Clinical Studies of Human Pancreatic Enzyme Synthesis

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Very little is known of the effects of diet and disease on pancreatic enzyme synthesis in humans as conventional tests measure the secretory response to secretagogues, such as CCK, and secretion may be unrelated to synthesis because of the masking effect of a large intracellular pool of stored enzymes (zymogens). In order to obtain information on enzyme synthesis, as well as secretion, we have measured the incorporation characteristics of isotopically labelled amino acids (e.g., $^{14}$C or $^{13}$C leucine tracer) into amylase and trypsin protein, extracted by affinity chromatography from duodenal secretions during pancreatic stimulation with CCK-

The results of our studies in healthy volunteers and patients have suggested that (a) it takes between 75 and 101 min for the participation of newly synthesized pancreatic enzymes in the digestive process, and that zymogen stores are replaced at a rate of between 12 percent and 47 percent per hour in normal healthy subjects, (b) the synthesis and production rates of trypsin and amylase are parallel in healthy subjects, but can diverge under stressful conditions such as hypersecretory states, post-acute pancreatitis and protein malnutrition, (c) hyperphagia stimulates the synthesis of enzymes whilst malnutrition diminishes the synthesis of trypsin to a greater extent than amylase, (d) intravenous glucose and amino acids exert negative feedback control on the synthesis and release of amylase and trypsin, and (e) the decreased secretion of pancreatic enzymes in Type 1 insulin-dependent diabetics is more a consequence of defective enzyme release from zymogen stores than defective synthesis.

In conclusion, our results indicate that changes in pancreatic enzyme secretion noted in patients do not always reflect changes in enzyme synthesis, and that the production of individual enzymes may diverge under certain circumstances. Based on the methodology described, it should be possible to develop more sensitive clinical tests of pancreatic function that provide information not only on the ability of the pancreas to secrete enzymes under certain disease states, but also information on the gland’s synthetic activity.

INTRODUCTION

Interest in the use of radio-labelled amino acids for the measurement of protein synthesis rates in humans was stimulated by a series of studies conducted by Waterlow working in Jamaica in the mid-1960s. Using $^{14}$C and $^{15}$N labelled amino acids, he developed a method based on the continuous intravenous infusion of tracer labelled amino acids to calculate rates of whole body protein metabolism [1]. His calculations depended upon the establishment of an isotopic steady-state in the plasma and the conceptualization of a common metabolic pool of amino acids from which amino acids were either taken up into protein synthesis or removed by oxidation. He was also able to demonstrate that, during the isotopic steady-state, the uptake of label into body proteins was linear and that the measurement of the slope of the curve provided a measure of the fractional turnover rate of the protein.

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Abbreviations: CCK, cholecystokinin; i.v., intravenous.
Early studies of ours in patients with chronic pancreatic disease, patients without pancreatic disease ("controls") and patients with diseases causing severe malnutrition showed that, after a delay period, there was a curvilinear increase in the labelling of pancreatic enzymes secreted into the duodenum (Figure 1). Our studies showed that the rate of labelling was reduced in patients with chronic pancreatic disease and we, as will be shown below, mistakenly assumed that this represented a decrease in enzyme synthesis [2]. Our conclusions were incorrect because, (a) we assumed that pancreatic duodenal juice protein was entirely made up of enzyme protein and (b), we did not take into consideration compartmentation of enzymes in the zymogen pool.

In order to solve these problems, we developed methods of extracting pure enzymes from pancreatic juice using affinity chromatography. Amylase was extracted by passing the juice through a column containing the affinity ligand acarbose [3] and trypsin was extracted from a column containing anti-trypsin antibody [4]. When we then repeated measurements of isotope incorporation into pure enzymes, we were able to show that incorporation of label into amylase was delayed in patients who had post-acute and early chronic pancreatitis [5]. However, the delay in synthesis and turnover of zymogen stores was much less than that suggested by our initial studies where the changes had been exaggerated by contamination with nonenzyme proteins, such as albumin, which have far slower turnover rates.

We then turned our attention to the interpretation of the isotope incorporation curve. Figure 2 summarizes the incorporation characteristics obtained from measurements in a group of 10 healthy volunteers. It is clear that the curve can be divided into two sections: (a) a delay period "D" when all enzymes secreted were unlabelled followed by (b) a sim-
ple non-linear exponential isotope incorporation curve, which achieved a maximal value similar to that of plasma ketoisocaproic acid [6]. In order to interpret these characteristics, we referred to the classic studies reported by Jamieson and Palade where they describe the process of enzyme production by following the sequential labelling of acinar cell protein components with $^{14}$C leucine, using pulse/chase technique and autoradiography on incubated slices of guinea pig pancreas [7]. Their results are summarized on Figure 3, showing that the labelled amino acids become attached to proteins that initially pass through the rough endoplasmic reticulum, then the Golgi apparatus, then the condensing vacuoles, before finally appearing in zymogen granules.

