Response of Human Growth Hormone, Prolactin and Thyrotropin to Thyrotropin Releasing Hormone in Liver Cirrhosis and Diabetes Mellitus

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Synopsis

Serum HGH, PRL and TSH responses to intravenous injection of 500 μ g of TRH were investigated in nine patients with liver cirrhosis and in patients of the same number with diabetes mellitus who served as controls. They were roughly matched in age, sex and body weight. The basal serum HGH levels in the cirrhotic group were significantly high with a value of 4.7 ± 1.7 ng/ml compared to the values of 1.5 ± 0.9 ng/ml in the control diabetic group. Serum HGH levels in the cirrhotic group at 15, 30, 60 and 90 min intervals after TRH were significantly higher than the basal serum HGH levels. The control diabetic group showed no positive response. Similar responses were observed again in three subjects of the cirrhotic group after treatment for hepatic insufficiency. Two subjects of the cirrhotic group showed an elevation of serum HGH in response to TRH even under hyperglycemia induced by glucose administration. The basal serum PRL levels were identical in both groups. The serum PRL levels in both groups evidently increased in response to TRH with significantly higher response in the cirrhotic group than in the control diabetic group at 15, 30 and 60 min intervals after TRH. There was no significant difference in the basal levels of serum TSH or the levels after TRH between both groups. It was concluded that the serum HGH levels in cirrhotic patients were elevated by TRH. Since the response was independent of clinical severity, the possibility exists that it could be attributed to some basic metabolic abnormality of the underlying liver cirrhosis. Since the abnormal HGH response to TRH was not seen in the control diabetic group and was not altered by hyperglycemia in the cirrhotic group, an abnormality of the glucose metabolism was eliminated as a possible cause.

The promotion of paradoxical human growth hormone (HGH) response by thyrotropin releasing hormone (TRH) was reported in the case of a variety of conditions and diseases (Irie *et al.*, 1972; Gonzalez-Barcena *et al.*, 1973; Faglia *et al.*, 1973; Maeda *et al.*, 1975; Hasegawa *et al.*, 1975; Maeda *et al.*, 1976; Czernichow *et al.*, 1976).

Recently, when investigating the response in diabetics, we encountered a patient with liver cirrhosis who exhibited a hyperresponse

of HGH to TRH. Therefore, we compared the response in nine patients with liver cirrhosis with that in nine diabetics without any clinical evidence of liver disease matched in age, sex and body weight. The results confirmed the hyperresponse of HGH to TRH in cirrhotics but not in diabetics who served as controls, and were reported at the 50th annual meeting of Japan Endocrine Society (Yamaguchi *et al.*, 1977). Shortly after our report, almost the identical results were published separately by Panerai *et al.* (1977) and Zanoloni and Zanoloni-Mucaccia (1977). However, they did not

describe the relationship between the response and the severity of hepatic dysfunction, and thyroid stimulating hormone (TSH) response to TRH in liver cirrhosis, although Panerai *et al.* (1977) reported prolactin (PRL) response to TRH in this disease. In this paper, we present the obtained results concerning these issues mentioned above.

Materials and Methods

Subjects

(Table 1, 2): Two groups of subjects were studied: one group of nine patients with liver cirrhosis (five males and four females; mean age and body weight, 52.3 years and 55.8 kg) and the other group of nine patients with diabetes mellitus (five males and four females; mean age and body weight, 54.0 years and 52.4 kg) who served as controls. None of the patients with liver cirrhosis and diabetes mellitus were azotemic. Their thyroid functions were within normal limits.

