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INTESTINAL ABSORPTION OF L-TRYPTOPHAN IN SCLERODERMA

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Abstract. The purpose of this investigation was to study the intestinal absorption of L-tryptophan and to assess the absorptive function of the intestine in scleroderma. The oral L-tryptophan loading test was performed in 31 cases of systemic scleroderma (progressive systemic sclerosis, PSS) and 3 cases of localized scleroderma. Serum levels of tryptophan and urinary excretion of indole-acetic acid (IAA) and indican (IS) were determined in order to assess intestinal absorption of tryptophan. In 10 cases the D-xylose test and in 4 cases Schilling's test was also performed. Furthermore, in vitro binding of L-tryptophan by plasma proteins in PSS and in other skin diseases as controls was studied. The normal increase in serum tryptophan after loading was noted in 17 cases (in 14 cases of PSS with a mild, slow progression and in 3 cases of PSS with a severe, rapidly progressing course). In 10 of these cases, urinary excretion of IAA was higher than normal and in 3 cases excretion of urinary IS was also above normal. On the other hand, in 14 cases of severe, rapidly progressing PSS and in 2 of 3 cases of widespread linear scleroderma, serum levels of tryptophan were markedly depressed after loading, while urinary excretion of IAA and IS was normal. In all 4 cases studied, Schilling's test was normal, and only in 2 of 10 cases of PSS was the D-xylose test abnormal. It is concluded that in the majority of cases of PSS, intestinal absorption of tryptophan is normal as also is the absorptive function of the intestine. The slight rise in serum tryptophan after loading in some cases of PSS may be a result of increased binding of tryptophan by albumin.

Key words: Scleroderma; Tryptophan metabolism; Intestinal absorption; D-xylose test

Changes in the small intestine in progressive systemic sclerosis (PSS) are relatively frequent (third in rank after esophagus and lungs), usually appearing after cutaneous lesions (5, 7, 8, 14, 15, 17, 20, 21, 22, 27, 30, 31, 32, 34, 35). However, there are also cases in which typical clinical gastrointestinal symptoms and radiographic and pathologic changes precede the appearance of cutaneous lesions, by months or even years (7, 20).

Systemic sclerosis of the small intestine may be relatively asymptomatic or may be associated with various degrees of dyspepsia, abdominal distention or distress, symptoms of intestinal obstruction, or evidence of malabsorption syndrome.

Radiographic changes are localized mainly in the duodenum and the initial part of the jejunum, i.e., at sites of most intense absorption, and occur in about 50% of cases of PSS (32). Characteristic features include dilatation of the intestinal lumen, hypotonia and feeble intestinal peristalsis, though the villous structure and the mucosa are usually normal, except for the minimal infiltration of inflammatory cells. Alteration in intestinal motility may lead to an abnormal bacterial overgrowth and consequently to malabsorption of sugars, fat, fat-soluble vitamins and vitamin B_{12} (5, 21, 30, 34).

A possible malabsorption of tryptophan (TRY) seems particularly interesting. Price et al. (33) called attention to the relation between tryptophan metabolism and diseases of connective tissue. Reports on the occurrence of scleroderma-like lesions in the carcinoid syndrome (12, 41) prompted a few investigations on TRY metabolism in the serotonin and 5-hydroxyindole-acetic acid (5-HIAA) pathway (6, 38). Subsequent studies on scleroderma were concerned mainly with the kynurenine–niacin pathways of TRY metabolism (4, 16, 18, 36).

No studies dealing *sensu stricto* with intestinal absorption of amino acids in scleroderma have come to our attention in the available literature. In the studies on the metabolism of tyrosine in collagen diseases, normal intestinal absorption of this amino acid has been found in scleroderma (1), which also would indicate a normal intestinal absorption of phenylalanine. On the other hand, impaired intestinal absorption of TRY indicated indirectly by excessive urinary excretion of indican,

Table I. *Increase in indole-acetic acid (IAA) and indican (IS) in the urine after L-tryptophan loading test (0.1 g/kg body weight) in progressive systemic sclerosis (PSS)*

