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Glycine intestine
iminoacids type I hyperprolinemia

Type I Hyperprolinemia: A Study of the Intestinal Absorption of Proline, Hydroxyproline, and Glycine

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Extract

Intestinal absorption of proline, hydroxyproline, and glycine was interpreted by investigation of a type I hyperprolinemia patient and six control subjects. Intestinal perfusion was performed.

When proline (Pro), hydroxyproline (OH-Pro), and glycine (Gly) were infused together, an increase in proline concentration did not alter aminoacid uptake in the control subjects; however, in the hyperprolinemia patient, uptake of aminoacids became negligible (Pro, 17–6 μM/min; OH-Pro, 15–0.3 μM/min; and Gly, 13.5–0 μM/min).

When each aminoacid was infused alone at increasing concentrations aminoacid uptake increased in controls; in the hyperprolinemic patient, intestinal absorption was less for glycine and hydroxyproline but aminoacid uptake increased with substrate concentration; however, for proline, the uptake remained constant (16.5–17 μM/min/20 cm of intestinal test segment) (Table 1).

When hydroxyproline was infused with an increased concentration of proline in the hyperprolinemic patient, hydroxyproline uptake first increased (9.8–14.3 μM/min/20 cm) then decreased to its basal value, whereas, in the control subjects, uptake increased without decreasing subsequently.

Speculation

The chronic hyperprolinemia state might entail adaptation of the transport mechanism with the three infused aminoacids (Pro, OH-Pro, and Gly), bringing about an "overflow" of the system similar to that observed in the kidney. However, the inhibition of intestinal iminoacids and glycine transport seems to be due to mechanisms more complex than that of a simple inhibition by proline.

The mechanisms of membrane transport of proline, hydroxyproline, and glycine have been investigated in some recent studies, the results of which seem to indicate the presence, *in vivo*, of a single transport system for iminoacids and glycine (7, 10, 11, 13).

Investigation of a type I hyperprolinemia patient allowed us to suggest a new approach to the problems of intestinal absorption of these three aminoacids.

EXPERIMENTAL PROCEDURE

SUBJECTS

The subjects were one patient with type I hyperprolinemia whose case is described in an earlier report (4) and six control subjects of the same age and weight as the propositus; none had evidence of small bowel or metabolic diseases and plasma aminoacid levels (Pro, Gly, OH-Pro) were normal.

METHODS

A method of intestinal perfusion with which we were already familiar was adopted (3).

Intubation. This was carried out with a double lumen tube in accordance with the procedure previously described elsewhere (3).

Perfusion. Six intubations (one per week) were performed on the patient with hyperprolinemia, with the following infused solutions: (*1*) proline (5, 10, 20, 30, and 40 mM); (*2*) hydroxyproline (5, 10, 20, 30, and 40 mM); (*3*) glycine (5, 10, 20, 30, and 40 mM); (*4*) proline (10, 20, and 40 mM)-hydroxyproline (10 mM); (*5*) proline (10, 20, and 40 mM)-glycine (10 mM); (*6*) proline (10, 20, and 40 mM)-hydroxyproline (10 mM)-glycine (10 mM).

Samples. After an equilibration period (40 mM) to allow examination of the composition of the intestinal fluid arriving in the test segment, three 10-min samples were taken for each concentration.

Assays. Aminoacids were estimated by ion exchange chromatography with a Unichrom-Beckman Auto Analyzer and polyethylene glycol (PEG) was estimated by Hyden's turbidimetric method (6).

Results. For each sample, absorption was calculated with correction of the dilution factor by the PEG determination (PEG 4,000 infused with the amino acid solution). For each infused concentration, we calculated the average of the sample results from the three 10-min periods.

RESULTS

Our method did not allow an analytic study of all the variables present; compared the propositus (16) only with control subjects for each solution infused.

INTESTINAL ABSORPTION, WHEN PROLINE, HYDROXYPROLINE, OR GLYCINE WAS INFUSED ALONE, (TABLE 1)

Control Subjects. The quantity of aminoacid taken up (as expressed in micromolar concentration per min per 20 cm of intestinal test segment) increased with increasing substrate concentration.

Hyperprolinemic Patient. The intestinal absorption was less for glycine and hydroxyproline, but the aminoacid uptake increased with the substrate concentration. However, when a higher proline concentration was infused, the quantity of proline absorbed remained constant of 16.5–17 μM/min.

INTESTINAL ABSORPTION WITH INFUSIONS OF AMINOACID MIXTURES

Proline-glycine infusion. In the control subjects proline uptake increased but did not alter the glycine uptake, which remained constant (20–21.5 μM/min/20 cm). In the hyperprolinemia patient, the proline uptake increased (from 7 to 32.5), whereas the glycine uptake decreased (Table 2). Unfortunately, we were unable to make the 40 mM infusion for technical reasons.)

Proline-Hydroxyproline Infusion. In the control subjects both proline and hydroxyproline uptake increased, although only the proline concentration in the infused solution was increased. In the patient, when the concentration of infused proline was raised, the absorption rate of proline increased whereas that of hydroxyproline first increased (9.8–14.3 μM/min) and then decreased to its basal value (14.3–9.8 μM/min) (Table 3).

Proline-Hydroxyproline-Glycine Infusion. In the control subjects, hydroxyproline and glycine uptake was not significantly altered when proline uptake increased (12.5–58 μM/min). In the patient, raising the concentration of infused proline was accompanied by a large decrease in uptake of all aminoacids; uptake became negligible (Table 4).