Table 1. Clinical data of the cirrhotic patients

Case	Sex	Age (yrs)	Body weight (kg)	GOT* (u.)	GPT* (u.)	Bili- rubin* (mg/dl)	γ -Glo- bulin* (g/dl)	Crea- tinine* (mg/dl)	Thyro- xine* (μ g/dl)	ICG** (%)	FBS# (mg/dl)	GTT##
1	m	65	44.0	84	38	1.0	2.1	1.1	6.4	26.6	140	diabetic
2	m	49	74.0	118	77	1.8	3.1	1.4	5.3	60.6	185	diabetic
3	m	41	49.5	92	28	1.4	3.6	1.0	3.9	47.5	92	border line
4	m	39	62.5	47	39	0.9	1.1	1.0	5.9	62.5	207	diabetic
5	m	39	64.0	48	24	1.9	2.2	1.1	5.6	43.3	79	diabetic
6	f	62	40.0	122	74	1.5	2.3	1.1	7.6	32.7	136	diabetic
7	f	56	52.0	61	21	1.1	2.7	0.7	2.6	54.6	122	border line
8	f	62	56.5	75	40	0.8	2.0	0.9	3.3	32.5	80	diabetic
9	f	58	59.5	72	24	1.9	2.1	0.5	4.2	67.0	84	diabetic
Mean		52.3	55.8	79.9	80.6	1.4	2.4	1.0	5.0	47.5	125.0	
S. D.		10.5	10.6	27.2	21.0	0.4	0.7	0.3	1.6	14.7	46.9	

* Normal value: GOT; 8-40, GPT; 5-30, Bilirubin; 0.03-1.2, γ -Globulin; 0.82-1.71, Creatinine; 0.8-1.5, Thyroxine; 3-12

** Indocyanine Green Retention (15 min); normal < 10%

Fasting Blood Sugar

Glucose Tolerance Test

Table 2. Clinical data of the diabetic patients*

Case	Sex	Age (yrs)	Body weight (kg)	GOT (u.)	GPT (u.)	γ -Glo- bulin (g/dl)	Crea- tinine (mg/dl)	Thyro- xine (μ g/dl)	FBS (mg/dl)	Treatment
1	m	37	44.0	28	22	1.3	0.8	7.5	180	Insulin
2	m	65	44.0	15	13	0.9	1.2	6.7	244	Acetohexamide
3	m	43	70.0	40	44	1.6	1.2	7.9	196	Diet only
4	m	40	61.5	27	35	1.4	1.0	7.9	176	Diet only
5	m	65	54.5	23	24	1.7	1.0	5.3	224	Insulin
6	f	60	51.0	24	8	1.8	0.8	6.3	176	Diet only
7	f	59	46.0	19	21	2.0	0.5	6.4	148	Diet only
8	f	66	46.5	20	16	1.2	1.1	9.4	118	Diet only
9	f	51	53.8	19	9	0.9	0.8	6.8	194	Insulin
Mean		54.0	52.4	23.9	21.3	1.4	0.9	7.1	184.0	
S. D.		11.5	8.9	7.3	11.9	0.4	0.2	1.2	37.5	

* Abbreviations and normal values: See Fig. 1.

The diagnosis of the patients with liver cirrhosis was verified by an increased retention of ICG (>25%), hypergammaglobulinemia and other clinical findings (hepatomegaly, palmar erythema, vascular spider and history of hepatic encephalopathy, etc.). Also, they all had glucose intolerance (seven diabetic and two border line cases) which were confirmed by the 50 g oral glucose tolerance test (normal limits; lower than 200 mg/dl at 60 min and 140 mg/dl at 120 min). Two of them were treated with insulin as diabetes mellitus associated with liver cirrhosis (case #1 and #6).

All of the patients with diabetes mellitus had normal liver function with normal serum enzyme levels, no increase of serum gammaglobulin and no clinical findings suggesting liver function derangement. Their diagnosis was verified by the oral glucose tolerance test and the evidence of microangiopathy.

Studies

All studies were performed in the morning after overnight fasting with the subjects recumbent throughout the experiment. All subjects were given 500 µg of synthetic TRH (Tanabe Co.) intravenously. Saline solution was injected intravenously in some of these patients as a control study on different occasions before or after TRH administration (five of the cirrhotics and eight of the control diabetics).

Three patients with liver cirrhosis were re-examined after a minimal one month period of treatment for hepatic insufficiency to assess the reproducibility of the response.

In two patients with liver cirrhosis, hyperglycemia was induced by an intravenous injection of 20 ml of 50% glucose followed by an intravenous infusion of 20% glucose 15 min prior to the injection of TRH to observe the response of serum HGH to TRH under the induced hyperglycemia. As the control study for this portion of the experiment, the changes in serum HGH were observed without the TRH injection under otherwise identical conditions.

