Endogenous Oxalate Synthesis and Glycine, Serine,
Deoxypyridoxine Interrelationships in
Vitamin B\textsubscript{6}-deficient Rats*

STANLEY N. GERSHOFF AND FAROUK F. FARAGALLA

From the Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts

(Received for publication, May 18, 1959)

Attempts to study the etiology of diseases associated with oxaluria or oxalate deposition or both, have been handicapped by the misconception that very little urinary oxalate is endogenous in origin. However, Gershoff et al. (1) have demonstrated oxalate nephrocalcinosis and oxaluria in vitamin B\textsubscript{6}-deficient cats. In vitamin B\textsubscript{6}-deficient rats consuming diets free from oxalate, renal calculi of calcium oxalate monohydrate have been observed (2). Such renal calculi and the obstructive sequelae they produce, closely resemble the conditions found in human cases of kidney disease accompanied by oxalate stones. The possibility that these findings relating oxalate production and vitamin B\textsubscript{6} may be pertinent in human nutrition is indicated by the finding (3) that vitamin B\textsubscript{6} supplements decreased oxalate excretion in human subjects receiving diets thought to be more than adequate in vitamin B\textsubscript{6}.

In the present paper, the effect of glycine, deoxypyridoxine, and isonicotinic acid hydrazide supplements on oxaluria in vitamin B\textsubscript{6}-deficient rats is reported. The effect of L-serine and glycine on deoxypyridoxine toxicity has also been studied.

EXPERIMENTAL AND RESULTS

Male weanling rats of the Charles River CD strain were used. The diets fed contained 15 or 40 per cent casein, 4 per cent salts IV (4), 4 per cent corn oil, 1 per cent cod liver oil, and 0.3 per cent choline. In a number of instances different levels of glycine or L-serine were added to the diets. Sucrose was used to bring each diet to 100 per cent. All diets were supplemented with 4 mg. of thiamine, 8 mg. of riboflavin, 40 mg. of niacin, 20 mg. of Ca pantothenate, 1 mg. of folic acid, 1 mg. of menadione, 0.2 mg. of biotin, and 0.1 mg. of vitamin B\textsubscript{12} per kilogram of diet. When used, 4 mg. of pyridoxine HCl, 500 mg. of deoxypyridoxine, and 2 gm. of isonicotinic acid hydrazide were added per kilogram of diet.

In the first experiment 12 groups of 9 rats were used. The diets fed contained 15 or 40 per cent casein with or without 3 per cent added glycine. Some of the vitamin B\textsubscript{6}-deficient diets contained deoxypyridoxine. At the end of each week during the 30-day experimental period, subgroups of 3 rats from each group were placed in metabolism cages and 48-hour urine collections made. The oxalic acid content of the urine was determined by the method of Powers and Levatin (5). The results of this experiment (Table I) clearly show that in vitamin B\textsubscript{6}-deficient rats there is a marked increase in urinary oxalate excretion. The addition of 3 per cent glycine to the 15 per cent casein diets and of deoxypyridoxine to both 15 per cent and 40 per cent casein diets, resulted in a further increase in oxalate excretion. Oxaluria was most pronounced when 40 per cent casein diets containing both added glycine and deoxypyridoxine were fed. Although the addition of deoxypyridoxine inhibited growth, as expected when added to the basal diet, the further addition of glycine provided considerable protection against the growth-inhibiting and lethal effects of the deoxypyridoxine. Three per cent glycine had no significant effect on the growth of animals receiving vitamin B\textsubscript{6}, but it caused some growth inhibition in deficient rats not receiving deoxypyridoxine.

Isonicotinic acid hydrazide, commonly used in the treatment of tuberculosis, is known to increase vitamin B\textsubscript{6} requirements (6). Its effect on oxalate production in rats fed 15 per cent casein diets without added glycine has been studied in groups of 9 rats. At the end of the first and second experimental weeks, urines were collected (over a 48-hour period) for oxalate analysis. The mean results of this study shown in Table II, indicate that isonicotinic acid hydrazide is effective in increasing urinary oxalate excretion by rats particularly when they are vitamin B\textsubscript{6} deficient.

