Letter to the Editor: A Mechanism for Valproate-Induced Hyperammonemia

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Valproate induces hyperglycinuria (6-8) and hyperammonemia (4) in children. Its experimental use in rats to obtain a propionic acidemia model was proposed (8) because propionic acid is known to accumulate probably as an intermediary metabolite in valproate-treated patients. In the search of the mechanism by which propionate inhibits ureagenesis (1, 3, 10) and because of the analogy between some toxic effects of valproate and the ketotic hyperglycinemia syndrome (hyperglycinuria, leucopenia and thrombocytopenia), we have studied the *in vivo* metabolic effects of valproate on the mitochondrial steps of ureagenesis in rat.

Rats were killed 2 hr after intraperitoneal injection of sodium valproate (100 mg/kg). Mitochondria were prepared immediately from livers (5). In valproate-treated rats, we observed (Table 1) a

have shown previously (10) indicates that NAGA must be the key factor. The addition of ATP increases the citrullinogenesis in both groups, but it remains significantly lower in valproate-treated patients. This implies that when ATP freely enters the mitochondria and is not any more a rate-limiting factor, the citrullinogenesis is limited by the NAGA level. This valproate effect is analogous to the effect of propionate which we have observed in intact mitochondria (1, 10). Nevertheless, the intraperitoneal injection of propionate at the same levels in rat does not decrease the citrullinogenesis (2). Therefore, propionyl-CoA does not seem to be responsible for the valproate inhibition and valproyl CoA or some closely related compounds must be the effective inhibitor. We are proposing that the valproate-induced hyperammonemia is second-

Table 1. Valproate effects on citrullinogenesis and N-acetylglutamate levels in rat liver¹

	Controls (n = 3)	Treated (n = 3)	Significance (P)
CIT (nmole CIT ² min ⁻¹ mg ⁻¹)			
+ succinate 16 mM	4.38 ± 1.06 ³	0.52 ± 0.34	<0.01
+ glutamate 16 mM	6.68 ± 0.90	4.37 ± 1.80	NS ⁴
+ ATP 4 mM, oligomycin 10 µg/ml, 2,4-dinitrophenol (0.04 mM)	8.57 ± 1.46	3.16 ± 0.90	<0.01
N-acetylglutamate (nmole mg ⁻¹)	0.81 ± 0.09	0.61 ± 0.04	<0.01
N-acetylglutamate synthetase (nmoles NAGA min ⁻¹ mg ⁻¹)	0.20 ± 0.04	0.17 ± 0.06	NS
CPS-I (nmoles CIT min ⁻¹ mg ⁻¹)	71.0 ± 4.2	63.5 ± 3.5	NS
Ornithine transcarbamylase (nmoles CIT min ⁻¹ mg ⁻¹)	2032.5 ± 77.1	1954.5 ± 78.5	NS

¹ Citrullinogenesis, NAGA level, NAGA synthetase, CPS-I, and ornithine transcarbamylase are measured in isolated mitochondria as previously described (3, 4, 6).

² CIT, citrullinogenesis.

³ Mean ± S.D.

⁴ NS, not significant.

highly significant inhibition of citrullinogenesis in the presence of succinate but not in the presence of glutamate. In the presence of ATP, oligomycin, and 2,4-dinitrophenol, the citrullinogenesis was increased, but there was always a significant inhibition in valproate-treated rats. Concomitantly, there was a significant decrease of mitochondrial N-acetylglutamate (NAGA) level in valproate-treated rats. NAGA synthetase, carbamoylphosphate synthetase (CPS-I), and ornithine transcarbamylase activities were in the same range in both groups.

These results show that valproate or one of its metabolites is a potent inhibitor of the mitochondrial steps of ureagenesis. A direct enzymatic inhibition may be excluded because there was no change in the CPS-I, ornithine transcarbamylase, and NAGA synthetase activities in valproate-treated rats. The normalization of the citrullinogenesis in the presence of glutamate which resulted in a de novo synthesis of NAGA in intact mitochondria as we

ary to an inhibition of the mitochondrial NAGA synthesis. In this way, N-carbamyl-glutamate which seems to cross freely the biologic membranes and activates CPS-I (9) might be useful in the management of patients with these valproate adverse effects.

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Erratum

In the May, 1981 issue, Vol. 15, No. 5, the article, "Different Properties of Residual N-Acetylgalactosamine-6-Sulfate Sulfatase in Fibroblasts from Patients with Mild and Severe Forms of Morquio Disease Type A" by J. Glossl, P. Maroteaux, P. Di Natale, and H. Kresse was listed in the table of contents.

However, because of a printer's error, it was inadvertently omitted from the printed issue. The article now appears immediately following this Erratum on pages 976-978.

Waverly Press, Inc. regrets the error.