Ompi-to relieves acidosis in rats given adenine

Takako YOKOZAWA,*[a] Ping Dong ZHENG,[b] Hikokichi OURA,[b]
Masao HATTORI,[a] Naoya KUWAYAMA[c] and Akira TAKAKU[c]

[a] *Department of Cell-resource Engineering, Research Institute for Wakan-Yaku, Toyama Medical and Pharmaceutical University*
[b] *Department of Applied Biochemistry, Research Institute for Wakan-Yaku, Toyama Medical and Pharmaceutical University*
[c] *Department of Neurosurgery, Faculty of Medicine, Toyama Medical and Pharmaceutical University*

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Abstract

In rats given an adenine diet, the presence of acidosis was corroborated by decreases in pH, partial pressure of carbon dioxide, base excess and standard bicarbonate. Ompi-to administration relieved acidosis under conditions of renal failure.

Key words Acidosis, adenine, Ompi-to, rat.

Abbreviations BE, base excess ; Ompi-to (Wen-Pi-Tang), 温脾湯 ; Pco_2, partial pressure of carbon dioxide ; SBC, standard bicarbonate.

Introduction

We have found previously that renal failure is induced gradually with the course of administration, in rats given adenine orally, and reported the physiological, biochemical and histological features of the renal failure thus induced.[1-7] Rats given an adenine diet exhibited anorexia, tremor of the limbs, spasm or decreased responsiveness to stimulation, and finally coma and death. These findings suggested the presence of acidosis in the body. In the present study, we determined pH, partial pressure of carbon dioxide (Pco_2), base excess (BE) and standard bicarbonate (SBC) in the blood of rats given an adenine diet in order to examine this possibility. The effects of Ompi-to administration in these rats were also studied ; Ompi-to is an Oriental medical prescription which is known to improve uremia, hypertension and decreased blood flow or to suppress their progression.[8-17]

Materials and Methods

Animals and treatment : Male rats of the LWH : Wistar strain, with a body weight of about 200 g, were used in this experiment. The rats were kept in a wire-bottomed cage under a conventional lighting regimen with a dark night. The room temperature (about 23°C) and humidity (about 60%) were controlled automatically. The animals were fed on an 18% casein diet containing 0.75% adenine, which produced experimental renal failure.[1-7] In rats with renal failure induced by adenine, renal impairment becomes aggravated as the period of adenine feeding increases. It has been confirmed previously by histological and biochemical procedures that renal failure was present after 6 days of adenine ingestion. Ompi-to extract was dissolved in water, and given to rats orally every day as drinking water with the adenine diet. The dose was adjusted to 200 mg/kg body weight by regulating its concentration in relation to water consumption. Control rats

*〒 930-01 富山市杉谷2630
富山医科薬科大学和漢薬研究所細胞資源工学部門 横澤隆子
2630 Sugitani, Toyama 930-01, Japan

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were given a corresponding amount of water. Throughout the experiment there were no significant differences in body weight change between the control and extract-treated rats. The food intake of each rat was essentially proportional to weight change. Six rats were used for each experimental group. Values are expressed as mean±S. E.

Ompi-to : The Ompi-to preparation was the same as that described previously.[8] The composition of Ompi-to used in this experiment was as follows : 15 g of Rhei Rhizoma (*Rheum officinale* BAILLON), 3 g of Ginseng Radix (*Panax ginseng* C. A. MEYER), 5 g of Glycyrrhizae Radix (*Glycyrrhiza glabra* LINN. var. *glandulifera* REGEL et HERDER), 3 g of Zingiberis Rhizoma (*Zingiber officinale* ROSCOE) and 9 g of Aconiti Tuber (*Aconitum japonicum* THUNBERG). Ginseng Radix was a product of Korea, Aconiti Tuber was from Japan, and the other ingredients were from China.

Statistics : The significance of differences between the normal rats and those with renal failure treated or not-treated with Ompi-to was tested using Student's *t* test.

Analyses : After 24 days, each rat was anesthetized with pentobarbital sodium, and a catheter was inserted into the right iliac artery. Blood samples were obtained under spontaneous respiration every 10 min in order to regard the degree of contribution of anesthesia thereafter for measurement of pH, Pco_2, BE and SBC, using a Blood Gas Analyzer (model ABL2, Radiometer Co., Copenhagen).

Results

pH : As shown in Table I, the pH value in normal rats was 7.38 just after cannulation. This was increased slightly to 7.40, 7.42 and 7.44 on three subsequent occasions of measurement repeated at 10-min intervals. On the other hand, in rats with adenine-induced renal failure, the pH value was 7.04 just after cannulation, showing an inclination to the acidic side in comparison with normal rats. The subsequent pH values obtained at 10-min intervals were all significantly lower than those in normal rats. In contrast, rats with renal failure given Ompi-to showed a significantly high pH value on each occasion of measurement in comparison with rats with renal failure given no Ompi-to.

Pco_2 : In normal rats, Pco_2 was 34.3-36.9 mmHg just after cannulation and on subsequent measurements at 10-min intervals. In rats with renal failure, Pco_2 tended to be lower than in normal rats just after cannulation and 10 min later. At 20 and 30 min, the partial pressure was significantly lower than in normal rats. In rats with renal failure given Ompi-to, Pco_2 was higher by 8% and 14 % 20 min and 30 min, respectively, after cannulation than in control rats with renal failure. However, these differences were not statistically significant (Table I).

