4). At increasing time periods, 0.2 ml portions of the homogenates were put in 0.4 ml of ethanol and mixed for 30 s on a vortex mixer. The ethanolic extracts were then

centrifuged at 1500 g for 15 minutes and the T₃ concentration of the supernatants was measured with radioimmunoassay after 10-fold dilution with sucrose/Tris buffer (6).

Protein concentration in the homogenates was measured by biuret reaction.

Measurement of Hepatic GSH-Px (Glutathione peroxidase) activity

Liver tissues were homogenized in 3 volumes of 20 mM phosphate buffer containing 150 mM NaCl (pH 7.4) and used for the measurement of GSH-Px activity.

GSH-Px activity was measured, with 0.25 mM-H₂O₂ as the substrate, in the presence of 5 mM-GSH (13).

The data were expressed as Mean±SD. Differences among groups were compared using the Mann-Whitney U-test.

Results

Diagnosis of cirrhosis was confirmed histopathologically. The results of the liver function tests are shown in Table 1.

GSH-Px activity was measured as an index of selenium deficiency. Hepatic GSH-Px activity was significantly low in the CCl₄ group (P<0.001). By administering selenium, hepatic GSH-Px activity increased. Hepatic GSH-Px activity was higher in the CCl₄+Selenium group (790.81±78.45 mU/mg protein) than in the CCl₄ group (612.15±71.00 mU/mg protein) (P<0.01). By administering selenium, hepatic GSH-Px activity was also increased in the selenium group relative to the control group (P<0.01).

5'-deiodinase (5'DI) enzyme activity decreased 50% in the CCl₄ group and 20% in the CCl₄+Selenium group. After administering selenium, 5'DI enzyme activity was increased significantly in the selenium group relative to the control group (P<0.05).

Serum T₄ level decreased insignificantly in the CCl₄ group and increased insignificantly in the CCl₄+Selenium group. However, T₄ level increased significantly in the Selenium group (P<0.05).

T₃ levels in the CCl₄ group and CCl₄+Se group were significantly lower than in the control group (P<0.01, P<0.05, respectively). In the CCl₄+Se group, the level of T₃ was higher than in the CCl₄ group (P<0.05). These results are shown in Table 2.

In the control group, the correlation between GSH-Px activity and 5'-Deiodinase was r=0.472 (P>0.05) and

Table 1. Liver function tests.

	Control Group (n=10)	CCl ₄ Group (n=10)		CCl ₄ +Se Group (n=10)		Se Group (n=10)
AST (U/L)	70.20±12.21	807.15±98.06	A	708.57±100.90	A	73.21±11.05
ALT (U/L)	50.80±9.70	383.86±67.09	A	354.44±50.71	A	49.01±7.00
LDH (U/L)	504.67±81.90	2910.54±275.87	A	2900.60±265.98	A	512.32±79.00
ALP (U/L)	250.29±40.50	600.13±96.23	A	588.13±90.30	A	275.41±34.09
GGT (U/L)	3.90±0.70	7.80±1.72	A	4.79±0.98	A	4.01±0.40
T. Bilirubin (mg/dl)	0.24±0.02	3.60±0.65	A	3.03±0.70	A	0.26±0.03
C. Bilirubin (mg/dl)	0.18±0.01	2.80±0.70	A	2.52±0.45	A	0.17±0.02

CCl₄ = Carbon tetrachlorideCCl₄+Se = Carbon tetrachloride+selenium

Se = Selenium

AST = Aspartate aminotransferase

ALT = Alanine aminotransferase

LDH = Lactic dehydrogenase

ALP = Alkaline phosphatase

GGT = Gamma-glutamyltranspeptidase

T. Bilirubin = Total Bilirubin

C. Bilirubin = Conjugated Bilirubin

A = P<0.001 versus control

Table 2. Hepatic 5'-Deiodinase and Glutathione peroxidase (GSH-Px) enzyme activities and serum thyroxin (T₄) and triiodothyronine (T₃) values.