No.	Case	Sex	Age (y.)	Time between Raynaud's s. and indurations (y.)	Duration of the disease (indurations) (y.)	Internal organs: Oesophagus	Lungs	Heart	Osteolysis	ESR
Group I										
1	J. A.	♂	51	5	25	+	−	±	+	6/15
2	D. G.	♀	15	1	5	−	−	+	+	4/11
3	C. H.	♀	57	24	3	+	−	−	+	37/67
4	F. C.	♀	49	10	2	+	+	+	−	10/25
5	S. L.	♀	45	1	3	−	+	−	+	4/11
6	W. J.	♀	40	1	2	−	−	−	−	37/50
7	E. K.	♀	35	3	3	+	−	+	−	12/33
8	R. A.	♀	55	11	3	−	−	+	−	13/29
9	J. A.	♀	51	3	2	−	−	−	+	3/8
10	K. T.	♀	34	1	2	−	−	−	−	42/73
11	F. M.	♀	45	1	2	−	−	+	+	17/38
12	R. Z.	♀	30	3	1	−	−	−	+	10/27
13	C. M.	♀	15	3	1	−	−	−	+	12/31
14	Z. K.	♂	57	1	19	+	+	−	+	11/34
15	W. J.	♂	57	3	3		−	−	+	18/42
16	F. J.	♀	51	24	10	+	+	+	+	28/63
Group II										
1	K. A.	♀	33	1½	½	−		−	−	8/9
2	P. J.	♀	49	½	½	+	+		−	17/36
3	Z. J.	♂	63	0	½	+	+	+	−	26/60
4	L. S.	♂	60	½	0	−	+	+	−	80/113
5	B. A.	♀	46	½	1	−	+	−	−	10/19
6	K. A.	♂	67	½	1½	+	+	+	−	34/62
7	B. C.	♀	51	1	½	+	+		−	32/72
8	K. M.	♂	37	2	4	−	−	−	−	5/18
9	B. W.	♂	63	3	1	+	+	+	−	17/36
10	K. I.	♀	44	2	1	−	−	+	−	8/16
11	B. C.	♀	17	3	3	+	+	−	+	−
12	N. A.	♂	37	1	½	+	−	−	−	54/85
13	S. I.	♀	34	¼	⅙	−	−	−	−	25/39
14	W. S.	♂	50	½	½	+	−	−	−	10/19
15	M. F.	♂	46	1	½	+	+	+	+	38/70
Normal (10 persons)										

[a] Values calculated by subtracting basal values (before load test) from values after loading; ESR after 1 and 2 hours.

has been demonstrated in some cases of scleroderma with intestinal malabsorption (5, 14, 20). Malabsorption in these cases has been established by an increased faecal fat excretion, flat glucose curve, D-xylose test, as well as by clinical symptoms. In our previous studies (37), we found that in some cases of PSS, urinary excretion of total indoles and indole-acetic acid (IAA) is increased, suggesting disturbances in intestinal absorption of TRY. These observations prompted us to undertake the present studies.

MATERIAL

The study material consisted of 31 cases of PSS (20 women, 11 men) and 3 cases of localized scleroderma (2 women, 1 man) aged 15–70 years. Tables I and II present data on the course and duration of the disease, visceral involvement, ESR and serum γ-globulin levels. The patients were divided into two clinical groups. Group I comprised 16 patients with acrosclerosis with relatively mild and slow progression, Raynaud's symptom preceding scleroderma by several years, and minor abnormalities in ESR and serum γ-globulin levels. Group II consisted of 15 cases of diffuse scleroderma of the type usually rapidly progressive, generalized, and with the Raynaud's symptom appearing simultaneously with, or only shortly before indurations appeared. ESR and serum γ-globulin levels were high. Three patients of this group died.

METHODS

Oral loading with L-tryptophan was done always at the same time of day after an overnight fast and using the dosage 0.1 g/kg body weight. Tryptophan was assayed in

Level of γ-glob. (relative %)	Maximal level of TRY in the serum after loading (mg%)	IAA[a] (μmol/ kg/24 hr)	IS[a] (μ mol/ kg/24 hr)
15.9	22.7	11.4	1.5
15.5	22.0	8.0	0.1
25.0	21.6	1.7	3.7
21.4	20.8	7.3	0
23.8	18.1	5.5	0.1
19.4	18.0	8.7	0
19.6	18.1	5.8	0
22.8	18.0	6.4	0
20.0	17.7	3.8	2.0
22.5	17.4	10.2	2.5
–	16.2	1.2	1.4
18.5	15.7	2.5	2.5
21.2	15.4	7.8	0.4
23.8	14.4	3.0	5.5
30.9	12.5	4.1	0
28.5	12.3	5.2	0
24.5	14.9	8.0	0
27.1	14.9	10.6	5.5
24.4	14.9	6.7	0
38.5	12.0	2.3	0
20.8	13.6	9.0	0.8
32.3	11.5	1.4	1.4
35.0	11.4	3.6	0.4
25.3	11.0	20.4	1.5
27.5	11.0	2.7	1.2
22.5	10.8	3.5	0
22.6	10.3	1.9	1.7
21.3	10.0	2.7	2.6
28.3	9.6	1.9	0
22.4	8.7	2.5	0
35.0	7.6	0.1	6.7
	15–17	3.0–5.0	0–2.0