Blood samples were taken from the antecubital vein prior to and at 15, 30, 60, 90 and 120 min intervals after the injection of TRH. After centrifugation, the serum was frozen at -20°C until assayed. Serum HGH (Utiger *et al.*, 1962), PRL (Reuter *et al.*, 1976) and TSH (Odell *et al.*, 1976) were determined with radioimmunoassay using double antibody methods. Kits for assays of HGH, PRL and TSH were obtained from Dainabott RI institute, CIS and Daiichi RI Laboratory, respectively. Blood sugar levels were measured with an autoanalyzer. Serum HGH response was defined as "positive" only when a peak value greater than 10 ng/ml was obtained within 60 min after TRH administration.

Results

Serum HGH levels after TRH

The basal serum HGH levels were 1.5 ± 0.9 ng/ml (mean $\pm$ S.D.) and no significant change was observed following TRH administration in control diabetics (Table 3, Fig. 1). The basal serum HGH levels (mean $\pm$ S.D.) in cirrhotics were 4.7 ± 1.7 ng/ml and significantly higher than those in control diabetics. TRH caused a remarkable increase in serum HGH in all of the cirrhotics showing peak values ranging from 10.7 to 25.7 ng/ml. But in one patient (Case #5), the peak appeared at 90 min

Table 3. HGH response to TRH in liver cirrhosis and diabetes mellitus

Case	Before	15	30	60	90	120 min
Liver cirrhosis						
1	7.8	16.8*	15.7	11.3	7.9	5.8 ng/ml
2	5.4	16.5	23.5*	17.7	11.6	7.6
3	5.2	14.3*	12.6	9.8	8.4	4.0
4	4.5	11.7*	9.5	5.2	/	2.0
5	5.8	7.8	7.8	10.5	10.8*	10.8*
6	4.3	11.7	12.7*	6.3	3.3	0.8
7	4.0	18.7*	13.7	5.8	3.6	2.8
8	3.3	18.0	25.7*	15.3	9.0	5.1
9	1.6	10.7	8.3	11.0*	/	3.3
Mean	4.7	14.0	14.4	10.3	7.8	4.7
S. D.	1.7	3.7	6.4	4.2	3.2	3.0
(Mean peak value: 16.1 ± 5.5)						
Diabetes mellitus						
1	3.4	2.5	2.4	2.3	2.9	4.5*
2	1.8	2.3	2.2	2.4	2.8*	2.0
3	0.4	2.0	1.0	0.4	6.3	6.6*
4	1.2	1.0	1.0	0.8	0.8	1.2*
5	1.2	5.2*	4.5	2.7	2.0	1.7
6	2.3	1.5	1.3	1.5	1.5	1.7*
7	0.6	0.5	0.4	0.7*	0.7*	0.4
8	1.2	1.7	2.1*	1.5	1.7	1.2
9	1.3	2.0	2.7*	1.2	1.7	1.5
Mean	1.5	2.1	2.0	1.5	2.3	2.4
S. D.	0.9	1.3	1.2	0.8	1.7	2.0
(Mean peak value: 3.1 ± 2.0)						
p value #						
<0.001 <0.001 <0.001 <0.001 <0.005 >0.05						

Liver cirrhosis vs. diabetes mellitus

* peak value

(10.8 ng/ml), which was not regarded as a positive response. Seven of the eight patients with positive responses showed a peak value within 15–30 min. So far in liver cirrhosis, mean serum HGH levels after TRH were significantly higher at 15, 30, 60 and 90 min than mean basal levels (Fig. 1). The mean ($\pm$ S.D.) peak value of serum HGH response to TRH in the nine cirrhotic patients was significantly higher than in the control diabetic patients (16.1 ± 5.5 ng/ml *vs.* 3.1 ± 2.0 ng/ml, $p < 0.001$).

In the control test by saline injections in six of the nine cirrhotic patients, the mean levels after injection at intervals of respective minutes described above did not show any significant change from the basal level (Table 4, Fig. 1). However, in one patient (Case #2), the levels after saline administration were lower at 15, 30 and 60 min intervals than the basal level of 5.3 ng/ml, and increased to 11.0 ng/ml at 90 min interval and finally to 16.7 ng/ml at 120 min interval.

