Annu. Rev. Nutr. 1990. 10:85–105

ADAPTATION OF THE EXOCRINE PANCREAS TO DIET

P. M. Brannon

Department of Nutrition and Food Science and Nutritional Sciences Program, University of Arizona, Tucson, Arizona 85721

KEY WORDS: gene expression, amylase, lipase, protease

CONTENTS

INTRODUCTION

Since the report of Pavlov (66) in the early 1900s, the adaptation of the exocrine pancreas to dietary changes in various species, including the rat (29, 34, 74), dog (4), pig (15, 26), and chicken (41), has been described. The content in both pancreatic tissue and its secretions (5, 7) of the major digestive enzymes, proteases, amylase, and lipase, changes in proportion to the dietary content of their respective substrates, protein, carbohydrate, and fat (29, 34,

0199-9885/90/0715-0085$02.00

35, 74). Pancreatic adaptation occurs through changes in the synthetic rates (17, 75, 76, 99) and mRNA levels (30, 31, 101, 102). Cholecystokinin (CCK), through the negative feedback regulation of its secretion by dietary protein and peptides, appears to be the mediator of the adaptation of the proteases. Various hormones and metabolites are proposed mediators of the adaptation of pancreatic amylase and lipase, but the mechanisms by which dietary carbohydrate and fat regulate these enzymes are not yet known.

The physiologic significance of pancreatic adaptation to diet is unclear. Teleologically, the coordinate regulation of a digestive enzyme by its dietary substrate would optimize digestion and utilization of that substrate, but the pancreas normally synthesizes and secretes a 10-fold excess of digestive enzymes (23). Protein digestibility correlates ($r = 0.998$) with increasing chymotrypsin activity induced by increasing dietary protein (51), but changes in digestibility are small (94–97.5%). As yet, the physiologic significance of pancreatic adaptation has not been determined.

After a brief description of the exocrine pancreas, this review focuses on pancreatic adaptation to dietary protein, carbohydrate, and fat, particularly on the effects of the amount and nature of these dietary components. The mechanisms by which these dietary components alter pancreatic gene expression and the proposed hormonal and nutritional mediators of pancreatic adaptation are discussed.

THE EXOCRINE PANCREAS

The pancreas contains 90–95% exocrine tissue and only 2–3% endocrine tissue. The exocrine acinar cells synthesize and secrete digestive enzymes, as much as 6–20 g daily in humans (78). The ductal cells secrete bicarbonate-rich fluid, and the endocrine islets of Langerhans secrete the hormones insulin, glucagon, somatostatin, and pancreatic polypeptide. Together, the exocrine and endocrine pancreas enable the digestion and utilization of ingested food.

Morphology

Acinar cells clustered in three-dimensional arrays known as acini surround a lumen, whereas ductal cells line the ducts. The islets of Langerhans are scattered throughout the acini.

ACINAR ULTRASTRUCTURE Acinar cells exhibit typical epithelial polarity. The plasma membrane of the acinar cell is surrounded by an extracellular matrix containing collagen type IV, laminin, and proteoglycans (45), and the basal portion of the cell contains its nucleus and copious rough endoplasmic reticulum (RER). The apical membrane of the cell faces the lumen of the duct

into which secretion occurs, and the apical portion of the cell contains the Golgi apparatus and the secretory vesicles, zymogen granules (ZG). Acinar polarization reflects the unidirectional flux of digestive enzymes during their synthesis and secretion.

Between acinar cells are gap junctions (45) through which small molecules can pass and may regulate neighboring acinar cells. Supporting such intercellular regulation is the increased basal secretion that occurs when gap junctions are disrupted (57) and the greater secretagogue responsiveness of acini (67).

RELATIONSHIP TO THE ENDOCRINE PANCREAS Acini nearest the islets of Langerhans (periinsular acini) exhibit different morphology from more distant acini (teleinsular acini) (55, 103). Periinsular acini have larger cells, which contain larger nuclei and more ZG (38). These changes in the periinsular acini are proposed to result from enhanced exposure to insulin (103) or glucagon (55).

Blood flow in the pancreas supports a potential islet-acinar axis (103). Arterial blood flows into the islets and exits into the exocrine tissue through acinar capillaries, but the magnitude of this arterial blood flow ranges from 25 to 100% in different species. Thus, acinar cells potentially encounter much higher concentrations (10- to 20-fold) of pancreatic hormones than peripheral cells do (44). This islet-acinar axis may be important for the integrated action of the pancreas in digestion.