serum by the method of Opieńska-Blauth (28). Blood for examination was drawn every 30 min for 3 hours. After 3 hours the patients took their common hospital diet. Most of the patients tolerated tryptophan well. Only 3 patients experienced transient nausea and had a weak pulse half an hour after ingesting tryptophan.

Intestinal absorption of tryptophan was evaluated on the basis of assays of IAA in 24-hr urine before and after loading according to the method of Fischl & Rabiah (11) and indican (IS) by the method of Meiklejohn (26). The patients did not take any drugs for at least 4–5 days before the test.

The degree of in vitro binding of L-tryptophan by serum proteins was determined by the method described by Opieńska-Blauth (29).

In some cases of PSS, roentgenographic and bioptic studies on jejunum have been performed. In 10 cases of PSS and one case of scleroderma-like lesions in multiple myeloma, intestinal absorption of L-tryptophan has been compared with D-xylose absorption test, and in 4 cases of PSS also with vitamin B_{12} absorption test. These preliminary studies were performed in order to assess intestinal function.

Student's test was used in the statistical analysis.

RESULTS

The results are presented in Tables I–V as well as in Fig. 1.

Serum tryptophan. The increase in serum TRY after loading was normal in nearly all cases of systemic scleroderma in group I, and markedly reduced in all except 3 cases in group II (Tables I, II and Fig. 1). The differences in increase of serum TRY after loading between group I and group II of PSS patients are statistically significant (Table III). In 2 cases of widespread linear scleroderma, the increase in serum tryptophan after loading was also distinctly reduced (Tables II and III). In all cases, peak levels of serum tryptophan were observed, on average, 2 hours after loading.

Indolce-acetic acid. In 7 of 16 cases of PSS group I of acrosclerosis type and in 5 of 15 cases of PSS group II of diffuse scleroderma type as well as in one case of generalized morphea, urinary excretion of IAA after loading was above normal (Tables I and II).

Indican (IS). After loading with L-tryptophan, an increase in urinary IS above normal occurred in only 4 cases of systemic scleroderma, i.e., in 2 cases of PSS group I and 2 cases of PSS group II. In addition, in one case of linear scleroderma, urinary excretion of IS was somewhat increased (Tables I and II).

Binding of L-tryptophan by serum proteins in vitro. Preliminary results of determinations of binding of L-tryptophan by serum proteins (Table IV) indicate significantly high mean values in cases of PSS of group II and in widespread linear scleroderma (mean, 0.596 and 0.733 mg of L-tryptophan per gram albumin) in comparison with other skin diseases and healthy subjects (mean, 0.280 and 0.218 mg of L-tryptophan per gram albumin).

Intestinal studies. Biopsy studies performed in 5 cases of PSS revealed slight flattening of villi in 2 cases. In only 2 of 10 cases of PSS and 1 case of scleroderma-like lesions in multiple myeloma the excretion of D-xylose in urine was low. Vitamin B_{12} test was normal in all 4 cases studied (Table V).

Table 11. *Increase in indole-acetic acid (IAA) and indican (IS) in the urine after L-tryptophan loading test (0.1 g/kg body weight) in localized scleroderma*

No.	Case	Sex	Age (y.)	Duration of the disease (indurations) (y.)	ESR[a]	Level of γ-glob. (relative %)	Maximal level of TRY in the serum after loading (mg %)	IAA[b] (μmol/kg/24 hr)	IS[b] (μmol/kg/24 hr)
1	K. J. (generalized morphea)	♂	70	4	34/63	23.0	14.4	6.8	2.9
2	K. T. (widespread linear)	♀	37	2	8/24	24.0	12.8	3.7	3.3
3	K. I. (widespread linear)	♀	34	1/4	3/6	18.6	9.6	0	1.2
Normal controls (10 persons)							15–17	3.0–5.0	0–2.0

[a] ESR after 1 and 2 hours.
[b] Values calculated by subtracting basal values (before load test) from values after loading.

