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Effects of acute hepatic damage on natriuresis and water excretion after acute normal saline loading in rats

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Abstract

AIM: To investigate the relationship between liver functional impairment and sodium and water retention.

METHODS: An animal model of acute liver damage model was established by administering carbon tetrachloride (CCl_4) to male Sprague-Dawley rats. Twenty-four and 48 h after CCl_4 administration, the excretion of acute sodium and water load was measured. In controls, the excretion of acute sodium and water load was measured 24 h after administration of normal saline. In addition, the concentration of plasma caffeine was analyzed using high pressure liquid chromatography (HPLC). The half-life of plasma caffeine (Caf $t_{1/2}$) served as a quantitative index of hepatic function. Plasma alanine aminotransferase (ALT) was measured using the Reitman method. Hepatic tissue sections from the same site were used for water content measurement and pathological observation. The serum and urinary sodium levels were measured with flame photometry.

RESULTS: Twenty-four hours after CCl_4 administration, plasma ALT level (n = 6, 37.5 ± 12.6 → 189.4 ± 34.4 U, P < 0.01) and water content of hepatic tissue (n = 6, 70.0% ± 0.11% → 73.0% ± 1.0%, P < 0.01) were significantly increased, and Caf $t_{1/2}$ was prolonged significantly (94.9 ± 18.9 → 326.4 ± 85.8 min, P < 0.01) compared to saline treated control. Renal function, as assessed by excretion of acute salt and water load, was significantly decreased (n = 6, Na^+: 92.4% ± 14.1% → 50.1% ± 13.1%, P < 0.01; H_2O: 86.3% ± 14.3% → 42.1% ± 8.8%, P < 0.01). The above indices had recovered somewhat 48 h later but were still markedly different from those of control. In addition, the relationships between Caf $t_{1/2}$ and ALT (r = 0.752, P < 0.01) and between Caf $t_{1/2}$ and excretory rate of sodium (r = 0.634, P < 0.05) and water remained significant (r = 0.612, P < 0.01) at 48 h.

CONCLUSION: Caf $t_{1/2}$ is a good index to assess the degree of hepatic damage. Hepatic dysfunction may contribute to impairments in renal excretion following acute sodium and water load.

Key words: Liver disease; Water-electrolyte imbalance; Kidney/Metabolism

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INTRODUCTION

Most data to date have shown that there is a significant relationship between hepatic functional damage and sodium retention, but it remains unclear whether acute liver dysfunction results in sodium and water retention. To understand further the relationship between liver function per se and sodium retention, we investigated renal excretion following acute salt and water load in a rat model of acute hepatic damage.

MATERIALS AND METHODS

Acute hepatic damage model

Eighteen male Sprague Dawley rats weighing 270-320 g were divided into three groups: control (n = 6), experimental group 1 (n = 6), and experimental group 2 (n = 6). Reduced salt chow (12.74 mmol/kg) and re-distilled water were available *ad libitum*. Three days later, carbon tetrachloride (CCl_4) (0.02 mL/100 g body wt) was administered intraperitoneally to experimental groups, and normal saline (0.02 mL/100 g body wt) was administered to the control group. Acute normal saline loading was conducted in experimental groups 2 and 3 24 and 48 h after CCl_4 administration, respectively, and 24 h after saline administration in the control.

Acute sodium and water loading experiment

Twelve hours after removing water and food, the animals received under urethane anesthesia normal saline (4 mL/100 g body wt) through the femoral vein. Urine was collected for 4 h and stored in an Eppendorf tube at -20 ℃ until analysis. One percent caffeine, 0.1 mL (1 mg/rat), was then administered to the femoral vein for

Table 1 Lesion indices of hepatic tissue and liver dysfunction after CCl_4 administration (n = 6, $\bar{x} \pm s$)

Group	Water content (%)	ALT (Reitman U)	Caf $t_{1/2}$ (min)
Control	70.1 ± 1.1	37.5 ± 12.6	94.8 ± 18.9
CCl_4 24 h	73.0 ± 1.0[b]	189.4 ± 34.4[b]	326.4 ± 85.8[b]
CCl_4 48 h	72.0 ± 0.8[b]	126.1 ± 59.1[a]	169.5 ± 37.9[b]

[a]$P < 0.05$; [b]$P < 0.01$ *vs* control. Liver water content (%)

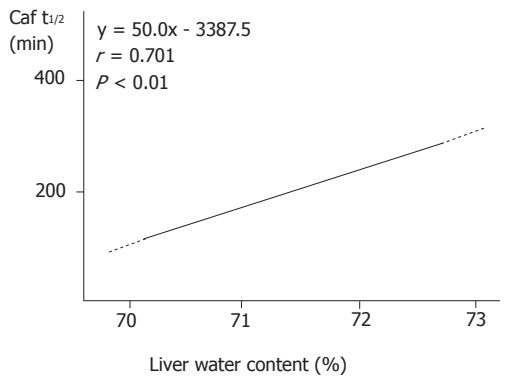

Figure 1 Relationship between liver water content and liver function

Table 2 Serum Na^+ and water salt excretory rate (n = 6, $\bar{x} \pm s$)

Group	serum Na^+ (mmol/L)	Na^+ excretory rate (%)	H_2O excretory rate (%)
Control	145.7 ± 5.7	92.4 ± 14.1	86.3 ± 14.3
CCl_4 24 h	143.0 ± 5.6	50.1 ± 13.1[b]	42.1 ± 8.8[b]
CCl_4 48 h	139.8 ± 2.1	64.3 ± 14.1[a]	56.6 ± 12.4[a]