Digestive Enzymes

SYNTHESIS AND SECRETION In the nucleus, mRNAs for these enzymes are transcribed and translocated to the cytoplasm. Translation begins on free ribosomes but continues on the RER through the interaction of the signal peptide encoded in the *N* terminus of these mRNAs, a signal peptide recognition particle (SRP) found free in the cytoplasm, and the SRP receptor (SRPR), an integral endoplasmic reticulum (ER) membrane protein. Signal peptides are highly hydrophobic but heterogeneous sequences (22) to which SRP (a complex of a 7SL RNA and six polypeptides) binds. Translation is delayed (98), and the ribosome–mRNA–nascent peptide–SRP complex then binds to the SRPR in the ER. Once complexed to the RER, the SRP dissociates from the complex in a GTP-dependent manner (13). As translation proceeds, the nascent peptide is translocated through the ER membrane, possibly through a proposed "translocon" membrane pore (98).

Intraluminally, signal peptidases cleave the signal peptides; the nascent proteins are further processed. In the Golgi complex, the secretory proteins are segregated from lysosomal and plasma membrane proteins (68); they leave the *trans*-Golgi complex in condensing vacuoles (64). Condensing

vacuoles mature into ZG by concentrating their contents. The ZG, which serve as storage vesicles and exocytosis vehicles, move toward the apical membrane, where the ZG membranes fuse by an unknown process with the apical membrane and release their contents into the ductal lumen.

Acinar secretion is regulated by the interaction of secretagogues with two classes of receptors that differ in their stimulus-coupling mechanisms (28). One class acts through a phosphatidylinositol- and calcium-mediated pathway (62, 93, 104), and the other class acts through a cyclic AMP (cAMP)-mediated pathway (42). Four receptors of the former class exist (on the basis of their ligand specificity): the CCK, bombesin, physalaemin, and muscarinic/cholinergic receptors. Two receptors of the latter class exist: the vasoactive intestinal polypeptide–preferring and secretin-preferring receptors. Both classes of receptors generate signals that alter the phosphorylation of regulatory or structural proteins, but these distal steps in stimulated secretion are not understood.

FUNCTION The pancreatic digestive enzymes hydrolyze macromolecules in food into smaller molecules that can be absorbed. Proteins, starch, and triglycerides make up the majority of the macromolecules in food and are hydrolyzed by the major pancreatic enzymes: the serine proteases, amylase, and lipase, respectively.

The pancreatic serine proteases, a family of endopeptidases, share a similar three-dimensional structure (85) and contain a reactive serine in the active site. Trypsin and chymotrypsin are the predominant pancreatic serine proteases, with elastase and kallikrein present in smaller amounts. Trypsin (EC 3.4.21.4) has several isozymes, depending on the species, and cleaves peptide bonds between basic amino acids (arginine and lysine) and the next amino acid (78). Secreted as an inactive precursor (zymogen), trypsinogen is activated (37) by the cleavage of an *N*-terminal octapeptide by enteropeptidase or by activated trypsin. Trypsin activates other pancreatic zymogens, including proteases and colipase. Chymotrypsin (EC 3.4.21.1) has multiple isozymes, depending on the species, and cleaves peptide bonds between aromatic residues (phenylalanine, tyrosine, and tryptophan) and the next residue (78). Chymotrypsinogen is activated by tryptic cleavage of four peptide bonds, releasing two small peptides, while the remaining three peptides are held by disulfide linkages (61). The resulting products of these proteases are oligopeptides, with specific C-terminal amino acids, that are subsequently hydrolyzed by intestinal oligopeptidases.

Amylase (EC 3.2.1.1) is secreted in its active form and hydrolyzes α-1,4-glucosidic bonds in oligosaccharides with at least four subunits (80). It binds five α-1,4-linked glucose residues and rapidly cleaves the glucosidic linkage between the second and third residues, forming maltose and small oligosac-

charides (81), which are further hydrolyzed by intestinal glucosidases prior to absorption.