What is fascinating is that the isotope incorporation curve for zymogen granules described by these workers was almost identical to the curve we measured in our human duodenal juice proteins. This suggests that what we are, in fact, sampling, during conditions of pancreatic stimulation, is the zymogen pool (Figure 4). Further support for this contention is provided by other studies which have shown that it only takes a few minutes for exocytosed enzymes to appear in duodenal juice during pancreatic stimulation [8]. Consequently our parameter “D” provides a measure of the rate of synthesis of new enzymes, incorporating the processes of uptake of labelled amino acid by the cell, incorporation into polysomes, enzyme modification in the Golgi apparatus, and passage via the condensing vacuoles into the zymogen pool. Secondly, the curvilinear increase thereafter will represent the rate of turnover of zymogen stores, and not the rate of synthesis of new enzymes as we originally suggested. Finally, the maximal (plateau) level of labelling of secreted enzymes (MX) will provide a measure of the labelling of the precursor amino acid pool for protein synthesis. In order to measure this value, we conducted studies in 8 more normal volunteers where the isotope infusion and period of pancreatic stimulation was continued for 8 hr [6]. Our results demonstrated that the value for MX was indistinguishable from that of plasma ketoisocaproic acid and approximately 20 percent lower than that of plasma $^{14}$C leucine. This provides evidence that the precursor pool for pancreatic enzyme synthesis is intracellular, rather than extracellular, as labelled ketoisocaproic acid is a product of intracellular $^{14}$C leucine.
Figure 3. Results of classic studies by Jamieson and Palade [6] on isolated incubated slices of guinea pig pancreas where cellular proteins were labelled by pulse/chase technique with $^{14}$C leucine. Results show sequential labelling of proteins contained in the RER, the Golgi, the condensing vacuoles, with the eventual accumulation of labelled proteins (enzymes) in zymogen granules.

Figure 4. Proposed physiological explanation for the characteristic isotope incorporation curve observed when pancreatic enzyme proteins are labelled by primed/continuous intravenous infusions of $^{14}$C labelled leucine tracer during conditions of pancreatic stimulation with CCK-8. The delay parameter "D" provides a measure of the time taken for mature enzymes to be synthesized from amino acids and deposited in the zymogen pool. The exponential rate A provides a measure of the rate of turnover of zymogen stores. MX provides a measure of the specific activity of amino acids in the precursor pool for pancreatic enzyme synthesis [8].
Our measurements of the rate of zymogen pool turnover also permit us to calculate zymogen pool size since we simultaneously measure the rate of enzyme secretion during our studies. Clearly zymogen pool size will be equal to the secretion rate divided by the zymogen pool turnover rate.

Based on measurements on 10 healthy adult volunteers, we calculated that enzyme synthesis time varied between 75 and 101 min (median 86 min), and zymogen turnover rate was 29 percent/hour (range 12 percent-47 percent/hr) [9]. Zymogen pool size for amylase was estimated to be 361,800 kIU, for trypsin 35,600 kIU and for lipase 248,300 kIU.

The physiological importance of our observations is that conventional pancreatic function tests will be unable to detect acute changes in enzyme synthesis, as the secretions will be derived from preformed stores which would be related to previous dietary intake and hormonal balance. Figure 5 illustrates that secretions between 0 and 60 min will be exclusively derived from preformed zymogen stores. Those secreted between 60 min and 270 min will consist of a mixture of old and new enzymes. Only those enzymes secreted after 270 min will consist entirely of newly synthesized enzymes.

**THE STUDY OF NUTRITIONAL AND HORMONAL REGULATION OF PANCREATIC ENZYME SYNTHESIS IN HUMANS**

*The effect of food and intravenous nutrients*

The ability of digestive function to adapt to changes in dietary intake accounts for man's survival in a hostile environment. The pioneering studies by Grossman's group led to the exciting discovery that the composition of pancreatic enzyme secretions in animals changes in response to changes in dietary composition. Intense investigation, chiefly in experimental animals, has concluded that the increase in trypsin production in response to a high protein diet, is mediated by duodenal protein-induced CCK release. CCK is also thought to play a role in the adaptation of lipase to high fat feeding, but the amylase response to high carbohydrate feeding is considered not to be gut-mediated, but rather a response to the absorbed products of digestion i.e., portal blood glucose. The mechanism may involve a direct effect of glucose on the acinar cell, or an indirect effect via glucose-
induced insulin release and the islet-acinar cell axis. There is, however, considerable controversy about the effects of glucose and insulin on amylase production, and to our knowledge, no studies have attempted to measure their effects in humans subjects.