[a]$P < 0.05$, [b]$P < 0.01$ *vs* control

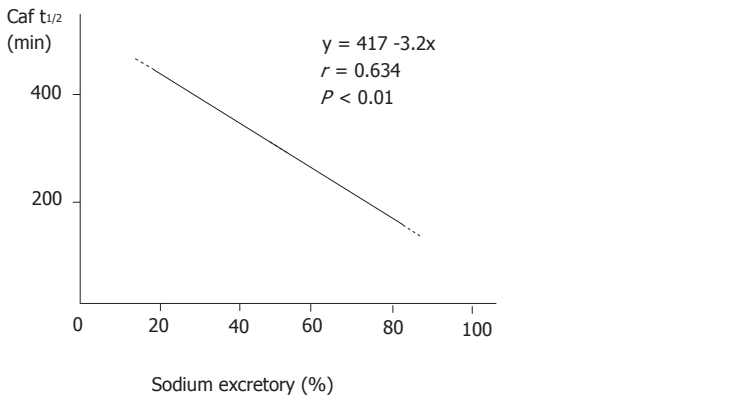

Figure 2 Relationship between excretory rate of salt load and liver function

3 h. Four milliliters of blood were taken from the inferior vena cava and anti-agglutinated with heparin. The plasma was separated to measure caffeine, ALT, and sodium. At this time, liver tissues were taken for pathologic examination and water content calculation.

Examination method

The plasma caffeine concentration was analyzed with high pressure liquid chromatography (HPLC). Plasma ALT was examined with Reitman method, and serum and urinary sodium levels were measured with flame photometry.

Calculation and statistics

The Caf $t_{1/2}$ was calculated using the following formula:

$$\text{Caf } t_{1/2} = \ln 2 \times (t / \ln (D / (avd \times \text{body wt}) \ln C_{caft})$$

where D = the dosage of caffeine (1 mg in this experiment); t = time from caffeine injection to blood collection (180 min); C_{caft} = caffeine concentration when blood was taken (mg/L); adv = apparent distribution volume (0.64 mL/kg). Data for each parameter were compared between two groups with a t test and among the three groups with an F test. Regression analysis was used to correlate Caf $t_{1/2}$ and water content in hepatic tissue, sodium excretory rate, water excretory rate, and plasma ALT. p values less than 0.05 were considered to be statistically significant.

RESULTS

The changes of hepatic tissue

In the control group, the hepatic cells were arranged regularly, and the plates radiated from the central vein to the portal canals. Twenty four hours after CCl_4 administration, the hepatic tissue exhibited extensive necrosis, hepatocyte swelling, and vacuolization under light microscopy. In the 48 h group, hepatocyte necrosis, swelling, and vacuolization were still clearly seen but to a lesser extent than the 24 h group. Consistent with the histological changes in the hepatic tissue, water content was significantly higher in both experimental groups than the control group.

Liver function decline

Following structural damage to the liver tissue, the capability of the liver to metabolize caffeine was impaired. The Caf $t_{1/2}$ was prolonged significantly in the 24 h and 48 h groups compared to that in the control group (Table 1). Caf $t_{1/2}$ and water content in hepatic tissue were significantly correlated (r = 0.701, $P < 0.01$, Figure 1).

Consistent with our findings on water content in hepatic tissue and Caf $t_{1/2}$, plasma levels of ALT rose significantly in both experimental groups. There was a significant positive correlation between ALT levels and Caf $t_{1/2}$ (r = 0.753, $P < 0.01$).

Relationship between liver dysfunction and sodium and water excretion

Following the impairment in liver function, the capability of the kidney to excrete acute water and sodium load declined significantly. Although this decline recovered somewhat in the 48 h group, it remained significantly different from that of the control (Table 2). The relationship between Caf $t_{1/2}$ and renal excretory rate of sodium (Figure 2) and water was significantly correlated (r = -0.612, $P < 0.01$). There was no significant difference among the three groups in serum sodium level (F = 2.34, $P > 0.05$, Table 2).

DISCUSSION

Recently, different models of hepatic damage[1-3] have demonstrated that the decline in liver function is an important cause of salt and water retention. Caffeine is metabolized by hepatic cytochrome P-450, and the ability of the body to clear caffeine reflects metabolic function of the liver. Jost *et al*[4] showed that the clearance rate of plasma caffeine is in significant agreement with the aminopyrine breath test (r = 0.80, $P < 0.01$), prothrombin time (r = 0.59, $P < 0.01$), indo cyanogreen test (r = 0.51, $P < 0.01$), and galactose clearance rate (r = 0.46, $P < 0.01$). Therefore, use of Caf $t_{1/2}$ to quantitate liver function is reliable; HPLC is an efficient and stable means to measure caffeine. Our results found that 24 and 48 h after CCl_4 administration, Caf $t_{1/2}$ was prolonged significantly. Changes in ALT levels and hepatic tissue water content paralleled Caf $t_{1/2}$. There was a significant relationship between Caf $t_{1/2}$ and ALT and between Caf $t_{1/2}$ and water content of hepatic tissue. These results illustrate that the decrease in liver function is linked to the degree of hepatic tissue damage. Thus, Caf $t_{1/2}$ may be considered a sensitive index that reflects the degree of acute hepatic tissue damage.

Importantly, following pathological damage of the liver, the plasma Caf $t_{1/2}$ was prolonged significantly and the ability of the kidney to excrete acute water and sodium load was declined significantly. Caf $t_{1/2}$ and renal excretory rate of sodium and water were negatively correlated. These results are consistent with the report by Wong *et al*[5] and identity hepatic tissue damage and liver function decline as important contributors to salt and water retention.

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