Pancreatic lipase (EC 3.1.1.3) is secreted in its active form (78) and acts at lipid/water interfaces to hydrolyze triglycerides at the *sn*-1 and *sn*-3 positions. Lipase has a histidine residue in its catalytic site and a serine residue active in its interfacial binding site (12). It has a complex interaction with bile salts, which shift its pH optimum to pH 6–7 and inhibit its activity (8), possibly by displacing it from the surface of the emulsified triglyceride. Colipase, a small pancreatic peptide (10,000 daltons), reverses this inhibition by bile salts, possibly by allowing lipase access to its interfacial substrate (8, 9). Colipase is secreted as procolipase, which is activated by *N*- and *C*-terminal tryptic cleavage (9). Pancreatic lipase is maximally activated by a 1:1 molar ratio with colipase, but the two proteins are secreted in a 0.5 ratio (colipase:lipase) (24). The products, monoglycerides and free fatty acids, partition into mixed micelles, cross the unstirred water layer, and are absorbed by the enterocyte.

PANCREATIC ADAPTATION TO DIETARY COMPONENTS

Pancreatic adaptation to dietary protein, carbohydrate, and fat has been investigated widely in various species, but unless stated otherwise, results discussed here are from rats. The consensus of these studies is that proteolytic, amylolytic, and lipolytic content and synthesis change proportionately in response to the amounts of their respective dietary substrates protein, carbohydrate, and fat (Table 1). The magnitude of these adaptive changes is similar whether expressed as enzyme activity per pancreas, per gram of pancreas, or per milligram of pancreatic protein (83, 86).

The kinetics of these adaptations are similar. Changes in content begin in the first 24 h after the dietary change and continue until 5–7 days, when new steady-state levels are reached (7, 102). Changes in synthetic rates precede those in content. Within the first 2 h after a dietary change, the synthetic rates of amylase and the proteases change (17). By 24 h after starting a high-protein (HP) diet, chymotrypsinogen and trypsinogen synthesis increases by 70 and 50%, respectively, and amylase synthesis decreases by 25% (17). Synthetic rates continue to change more slowly thereafter until day 9 for chymotrypsin and trypsin (300 and 200%) and until day 5 for amylase [60% (49)]. By 24 h after starting a high-carbohydrate (HC) diet, amylase synthesis increases by 15% and continues to increase (200%) until day 3, whereas chymotrypsinogen and trypsinogen synthesis decreases by 25% and continues to decrease (50%) until day 5 (49). By 24 h after starting a high-fat (HF) diet, lipase synthesis increases by 36% and continues to increase (217%) until day 5, whereas amylase synthesis decreases by 17% and continues to decrease (61%)

Table 1 Pancreatic adaptation to dietary components[a]

Stimulus		Adaptive response				
		Proteases		Amylase		Lipa
Dietary	Intravenous	Content and synthesis	mRNA	Content and synthesis	mRNA	Content and synthesis
Protein, oligopeptides	none	▲	▲	▼	▼	—[b]
Starch, glucose[d]	Glucose	▼[e]	▼[e]	▲	▲	▼[f]
Triglycerides, fatty acids	Triglycerides	—[b]	ND	▼	—[b]	▲

[a] When responses conflict, the majority effect is indicated.
[b] Unchanged.
[c] ND, not determined.
[d] Sucrose and fructose are less effective than starch.
[e] Observed when dietary carbohydrate increased at the expense of protein.
[f] Observed when dietary carbohydrate increased at the expense of fat.

until day 5 (100). Adaptation of synthetic rates exhibits a rapid change in the first several hours after the dietary change and a prolonged, slower change thereafter until days 3–9, when new steady-state rates are established. These adaptations to diet are then maintained long-term in the rat [9 months (39)] and pig [1 month (26)].

Caution must be used in comparing synthetic rates of individual enzymes or total protein among dietary groups because of the demonstrated dietary effects on the specific activity (expressed as dpm per mole of labeled amino acid) of pancreatic amino acid pools in vivo (91) and in vitro (11). HP diets decrease the [^{3}H]leucine specific activity by 50% in vivo, whereas HF diets increase the [^{3}H]phenylalanine specific activity by 30% in vitro. The synthetic rates discussed above are compared as relative rates (the ratio of labeled amino acid incorporated into the specific enzyme to that incorporated into total protein); this technique eliminates the problem of differing specific activities among dietary treatments.