In all patients, the blood sugar level did not show any significant change after intravenous injection of TRH or saline.

Fig. 1. HGH response to TRH or saline in liver cirrhosis and diabetes mellitus. Mean $\pm$ S.D.

Examination of reproducibility (Table 5)

The TRH test was repeated after one month interval following the treatment of hepatic insufficiency in the three patients. The results showed good reproducibility. For test 1 and test 2 respectively, case #1 reached a peak value of 16.0 ng/ml (30 min) and 16.8 ng/ml (15 min); case #2 19.0 ng/ml (15 min) and 23.5 ng/ml (30 min); case #5 7.0 ng/ml (90 min) and 10.8 ng/ml (90 min).

The first and second tests for each of the patients were performed under the different condition: those on case #1 were performed when hepatic encephalopathy appeared frequently and when it was controlled, respectively; those on case #2 when ascites was evident and when it was absent, respectively; and those on case #3 when jaundice was heavy and when it was light (serum bilirubin: 2.7 to 1.0 ng/dl), respec-

Table 4. HGH response to saline in liver cirrhosis and diabetes mellitus

Case	Before	15	30	60	90	120 min
Liver cirrhosis						
1	6.4	5.7	4.6	2.9	2.3	2.8 7g/ml
2	5.3	4.2	3.2	3.3	11.0	16.7
3	6.0	3.8	5.3	4.3	4.8	4.4
4	5.8	6.8	8.2	7.8	5.3	5.0
7	4.8	3.8	2.8	1.7	1.7	1.2
8	5.4	4.3	3.2	2.3	1.7	2.2
Mean	5.6	4.8	4.6	3.7	4.5	5.4
S. D.	0.6	1.2	2.0	2.2	3.6	5.7
Diabetes mellitus (n=8)						
Mean	1.7	1.4	1.2	1.5	1.3	1.3
S. D.	1.7	0.7	0.6	1.1	0.7	0.8

Table 5. HGH responses to TRH in liver cirrhosis before (1) and after (2) the treatment of hepatic insufficiency

	Before	15	30	60	90	120 min
Case 1 (1)	2.5	12.5	16.0	8.7	4.5	3.1 ng/ml
(2)	7.8	16.8	15.7	11.3	7.9	5.8
Case 2 (1)	13.7	19.0	17.2	15.0	11.5	7.2
(2)	5.4	16.5	23.5	17.7	11.6	7.6
Case 5 (1)	1.8	2.5	3.0	5.7	7.0	5.7
(2)	5.8	7.8	7.8	10.5	10.8	10.5

tively. This shows little change in the response of serum HGH to TRH due to the change in the state of treatment. In each patient the response in the first test was similar to that in the second.

The effect of hyperglycemia on serum HGH response to TRH (Table 6)

The increase in serum HGH in response to TRH in liver cirrhosis could not be blocked with hyperglycemia. The response to TRH, with the blood sugar level maintained at 300–400 mg/dl, was the same as that to TRH only. The peak values from TRH injection, with and without hyperglycemia, were 17.5 ng/ml (30 min) and 16.8 ng/ml (15 min) for case # 1, and 29.7 ng/ml (30 min) and 19.0 ng/ml (15 min) for case # 2, respectively. In case # 1, hyperglycemia without TRH administration caused no significant change in serum HGH levels.

Serum PRL levels after TRH (Table 7)

The basal PRL levels were 4.6 ± 2.1 ng/ml (mean $\pm$ S.D.) and serum PRL increased significantly following TRH administration with the peak values ranging

