Formiminoglutamicaciduria in Humans with Megaloblastic Anemia: Diminution by Methionine or Glycine.* (28023)

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Excretion of large amounts of formiminoglutamic acid (FGA), a catabolite of histidine, has been observed in rats, chicks and humans deficient in folic acid(1-7) or Vit. B_{12}(1,2,4-7), especially after an oral histidine load. In rats(8) and chicks(2) administration of methionine markedly reduced FGA excretion. In the present study this observation is extended to humans and it is noted that glycine may also reduce FGA excretion.

Materials and methods. Five subjects with megaloblastic anemia due to Vit. B_{12} and/or folic acid deficiency were studied while on a diet low in folate and Vit. B_{12}. All had excessive FGA excretion, determined as previously described(4). Normal subjects were not studied because they have negligible FGA excretion, with spontaneous daily variability between 0 and 50 mg/12 hours after a 20 g L-histidine load. Serum Vit. B_{12} levels were determined with *Euglena gracilis* var. *bacillarus* by the method of Lear *et al.*(9) with various slight modifications. By this method, values below 100 $\mu\mu$g per ml of serum are indicative of Vit. B_{12} deficiency, and values of 200-900 $\mu\mu$g per ml are normal.

Serum folate activity for *Lactobacillus casei* was determined using the "aseptic addition method," with 1% ascorbate added (10). By this method, levels below 3 mμg/ml are indicative of folic acid deficiency, 3-5 are strongly suggestive of folate deficiency, 5-7 are diagnostically indeterminate, and 7-16 mμg/ml are normal. However, with Vit. B_{12} deficiency, serum folate levels greater than 3 mμg/ml may be compatible with folate deficiency, due to the "pile up" of folate in the serum of such subjects(11).

*This study has been aided by research grants from N. I. H., U. S. P. H. S., and National Vitamin Foundation.

Results. As indicated in Table I, all subjects excreted abnormally large quantities of FGA, after an oral load of 20 g L-histidine · HCl. In subsequent tests, performed after intervals of at least 48 hours all 4 subjects given a simultaneous oral load of 20 g DL-methionine had a sharp drop in FGA excretion. One subject given methionine one hour before histidine had a significant but lesser drop in FGA excretion, and a slightly smaller drop when methionine administration followed histidine by one hour.

Two subjects given 20 g of glycine together with histidine also had a sharp fall in FGA excretion (Table I). Of 3 subjects given 20 g DL-serine orally together with histidine, 2 showed moderate falls in FGA excretion and the third showed no fall. The subject with a serum B_{12} level of 15 $\mu\mu$g/ml was given 20 g of DL-tryptophane together with histidine with no fall in FGA excretion (not charted).

Discussion. The mechanism whereby methionine administration lowers FGA excretion is uncertain. One possibility suggested is that methionine may supply a methyl-acceptor in the form of S-adenosylhomocysteine *via* demethylation of S-adenosylmethionine to liberate tetrahydrofolic acid (THFA)(12). Another possibility is that methionine may, by negative feedback, spare the entire pathway involving N^5-methyl-THFA, allowing greater production of THFA *via* other pathways(11). A third possibility is that methionine and histidine may be absorbed from the human intestine, as from the chicken intestine(13), by a common specific transport mechanism, so that orally administered methionine could block the absorption of orally administered histidine. This possibility is supported by the finding that FGA excretion is not reduced as much when methionine administration precedes administra-

TABLE I. Effect of DL-Methionine, Glycine, and DL-Serine on Formiminoglutamicaciduria of Humans Deficient in Vit B_{12} and/or Folic Acid.

Diagnosis	Hct (%)	Serum level: μμg/ml B_{12}	Serum level: mμg/ml folate	mg FGA/12 hr after administration of 20 g L-histidine • HCl: Alone	+ 20 g DL-methionine: Simultaneously	+ 20 g DL-methionine: 1 hr later	+ 20 g DL-methionine: 1 hr earlier	+ 20 g DL-serine	+ 20 g glycine
Megaloblastic anemia in pregnancy	22.2	<25	<1	268	59	—	—	—	—
Pernicious anemia	22.8	15	4.8	700*	248	459	377	—	—
" "	23	11	7.0	556*	194	—	—	559	154
" "	16.1	37	9.1	119	23	—	—	82	—
Nutritional folate deficiency (alcoholism)	23.5	241	1.1	880	—	—	—	612	323

* Avg of values with histidine alone before and after studies with other agents.

tion of histidine by one hour and is reduced still less when methionine is given one hour after histidine. However, more than competitive intestinal absorption is probably involved since, in the rat, parenteral administration of methionine both reduces excretion of FGA and increases excretion of 2-C^{14} of L-histidine as expired $C^{14}O_2$(8).

If further studies confirm the present finding that glycine also suppresses FGA excretion, the most likely mode of action is that glycine accepts the 1-carbon unit of $N^{5,10}$-methylene THFA, converting it to THFA which then removes formimino units from FGA. This is one of the "alternate pathways to THFA whose variable activity may explain why FGA 'piles up' in only a third of patients with pernicious anemia."(11). The uncertain effect of serine deserves further study.

Summary. Five patients with megaloblastic anemia due to Vit. B_{12} and/or folic acid deficiency who excreted abnormally large quantities of formiminoglutamic acid (FGA) after a 20 g oral L-histidine • HCl load were studied. FGA excretion was markedly reduced in all 4 subjects given 20 g DL-methionine and in both subjects given 20 g glycine together with L-histidine • HCl. Of 3 subjects given 20 g DL-serine, one showed no reduction in FGA excretion and 2 showed moderate reduction.

We are indebted for technical assistance to Miss Brenda Conti and Mrs. Nancy Cunneen Boardman.

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Received July 30, 1962. P.S.E.B.M., 1963, v112.