DIFFERENT EFFECTS OF ORAL GLYCINE AND METHIONINE ON URINARY LITHOGENIC SUBSTANCES

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Summary

Nine male healthy volunteers were examined during a control period, during an oral glycine load (45g/day, 600mmol) and oral methionine (6g/day, 40mmol). Glycine caused a significant increase of urinary oxalate above baseline (from 644 to 797μmol/day) without change in calciuria (4.74 vs 4.84mmol/day). In contrast methionine caused no change of oxaluria, but a significant increase in calciuria (from 4.74 to 6.9mmol/day). Alterations of lithogenic ions in urine after protein ingestion are mediated by different amino acids. The particular lithogenic risk of animal protein may be related to its high methionine/cystine and glycine content.

Introduction

The pandemic of nephrolithiasis in Western societies has been related to dietary factors, in particular to high animal protein consumption [1]. Both high urinary Ca and high urinary oxalate have been identified as important lithogenic risk factors [2]. While an increase of urinary Ca with protein ingestion is well documented [3–5], information on the action of dietary protein or amino acids on urinary oxalate is conflicting. Several recent communications failed to demonstrate an increase of urinary oxalate in response to glycine loads [6, 7].

The present study examines to what extent calciuria and oxaluria are affected by methionine (a calciuric sulphur containing amino acid and glycine (a putative oxalate precursor).

Proband and methods

Nine male healthy volunteers, physicians of the nephrological staff, age 31 ± 5 years, were examined under constant self-selected diet with known energy and protein content under ambulatory conditions. Studies were carried out during three metabolic periods of five days each with no study on the intervening
After a control period the probands received in a second period glycine (45g/day, 600mmol) as three divided doses dissolved in distilled water taken together with meals. In a subsequent third period they received methionine (6g/day, 40mmol). Urine was collected in plastic bottles with thymol. Fasting morning plasma samples and 24 hour urinary samples were examined for: Plasma-SMA 12 Autoanalyser; RIA for PTH (carboxyterminal), glucagon, insulin, GH; urine-oxalate with isothachophoresis [8]; citrate (lyase method); pH; cAMP (RIA); electrolytes with emission or AA spectrophotometry; sulphate with indirect AAS.

Results

As shown in Table I, 600mmol/day, glycine increased urinary oxalate in seven of the nine probands by an average of 153μmol/day. This was not associated with any significant change of calciuria. A preliminary dose response curve in one single proband showed a dose-related increase of oxaluria (baseline 476μmol/day; 3 x 4g glycine: +239μmol/day; 3 x 8g: +354; 3 x 16g: +506).

<table>
<thead>
<tr>
<th></th>
<th>Control period</th>
<th>Oral glycine (600mmol/day)</th>
<th>Oral methionine (40mmol/day)</th>
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</thead>
<tbody>
<tr>
<td>(U_{V_{oxalate}}) (μmol/day)</td>
<td>644 ± 155</td>
<td>797 ± 194*</td>
<td>598 ± 150</td>
</tr>
<tr>
<td>(U_{V_{Ca}}) (mmol/day)</td>
<td>4.74 ± 2.36</td>
<td>4.84 ± 1.19</td>
<td>6.90 ± 3.2**</td>
</tr>
<tr>
<td>(U_{V_{cAMP}}) (μmol/day)</td>
<td>4.0 ± 1.7</td>
<td>4.5 ± 0.79</td>
<td>4.25 ± 1.03</td>
</tr>
</tbody>
</table>

The values represent \(\bar{x} \pm SD\) for the average values of nine probands.

* \(p < 0.05\) (Wilcoxon test for paired differences)

** \(p < 0.01\)

In contrast, oral methionine caused no significant change of oxaluria, but a consistent increase of calciuria in all probands, the mean increment being 2.16 mmol/day. Complete intestinal absorption was suggested by an increase of urinary sulphate above baseline of 36mmol/day and by a corresponding increase of urea generation rate (urinary excretion plus Δ plasma urea x space of distribution). No significant associated change of iPTh or urinary cAMP/GFR was noted.

