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THYROXINE METABOLISM IN UNTREATED AND TREATED PANCREATIC STEATORRHEA *

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The peripheral metabolism of a variety of hormones is conditioned in part by an enterohepatic circulation. Thus, both steroid hormones and thyroxine are taken up by the liver from the circulation, presumably by means of binding equilibria between specific circulating binding proteins and hepatocellular binding sites (1–3). Along with their metabolites, portions unaltered by degradation or transformation of the molecule are excreted into the gastrointestinal tract in free or conjugated form. A variable quantity is then hydrolyzed, reabsorbed, and restored to the circulation.

Since enteric losses of thyroxine from this cycle may be appreciable in man, particularly in infancy and childhood (4), it was of interest to examine the fecal losses of hormonal iodine under circumstances in which it is theoretically possible to control a discrete abnormality in digestive function. Pancreatic steatorrhea was selected as such a condition. In this disorder defective pancreatic exocrine function causes great increase in the volume of the gastrointestinal contents which, it was reasoned, might lead to entrapment of organic iodine secreted in the bile and thereby prevent absorption of thyroxine. While no clinical evidence suggests that pancreatic steatorrhea leads to peripheral thyroxine deficiency, compensatory thyroid hyperfunction, or goiter, no laboratory evidence exists that precludes an effect of the disease on iodine metabolism.

The studies to be described reveal that patients with treated or untreated steatorrhea lose significantly greater than normal quantities of organic iodine in the stool and exhibit accelerated fractional rates of turnover of hormone. Only small changes in thyroxine metabolism were found before and after treatment of these patients; however, estimated fecal excretion of organic iodine was increased significantly in the untreated state.

MATERIALS AND METHODS

Eight male patients with well established chronic pancreatic insufficiency were selected for study. Five were considered to have severe insufficiency, two had moderate, and one had mild insufficiency, based on the number and volume of stools during the untreated state. The mean duration of insufficiency was 5.5 years, the longest period being 12 years and the shortest 2 months. Three patients had undergone total pancreatectomy, two for recurrent pancreatitis and one for pancreatic carcinoma. All eight had easily controlled diabetes mellitus: one patient could be controlled by diet and the others required moderate doses of long-acting insulin. All demonstrated a good response to pancreatic enzyme therapy (Viokase) given as two tablets every waking hour.

Paired studies of thyroxine metabolism were performed by the methods of Ingbar and Freinkel (5), before and after treatment of the steatorrhea. The intervals between studies of individual patients are presented in Table I. The initial study was performed in six untreated patients, and during treatment in Subjects 5 and 6. The techniques employed were briefly as follows: 50 μc of I^{131}-labeled thyroxine was given intravenously, and blood samples were collected daily or twice daily for a 9-day period. In order to prevent thyroidal recycling of I^{131}, liberated from labeled thyroxine degradation, methimazole was given throughout the study in an oral dose of 30 mg every 6 hours. Suppression of I^{131} uptake was confirmed by direct measurement. Samples of urine were collected over 24-hour periods and feces over 72-hour periods. Appropriate aliquots of these specimens were then counted for radioactivity in a well-type scintillation counter and compared with counts obtained from an appropriate dilution of the injected dose placed in vessels corresponding to the geometry of the samples. However, due to stool bulk and variable rates of fecal excretion, fecal thyroxine clearance was indirectly calculated by methods published elsewhere (5, 6). Serum thyroxine binding in four cases was assessed by electrophoretic methods described elsewhere in detail (7, 8).