Protein

In response to HP diets (64–71% casein), the trypsinogen and chymotrypsinogen content increases by 80–600% (5, 7, 34, 43, 74, 76, 79, 87, 88, 91), while their synthesis also increases by 250–1800% (69, 75, 76, 91). This adaptive response increases as the amount of dietary protein increases from 10 to 80% casein (51, 84, 95). The quality of dietary protein also affects this adaptation. Increasing the intake of high-quality proteins such as casein or fish protein increases chymotrypsinogen, whereas increasing the intake of low-quality proteins such as gelatin or zein does not (43). If dietary zein is

supplemented with its two most limiting amino acids, lysine and tryptophan, adaptation of chymotrypsinogen occurs (43). Furthermore, whole-egg protein increases chymotrypsinogen more than casein does (87), in part because of its higher biological value and in part because of its content of trypsin inhibitor (88) (see below for further discussion of trypsin inhibitors). Supplementation of casein with methionine improves its biological value and increases chymotrypsinogen (88). Thus, sufficient availability of the essential amino acids is required for pancreatic adaptation.

Hydrolyzed protein consisting of oligopeptides affects protease content and synthesis to the same degree that the intact protein does (43, 95). Neither consumption of an amino acid mixture identical to that contained by the intact protein (43, 95) nor intravenous infusion of amino acids (50) affects the proteases. The adaptation of proteases to dietary protein requires intact protein or small peptides and does not involve the end products of their digestion, namely, amino acids.

This pattern of adaptation to dietary protein changes when severe protein malnutrition is induced by a nitrogen-free or protein-free diet. A nitrogen-free diet fed to rats decreases the content of chymotrypsinogen (by 75%), trypsinogen (by 50%), and amylase (by 72%) (87); and a nitrogen-free diet fed to pigs decreases the content of chymotrypsinogen (by 30%), amylase (by 35%), and lipase (by 23%), but not trypsinogen (14). A protein-free diet compared with a protein-sufficient diet (22% casein) decreases the synthesis of amylase and the cationic protease isozymes but paradoxically increases the synthesis of the anionic protease isozymes (84). The decreased content and synthesis of most enzymes during protein deprivation may reflect limited availability of essential amino acids and an adaptive response to spare amino acids for other tissue. The paradoxical increase of the anionic protease isozymes is proposed as a protective mechanism to ensure the availability of proteases to digest any consumed protein (84).

Carbohydrate

In response to a HC diet (65–73% of the total energy content as carbohydrate), the amylase content increases by 50–500% (5, 21a, 34, 69, 75, 76, 79, 89), while its synthesis increases by 200–800% (43, 56, 75, 76, 99). This adaptive response increases as the level of dietary carbohydrate increases at the expense of dietary fat (82, 89, 99) or protein (84); which implies a response primarily to the amount of carbohydrate. Maximal response of amylase content and synthesis occurs when dietary carbohydrate is 58–71% of the total energy content, provided that the dietary protein content is adequate (82, 84, 89, 99). Even a modest reduction of protein intake to 10% casein decreases amylase synthesis slightly [by 24% (84)]. Supplementation of a 15% casein HC diet with methionine improves the quality of the protein and

increases the amylase content (by 260%) with no change in carbohydrate intake (87). Although amylase adapts primarily to the amount of dietary carbohydrate, this adaptation requires adequate availability of essential amino acids.

Many different carbohydrates (complex carbohydrates, disaccharides, and monosaccharides) affect pancreatic amylase levels. Dietary starch and glucose increase the amylase content similarly (21a, 40, 79), whereas sucrose and fructose increase the amylase content less than starch does (40). Lactose and galactose do not affect the pancreatic amylase content (21a). In general, dietary carbohydrates that lead to maximal increases in postprandial blood glucose levels also lead to maximal adaptation of amylase.

Intravenous infusion of glucose increases the pancreatic amylase content, whereas infusion of lipid decreases it (50). Also supporting a role of the end product of starch digestion in amylase adaptation is the decrease in the amylase content when starch digestion is inhibited (27). This response of amylase to oral or intravenous glucose contrasts the nonresponse of the proteases with oral or intravenous amino acids.