DISCUSSION

The slight increase in serum TRY after oral loading in 14 of 31 cases of PSS and 2 cases of linear scleroderma suggests an impaired absorption of L-tryptophan from the digestive tract. Twelve of these 14 patients were assigned to group II, characterized by the rapid and severe course of the disease, and only 2 patients to group I. No correlation was noted between maximum values of TRY in serum after loading, and visceral involvement (esophagus, lungs, heart), age, sex or the ingested dose of L-tryptophan. Peak values of TRY in blood were observed on average 2 hours after loading, in patients as well as in healthy subjects, thus indicating normal dynamics of intestinal absorption of tryptophan in PSS and localized scleroderma.

Three possible reasons for the markedly diminished rise in TRY in the serum after loading are: (*a*) the amino acid is not completely absorbed from the intestine; (*b*) the amino acid is intensively and rapidly metabolized in the liver via different pathways, for example kynurenine or IAA; and (*c*) the amino acid crosses the intestine and passes into the blood, but is firmly bound by serum proteins and is not released during trichloroacetic acid precipitation.

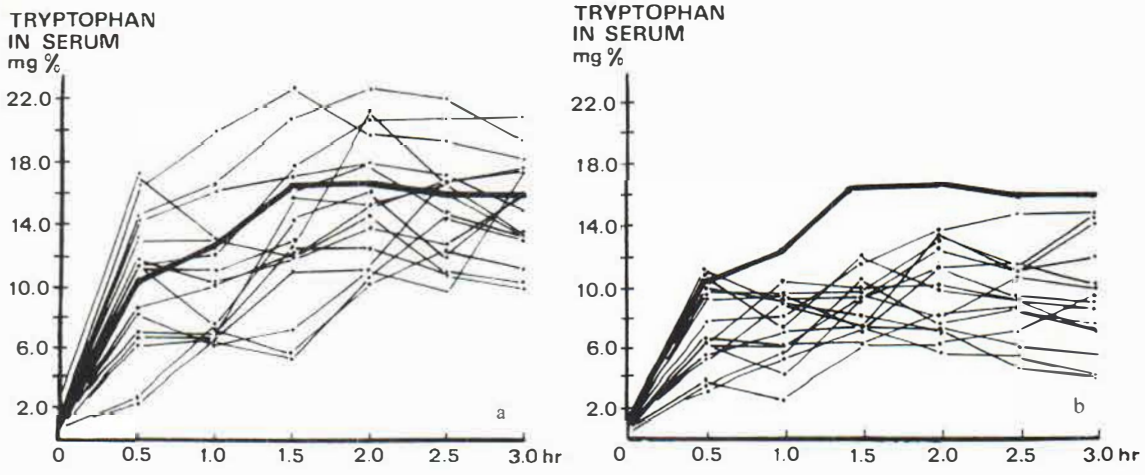

Fig. 1. Rise in serum tryptophan after oral loading with 0.1 g of L-tryptophan per kg body weight. (a) PSS, group I—16 cases; (*b*) PSS, group II—15 cases. Note: thick line = normal controls.

Table III. *Serum tryptophan levels after oral loading with L-tryptophan at a dosage of 0.1 g/kg body weight*

Minutes after loading	Levels of tryptophan in serum (mg%) 0	30	60	90	120	150	180	Peak values (mg %)
Progressive systemic sclerosis								
16 pats. (group I)	1.23[a] ±0.42	10.5[a] +4.4	11.0[a] ±4.2	13.8[a] ±4.5	15.9[a] ±3.9	15.2[a] ±3.8	15.2[a] ±3.3	17.5[a] ±3.3
15 pats. (group II)	0.99[a] ±0.40	6.6[a] ±2.7	7.0[a] ±2.3	8.8[a] ±2.0	9.6[a] ±2.8	9.5[a] ±3.2	9.4[a] ±3.6	11.5[a] ±2.4
				$P<0.0005$				
Localized scleroderma (3 cases)								
Generalized morphea	1.18	8.4	7.9	14.4	11.9	6.9	6.6	14.4
Widespread linear	1.25	9.1	9.5	10.4	12.8	12.0	12.6	12.8
Widespread linear	1.00	7.3	7.5	9.1	9.6	7.9	6.9	9.6
Normal controls								
10 pats.	1.40[a] ±0.31	10.5[a] ±3.9	12.5[a] ±4.1	16.0[a] ±3.8	16.7[a] ±2.9	16.0[a] ±2.5	16.0[a] ±2.1	16.6[a] ±2.3

[a] Mean values ±standard deviations.