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TABLE I

Clinical features of subjects with pancreatic steatorrhea

Patient	Age, Wt	Pancreatitis		Pancreatectomy	Diabetes mellitus	Response to Viokase	Serum carotene	Wet stool wts		Triolein* at:		Oleic acid* at:	
		Duration	Severity					Off Viokase	On Viokase	5 hrs Blood	72 hrs Stool	5 hrs Blood	72 hrs Stool
	yrs, lbs						*μg %*	*g/72 hrs*		*%/L*	*%*	*%/L*	*%*
1	34 145	8 yrs	++++	No	25 U NPH‡	Good	34	2,324 3,005 1,983 (2,437)§	1,786 1,296 1,962 (1,713)	0.1	9.6		
2	65 100	5 yrs	++	No	Diet	Good	225	1,138 973 1,014 (1,661)	302 573 627 (500)	1.3	26.5	2.36	22.1
3	39 138	8 yrs	++++	No	45 U NPH	Good	135	1,809 1,308 1,506 (1,541)	1,196 1,214 1,187 (1,199)	0.16	23.5	1.27	12.2
4	45 120	12 yrs	++++	Total, 1954	Postop. 35 U NPH	Good	16	1,308 819 1,571 (1,233)	540 681 459 (560)	0.48	57.0		
5†	47 136	2 mos	++++	Total, 1961	Postop. 20 U NPH	Good		1,102 864 1,143 (1,036)					
6†	46 140	6 yrs	++++	No	35 U Lente	Good	50	1,879 1,318 1,602 (1,599)	1,228 1,271 1,200 (1,233)	0.49	36.0	1.37	3.27
7	47 134	2 yrs	+++	No	40 U NPH	Good	88	1,025 918 1,119 (1,020)	986 777 889 (884)	2.29	9.6		2.83
8	69 140	3 mos	+++	No	15 U NPH	Good	99	792 720 484 (665)	373 310 241 (308)	2.01	18.7	3.04	4.38
Approximate limits of normal								<450		>1.0	<5.0	>1.0	<5.0

* Performed while off Viokase.
† Study on Viokase performed first.
‡ Neutral protamine Hagedorn.
§ Mean of three.

TABLE II

*Several parameters of iodine metabolism in subjects with pancreatic steatorrhea before and after treatment**

Patient	Interval between turnovers	$t_{\frac{1}{2}}$	k	TDS	C	ETT	D	PBI	U_{max}	F_{max}	T_{max}	Fecal clear.	Degrad. clear.	Fecal excre.	Change in fecal excre.	Degrad. rate
	days	*days*	*%/day*	*L*	*L/day*	*μg I*	*μg I/day*	*μg %*	*% dose*	*% dose*	*% dose*	*L/day*	*L/day*	*μg I/day*	*%*	*μg I/day*
1	3.5 mos	4.7†	14.7	12.0	1.764	552.0	81.1	4.6	61.7	36.0	2.3	0.635	1.129	29.2		51.9
		5.5‡	12.6	12.8	1.613	512.0	64.5	4.0	62.2	36.2	1.7	0.584	1.029	23.4	19	41.1
2	6	7.6	9.1	10.9	0.992	512.3	46.6	4.7	63.9	33.1	3.0	0.328	0.664	15.4		31.2
		8.0	8.6	9.4	0.808	376.0	32.3	4.0	50.2	41.9	7.9	0.339	0.469	13.6	12	18.7
3	6	5.5	12.6	14.9	1.877	879.1	110.7	5.9	50.5	47.6	1.9	0.893	0.984	52.7		58.0
		7.0	9.9	15.4	1.525	908.6	89.9	5.9	57.1	36.9	6.0	0.563	0.962	33.2	37	56.7
4	5	4.3	16.1	9.9	1.594	465.3	74.9	4.7	51.7	46.2	2.1	0.736	0.858	34.6		49.3
		4.4	15.8	9.7	1.533	455.9	72.0	4.7	58.0	39.9	2.1	0.612	0.921	28.8	17	43.2
5	35	6.2	11.2	15.2	1.702	805.6	90.2	5.3	45.1	53.1	1.8	0.904	0.798	47.9		42.3
		6.0	11.5	14.2	1.633	710.5	81.7	5.0	41.1	57.1	1.8	0.933	0.700	46.7	3	35.0
6	6	5.7	12.2	13.9	0.963	750.6	52.0	5.4	60.1	33.4	6.5	0.322	0.641	17.4		34.6
		5.6	12.3	10.8	1.328	540.0	66.4	5.0	66.9	20.6	12.5	0.274	1.054	13.7	21	52.7
7	6	4.6	15.0	12.5	1.875	687.5	103.1	5.5	59.9	38.8	1.3	0.728	1.147	40.0		63.1
		6.2	11.0	15.2	1.672	836.0	91.9	5.5	47.1	45.7	7.2	0.764	0.908	42.0	−5	49.9
8	5	5.3	13.1	10.0	1.310	620.0	81.2	6.2	57.8	39.1	3.1	0.512	0.798	31.7		49.5
		5.6	12.4	9.7	1.203	601.4	74.6	6.2	66.6	30.3	3.1	0.365	0.838	22.6	29	52.0

* See Appendix for abbreviations.
† Value in upper row: off treatment.
‡ Value in lower row: on treatment.

