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Growth Hormone Responses to Arginine Infusion in Patients with Chronic Pancreatitis: Relationship to Glucose Intolerance and Insulinopenia

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Summary. The growth hormone (HGH) and insulin responses to intravenous arginine infusion were studied in 21 patients (13 males and 8 females) with chronic pancreatitis. Ten of these patients had glucose intolerance, 5 with fasting hyperglycaemia, while 11 patients had subnormal insulin responses to arginine. Basal HGH levels and peak responses to arginine were normal but were uninfluenced by sex, glucose intolerance, fasting hyperglycaemia or insulinopenia.

Key words: Human growth hormone, pancreatitis, insulinopenia, diabetes, arginine.

Patients with genetic diabetes mellitus may have increased spontaneous human growth hormone (HGH) secretion [1, 2]. Abnormalities of plasma HGH responses to various provocative stimuli have also been demonstrated and have been reported as subnormal, paradoxical or exaggerated [3, 4, 5, 6, 7, 8, 9, 10]. The present study presents data on the HGH responses to intravenous arginine infusion in patients with chronic pancreatitis. Since many of these patients are diabetic [11], and may be insulinopenic [12, 13], the effects of glucose intolerance, chronic hyperglycaemia and insulinopenia could be studied independently of the genetic effects of spontaneous diabetes mellitus. Our results indicate that most patients with chronic pancreatitis have substantial HGH responses to arginine, uninfluenced by sex or by the presence or absence of glucose intolerance or insulinopenia.

Material and Methods

Twenty-one patients, 13 males and 8 females, aged from 21 to 64 years were studied. All had suffered typical episodes of acute pancreatitis with elevated serum and/or urinary amylase levels [11]. The presence of chronic pancreatitis was confirmed by radiologically evident pancreatic calcification, by the development of pancreatic pseudocysts, or by laparotomy. All patients underwent standard tests of pancreatic exocrine function, which were shown to be abnormal in all but 3 patients [14] (Table 1).

Only 1 patient had a family history of diabetes mellitus. No patient was on insulin or oral antidiabetic therapy or was taking drugs known to effect HGH secretion at the time of testing.

A 50 g oral glucose tolerance test was performed on all patients as a screening procedure. Blood was taken before and at 30 min intervals after the glucose load for 2 hrs.

Intravenous arginine infusions were performed at rest after an overnight fast. A polythene cannula was inserted into an antecubital vein, after which 3 basal blood samples were taken. 30 g of buffered arginine monohydrochloride in 100 ml of 0.9% saline was then infused over 30 min. Further blood samples were taken 10, 20, 30, 40, 50, 60, 75 and 90 min after the commencement of the infusion. Blood glucose was estimated immediately by the ferricyanide, reduction method of Hoffman [15], using an auto-analyser. Aliquots of plasma were deep frozen until assayed for immunoreactive insulin (IRI) by the method of Hales and Randle [16] and for HGH by the method of Morgan and Lazarow [17], using HGH obtained from the National Pituitary Agency, U.S.A. (HS 1394) for iodination and as reference standard. HGH assay sensitivity was 1 ng/ml.

The incremental insulin values above mean basal levels for the 0—60 min period were plotted and the total area under this insulin incremental curve was calculated using an Olivetti P203 desk computer. These data were compared to values obtained in 7 normal male subjects tested in an identical manner. Results were analysed statistically using the Mann-Whitney-U test.

Results

Glucose Tolerance, Insulin and Growth Hormone Responses to Arginine

Ten patients were considered to have 'diabetic' glucose tolerance tests according to the criteria of Jackson and Vinik [18]; 5 of these had fasting hyperglycaemia (fasting blood glucose above 120 mg/100 ml). The remaining 11 subjects had normal oral glucose tolerance.