The protective effect of glycine on deoxypyridoxine toxicity and the fact that glycine is rapidly converted to serine in animal tissues, led to the third study in which the effect of L-serine and glycine in sparing vitamin B\textsubscript{6}-deficient rats from the toxic effects of deoxypyridoxine was studied. The results of this experiment, Table III, demonstrate again the protective effect of glycine and that L-serine is more effective than glycine when fed on an equal molecular basis.

DISCUSSION

The quantity of endogenous oxalate produced in these experiments must be related to the amount of oxalate precursors ingested and the degree of vitamin B\textsubscript{6} deficiency produced. It appears from this study that and that of Calhoun et al. (7) in vitamin B\textsubscript{6}-deficient rats and the work of Archer et al. (8) and Seowen...
glycine-containing diets when the deficiency became intensified.

Increased oxalate formation. The slightly decreased oxalate excretion of some of the deficient groups as the first experiment

glyoxylic acid plus glutamic acid c) glycine plus a-ketoglutaric acid, could result in an accumulation of glyoxylic acid with
derived in great part from glycine. Oxalate has been shown to
be formed from glycine via glyoxylic acid (10, 11) and inhibition
standard error of the mean.

parentheses represent survivors.

Each value represents the mean of six determinations plus
standard error of the mean.

* Five rats per group.
† Diets contained 15 per cent casein.

Two vitamin B6 antagonists, deoxypyridoxine and isonicotinic acid hydrazide, have been used to accelerate the production of the
deficiency state. The feeding of either of these compounds, particularly to animals not receiving dietary vitamin B6, was
accompanied by an increase in oxaluria. This is presumably due to an acceleration in the rate of development or severity of the
deficiency. Some practical significance may be attached to this action of isonicotinic acid hydrazide, since it is widely used in the
treatment of tuberculosis. It has not yet been determined whether the administration of isonicotinic acid hydrazide to patients results in increased oxalate production. It seems probable that this would occur unless adequate pyridoxine
supplementation was provided.

Although serine and glycine are “nonessential” amino acids, they are necessary for the synthesis of body proteins and a
number of essential metabolites. The use of deoxypyridoxine in these studies apparently resulted in a deficiency of glycine and
serine since dietary supplementation with these amino acids reversed the growth inhibition caused by the antivitamin.
Deoxypyridoxine may inhibit the formation of serine and glycine or enhance their degradation.

Excessive amounts of glycine are toxic (13) particularly when
the diet is vitamin B6 deficient (14). Thus, it would appear
that whether glycine supplementation accentuates or ameliorates
the vitamin B6 deficiency depends on the different degrees to which
they are necessary for the synthesis of body proteins and a
number of essential metabolites. The use of deoxypyridoxine in these studies apparently resulted in a deficiency of glycine and
serine since dietary supplementation with these amino acids reversed the growth inhibition caused by the antivitamin.
Deoxypyridoxine may inhibit the formation of serine and glycine or enhance their degradation.

et al. (9) in cases of primary hyperoxaluria, that a considerable
amount of urinary oxalate may be of endogenous origin and
derived in great part from glycine. Oxalate has been shown to
be formed from glycine via glyoxylic acid (10, 11) and inhibition
of the system described by Cammarata and Cohen (12), i.e.
glyoxylic acid plus glutamic acid → glycine plus α-ketoglutaric
acid, could result in an accumulation of glyoxylic acid with
increased oxalate formation. The slightly decreased oxalate
excretion of some of the deficient groups as the first experiment
progressed, may have been due to lessened consumption of the
glycine-containing diets when the deficiency became intensified.

SUMMARY

Urinary excretion of endogenous oxalate by rats is markedly
increased in vitamin B6 deficiency. This effect can be enhanced
by dietary supplementation with glycine, deoxypyridoxine, or
isonicotinic acid hydrazide.

Deoxypyridoxine toxicity can be overcome by serine or glycine
supplementation suggesting that deoxypyridoxine interferes with
the availability of these amino acids.

REFERENCES

(1944).
85, 389 (1954).
Endogenous Oxalate Synthesis and Glycine, Serine, Deoxypyridoxine Interrelationships in Vitamin B₆-deficient Rats
Stanley N. Gershoff and Farouk F. Faragalla


Access the most updated version of this article at http://www.jbc.org/content/234/9/2391.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC’s e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/234/9/2391.citation.full.html#ref-list-1