Evidence in man for different specialized intestinal transport mechanisms for riboflavin and thiamin

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Man has a limited capacity to absorb riboflavin (1–3) and thiamin (4, 5). The gastrointestinal absorption of these vitamins is describable by Michaelis-Menten type kinetics, characteristic of saturable, specialized absorption processes (6). Both vitamins are phosphorylated in the intestinal mucosa during absorption (7–9) and there is evidence suggesting that this process is the basic mechanism for the intestinal transport of thiamin (9). The absorption of riboflavin-5'-phosphate (FMN) in man exhibits the same saturation kinetics as does riboflavin (2), but this is probably due to the rapid dephosphorylation and subsequent rephosphorylation of this vitamin during absorption (2). The available evidence suggests that phosphorylation may be involved in the specialized transport of riboflavin and thiamin, and that both vitamins may share the same transport process. This is not only of mechanistic but of practical interest; concomitant oral administration of large (“therapeutic”) doses of riboflavin and thiamin could result in mutual inhibition of absorption if both vitamins must compete for the same transport process.

In the investigation to be described here, the effects of a large dose of riboflavin on the absorption of a large dose of thiamin, and vice versa, have been determined in healthy adult volunteers. It has been shown previously that the absorption of large doses of riboflavin is increased substantially if the vitamin is taken after breakfast rather than on an empty stomach (1, 2). A similar effect may be anticipated in the case of thiamin if this vitamin is absorbed by the same process. Therefore, the absorption of riboflavin and thiamin was determined upon concomitant administration of both vitamins on an empty stomach and after a standard breakfast.

Material and methods

Four young men, 24 to 28 years old, weighing 62 to 85 kg, served as test subjects. They received 41 mg riboflavin-5'-phosphate·2H₂O (FMN),* equivalent to 30 mg riboflavin; 26.9 mg thiamin hydrochloride (molar equivalent of 30 mg riboflavin); and 41 mg FMN together with 26.9 mg thiamin hydrochloride. The vitamins were administered in 50 ml aqueous solution, which also contained 1.0% citric acid and 0.06% sodium saccharin as flavors. The solutions were given in random order in the morning, on an empty stomach, at least one week apart. The combined FMN and thiamin solution was also given after a standard breakfast of 60 g cornflakes with sugar and 500 ml milk.* The bottle containing vitamin solution was rinsed with 30 ml water that was also taken. There was no restriction on lunch and dinner but the subjects were instructed not to take any vitamin preparation or drugs for at least one week preceding and during the study.

Each subject emptied his bladder immediately before taking the vitamin solution. Urine was then collected every 30 min for 4 hr, every hr for the next 4 hr, every 2 hr until bedtime, and at desired intervals thereafter for a total of 36 hr. About 3 ml glacial acetic acid was added to each 100 ml urine immediately after collection, and the urine sample was placed in a refrigerator until the assays could be performed. All samples were protected from light. The subjects drank 50 to 100 ml water after each voiding to maintain an adequate urine output. Twelve-hour blank collections of urine were also carried out on each subject.

Riboflavin in the urine was determined fluorometrically by a modification of the USP XVI procedure (1). Thiamin was determined by the thio-

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*Riboflavin itself is not sufficiently water soluble to be administered in solution at this dose.

*The breakfast contained less than 0.9 mg riboflavin and less than 0.6 mg thiamin, i.e., negligible amounts compared with the test doses of these vitamins.

Thiamin had no effect on the time course of riboflavin excretion (Fig. 1) and on the total excretion of riboflavin (Table 1) after oral administration. Riboflavin did not inhibit the absorption of thiamin, as reflected by the time course (Fig. 2) and total excretion (Table 2) of thiamin. Concomitant administration of riboflavin and thiamin after a standard breakfast, rather than on an empty stomach, resulted in a pronounced and statistically highly significant \( P < 0.01 \) increase in riboflavin absorption (Fig. 3; Table 2). Thiamin absorption after the meal was delayed and prolonged (Fig. 4) but total absorption did not differ significantly from that after administering the vitamin on an empty stomach (Table 2).

**Comments**

The doses of riboflavin and thiamin employed in this study were at least twice the amount required to achieve 50% of theoretical maximum absorption (4–6). Thus, they are sufficient to demonstrate saturation ef-
TABLE 2
Effect in man of riboflavin and food on gastrointestinal absorption of thiamin

<table>
<thead>
<tr>
<th>Subject</th>
<th>% Dose recovered in urine*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B1 alone</td>
<td>B1 with Bs</td>
</tr>
<tr>
<td>SF</td>
<td>5.16</td>
<td>7.57</td>
</tr>
<tr>
<td>WJ</td>
<td>3.67</td>
<td>5.02</td>
</tr>
<tr>
<td>VS</td>
<td>5.66</td>
<td>9.62</td>
</tr>
<tr>
<td>WH</td>
<td>6.51</td>
<td>3.47</td>
</tr>
<tr>
<td>Mean</td>
<td>5.25</td>
<td>6.42</td>
</tr>
</tbody>
</table>

* 26.9 Mg thiamin hydrochloride (B1) was administered alone or with 41 mg riboflavin-5'-phosphate (Bv), in the morning on an empty stomach or after a standard breakfast. Urine was collected for 36 hr.

...effects and they should inhibit competitively the absorption of any other substance which is transported by the same process. The absence of such inhibitory effects, as found in the present study, suggests that in man riboflavin and thiamin do not share a common pathway for intestinal absorption. This conclusion is supported by the different effect of food on the absorption of the two vitamins, i.e., administration after breakfast enhanced appreciably the absorption of riboflavin but had no significant effect on the amount of thiamin absorbed from a 26.9-mg dose. Though the two vitamins were administered together and in solution (the latter to rule out dissolution rate limited absorption), the absorption of riboflavin was rapid and increased (Fig. 3), whereas that of thiamin was delayed, prolonged, and not significantly increased (Fig. 4), as judged by the urinary excretion data. The effect of food on thiamin absorption is consistent with the known retarding effect of food on gastric emptying. The effect on riboflavin absorption is such as to suggest that food, either directly or indirectly, increases riboflavin absorption. This may be due to stimulation of bile output since riboflavin absorption is decreased in subjects with biliary obstruction (12).

Studies in man do not readily afford the opportunity for a rigorous kinetic investigation of specialized absorption processes under widely different but controlled conditions, as is possible with in vitro studies on everted intestinal segments and with in situ isolated...
intestinal loops in animals. The absence of any apparent mutual inhibition in the absorption of riboflavin and thiamin in man suggests strongly that these vitamins do not share a common rate-limiting pathway for absorption. However, this interpretation is limited by and subject to the complexity of the experimental system. Irrespective of such limitation, the results of this study lead to the clinically significant conclusion that riboflavin and thiamin may be administered together orally in therapeutic doses without concern for mutual inhibitory effects on their respective absorption.

Summary

Large oral doses of riboflavin and thiamin do not affect the absorption of one another in man. The absorption of a large dose of riboflavin is much greater when given after breakfast than on an empty stomach, whereas the extent of absorption of thiamin is not affected significantly by food. Although riboflavin and thiamin are absorbed by saturable intestinal transport mechanisms and are both phosphorylated during absorption, the results of this investigation suggest that the two vitamins do not share a common specialized absorption pathway.

References