The basal HGH concentration was regarded as the lowest fasting HGH level in each patient before the

Table 1. *Oral glucose tolerance (OGTT), mean fasting blood glucose and plasma immunoreactive insulin (IRI), area of IRI increment after IV arginine, basal and peak post arginine plasma human growth hormone (HGH) in 21 patients with chronic pancreatitis. OGTT is classified as either normal (N) or diabetic (D) as explained in text. The fasting glucose and IRI values are a mean of 3 samples taken in the basal state (see text). The asterisk* marks the IRI responses to arginine below the range of the controls i.e. $< 300\,\mu U \cdot ml^{-1} \cdot 60min$ (Mean of 7 controls $1424.7 \pm 533.4\,\mu U \cdot ml^{-1} \cdot 60min$). Pancreatic function tests (PFT) are included for all but 2 patients who had a history of recurrent acute pancreatitis and pancreatic calcification radiologically (see text). Normal values for PFT are volume > 140 ml, $HCO_3 > 80$ mEq/L; Amylase > 5 U/ml and Lipase > 300 U/ml*

Patient	Sex	OGTT	Mean fasting glucose mg/100 ml	Mean fasting IRI μU/ml	IRI increment after IV arginine* μU·ml⁻¹·60min	Basal HGH ng/ml	Peak HGH ng/ml	Pancreatic response to CCK-PZ secretin			
								Volume ml	HCO_3 mEq/l	Amylase U/ml	Lipase U/ml
TD	M	N	82	18.0	262*	3.3	23.5	112	34	10.6	1120
JE	M	N	93	17.7	252*	0.8	6.2	191	45	5.4	—
TB	M	N	100	20.3	47*	13.7	25.0	38	48	2.8	354
BT	M	N	98	24.7	1979	0.5	4.9	164	46	3.2	229
JP	M	N	96	8.0	280*	6.2	50.0	121	65	4.3	318
JB	M	N	95	20.3	1015	0.5	3.9	—	—	—	—
JF	M	N	100	20.3	0*	2.5	66.1	182	51	3.2	495
MW	F	N	94	16.3	3110	1.7	10.5	241	83	11.9	729
MP	F	N	74	8.0	887	0.4	26.1	211	68	6.5	323
MP	F	N	88	10.0	307	6.8	36.0	103	38	6.1	881
JS	F	N	85	10.7	32*	6.4	8.3	129	88	10.5	1177
PP	M	D	355	16.7	0*	1.7	24.0	66	31	2.8	198
MI	M	D	116	15.7	564	2.6	29.0	120	32	1.3	63
JM	M	D	72	22.3	506	2.1	19.8	247	38	3.4	297
WH	M	D	139	24.0	147*	1.8	28.5	145	59	4.9	375
JM	M	D	124	18.0	310	0.6	9.2	138	50	1.5	209
WR	M	D	87	17.7	198*	1.4	50.0	159	35	2.4	459
MP	F	D	83	12.7	380	1.3	20.9	—	26	10.5	—
LM	F	D	259	28.0	0*	2.4	6.8	219	50	3.4	—
LH	F	D	159	11.0	245*	2.9	27.0	—	—	—	—
GduP	F	D	98	18.3	942	1.3	25.5	66	24	12.1	—

Table 2. *Fasting blood glucose, plasma IRI, basal and peak plasma HGH concentrations in pancreatitis patients with normal and diabetic glucose tolerance*

	Normal GTT (n = 11)	Diabetic GTT (n = 10)	Significance
Mean fasting glucose (±SEM) mg/100 ml	91.4±2.5	148.7±28.5	$p < 0.05$
Mean fasting IRI (±SEM) μU/ml	15.9±1.7	18.4±1.6	NS
Mean basal HGH (±SEM) ng/ml	3.9±1.3	1.8±0.2	NS
Range	(0.4—13.7)	(0.6—2.9)	
Mean peak HGH (±SEM) ng/ml	23.4±6.1	25.1±3.9	NS
Range	(3.9—66.1)	(6.8—35.5)	

Table 3. *Fasting blood glucose, plasma IRI, basal and peak plasma HGH concentrations in pancreatitis patients with normal and insulinopenic responses to IV arginine*

	Normal IRI responders (n = 10)	Insulinopenic patients (n = 11)	Significance
Range of insulin area after arginine ($\mu U \cdot ml^{-1} \cdot 60\,min$)	307—3110	0—280	
Mean fasting glucose (±SEM) mg/100 ml	94.2±5.2	141.1±26.5	$p < 0.05$
Mean fasting IRI (±SEM) μU/ml	16.6±1.7	17.5±1.8	N.S.
Mean basal HGH (±SEM) ng/ml	1.8±0.6	3.9±1.1	$p < 0.05$
Range	(0.4—6.8)	(1.4—13.7)	
Mean peak HGH (±SEM) ng/ml	18.6±3.5	28.7±5.9	N.S.
Range	(3.9—50)	(6.8—66.1)	

start of infusion, while the highest HGH level attained during or after the infusion was considered to be the peak concentration. Mean (± SEM) basal HGH value for all patients was 2.9±0.7 ng/ml. In 19 of the 21 patients a peak level above 6 ng/ml was elicited between 20 and 75 min after the start of the infusion. The mean peak value was 24.3±3.6 ng/ml. (Table 1)