Triglyceride

In response to a HF diet (41–75% of total energy as triglyceride), the lipase content increases by 170–800% (3, 21a, 29, 32, 60, 63, 79, 82, 83, 97, 99), and its synthesis increases by 200% (99). Why earlier studies of adaptation reported that dietary fat does not affect lipase is unclear (34, 74), but these studies predate the knowledge of lipase-colipase interactions and may have underestimated lipase levels because the assay used to measure lipase activity contained no additional colipase and the tissue homogenates may have contained insufficient colipase for full activation of the lipase present. Pancreatic lipase responds to dietary fat whether the fat content is increased at the expense of dietary protein (21a, 79) or carbohydrate (82, 99), implying that the primary effector is dietary fat. The response of lipase to the amount of dietary fat varies among the studies. These studies are difficult to compare because of their use of different fats and, in some cases, nonisocaloric diets, which can alter the intake of micronutrients, as the intake decreases with increasing fat content. In addition, some studies analyzed the effect of varying fat intake by Student's *t* test comparisons among the low-fat (LF) control diet and other diets instead of by using the more appropriate analysis of variance (ANOVA). Ouagued and co-workers (63) found increased lipase levels with 61% of total energy as lard but not with 16%. Saraux et al (83) found increased lipase levels with 45% or more of total energy as corn oil but not with 27% or less. Sabb and co-workers (82) found increased lipase levels with 54% or more of total energy as corn oil but not with 47% or less. Two studies reported increased lipase levels with increased fat content after analyzing their

data by Student's *t* test. Wicker and co-workers (99) reported a significant increase in the lipase content and synthesis when the amount of sunflower oil was increased from 7.4 to 74% of total energy. When reanalyzed by ANOVA, lipase content and synthesis are significantly increased by 49% or more dietary fat but not by 25% or less (unpublished data). Bazin et al (3) reported an increasing lipase content as the dietary lard level was increased from 9 to 72% of kcal; these increases are also significant when the data are reanalyzed by ANOVA (unpublished data). Although lipase adapts to increasing dietary fat levels, there may be a threshold of fat content below which there is little adaptation and above which there is significant adaptation.

Considerable controversy exists whether the adaptation of lipase is affected by the type of dietary fat, i.e. its degree of saturation or its chain length. Deschodt-Lanckman and co-workers (21a) reported a twofold-greater response of lipase to unsaturated dietary fats than to saturated fats, although both types of fat increased the lipase content compared with a LF diet. However, the more highly unsaturated sunflower oil (polyunsaturated/saturated ratio = 6.5) increases the lipase content less than the equivalent amount of corn oil (P/S ratio = 4.6). In contrast, Saraux et al (83) found no difference in lipase adaptation to the highly saturated butter fat (P/S ratio = 0.1) and highly unsaturated sunflower oil. Rather, long-chain triglycerides increased the lipase content more than medium-chain triglycerides did. Sabb et al (82) reported equivalent adaptation to saturated and unsaturated fats and to long-chain and medium-chain triglycerides when the total fat content is high (67% of total energy). However, when dietary fat content is moderate (40–44% of total energy), only the highly unsaturated safflower oil (P/S ratio = 7.9) increases the lipase content in the rat [by 160% (82)] and the pig [by 170% (86)]. Finally, monounsaturated oleic acid increases the lipase content more than saturated palmitic acid does when fed as 55% of kcal (3). Both the type and amount of dietary fat influence the adaptation of pancreatic lipase, and these two factors interact. Unsaturated fat induces lipase more than saturated fat does when dietary fat intake is moderate and the lipase content is not maximal, but it is generally not more effective when dietary fat intake is high and the lipase content is maximal.

Dietary fatty acids also increase pancreatic lipase levels (3, 21a). Oleic acid as 37% of total energy increases the lipase content equivalently to olive oil (21a), whereas oleic acid as 55% of total energy increases the lipase content, but to a lesser extent than does the triglyceride lard (3). Unfortunately, in the latter study, dietary oleic acid ($C_{18:1}$) was compared with lard, which contains 23% stearic acid ($C_{18:0}$) and 33% oleic acid, but was not compared with olive oil, which contains 65% oleic acid. Oral consumption of dietary fat is not required for the adaptation of lipase. Constant intravenous infusion of emulsified triglyceride increases the lipase content comparably to a HF diet (50).

The adaptation of lipase resembles that of amylase and not the proteases, in that the end product of its hydrolysis or intravenous delivery of the absorbed product of fat digestion affects lipase as well as its intact substrate.

Adaptation of colipase to dietary fat is controversial. Two studies report no adaptation to increasing fat levels (63, 97), whereas four other studies report an adaptation (32, 60, 83, 99). When adaptation to dietary fat is seen, colipase responds less strongly than lipase (60), leading potentially to less than fully activated lipase in the lumen. The correlation coefficient of colipase with fat intake is 0.63 but is even stronger (0.85) with protein intake (83). Ouagued and co-workers (63) also report adaptation of colipase to increasing dietary protein levels. Unlike lipase, then, colipase adapts to both dietary fat and protein, but whether fat and protein interact in this adaptation is unknown.