TABLE III

Comparison of normal mean turnover values from other studies and pancreatic steatorrhea off and on Viokase

Series from literature	No. of cases	$t_{\frac{1}{2}}$	k	TDS	C	ETT	D	PBI	U_{max}	F_{max}	T_{max}	Fecal clear.	Degrad. clear.	Fecal excre.	Degrad. rate
		days	*%/day*	*L*	*L/day*	*μg I*	*μg I/day*	*μg %*	*% dose*	*% dose*	*% dose*	*L/day*	*L/day*	*μg I/day*	*μg I/day*
Ingbar and Freinkel (5)															
Euthyroid	9	6.6	10.6	9.4	1.000	508.0	54.0	5.4		26.9		0.269	0.731	14.4	39.2
Treated myxedema	9	6.8	10.1	8.8	0.894	464.0	48.0	5.4		20.8		0.186	0.708	10.0	37.5
Dowling *et al.* (6)															
	10	6.6	10.7	8.8	0.940	506.0	54.0	5.8							
	5	6.8	10.2	9.2	0.950	505.0	52.0	5.5							
	7									29.7		0.310	0.740	18.0	43.3
Sterling and Chodos (21)	8	6.7	10.5	8.8	0.924	548.0	57.0	6.2							
Rasmussen (22)	1	7.1	11.0	8.2	0.902	590.0	65.0	7.2							
Federman *et al.* (23)	4	5.7	13.2	7.4	0.977	412.0	53.0	4.9							
Austen *et al.* (24)	8	6.2	11.3	10.9	1.232	598.0	68.0	5.5							
Grand mean		6.6	10.7	9.1	0.986	514.0	55.0	5.6		25.5		0.251	0.725	14.2	39.7
Present study															
Mean, off Viokase	8	5.5	13.0	12.4	1.510	659.1	80.0	5.3	56.3	41.0	2.8*	0.632	0.877	33.6	46.4
Mean, on Viokase	8	6.0	11.8	12.2	1.414	617.6	72.0	5.0	56.2	38.6	5.3	0.554	0.860	28.0	43.7
SE			0.54	0.93	0.074	30.4	3.61	0.87	3.25	3.0	1.04	0.043	0.021	2.36	3.75
p			0.10	0.10	0.30	0.60	0.10	0.05	0.9	0.5	0.05	0.5	0.5	0.05	0.5

* Patients on blocking dose of methimazole.

For definition of terms and symbols see Appendix. Statistical comparisons were made by the "paired" t test.

RESULTS

The clinical characteristics of the individual patients are presented in Table I. Data obtained from studies of iodine metabolism in these patients are given in Table II. Statistical analyses of these data and their comparison with results of previously recorded studies of normal persons are presented in Table III. The clinical severity of steatorrhea was least in Subjects 2, 7, and 8. Whereas 3-day wet stool weights ranged from a mean of 665 to 2,437 g while patients were off Viokase, they decreased to a range of from 308 to 1,713 g during treatment. Improvement in the defect was greatest, as judged by change in fecal weight, in Subjects 2, 4, and 8.

In the paired studies no significant difference could be ascertained in the fractional rate of removal of I^{131}-labeled thyroxine from the circulation (k),[1] in the volume of distribution of hormone (TDS), in its rate of clearance from the circulation (C) or in over-all degradation or utilization of hormone (D). The partition of radioactivity between urine and feces as indicated by the calculated maxima (U_{max} and F_{max}) also failed to reveal statistically significant differences. Fecal clearance and degradative clearance similarly were not different before and after treatment. However, fecal excretion of organic iodine was somewhat reduced after treatment in six of the eight patients, and for the group the difference reached the 95 per cent level of confidence. When the magnitude of the defect in the untreated state was taken into account by expressing the difference after treatment as the per cent reduction, fecal excretion of organic I^{131} improved significantly by 19.4 per cent ($p = 0.01$).

In comparing these data with those obtained from other studies of thyroxine metabolism, it was noted that the thyroxine distribution space, fractional rate of hormonal turnover, and total daily degradation were considerably greater than normal. Fecal losses of hormone in both the treated and untreated states (means, 28.0 and 33.6 μg I per day) were excessive when compared with normal values (mean, 14.2 μg I per day). The degradative rate (net daily tissue turnover), however, was within the normal range (steatorrhea means, 43.7 and 46.4 μg I per day; normal mean, 39.7 μg I per day; Table III).

[1] Definition of all abbreviations and terms is given in the Appendix.