Table 7. PRL response to TRH in liver cirrhosis and diabetes mellitus

Case	Before	15	30	60	90	120	min
Liver cirrhosis							
1	3.6	14.5*	13.0	13.0	10.0	8.0	ng/ml
2	5.9	30.0	33.0*	25.0	18.5	18.0	
3	4.4	24.5	26.0*	19.0	11.5	8.0	
4	15.5	35.0	50.0*	33.0	/	20.0	
5	3.6	37.0*	34.0	25.5	16.0	11.5	
6	3.4	20.5	27.0*	19.5	13.0	10.7	
7	1.7	15.5*	15.5*	10.0	6.7	4.9	
8	5.4	43.0*	42.0	32.5	22.5	19.0	
9	7.4	15.5*	12.0	12.5	/	7.5	
Mean	5.7	26.2	28.1	21.1	14.0	12.0	
S. D.	4.0	10.6	13.1	8.4	5.3	5.6	
(Mean peak value: 28.6 ± 12.4)							
Diabetes mellitus							
1	2.5	16.7*	10.0	10.3	6.0	4.6	
2	7.6	16.0	18.5*	16.7	14.2	15.3	
3	3.4	15.7	20.5*	14.5	10.5	8.0	
4	2.5	13.5*	12.5	7.8	6.3	4.5	
5	4.6	9.6*	7.2	8.8	7.5	6.9	
6	6.5	16.0*	14.8	9.7	6.5	6.2	
7	3.2	24.0*	23.5	15.7	7.7	6.1	
8	7.6	28.0	31.0*	24.0	10.0	14.5	
9	3.5	11.7	13.2*	7.2	5.8	4.2	
Mean	4.6	16.8	16.8	12.7	10.4	7.8	
S. D.	2.1	5.8	7.4	5.5	5.4	4.2	
(Mean peak value: 18.1 ± 6.4)							
p value #							
	>0.05	<0.05	<0.05	<0.05	>0.05	>0.05	
# Liver cirrhosis vs. diabetes mellitus							
* peak value							

Table 6. HGH responses to TRH in two patients with liver cirrhosis under hyper- and normoglycemia

Case	1	-15	0	15	30	60	90	120	min
TRH under normoglycemia									
HGH			7.8	16.8	15.7	11.3	7.9	5.8	ng/ml
B. S.#			134	138	136	128	130	122	mg/dl
TRH under hyperglycemia									
HGH		5.5	4.3	15.0	17.5	10.0	7.7	10.0	
B. S.		122	450	280	370	346	364	292	
Saline under hyperglycemia									
HGH		5.4	3.8	2.5	2.4	3.8	8.3	6.0	
B. S.		270	504	362	188	188	330	324	
Case 2									
TRH under normoglycemia									
HGH			13.7	19.0	17.2	15.0	11.5	7.2	
B. S.			111	115	108	113	108	106	
TRH under hyperglycemia									
HGH		*	*	24.0	29.7	28.5	16.3	8.7	
B. S.		*	*	209	216	205	209	217	

* Samples were missed with technical reasons.

Blood sugar.

from 9.6 to 31.0 ng/ml in the control diabetics. The basal serum PRL levels in cirrhotics were 5.7 ± 4.0 ng/ml (mean $\pm$ S.D.) and were not significantly different from those in control diabetics. The mean ($\pm$ S.D.) peak value for the cirrhotic group (28.6 ± 12.4 ng/ml) was significantly higher than that in control diabetics (18.1 ± 6.4 ng/ml) at $p < 0.05$. The mean levels of serum PRL in the cirrhotic group after TRH exceeded those in the control diabetic group at any intervals in the test, and were significantly higher ($p < 0.05$) at 15, 30 and 60 min intervals.

Serum TSH levels after TRH (Table 8)

The basal serum TSH levels in cirrhotics (6.9 ± 3.6 μ U/ml, mean $\pm$ S.D.) were not significantly different from those in control diabetics (6.4 ± 3.2 μ U/ml). The injection of TRH raised TSH levels in all cirrhotic and control diabetic patients with mean peak values of 21.5 ± 6.5 μ U/ml and 26.5 ± 19.2 μ U/ml, respectively. There was no significant difference between them.

Discussion

This study clearly demonstrated that in liver cirrhosis the basal serum HGH levels were higher than those of controls and that serum HGH increased in response to TRH, reaching a peak value within 15–30 min after the injection (Fig. 1 and Table 3). The early response of HGH to TRH introduction was nearly consistent when observed in cirrhotics but not in control diabetics (Table 3). As mentioned above, these results were compatible with those reported by Paneral *et al.* (1977) although they used normal subjects rather than diabetics as controls.

As for the mechanism of high resting level of serum HGH in liver cirrhosis, Pimstone *et al.* (1975) claimed its hypersecretion based on their clinical experiment

using somatostatin.