In order to investigate some of these aspects of pancreatic adaptation in humans, we have measured pancreatic enzyme synthesis and secretion in hyperphagic short-bowel and diabetic patients, as well as in normal volunteers infused intravenously with the digestive end-products of carbohydrate and protein.

**Hyperphagic short-bowel patients**

In order to examine the effects of increased dietary intake on pancreatic enzyme synthesis, we studied 10 patients with extreme short bowel syndrome who, as part of the adaptive response, had developed hyperphagia. Dietary studies had demonstrated that, despite receiving intravenous nutrition, average food intake in this group of patients was increased to approximately twice recommended daily allowance levels [10]. Measurement of the secretory response to CCK confirmed that the secretion of trypsin, lipase and amylase was 30 - 40 percent higher than that of healthy controls [11]. Analysis of the isotope incorporation curve showed that there was a generalized acceleration in the synthesis of trypsin and amylase, as well as an increased rate of turnover of zymogen stores (Figure 6) [12]. Consequently zymogen pool was also expanded suggesting a state of pancreatic

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**Figure 6.** Group mean values for the isotope incorporation curves for patients with adapted short bowel syndrome and end-jejunostomies in comparison to normal healthy volunteers. Results demonstrated significant increases in the rate of synthesis and turnover of zymogen stores in short bowel patients. Following treatment of octreotide (somatostatin) 100 µg s.c., a marked suppression of the synthesis and turnover of enzyme proteins was observed, accounting for the decrease in secretion of enzymes [15].
hyperplasia. While no direct measurements of pancreatic size have been made in humans with adapted short bowel, studies in rats have demonstrated pancreatic hyperplasia as part of the adaptive response [13].

There were a number of possible explanations for these findings, including the well-recognized hypergastrinemic response to short bowel syndrome, a chronic elevation of CCK release due to chronic over-stimulation by hyperphagia, increased plasma amino acids concentrations due to i.v. feeding resulting in increased substrate for enzyme synthesis, and finally the loss of negative feedback control - as most patients had end-jejunostomies [12].

**Intravenous infusions of amino acids and glucose**

As a general rule, protein synthesis is substrate dependent and amino acids stimulate production. The observation that pancreatic stimulation with CCK depletes circulating levels of amino acids also suggests that pancreatic enzyme synthesis may be rate-limited by amino acid availability as the demand for substrate is clearly great. In order to test this hypothesis, we gave 5 healthy volunteers i.v. infusions of a balanced amino acid solution at 0.08 g/kg/hr, whilst measuring amylase and trypsin synthesis. Despite significant increases in plasma amino acid concentrations from 2298 ± 98 to 3132 ± 59 mmol/l, no stimulation of enzyme synthesis was detected (Figure 7). In fact, the reverse was apparent suggesting that the influx of amino acids into the systemic circulation exerts negative feedback control on trypsin production. Similarly, we also demonstrated that intravenous glucose (0.3 g/kg/hr) suppressed rather than increased enzyme secretion, despite the stimulation of endogenous insulin release increasing plasma levels from 6.9 ± 3.4 to 21.2 ± 5.2 μIU/ml. Consequently, we were unable to support the explanation that amylase production is induced by the end-products of digestion, but rather that it is inhibited - again suggesting negative feedback control (Figure 7) [14]. To our knowledge, negative feedback control of pancreatic enzyme synthesis due to plasma increases has not previously been suggested, and the general opinion is that enzyme secretion turns off only when no food remains in the bowel lumen [15]. However, it seems more likely that physiological control would include negative feedback from the end-products of the process, rather than the proposed positive feedback for absorbed glucose.

**The effect of pancreatic hormones: endocrine/exocrine interaction**

**Somatostatin**

In the same series of studies in short bowel patients described above, we examined the effects of the negative regulatory hormone, somatostatin, in the form of its long-acting synthetic analogue, octreotide. Octreotide was given as a single bolus (100 μg) a half an hour before the infusion study commenced. Our results confirmed those of others showing approximately a 50 percent reduction in gastric acid and pancreatic enzyme secretion [11]. By labelling secreted enzymes, we were able to show that the mechanism behind the inhibition was a reduction in the rate of release of enzymes from zymogen stores [12]. Enzyme synthesis was also delayed, but to a lesser degree, resulting in an increase in calculated zymogen pool size (Figure 6). The possible expansion of the zymogen pool of stored enzymes is of concern as octreotide has been advocated by some for the treatment of acute pancreatitis. If intracellular activation of digestive enzymes is etiological in acute pancreatitis [16], treatment with octreotide might therefore enhance acinar cell disruption. Indeed, recent reports have not found octreotide useful in the clinical management of the condition.

