Hypercalcitoninemia in pancreatitis – evidence for immunochemical heterogeneity

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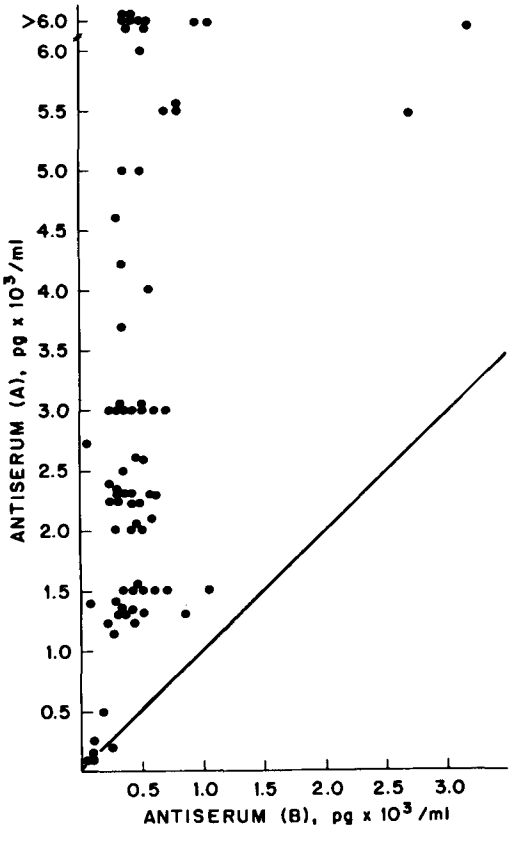
Summary. Recently in our laboratory we have demonstrated increased immunoreactive calcitonin (iCT) levels in 4 patients with acute pancreatitis and hypocalcemia[1]. The present study consists of 17 additional patients in whom serial determinations for (iCT) were performed. Furthermore, with the use of 2 different antisera directed against human calcitonin we present evidence for immunochemical heterogeneity of this hormone in acute pancreatitis.

Hypocalcemia occurs commonly in acute pancreatitis. The traditional explanation offered for the hypocalcemia has been peripancreatic calcium saponification found in areas of fat necrosis. It has been demonstrated, however, that calcium supplementation often does not restore serum calcium to normal levels even when very large amounts are used – much greater than that removed through saponification[2,3]. Also if parathyroid hormone function is normal, serum calcium should be rapidly restored by mobilization from bone[4]. However, the hypocalcemia associated with pancreatitis may persist for several days suggesting an alteration of parathyroid hormone activity or the presence of an actual inhibitor of parathyroid hormone mediated bone resorption.

Methods and materials. 17 patients with acute pancreatitis associated with hypocalcemia (calcium less than 8.5 mg/dl) were studied. All patients had clinical signs and symptoms of pancreatitis and elevated serum amylase and lipase. Sera from patients and normals were kept at −20 °C until assayed, in duplicate, for immunoreactive calcitonin (iCT) by the radioimmunoassay method of Deftos[5]. Sera were assayed for iCT using two different antisera against synthetic human calcitonin. Antiserum (A), obtained from Cal-Biochem (La Jolla, California), was raised in rabbits. Antiserum (B), a gift from Dr Glen W. Sizemore (Mayo Clinic), was raised in goats. In both cases, animals were immunized against synthetic human calcitonin. The radioimmunoassays utilized were identical except for the antisera. Synthetic human calcitonin obtained through the courtesy of Dr Dixon, Ciba-Geigy (Summit, New Jersey), was used for iodination and for standards. Calcium, phosphate and total protein were measured according to published methods[6–8]. Amylase and lipase were measured nephelometrically[9,10].



Comparison of iCT concentrations in 17 patients with acute pancreatitis measured by two antisera. iCT concentrations are consistently higher when measured with antiserum (A).

Results and discussion. In normal subjects, immunoreactive calcitonin values, with both antiserum A and antiserum B, were less than 100 pg/ml. In the patients with pancreatitis, iCT was significantly elevated in every serum when assayed by either antiserum A or antiserum B or both. However, values obtained with antiserum A were consistently greater than with antiserum B (figure). Although all patients demonstrated hypocalcemia during their course (calcium less than 8.5 mg/dl with a range of 3.9 to 8.3 mg/dl), there was variation in the time of onset of hypocalcemia relative to the peak iCT level. This variability may at least in part be due to the degree of peripancreatic saponification and the variable onset of hypomagnesemia which is known to interfere with parathyroid hormone mediated calcium mobilization from bone[11]. In the patients in whom serum phosphate was measured, there was a consistent hypophosphatemia during the clinical course which may result from the known phosphaturic effect of calcitonin[12,13].