The HGH response to TRH in three cirrhotics was unaffected by any clinical condition usually associated with liver cirrhosis such as encephalopathy, ascites and jaundice (Table 5). Furthermore, the time course of HGH after TRH injection was very similar regardless of the clinical condition for almost all the cirrhotic patients (Table 3). These findings suggest that the response is independent of any clinical condition and that it might be associated with some basic metabolic abnormality underlying liver cirrhosis.

Liver cirrhosis is often accompanied by glucose intolerance and this was borne out

Table 8. TSH response to TRH in liver cirrhosis and diabetes mellitus

Case	Before	15	30	60	90	120	min
Liver cirrhosis							
1	5.2	13.2	12.2	14.9	19.1*	17.3	μ U/ml
2	8.1	17.5	20.0*	19.0	18.5	16.5	
3	4.2	12.9	18.0*	14.1	15.1	11.9	
4	3.8	8.6	9.3*	7.0	/	8.7	
5	11.0	22.0	29.0*	26.5	26.5	24.5	
6	13.6	24.6	27.5	28.5*	22.5	21.9	
7	4.4	19.1	26.4*	22.3	19.6	14.5	
8	3.6	11.3	16.3*	14.0	12.3	10.4	
9	8.0	24.5*	24.0	22.4	/	15.1	
Mean	6.9	17.1	20.3	18.7	19.1	15.6	
S. D.	3.6	5.9	7.0	6.9	4.6	5.2	
(Mean peak value: 21.5 ± 6.5)							
Diabetes mellitus							
1	5.1	14.9	16.7	18.9*	17.5	14.2	
2	4.0	9.6	14.8	17.4*	12.2	13.8	
3	6.9	12.1	13.2*	12.3	12.4	10.7	
4	6.9	26.5	40.5*	31.5	30.5	24.8	
5	7.8	20.0	21.5*	20.5	17.1	17.0	
6	3.1	11.6	13.4*	10.1	9.3	6.7	
7	5.1	17.9	22.6*	19.3	15.1	11.8	
8	4.9	13.3	18.2*	14.2	14.1	11.4	
9	13.8	41.0	73.0*	55.0	44.0	31.0	
Mean	6.4	18.5	25.9	22.1	19.1	15.7	
S. D.	3.2	9.9	19.5	13.7	11.1	7.6	
(Mean peak value: 26.5 ± 19.2)							
p value #							
	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	

Liver cirrhosis vs. diabetes mellitus

* peak value

by the subjects under study (Table 1). As shown in Table 6, the HGH response of cirrhotics to TRH did not change when their blood glucose was raised by continuous glucose infusion. Furthermore, the patterns of HGH response to TRH were similar to one another, apparently independent of any direct effect from glucose intolerance (Table 1 and 3). These results indicate that the difference observed between the cirrhotics and diabetics in the HGH response to TRH can not be attributed to any disturbances in carbohydrate metabolism.

Hyperestrogenism in liver cirrhosis is well known (Kley *et al.*, 1976). All of the cirrhotics in this study had vascular spider and palmar erythema, acknowledged clinical signs of hyperestrogenism. It was reported that estrogen administration to male subjects resulted in the enhancement of the PRL response—but not in the HGH response to TRH,—and in the elevation of basal HGH levels, while the TSH response to TRH remained unchanged (Carlson *et al.*, 1973; Rutlin *et al.*, 1977). However, in our cirrhotic patients, the HGH increased markedly in response to TRH, although other findings such as the TSH and PRL responses were compatible with those reported by them (Table 3, 7 and 8). Panerai *et al.* (1977) also commented on this discrepancy of HGH response between the estrogen-administered subjects and cirrhotics, and stated that the HGH response to TRH can not be attributed solely to hyperestrogenism.

Since the high resting level of serum HGH and paradoxical serum HGH elevation after TRH administration were frequently observed in various conditions of impaired protein metabolism such as renal failure (Gonzalez-Barcena *et al.*, 1973; Hasegawa *et al.*, 1975; Czernichow *et al.*, 1976) and anorexia nervosa (Maeda *et al.*, 1976), the similar findings in liver cirrhosis in this study might be the results of im-

paired protein synthesis in this disease.

However, the true mechanisms underlying the abnormal response remain to be explored.

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