Table 1. *Intestinal absorption of proline (Pro), hydroxyproline (OH-Pro), and glycine (Gly) (aminoacids infused alone)*

	Intestinal absorption, μM/min/20 cm					
	Pro		OH-Pro		Gly	
	Controls	Patient	Controls	Patient	Controls	Patient
5 mM	4.1		7.9		8.8	
10 mM	13.8	16.8	17.5	5.8	16.5	14
20 mM	22	16.5	32	19.5	43.5	25
30 mM	41.4		63		66	
40 mM				35		50

Table 2. *Intestinal absorption (μM/min/20 cm) of proline (Pro)-glycine (Gly) mixture*

	Control subjects		Patient	
	Pro	Gly	Pro	Gly
Gly 10 mM + Pro 10 mM	22	21.5	7	21
Gly 10 mM + Pro 20 mM	41	20.7	32.5	15.3
Gly 10 mM + Pro 40 mM	80	20		

Table 3. *Intestinal absorption (μM/min/20 cm) of proline (Pro)-hydroxyproline (OH-Pro) mixture*

	Control subjects		Patient	
	Pro	OH-Pro	Pro	OH-Pro
OH-Pro 10 mM + Pro 10 mM	5.5	4	14	9.8
OH-Pro 10 mM + Pro 20 mM	37	6.5	32.5	14.3
OH-Pro 10 mM + Pro 40 mM	47	15.5	36	9.8

Table 4. *Intestinal absorption (μM/min/20 cm) of proline (Pro)-hydroxyproline (OH-Pro)-glycine (Gly) mixture*

	Control subjects			Patient		
	Pro	OH-Pro	Gly	Pro	OH-Pro	Gly
OH-Pro 10 mM-Gly 10 mM-Pro 10 mM	12.5	10	12.5	17	15	13.5
OH-Pro 10 mM-Gly 10 mM-Pro 20 mM	23	12.8	11.8	21	5.8	9
OH-Pro 10 mM-Gly 10 mM-Pro 40 mM	58	9	14.5	6	0.3	0

DISCUSSION

In hyperprolinemia, the typical "combined" aminoaciduria (proline, hydroxyproline, and glycine) has been interpreted by Scriver (11) in relation to an inhibition of aminoacid transport in the renal tubule. Among the known transport systems are (*1*) two types of genetically controlled mechanism (10, 12): the first of these, a common system, has low specificity and high capacity; the other has lower capacity and high substrate specificity for either iminoacids or glycine; (*2*) other more dissociated mechanisms apparently existing in the kidney (5, 8).

Is this conception of membrane transport applicable to the small bowel? In attempting to find an answer to this question we feel that the following observations arising from our study are particularly significant. (*1*) The control subjects do not show any significant inhibition of transport, which allows us to assume the apparent independance of glycine, proline, hydroxyproline transports; however, this is perhaps due to our relatively limited protocol (3). (*2*) The hyperprolinemic patient exhibits a special state characterized by a high proline concentration in all body fluids. In an identical

case, Dodinval (2) indicates the competitive inhibition of hydroxyproline and glycine uptake by proline in the kidney. During a proline load, an "overflow stage" occurs with an increase in the clearance of three aminoacids, followed by a decrease in clearances to basal values ("recovery stage"). This probably corresponds to a tubular adaptation of the transport system and is perhaps dependent on the induction of an enzymatic system.

The studies on our hyperprolinemic patient may lead to two conclusions. (*1*) During the perfusion of the three aminoacids, one by one, uptake of both glycine and hydroxyproline increased, but by lower amounts than in the control subjects. On the contrary, the proline uptake remained constant (16.5–17 μM/min) despite the increase of infused proline concentration; this makes us believe that the transport systems are saturated, particularly that for proline. (*2*) The proline-hydroxyproline and proline-glycine infusions involve similar variations of proline uptake for the hyperprolinemic patient and the control subjects, still, however, with lower values for the patients. However, glycine and hydroxyproline uptake differs in the patient (Tables 2 and 3); therefore, transports for these aminoacids seem to be slightly inhibited. (*3*) During the proline-hydroxyproline-glycine infusion in the patient, marked and general decrease in absorption appears.

The chronic hyperprolinemia state might therefore entail adaptation for the transport system, which would account for the low differences of absorption between the patient and the control subjects when aminoacids are infused one by one or two by two. On the other hand, when the three amino acids are infused together, an "overflow stage," similar to that observed by Dodinval in the kidney (2), appears, which is responsible for the fall in uptake of the three aminoacids.

In summation, the intestinal iminoacids and glycine transport seems to be due to complex mechanisms. (*1*) In normal subjects, glycine, proline, and hydroxyproline absorptions seem to be independent from one another. (*2*) In the hyperprolinemic patient, a strong inhibition of these transports occurs only when the three aminoacids are infused together and with an increasing concentration of proline. It remains that the values of aminoacid uptake are lower in the hyperprolinemic subject than in the control subject, a consequence perhaps of the fact that the patient with hyperprolinemia exhibits a special state characterized by a constant "overflow" of proline.

SUMMARY

Carrying out an investigation on a type I hyperprolinemia patient, our aim was to study iminoacids and glycine intestinal absorption.

It is difficult to compare the intestinal absorption mechanisms with those of the kidney. However, it appears that in the hyperprolinemic patient the intestinal absorption is not really disturbed, but the adaptation possibilities by comparison with control subjects are limited, particularly when hydroxyproline and glycine are infused with proline.

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