BE : The BE level was -2.9 mEq/ℓ in normal rats just after cannulation, as shown in Table I. The level increased with time, reaching -0.2 mEq/ℓ 30 min later. In contrast, in rats with renal failure, there were no such time-related changes, the levels ranging from -21.1 to -21.6 mEq/ℓ, although they decreased markedly in comparison with normal rats. On the other hand, in rats with renal failure given Ompi-to, the BE level was significantly higher than in control rats with renal failure on each occasion of measurement during the 30-min period after cannulation.

SBC : The SBC level in normal rats increased slightly with time after cannulation ; the level was 21.8 mEq/ℓ just after cannulation, whereas it was 24.2 mEq/ℓ 30 min later. In rats with renal failure, similar variations in the level in relation to time after cannulation were found, although the level itself, ranging from 8.8 to 9.0 mEq/ℓ, was significantly lower, by 60-63%, than in normal rats. In rats with renal failure given Ompi-to, the level was significantly higher, by 70-85%, than in control rats with renal failure on each occasion of measurement (Table I).

Discussion

Causative factors of renal acidosis include disturbed secretion of H^+ into urine, reversed diffusion of acids in the kidney, disturbed excretion of acids due to a decrease in the number of

Table I Effect of Ompi-to on acid-base balance.

Time after cannulation (min)	Group	pH	Pco_2 (mmHg)	BE (mEq/l)	SBC (mEq/l)
0	Normal rats	7.38±0.01	36.9±2.9	-2.9±1.6	21.8±1.3
	Rats with renal failure				
	Control	7.04±0.04[c]	33.6±2.3	-21.4±1.3[c]	8.8±0.8[c]
	Ompi-to	7.26±0.02[b,d]	36.2±1.4	-10.3±1.0[b,d]	16.3±0.7[b,d]
10	Normal rats	7.40±0.03	34.4±1.7	-2.1±2.4	22.6±2.0
	Rats with renal failure				
	Control	7.04±0.04[c]	34.5±0.6	-21.6±1.3[c]	8.8±0.9[c]
	Ompi-to	7.25±0.02[b,d]	33.0±1.5	-12.0±0.7[b,d]	15.1±0.5[b,d]
20	Normal rats	7.42±0.02	35.2±1.0	-1.0±1.4	23.5±1.2
	Rats with renal failure				
	Control	7.05±0.03[c]	31.1±0.8[b]	-21.6±1.1[c]	8.8±0.8[c]
	Ompi-to	7.25±0.02[c,d]	33.6±2.7	-12.1±0.9[c,d]	15.0±0.6[c,d]
30	Normal rats	7.44±0.03	34.3±0.8	-0.2±1.4	24.2±1.2
	Rats with renal failure				
	Control	7.06±0.02[c]	31.4±1.1[a]	-21.1±1.0[c]	9.0±0.7[c]
	Ompi-to	7.25±0.02[c,d]	35.7±1.7	-11.4±0.7[c,d]	15.5±0.5[c,d]

Pco_2=partial pressure of carbon dioxide; BE=base excess; SBC=standard bicarbonate. Statistical significance: [a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ vs. normal rats, [d]$p<0.001$ vs. control rats with renal failure.

nephrons, and loss of HCO_3^- into urine. When chronic renal failure progresses, acidic metabolites accumulate in the body because of the decreased number of nephrons. In the proximal uriniferous tubule, reabsorption of HCO_3^- is decreased, resulting in loss of HCO_3^- into urine, while excretion of H^+ is disturbed in the distal uriniferous tubule, inducing metabolic acidosis.[18] In rats with adenine-induced chronic renal failure, a decrease in the number of glomeruli, crystalline deposits in the uriniferous tubules and stroma, and granuloma formation occurred in the renal tissue. In addition, there was dilation of Bowman's capsules, hypertrophy of the basement membranes of uriniferous tubules, hyaline droplet degeneration in the tubular epithelium, and vacuolation in the vascular wall of the stroma, suggesting systemic acidosis.[1,5,7] The presence of acidosis in rats with adenine-induced renal failure was corroborated by the decrease in pH, Pco_2, BE and SBC observed in the present study. We have previously found a marked renal function-improving effect of Ompi-to in rats with adenine-induced renal failure. We have also suggested that Ompi-to improves metabolism under conditions of renal failure and promotes urinary excretion of creatinine, methylguanidine and guanidinosuccinic acid through enhancement of renal function, on the basis of evidence of improved hyperazotemia, decreased or eliminated guanidino compounds, particularly methylguanidine and guanidinosuccinic acid, and improved hyperphosphatemia.[8-17] The results of the present study showed another beneficial effect of Ompi-to, *i.e.*, relief of renal acidosis. However, Ompi-to was administered simultaneously with adenine. It is unclear whether the relief in renal acidosis is attributable to an effect of Ompi-to against the nephrotoxicity of adenine, or to a direct effect of Ompi-to on renal acidosis. This issue requires further investigation. In conclusion, Ompi-to is an Oriental medical prescription of a newly recognized type which corrects various metabolic disorders resulting from renal failure, exerting multifarious actions.

和文抄録

アデニン投与ラットでは食欲不振，四肢振戦，痙攣あるいは刺激に対する応答性が低下し，昏睡から

死亡する経過を辿り，生体はアシドーシスになっていることが示唆されたが，測定したpH, partial pressure of carbon dioxide (Pco_2), base excess (BE), standard bicarbonate (SBC) はいずれも低下し，腎性アシドーシスをひき起こしていることが明らかとなった。一方，腎不全による尿毒症，高血圧，血流低下等を軽減あるいは進行を抑制する結果が得られている温脾湯に腎性アシドーシスを改善する作用が認められた。

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