Discussion

A precursor product relationship between glycine and oxalate has been demonstrated with \(^{14}\)C-radioglycine in man [9], 0.027–0.081 per cent of oral radioglycine tracer being recovered as urinary radio-oxalate. Subsequent investigations
showed inconsistent or no increase of urinary oxalate after oral [10] or intravenous [6, 7] non-labelled glycine. This may be due to several factors: (a) interindividual heterogeneity, possibly related to pyridoxal status; such heterogeneity was also noted in our study with only 7/9 probands showing increased oxaluria; (b) difficulties of measuring urinary oxalate; or (c) differences in the protocol of glycine administration. In particular, intravenous infusion of glycine [6, 7] may not achieve equally high glycine concentrations in portal blood as does oral administration of glycine. This is of note since glycine-oxalate interconversion is restricted to hepatic tissue. Our finding of 0.025 per cent of administered oral glycine appearing as urinary oxalate is in good agreement with the oral radioglycine study [9]. Although a 40g glycine load is high in relation to the usual daily protein consumption of 70g, preliminary dose-response data suggest that extrapolations into the range of usual dietary intake are legitimate. For physicochemical reasons [2], even a minor diet related increase in oxaluria may be relevant for lithogenesis.

The increase in calciuria upon ingestion of protein [3–5] and sulphur containing amino acids is well known. Our results show that such calciuria is not associated with detectable changes if iPTH and cAMP. This casts some doubt on evaluating these indices in clinical studies on the mechanism of calciuria in nephrolithiasis. No change of oxaluria with methionine suggests that the oxaluric action of protein is restricted to individual amino acids.

The particular lithogenicity of animal protein consumption [1] may be due, amongst other factors, to its high content of sulphur containing amino acids and glycine (or possibly aromatic amino acids). This may explain why the risk of nephrolithiasis is related to animal protein, but not total protein consumption [1].

References

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Open Discussion

PEACOCK (Leeds) Did you find any change in the glomerular filtration rate because some of the changes that one might see with protein feeding could be due to alteration in glomerular filtration rate?

TSCHÖPE We did not see any change in glomerular filtration rate: there was no increase in urinary creatinine. One explanation might be that we started from a normal dietary protein intake. The reports of an increase in glomerular filtration rate with protein intake started from a low protein diet (30–50g daily) and then added 100g protein and in these circumstances the glomerular filtration rate increases.

PARSONS (Chairman) Is there any significance between the fact that one of the amino acids was essential while the other was non-essential? Do you have any observations on other amino acids in similar studies?

TSCHÖPE No, to my knowledge these are the first studies showing these effects. There are several reports on the calciferic effect of dietary protein. The calciferic effect is associated with increased urinary excretion of uric acid, sulphate and probably with a negative calcium balance. It is possible that some of these patients consuming a high dietary animal protein are at risk of developing negative calcium balance and bone disease, and perhaps are those patients claimed by Dr Pak to have a renal leak.

ROBERTSON (Leeds) We can confirm at a lower dose the results you have obtained with methionine, in that we found an increased urinary calcium. As far as increases in urinary oxalate in response to a high animal protein diet, there are some other amino acids, other than glycine and tryptophan, which are present in higher concentrations in animal than vegetable protein. Perhaps hydroxyproline might be one of interest as other workers have shown this to increase urinary oxalate excretion. Have you looked at any other amino acids?

TSCHÖPE No, we have not looked at other substances. Before starting our experiments we would have anticipated no effect of oral glycine. The metabolic fate of glycine is very diverse and so the effect of a single dose of glycine is very difficult to assess. There is one explanation of how glycine might be capable of inducing hyperoxaluria. A marginal pyridoxine (Vitamin B₆) deficiency, not a deficiency in the true nutritional sense. It might be that some individuals do not exhibit clinical signs of pyridoxine deficiency, but are at risk for oxalate formation as the threshold for oxalate synthesis from glycine, in these individuals, might be lower than the threshold for developing clinical signs of pyridoxine deficiency. In German surveys the plasma pyridoxine concentrations in the general population tends to be lower than that recommended by the World Health Organisation.