TABLE IV

Values of serum thyroxine binding in four patients with pancreatic steatorrhea

Patient	TBG		TBPA	
	Off Viokase	On Viokase	Off Viokase	On Viokase
	saturation	μg %	*saturation*	μg %
4	22	21	65	85
5	21	15	80	84
7	15	16	120	120
8	17	16	85	5

Serum thyroxine binding (Table IV) was normal and did not change with therapy except in the case of Subject 8 whose serum binding to TBPA inexplicably fell during treatment. Despite the change the subject exhibited no alteration in the concentration, volume of distribution, or fractional rate of turnover of thyroxine.

DISCUSSION

It is evident from the present work that patients with untreated and treated pancreatic steatorrhea excrete two or more times the normal quantity of organic iodine in the stool. The volume of distribution of thyroxine appears to be increased, conceivably as a result of increased bowel content of hormone, and fecal losses of organic iodine amount to from 30 to 57 per cent of the quantity of hormone that is degraded in the peripheral tissues. The difference between the total daily hormone turnover in these patients and that derived from published data in normal subjects (which reveal remarkable agreement) is so great that it appears to be significant. When compared with the mean normal data (Table III), it is evident that fecal thyroxine losses are compensated for by an increase in total daily turnover of hormone of such a degree that net peripheral tissue turnover remains entirely normal. It will be noted that the increase results from a more rapid fractional rate of turnover rather than from an increased circulating concentration of hormone. Moreover, it was shown that, although there is a

significant reduction in fecal thyroxine loss and in fecal weight during treatment with Viokase, fecal hormone losses remained highly abnormal. Whether this failure to achieve normality resulted from persistence of a defect in gastrointestinal function, which is not correctible by exogenous pancreatic enzymes or was due to incomplete replacement treatment, cannot be established. However, it is likely that currently available substitution treatment does not fully correct the disorder. If it is assumed that thyroid hormone production is in equilibrium with peripheral hormone turnover (5), then the thyroid glands of these patients must chronically produce increased quantities of hormone. In the present subjects this postulated augmentation was not associated with clinically evident goiter.

Changes in serum thyroxine binding did not appear to contribute to these findings since, in the four subjects studied, binding by TBG was normal. Indeed, the electrophoretic finding of reduced TBPA during treatment of Subject 8 was *not* accompanied by changes in iodine metabolism that could be attributed to it. This single finding is contrary to earlier speculations concerning the possible significance of reduced binding by TBPA (9).

Since the suggestion by Kendall that an enterohepatic cycle of organic iodine might be important in thyroid economy (10), several quantitative studies of the cycle have been undertaken in animals and man. It became apparent that great differences exist in its magnitude in various species. Thus, the rat excretes into the bile every hour an amount of thyroxine equal to that present in the circulation; 97 per cent of the excreted thyroxine is returned to the circulation by gastrointestinal absorption (11). Direct studies in man by Myant suggest that the biliary clearance of thyroxine, on the average, is about one-third of total daily clearance (12). Estimated biliary thyroxine turnovers, calculated for four subjects from his data, are 19, 40, 32, and 20 μg of iodine daily. From fecal clearance measurements he concluded that only about one-half of this organic iodine is absorbed. With the average of the foregoing estimates, the mean daily fecal excretion of these subjects is 14 μg of iodine, a figure that favorably compares with the mean of 14.2 μg derived from those studies performed by different methods cited in Table III and with the estimate of Berson and Yalow of 12 μg per day, arrived at by a third technique (13).

If the foregoing estimate of biliary thyroxine turnover in man is correct, it is possible that some of the present patients excreted more organic iodine in the stool than can be accounted for solely by disruption of the enterohepatic circulation. Thus, biliary excretion may have been excessive or additional thyroxine was secreted into the bowel. The latter possibility gains support from the observation that a small quantity of thyroxine appears in the feces of rats even after ligation of the bile ducts (14) and from the likelihood that if there is an element of exudative enteropathy in pancreatic steatorrhea, protein-bound thyroxine would be lost into the gastrointestinal tract.

Further possible causes of excessive loss of hormone include defective hydrolysis of thyroxine-glucuronide, entrapment or adsorption of organic iodine in the bowel contents, or interference with the mucosal absorption of thyroxine by a compound in the bowel contents which is normally degraded by pancreatic enzymes. The first of these mechanisms is supported by the finding that thyroxine-glucuronide is poorly absorbed by rat gastrointestinal mucosa (14). That the two other possibilities might be important can be inferred from the work of Beck who, in studies of the effects of feeding soya flour upon the enterohepatic cycle, concluded that the observed fecal loss of thyroxine was not due to increased biliary excretion, addition of thyroxine to the gut from any other source, or alteration of the thyroxine molecule (15). Further studies of fecal thyroxine clearance in patients with other malabsorption syndromes and in patients with exudative enteropathy may shed light on the relative importance of these mechanisms.