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Although marked elevation of serum calcitonin occurred in the patients with pancreatitis, the fall in serum calcium was moderate in most. This may be due to the lesser responsiveness of adult bone to calcitonin and to the eventual 'escape' during which bone becomes essentially unresponsive to continuously high levels of calcitonin[14]. Furthermore, increased levels of parathyroid hormone in response to hypocalcemia may override the effects of calcitonin. The exact mechanism of hypercalcitoninemia in pancreatitis is unknown although the inflamed pancreas releases glucagon which is a potent stimulator of calcitonin release[15,16].

Although elevated iCT levels were demonstrated using 2 different antisera against calcitonin, the values obtained with antiserum A were consistently higher than with antiserum B. It is well established that many hormones exist in polymorphic forms which are differentially recognized by various antisera. Such is the case with calcitonin in patients with medullary carcinoma of the thyroid and the present study provides evidence that in pancreatitis as well there is immunochemical heterogeneity of calcitonin[17,18]. The mechanism of hypocalcemia in pancreatitis is complex. Calcitonin, a hypocalcemic hormone, is elevated in this syndrome and may be one of the important contributing or permissive factors.

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Caryométrie des cellules réticulaires thymiques de rat: Influence des hormones somatotrope et corticotrope

Caryometric study of thymic reticular cells in the rat: Action of GH and ACTH

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Summary. GH stimulates thymic epithelial secreting cells; ACTH inhibits these cells. Thymic involution following hypophysectomy is due to GH and/or corticosteroid deficiency.

Dans un travail précédent[2] nous avons mis en évidence, à l'aide d'une méthode d'analyse taxonomique basée sur l'étude de la surface de coupe des noyaux cellulaires, 3 types de cellules réticulaires dans le thymus de rat: mésenchymateuses, épithéliales et hypertrophiées. Dans le travail que nous rapportons nous avons utilisé cette technique caryométrique pour déterminer les rôles respectifs de la GH et de l'ACTH vis à vis des types cellulaires du thymus et le mode d'action de l'hypophyse sur le thymus. Des rats mâles (Charles River, France), âgés de 60 jours, sont répartis en 6 lots de 3 animaux. Le premier lot, représenté par des animaux normaux reçoit, à partir du 61e jour et durant 3 jours des injections i.p. quotidiennes d'une solution saline isotonique (0,5 ml). 3 autres lots (lots 2, 3, 4) sont constitués par des animaux hypophysectomisés à 50 jours; ces animaux reçoivent à partir du 61e jour et durant 3 jours des injections i.p. quotidiennes de NaCl (2e lot) ou de GH de rat (0,05 mg/100 g de poids corporel) (3e lot) ou d'ACTH (0,3 UI/100 g de poids corporel) (4e lot). Enfin les 2 derniers lots (lots 5, 6) surrénalectomisés à 50 jours, reçoivent à partir du 61e jour et durant 3 jours des injections i.p. quotidiennes soit de NaCl (5e lot) soit d'ACTH (0,3 UI/100 g de poids corporel) (6e lot).

Au 64e jour, tous les animaux sont sacrifiés par décapitation, les thymus sont prélevés et fixés. L'étude caryométrique est réalisée, selon la technique décrite antérieurement[2], sur les thymus de chaque lot fixés 24 h, dans le liquide de Zenker. Les coupes de 5 µm sont colorées au trichrome de Masson modifié par l'hématoxyline de Groat et le bleu d'aniline. Les cellules médullaires sont photographiées et les surfaces de coupe des noyaux sont mesurées par planimétrie (Planimètre Elphon Bender et Holèn). Les 3 types de cellules réticulaires sont séparées à l'aide d'un programme informatique faisant intervenir une méthode d'analyse taxonomique[3]. L'identification est réalisée par une technique d'imprégnation argentique[4] et par microscopie électronique.

Résultats et discussion. L'étude caryométrique permet de quantifier 2 paramètres, la surface nucléaire moyenne de chacun des 3 types cellulaires et leur pourcentage à l'in-

1 Les auteurs remercient le NIAMD pour l'envoi de la GH de rat.
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Tableau 1. Surfaces nucléaires moyennes (en mm²) et pourcentages des différents types cellulaires de la trame thymique chez des rats normaux ou hypophysectomisés

Traitements	Types cellulaires Mesenchymateuses Surface nucléaire	%	Epithéliales Surface nucléaire	%	Hypertrophiées Surface nucléaire	%
Témoin	44,44 ± 0,84	39	75,75 ± 1,00	44	116,09 ± 2,94	17
Hypophysectomisé	45,76 ± 0,74	33	72,13 ± 0,77	47	115,72 ± 2,41	20
	NS	NS	$p < 0,01$	NS	NS	NS