Short Report

Activity of the Glycine Cleavage System in Hyperammonemia Treated with Benzoate

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Department of Pediatrics, Jichi Medical School, Minamikawachi-machi Tochigi-ken 329-04, *Institute for Enzyme Research, Tokushima University School of Medicine, Tokushima 770 and †Department of Pediatrics, Osaka University School of Medicine, Fukushima-ku, Osaka 553

Kodama, H., Fujiwara, K., Motokawa, Y., Tajiri, H., Nose, O. and Kamoshita, S. Activity of the Glycine Cleavage System in Hyperammonemia Treated with Benzoate. Tohoku J. exp. Med., 1983, 140 (3), 337–338 — We investigated levels of the glycine cleavage system in livers of spf-fur mutant mice with ornithine transcarbamylase (OTC) deficiency treated with sodium benzoate. The activities of the glycine cleavage system in benzoate-treated spf/Y males and the control mice livers are not significantly different. We examined plasma folate level and Vitamin B6 status in a patient with OTC deficiency during the therapy with benzoate. Plasma folate level and Vitamin B6 status during the therapy period and during control period are not different and these data were within normal ranges. The observation suggests that the glycine cleavage system is not the candidate for the increase of the de novo synthesis of glycine in hyperammonemic patients treated with benzoate.

Glycine cleavage system; hyperammonemia; sodium benzoate; ornithine transcarbamylase deficiency

Brusilow et al. (1980) reported that treatment of patients with inborn errors of urea synthesis with benzoate led to a significant decrease in the plasma ammonium level and an increase in urinary hippurate. These results suggest that acylation of glycine by benzoate is a quantitatively alternative mechanism of the waste nitrogen disposal. This change is presumably a consequence of the incorporation of ammonium or glutamate in the de novo synthesis of glycine by one of three pathways; from ammonium via the glycine cleavage system, or from glutamate via glyoxylate transamination or via de novo serine synthesis.

We investigated levels of the glycine cleavage system in livers of spf-fur mutant mice with X-linked deficiency of ornithine transcarbamylase (OTC) (spf/Y males), kindly supplied by Dr. Eicher at Jackson Labolatory. The activity of the glycine cleavage system was assayed as described in a previous paper (Motokawa et al. 1977). Spf/Y males were killed after 2 weeks on diet added 1% sodium benzoate (protein 24%). Plasma ammonium level of spf/Y males was 114±19 µg/100 ml (n=5, M±s.d.) during the treatment with sodium benzoate and 196±34 (n=5) during control period. The OTC activity of spf/Y males livers was 2,682±1,027 µmol/hr/g wet weight (n=4, M±s.d., pH 8) and that of control mice (B6C3H F₁) livers was 13,817±2,389 µmol/hr/g wet weight (n=3). The rate of formation of 14CO₂ from [1-14C]glycine was 83.1±11.1 nmol/hr/mg protein (n=4) in

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liver homogenate of spf/Y males and 63.7±9.8 (n=3) in that of control mice livers. The rate of formation of [1-14C] glycine from 14C-bicarbonate was 3.6±0.3 nmol/hr/mg protein (n=4) in liver homogenate of spf/Y males and 3.4±0.2 (n=3) in that of the control livers. The activities of the glycine cleavage system in benzoate-treated spf/Y males and the control mice livers are not significantly different in these experimental conditions.

A pyridoxal phosphate enzyme is involved in the synthesis of glycine from methylene-tetrahydrofolate, ammonia and CO₂ via the glycine cleavage reaction. We examined plasma folate level and Vitamin B₆ status in a patient with OTC deficiency who was reported previously (Kodama et al. 1982). The plasma folate level was measured by microbiological assay (Waters and Mollin 1961). Vitamin B₆ status is evaluated by determining the erythrocyte glutamic oxaloacetic transaminase activity (Kishi and Folkers 1976). Her plasma ammonium level of 3 hr after breakfast during the therapy with benzoate (200 mg/kg/day) was 177±66 µg/100 ml (n=6) and significantly lower than that during control period (354±157, n=13). The plasma folate level and % deficiency of B₆ were 6.9±3.5 ng/ml and 22±5 % deficiency (n=3) during control period, and 8.2±2.8 ng/ml and 19±4 % deficiency (n=3) during therapy period respectively. These data were within normal ranges (folate, 3.8-13.3 ng/ml; B₆, 15-27% deficiency).

In vertebrates glycine is degraded through the reaction catalyzed by the glycine cleavage system (Yoshida and Kikuchi 1972). The reaction is reversible and there exists a possibility that glycine is synthesized in vivo by the catalytic action of the glycine cleavage system. The results reported here indicate that the level of the glycine cleavage system is unchanged by the treatment of hyperammonemia with benzoate. The observation suggests that the glycine cleavage system is not the candidate for the increase of the de novo synthesis of glycine in hyperammonemic patients treated with benzoate and that the system may not significantly participate in the synthesis of glycine in mammals.

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References