Although no goiter was observed in any of the present patients, a great deal of recent work in animals has suggested that excessive fecal loss of thyroxine might be goitrogenic. Thus, Van Middlesworth and Intoccia observed that rats fed soya flour develop hyperfunctioning thyroid glands (16); Van Middlesworth demonstrated that the probable mechanism was fecal wastage of thyroxine (17) and confirmed the magnitude of the enterohepatic cycle in the rat. Despite the lesser importance of the cycle in man, these data sug-

gested that the phenomenon might be important in the pathogenesis of simple goiter in man. However, the only reported human instances of goiter due to fecal loss of thyroxine are those that have developed in infants fed a soya flour substitute for milk (18–20).

Since the present patients excreted amounts of organic iodine which equaled or exceeded estimates of biliary excretion (12) without developing goiter, it seems unlikely that total disruption of the enterohepatic cycle in the adult would lead to significant goiter. However, when complicated by the presence of other stimuli toward goitrogenesis or increases in the amount of hormone secreted into the bowel from the bile or through the gastrointestinal mucosa, such a defect may conceivably be of importance. Indeed, there may be individuals without manifest gastrointestinal disease, who harbor specific absorptive defects, in whom fecal thyroxine loss contributes to goitrogenesis. Moreover, as suggested from studies of soya flour goiter, there may be unrecognized dietary agents that interfere with the enterohepatic circulation of thyroxine in susceptible individuals. These tentative possibilities can only be refuted or sustained by further similar studies of the metabolism of thyroxine in patients with hyperfunctioning goiter (16, 17).

SUMMARY

Paired studies of the kinetics of thyroxine metabolism in eight patients with well documented treated and untreated pancreatic steatorrhea revealed no significant difference in the fractional rate of removal of I^{131}-labeled thyroxine from the circulation in the volume of distribution of hormone, in its rate of clearance from the circulation, or in its over-all degradation.

The partition of radioactivity between urine and feces also did not differ in the treated and untreated states. However, fecal excretion of organic iodine was somewhat reduced after treatment in six of the eight patients.

Of significance was the finding that fractional rates of hormonal turnover, total daily degradation, and fecal losses of hormone were excessive when compared with normal values in both the treated and untreated states. Net peripheral tissue turnover, however, was within the normal range; thus, the production of thyroxine by the thyroid gland must increase in response to the fecal loss.

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APPENDIX

In the foregoing manuscript and tables the following terms have been employed.

TDS, thyroxine distribution space; the virtual volume of body fluids through which exchangeable thyroxine would be distributed were it present throughout at the same concentration at which it exists in the plasma.

PBI, concentration of hormonal iodine in the plasma and, by definition, the geometrical mean concentration of hormonal iodine in the TDS; assumed to represent solely iodine in thyroxine.

ETT, extrathyroidal thyroxine; the total quantity of thyroxine within the TDS, in terms of its content of iodine.

k, Fractional rate of turnover of thyroxine; the proportion of ETT removed from the TDS per unit time.

$t_{\frac{1}{2}}$, Thyroxine half-time; the time required for half of the ETT to be removed from the TDS.

C, thyroxine clearance rate; the volume of plasma containing an amount of thyroxine equal to that removed from the TDS per unit time. Defined as "volume turnover, V" in an earlier communication (5).

D, hormonal disposal rate; the quantity of hormone removed from the TDS per unit time, in terms of its content of iodine.

F_{max}, the proportion of D accounted for by fecal excretion of hormone; fecal clearance, the volume of plasma containing a quantity of hormone equal to that lost in the feces per unit time; degradative clearance, the volume of plasma containing a quantity of hormone equal to that removed by nonexcretory pathways per unit time; fecal excretion, the quantity of hormone excreted in the feces per unit time; degradative rate, the quantity of hormone removed by nonexcretory pathways per unit time. All quantities of hormone are expressed in terms of iodine content.

TBG, thyroxine-binding globulin.

TBPA, thyroxine-binding prealbumin.

ETT = PBI × TDS × 10. C = TDS × k. D = C × PBI = ETT × k. $t_{\frac{1}{2}} = 0.693/k$. Fecal clearance = $C \times F_{max}$. Degradative clearance = C − fecal clearance. Fecal excretion = fecal clearance × PBI = $D \times F_{max}$. Degradative rate = degradative clearance × PBI = D − fecal excretion.

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