	Control Group (n=10)	CCl ₄ Group (n=10)		CCl ₄ +Se Group (n=10)		Se Group (n=10)
GSH-Px	807.50±95.70	612.15±71.00	B	790.81±78.45		957.48±108.30 A
5'-DI	15.20±1.30	7.70±0.60	C	12.10±1.40	A	20.30±2.00 B
T ₄ (µg/dl)	5.37±0.95	4.60±0.87		5.20±0.98		6.50±1.05 A
T ₃ (ng/dl)	90.48±18.20	60.12±11.71	B	71.18±10.12	A,D	92.74±13.98

CCl₄ = Carbon tetrachlorideCCl₄+Se = Carbon tetrachloride+selenium

Se = Selenium

GSH-Px = Glutathione peroxidase (mU/mg protein)

5'-DI=5'-Deiodinase (fmol/min/mg)

T₄ = ThyroxinT₃ = Triiodothyronine

A = P<0.05 versus control

B = P<0.01 versus control

C = P>0.001 versus control

D = P<0.05 versus CCl₄ group

the correlation between GSH-Px activity and T₃ was r=0.403 (P>0.05).

In the CCl₄ group, the correlation between GSH-Px activity and 5'-Deiodinase was r=0.670 (p<0.01) and the

correlation between GSH-Px activity and T₃ was r=0.550 (P<0.05).

In the CCl₄+Se group, the correlation between GSH-Px activity and 5'-Deiodinase was r=0.690

($P < 0.01$) and the correlation between GSH-Px activity and T₃ was $r = 0.565$ ($P < 0.05$).

In the Se group, the correlation between GSH-Px activity and 5'-Deiodinase was $r = 0.560$ ($P < 0.05$) and the correlation between GSH-Px activity and T₃ was $r = 0.510$ ($P > 0.05$).

Discussion

T₄ produces T₃ and rT₃. This transformation is in balance under normal conditions. Several clinical states such as starvation, protein calorie malnutrition, acute or chronic illness, cirrhosis of the liver, chronic renal failure, systemic diseases, and exercise are associated with low serum T₃ and increased serum rT₃ levels due to changes in the T₄ metabolism (14–19).

Recently, it was concluded that hyperglucagonemia may be one of the factors responsible for low serum T₃ and high serum rT₃ concentrations in hepatic cirrhosis. Besides hyperglucagonemia, selenium deficiency occurs in cirrhosis, too. Kabadi et al have suggested that glucagon has a significant effect on the deiodination of T₄ (12, 16, 18, 20). The Se level decreases in hepatic cirrhosis. Se is present in the 5'-deiodinase enzyme structure and this enzyme has a role in the monodeiodination of T₄. Therefore, 5'-deiodinase enzyme activity decreases in Se deficiency (21, 22).

In this study, we observed that Se didn't affect the serum T₃ level in normal rats. But, the T₃ level decreased in the group in which hepatic failure was induced with CCl₄. The CCl₄+Se group had a significantly higher serum T₃ level than the CCl₄ group ($P < 0.05$), but a lower T₃ level than the control group ($P < 0.05$).

5'-deiodinase enzyme activity significantly decreased after hepatic failure. By administering Se, 5'-deiodinase enzyme activity increased. These findings were in parallel with changes observed in the serum T₃ level.

Se administered to cirrhotic rats increased GSH-Px activity, 5'-DI activity, and the T₃ level. Thus, we think that a low serum T₃ level in cirrhosis at least may originate from Se deficiency.

5'-deiodinase enzyme activity decreases in chronically Se deficient rats. Therefore, the serum T₄ level increases and the serum T₃ level decreases. Menhold et al (8) have observed that hepatic type I 5'-deiodinase enzyme activity significantly decreased in chronically Se deficient rats. They have reported that the T₃ level decreased and the T₄ level increased in these rats. Beckett et al (23) have demonstrated that Se deficiency for periods of 5 or 6 weeks in rats produced an inhibition of type I 5'-deiodinase enzyme activity in the liver and an inhibition of type II 5'-deiodinase enzyme activity in the brain. Inhibition of type I 5'-deiodinase and type II 5'-deiodinase activities decrease turnover of T₄ to T₃.

The Se level decreases in hepatic failure and the thyroid hormone metabolism is impaired in Se deficiency. Therefore, Se deficiency may be one of the factors responsible for low T₃ hormone levels in hepatic cirrhosis. In our study, we observed that Se, a trace element, played an important role in the thyroid hormone metabolism in cirrhosis. However, we couldn't increase the T₃ level to its normal value by administering Se to rats which had hepatic failure. Therefore, we suggest that other factors are also responsible for "Low T₃ syndrome" in hepatic failure. Nevertheless, we think that additional Se therapy may be beneficial to the thyroid hormone metabolism in hepatic failure.

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