(*a*) The reduction in intestinal absorption of TRY is usually accompanied by a rise in urinary excretion of indoles, particularly IS and IAA, as observed in Hartnup's disease (9), phenylketonuria (PKU) (39) and other intestinal diseases (13). However, in our study, despite the markedly diminished increase in TRY in the serum after loading in some cases of PSS (Table I), urinary excretion of IS was normal (except in cases 2 and 15 of group II). It is known (7, 20) that patients with scleroderma may have intestinal stasis and bacterial overgrowth. Conceivably, bacteria could be converting tryptophan preferentially to IAA, resulting in low serum levels of the former, high urine levels of the latter and normal values of IS. Such a situation could have occurred in only 3 cases, i.e., 1, 5 and 8 of group II of PSS. It is also possible that the bacterial population in the intestine of patients with scleroderma produces fewer indoles and consequently less IS. However, strains of *E. coli* cultured by us from the faeces of 4 patients with PSS were able to metabolize TRY to indoles in vitro. Thus, there is yet another possibility, that in some cases of PSS, intestinal absorption of indoles produced in the digestive tract may be impaired.

Our preliminary studies, which were performed to assess intestinal function, showed that only in 1 of 10 cases of PSS was the lowered serum TRY level after loading parallel to low excretion of xylose in the urine in the D-xylose test (Table V, case 9). The high level of indican in this case seems to confirm the true malabsorptive state of the patient.

In another case of scleroderma-like lesions accompanying multiple myeloma (19), low urinary excretion of xylose could be caused by impaired renal

Table IV. *In vitro binding of L-tryptophan by serum proteins in collagenoses and various skin diseases*

Diagnosis	No. of cases	Range of total serum proteins (g%)	Range of albumin in serum (g%)	mg L-tryptophan bound per g albumin Range	Mean
PSS (group I)	7	7.1–8.1	3.4–4.0	0.14–0.67	0.307
PSS (group II)	9	6.4–8.4	2.8–3.8	0.11–1.23	0.596
Localized scleroderma	3	5.9–7.9	3.1–3.7	0.50–1.02	0.733
Lupus erythematosus	5	5.5–7.9	3.0–4.0	0.08–0.72	0.296
Dermatomyositis	3	5.2–6.5	2.5–3.6	0.22–0.62	0.440
Various skin diseases	8	6.5–8.7	3.1–4.0	0.06–0.55	0.280
Normal controls	5	6.8–7.4	2.3–4.1	0.09–0.40	0.218

Table V. *Clinical features and results of intestinal function studies in 10 patients with systemic sclerosis and one patient with scleroderma-like lesions in multiple myeloma*
N=normal; n.d.=not done

No.	Case	Age (y.)	Sex	Years between onset of Raynaud's phenom. and of systemic scleroderma	Duration of the disease (indurations) (y.)	Intestinal absorption tests: D-xylose (normal) (17–35 %)	Intestinal absorption tests: Vitamin B_{12} (normal) (>10 %)	Maximal level of TRY in the serum after loading (normal) (15–17 mg%)
Progressive systemic sclerosis								
1	E. K.	35	♀	3	3	24.9	36.6	18.1
2	J. A.	51	♂	3	2	19.3	20.1	17.7
3	F. M.	45	♀	1	2	14.2	20.9	16.2
4	C. M.	15	♀	3	1	24.5	n.d.	15.4
5	Z. K.	57	♂	1	19	18.6	n.d.	14.4
6	S. S.	47	♀	1/2	1	31.7	22.1	12.2
7	B. C.	17	♀	3	3	22.0	n.d.	10.3
8	D. D.	20	♀	1	3	26.7	n.d.	9.6
9	M. F.	46	♂	1	1/2	6.3	n.d.	7.6
10	R. M.	20	♀	–	1/2	24.8	n.d.	13.3
Pseudoscleroderma in multiple myeloma (19)								
1	B. T.	45	♂	–	1	13.8[b]	n.d.	12.2

[a] Values calculated by subtracting basal values (before load test) from values after loading;
[b] Normal level of xylose in the blood after loading.

absorption rather than true intestinal malabsorption, as the blood xylose level after oral loading was normal. This observation indicates importance of serum xylose determination after loading. The determination of the xylose merely in the urine is proved to be insufficient, which is in agreement with Aung-Than-Batu et al. (2).