**Insulin**

Insulin is the key anabolic hormone in the body and has powerful effects on muscle protein synthesis. However, its effect on splanchnic protein synthesis is less well under-
AMYLASE ISOTOPE INCORPORATION CURVE
healthy volunteers; effects of i.v. nutrients
n=5x3

![Graph showing isotope incorporation curves for glucose, amino acids, fast, and healthy volunteers.](image)

Figure 7. Comparisons of the isotope incorporation curves in normal volunteers (groups of 5) studied under conditions of fasting, i.v. glucose infusion (0.3 g/kg/hr) or i.v. amino acid infusion (0.08 g/kg/hr). Results suggest that i.v. glucose and amino acids exert negative feedback control on enzyme production.

stood. Although we have not as yet examined the effect of insulin infusions on pancreatic enzyme synthesis, our observations in patients given intravenous glucose, which stimulated endogenous insulin release, failed to support a major stimulatory effect of insulin on pancreatic enzyme synthesis as described above [14]. Preliminary results of studies on insulin-dependent (type 1) diabetics showed, despite significantly lower rates of secretion of amylase and trypsin, no delay in the rate of appearance of label into secreted enzymes, suggesting once again that insulin may not be directly involved in the regulation of pancreatic enzyme synthesis (Figure 8). However, the rate of labelling of pancreatic secretions with newly synthesised enzymes was slower, indicating that zymogen turnover was delayed. Our preliminary evidence would therefore suggest that the decrease in pancreatic enzyme secretion in patients with diabetes is more a consequence of defective release from zymogen stores rather than a decrease in enzyme synthesis, but further investigations are required for confirmation.

PARALLEL VERSUS NON-PARALLEL ENZYME SYNTHESIS IN HUMANS?

The development of a method which can measure simultaneously synthesis and secretion of different enzymes provides a unique opportunity to investigate the controversial question of whether we are capable of altering the relative synthesis and secretion of digestive enzymes in response to dietary and hormonal change.

Clearly, the isotope incorporation curves should be identical for all enzymes if a parallel state exists. To date we have been able to examine differences in isotope labelling of
AMYLASE ISOTOPE INCORPORATION:
diabetics vs healthy volunteers; fasting

Figure 8. Preliminary results from 3 diabetic patients (type 1) suggesting that the decreased rate of enzyme (amylase) secretion is a consequence of decreased release from zymogen stores rather than inhibited enzyme synthesis, as the rate of appearance of new enzymes in digestive juice was not obviously delayed.

total enzyme protein, amylase protein, and trypsin protein in normal volunteers, short bowel patients, pancreatic patients and malnourished patients.

Normal volunteers
Studies during fasting conditions showed that the stimulated secretion of enzymes resulted in parallel processing of amylase, trypsin and total pancreatic juice proteins [9]. However, when glucose was co-infused intravenously, there was, as described earlier, a significant delay in the rate of appearance of label in amylase as compared to trypsin, suggesting non-parallel processing (Figure 7) [14].

Short bowel patients
Studies during both fasted conditions and after octreotide administration, showed that the rate of appearance of isotope label was faster in amylase and trypsin proteins as compared to total pancreatic juice proteins [12]. These results suggest the presence of enzymes or cellular proteins with slower synthesis rates than amylase and trypsin in pancreatic juice. Further studies are needed to determine whether these proteins are digestive enzymes or other exocytosed cellular components.

Post-acute pancreatitis
We examined enzyme secretion and synthesis in 10 patients who had recovered from acute attacks of pancreatitis between 2 and 29 months later on [5]. The results demonstrated variable effects on amylase and trypsin with non-parallel depression of amylase
secretion. Isotope incorporation into amylase was also reduced, indicating delayed synthesis and decreased zymogen pool turnover, whereas no significant changes were detected with trypsin. Thus it appeared that amylase production was more sensitive to the disease process and took longer to return to normal following an acute attack. The explanation for this was unclear, but may be related to the fact that amylase production is not subject to feedback regulation in the duodenum, whereas decreased trypsin release would stimulate further trypsin synthesis via the proposed "CCK sensitive protein releasing factor" [17].