Ten patients had serum insulin responses to arginine within the range of the controls (control range 305 to 3875 $\mu U \cdot ml^{-1} \cdot 60$ min) i.e. they were "normal" responders. A further 11 had either reduced IRI response (below 300 $\mu U \cdot ml^{-1} \cdot 60$ min) or no rise at all — designated the 'insulinopenic' patients (Table 1).

The Influence of Sex on HGH Responses

Mean basal HGH values were the same in males (2.9±1.0 ng/ml) and females (2.9±0.9 ng/ml) and the mean peak concentrations were insignificantly different (26.2±5.3 ng/ml — males, 21.4±4.2 ng/ml — females). Only 2 male subjects failed to achieve HGH peak above 6 ng/ml.

The Influence of Glucose Intolerance on HGH Responses

Mean basal and peak HGH levels of the 10 patients with normal glucose tolerance did not differ significantly from those of the 11 diabetic subjects (Table 2).

The Influence of Fasting Blood Glucose Concentration on HGH Response

Five patients had fasting hyperglycaemia (206.6 ±44 mg/100 ml). The remaining 16 patients had fasting glucose levels below 120 mg/100 ml. The mean basal HGH concentrations in the hyperglycaemic and normoglycaemic groups were similar (2.0±0.3 and 3.3±0.9 ng/ml respectively), as were the peak HGH levels (20.8±4.1 ng/ml and 25.8±4.8 ng/ml respectively).

The Influence of Insulin Responses to Arginine on Growth Hormone Responses

The patients were subdivided according to their insulin responses to the infused arginine. Ten were found to have insulin increments within the range of the controls (above 300 $\mu U \cdot ml^{-1} \cdot 60$ min); 11 had subnormal responses — the "insulinopenic" patients (see above). Mean basal HGH concentration was slightly greater in the "insulinopenic" group compared to "normal" (Table 3), whereas the peak HGH concentrations were not significantly different.

Only 5 "insulinopenic" subjects had glucose intolerance while 5 patients with "normal" IRI values were diabetic.

Discussion

Basal plasma HGH levels and responses to I.V. arginine in our patients with pancreatitis were within the normal range reported by others. This contrasts with a previously reported finding of rather poor HGH responses to insulin hypoglycaemia in 6 pancreatitic patients compared to matched controls [19]. However, in that study peak HGH concentrations were within the accepted range of normal in 5 of the patients [20].

When the patients were separated according to sex, the expected differences [8, 21] in basal and peak HGH concentrations were not found. The unexpectedly frequent high HGH responses in the males may be related to the fact that they were all chronic alcoholics and might have had relative oestrogen excess [22]. However, other authors have found high HGH responses to I.V. arginine in most male subjects [8].

As both fasting HGH levels and the peak responses to arginine were similar in patients with diabetic and normal glucose tolerance, glucose intolerance *per se* does not appear to influence the HGH responses in pancreatitis subjects confirming the reports that hyperglycaemia does not blunt HGH responses to arginine [23]. A similar finding in genetic diabetics has been reported [8], although there are contrary views [10, 24].

The slightly higher basal HGH levels in the insulinopenic patients may reflect increased spontaneous HGH secretion as reported in genetic diabetes [1, 2], but the levels are within the normal range. The good HGH responses in our insulinopenic group contrast with poor insulin and HGH responses found in maturity onset diabetics by Merimee *et al.* [24], but are similar to the reported normal HGH responses to arginine in juvenile, insulinopenic diabetics [25].

Conclusion

It appears that most patients with chronic pancreatitis have normal basal and post arginine plasma HGH levels. These responses appear to be indifferent to the effects of glucose intolerance, fasting hyperglycaemia or subnormal insulin responses to arginine. No sex differences were found.

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