In other cases of PSS (Table V, cases 6, 7 and 8), in spite of the low TRY level in the serum after loading, the D-xylose test was normal. These observations may suggest that in most cases of PSS the absorptive function of the intestine is well preserved. High indican excretion is very rare in PSS and, when present, may be caused by transient bacterial overgrowth.

In 10 of 16 cases of PSS with a high serum tryptophan level we also observed a high excretion of IAA in the urine. IAA is produced from TRY by the action of bacterial and tissue enzymes (40). Markedly increased urinary excretion of IAA has been reported in Hartnup's disease, PKU and idiopathic sprue (9, 39), i.e., in conditions with well established intestinal malabsorption of TRY, but also in hepatic cirrhosis and progressive muscular dystrophy (40), where the high level of IAA is presumably a result of the tissue metabolism of TRY, and is not of bacterial origin due to malabsorption. Thus, it seems that in our cases of PSS with normal intestinal absorption of TRY, IAA is a product of tissue metabolism (liver, muscles, kidneys).

(*b*) Another reason for the slight rise in the serum TRY after loading may also be an intensive and accelerated metabolism of this amino acid in the liver via different pathways. However, we did not find a concomitant increase in the urinary excretion of kynurenine, IAA, 5-HIAA or xanthurenic acid which are produced by liver enzymes. It is to be assumed that utilization of TRY in the liver is not the reason for the low increase in serum TRY level.

(*c*) Our studies seem to indicate that in some cases of PSS group II it is not intestinal malabsorption of TRY which is responsible for the small rise in serum TRY after loading. As is known, TRY is the only amino acid possessing the capacity of binding with serum albumin (24) and is released upon precipitation of plasma proteins with trichloroacetic acid. It has been suggested (23) that human connective tissue diseases may arise from modifications in the binding characteristics of plasma proteins, namely albumin. Denko et al. (10) reported that in patients with rheumatoid arthritis the circulating albumin possesses an abnormal amino acid composition and this would be expected to be associated with different binding affinities and capacities for small molecules, compared with normal serum albumin. The results of Aylward &

Urine		
IS[a] (μmol/kg/24 hr) (normal) (0.–2.0)	IAA[a] (μmol/kg/24 hr) (normal) (3.0–5.0)	Histology of jejunum
0	5.8	N
2.0	3.8	N
1.4	1.2	Slight flattening of villi
0.4	7.8	n.d.
5.5	3.0	n.d.
n.d.	n.d.	Slight flattening of villi
1.6	1.9	n.d.
0	4.9	n.d.
6.7	0.1	n.d.
4.2	5.5	n.d.
0	1.4	N

Maddock (3) seem to support this assumption. These authors found that in patients with active rheumatoid arthritis (who are not receiving antirheumatic drugs), free TRY concentrations are diminished in comparison with plasma values in corresponding healthy controls. Our preliminary results (Table IV) indicate that in some cases of PSS (with a severe and rapid course) and in generalized morphea as well as in widespread linear scleroderma, plasma proteins exhibit an increased affinity for L-TRY compared with normal plasma, and that this may be the reason for the slight rise in TRY in serum after loading, rather than impaired intestinal absorption. These assumptions required confirmation on a larger material.

One possible reason for variations in binding of TRY to albumin may also be the endogenous fatty acid (FA), which occupies the several classes of FA sites on the albumin molecule (25). However, since the abnormal metabolism of FA in scleroderma has not been described so far, the hypothesis is only theoretical.

CONCLUSIONS

In about 50% of PSS cases corresponding to diffuse scleroderma type with severe progressive course as well as in cases of linear scleroderma and generalized morphea, serum levels of TRY are decreased after oral loading with this amino acid in comparison with normal controls. However, intestinal absorption of TRY seems to be normal, as indicated by the normal rise in urinary IS after loading. The absorptive function of the intestine (normal D-xylose and Schilling's tests) is also efficient.

It is possible that the small rise in serum TRY after loading may be a result of increased binding of TRY by albumin. Marked hyperproduction of IAA with simultaneous normal intestinal absorption of TRY would seem to indicate a tissue origin rather than a bacterial origin of this metabolite.

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