**Malnutrition.**

In Africa, the combined effects of chronic malnutrition and diarrhoeal illness account for the alarmingly high rates of mortality in children. Adequate supplies of dietary protein are essential to provide the building blocks of digestive enzymes and absorptive cell proteins. It is therefore likely that a stage will be reached in severe malnutrition when refeeding via the oral route will become unfeasable, as digestive function will fail. In order to investigate whether digestive failure exists in the types of malnutrition commonly encountered in hospitalised patients, we have measured pancreatic enzyme secretion and synthesis in 10 such patients with weight losses in excess of 30 percent of ideal body weight [18]. Measurements were made before and after re-feeding in hospital.

The results of the enzyme secretion studies demonstrated an average 80 percent reduction in the rate of release amylase, trypsin and lipase in response to sub-maximal CCK infusion (40 ng/kg/hr). Decreases of this magnitude were associated with food malabsorption, indicating that less severe reductions of enzyme secretion in malnourished patients are clinically significant, presumably because absorptive cell function is also impaired. The decreases in amylase and trypsin synthesis and zymogen turnover were, however, less dramatic than those in secretion, and only the synthesis of trypsin was significantly delayed from 61.5 ± 5 to 98 ± 16 min.

Overall, our results suggested that malnutrition results in a) non-parallel changes in the rates of secretion and synthesis of pancreatic enzymes, and b) a state of glandular atrophy, as the calculated zymogen pool sizes for both trypsin (173 ± 75 units) and amylase (2087 ± 1075 u) were lower than our measurements in well-nourished controls (1625 ± 892 u and 9722 ± 2543 u respectively). All patients then received nutritional support delivered in the most appropriate form - i.e., total parenteral nutrition in severe malabsorption, elemental tube-feeding in moderate malabsorption. There was a fairly rapid return of trypsin secretion, whereas that of lipase remained significantly depressed, again showing non-parallel changes. What was interesting was that the improvement in body weight was marginal in comparison to the magnitude of the improvement of secretory function, indicating that changes in organ function may provide more sensitive indicators of nutritional recovery.

Unfortunately, we cannot compare the actual values and rates calculated in this series of studies to those reported in the earlier short bowel studies as they were measured in different laboratories using slightly different methods. Consequently, we had to use separate groups of normal control volunteers for each study.

**SUMMARY AND CONCLUSIONS**

The simultaneous infusion of labelled amino acids and collection of CCK stimulated secretions in the duodenum adds an extra dimension to the information gained from standard clinical tests of pancreatic function. Our results demonstrated that there are sufficient stored enzymes in the zymogen compartment to cover the digestive needs of a single meal. This also means that no data on enzyme synthesis can be obtained by the usual one to two
Figure 9. Graphic summary of our results in patients with different nutritional status comparing isotope incorporation curves following infusions of $^{14}$C leucine tracer. In comparison to normal volunteers, patients with hyperphagia (e.g., short bowel syndrome) had increased enzyme synthesis and zymogen pool turnover, resulting in increased secretion, whilst those who had severe malnutrition due to diseases other than pancreatic disease showed reduced enzyme secretion due to impaired synthesis and reduced zymogen stores.

hour secretory studies, and that such studies have to be continued beyond two hours in order to detect acute changes in enzyme synthesis brought about by hormonal or dietary change.

Our technique allows us to determine whether the decreased rate of secretion is due to defective exocytosis or impaired enzyme synthesis. As both processes are independent and regulated by different factors, our measurements make it now possible to determine in human subjects at what level pancreatic disease, hormonal imbalance or malnutrition disturbs organ function. The preliminary measurements that we have to date, allow us to construct the illustration shown on Figure 9 which shows that the reduction in enzyme secretion in malnourished patients is a result of delayed synthesis rather than abnormal release of zymogen stores, whilst the hypersecretion in patients with hyperphagia is the result of increased synthesis and increased turnover and release of zymogen stores. The control mechanisms behind the changes need to be further investigated, but our investigations to date support the inhibitory influence of pancreatic islet (D) cell derived somatostatin and intravenous nutrients. Our results support the view that enzyme production in humans is normally parallel, but that disease and malnutrition can induce nonparallel change.

Having outlined the process of enzyme production in human subjects, it is now possible to develop new tests of pancreatic function that include measures of the rate of pancreatic enzyme synthesis. Our studies have demonstrated that similar measurements can be made using stable isotope labels for amino acids, such as $^{13}$C or $^{15}$N [6], thereby making it possible to study enzyme synthesis in children and pregnant women where even the slightest trace of radio-labelling is best avoided.
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