MECHANISMS OF ADAPTATION TO DIET

The mechanism by which dietary macronutrients alter the expression of specific pancrcatic enzymes can occur at the level of the gene (transcription), its mRNA (processing, extranuclear transport, or cytoplasmic stability), and its translation. Recent studies of pancreatic adaptation focus on mRNA levels, stability, and translation; evidence supports a pretranslational mechanism of dietary regulation of pancreatic gene expression (18, 30, 31, 100, 102).

Another facet of the adaptive mechanisms is how the luminal content of a dietary macronutrient alters pancreatic gene expression. Clearly, mediators of this adaptation must exist that signal the dietary composition to the acinar cell (48). Three basic types of mediators are possible: (*a*) gastrointestinal hormones released in response to the luminal presence of the macronutrient or its hydrolytic product; (*b*) hormones released in response to the absorbed hydrolytic product of the macronutrient or its subsequent metabolites; or (*c*) the absorbed hydrolytic product or its subsequent metabolites directly. The apparent mediator of protease adaptation, CCK, exemplifies the first type; however, the mediators of amylase and lipase adaptation, although not established yet, must be of the second or third type to account for their adaptation to intravenous glucose or lipid.

Gene Transcription and Translation

The structure and sequences of the genes for amylase (36, 54a), serine proteases (16, 54), and lipase (58) are known, and all are members of respective multigene families. The serine proteases and amylase genes contain 5'-flanking, tissue-specific enhancer elements (10, 62a). The lipase gene contains two homologous sequences to the protease tissue-specific enhancer element (20 bp); however, as yet, tissue-specific transcription has not been demonstrated for these sequences (58).

AVAILABILITY OF mRNA Dietary composition alters the mRNA levels of the serine proteases, amylase, and lipase, as assessed by in vitro translation of isolated poly $(A)^+$ mRNA (30, 101) or cDNA hybridization of total RNA (18, 30, 31, 100, 102) (Table 1). A HP diet increases the mRNA levels of trypsinogen (by 360%), chymotrypsin (by 390%), and proelastase (by 190%) (31). In response to a protein-free diet, chymotrypsinogen mRNA levels increase by 390%; however, surprisingly, amylase mRNA levels also increase by 170%, despite the 50% decrease in its synthesis (18). A HC diet increases amylase mRNA levels by 900%, paralleling the 470% increase in its synthesis (30). Finally, a HF diet increases lipase mRNA levels by 387%, again paralleling the 77% increase in its synthesis, but does not affect amylase mRNA levels, despite the 50% decrease in its synthesis (100, 102). In each case the respective dietary substrate increases the mRNA level of its digestive enzyme in parallel to its synthesis, supporting a pretranslational mechanism by which dietary macronutrients regulate pancreatic adaptation. To date, the mechanisms of dietary regulation of mRNA levels have not been determined. None of the studies has examined transcription directly by nuclear run-on assay to determine whether the increases in protease, amylase, and lipase mRNA in response to their respective substrates result from transcriptional regulation.

The stability of trypsinogen and proelastase mRNAs increases by 67% and decreases by 50%, respectively, in response to HP diets according to one report (70) in which actinomycin D was used to inhibit transcription, but the inhibition of poly $(A)^+$ RNA synthesis was not assessed, which is a concern because of the greater sensitivity of rRNA, than mRNA, synthesis to actinomycin D (48a). Nonetheless, these reported changes in mRNA stability in response to dietary protein suggest that posttranscriptional regulation by diet is possible. The apparently greater adaptive changes in functional mRNA availability than in synthesis also raise the possibility of dietary regulation of nuclear transport (30). The mechanisms of dietary regulation of mRNA levels must be addressed, particularly focusing on transcription and cytoplasmic stability. Indeed, dietary changes of mRNA levels may result from multiple mechanisms acting in concert, but that remains to be determined.

TRANSLATIONAL CONTROL Alterations in the rate of synthesis of a specific protein without changes in its mRNA levels are interpreted as translational control, which alters the efficiency of translation of existing mRNAs. If mRNA levels are determined with cytoplasmic RNA, this interpretation of translational control is well supported. However, if mRNA levels are determined with total RNA, the interpretation of translational control ignores the other possibility: regulation of transport of preexisting mRNA from the nucleus to the cytoplasm. Increased nuclear transport could lead to a larger translatable cytoplasmic pool of mRNA without changing total mRNA levels.

Unfortunately, isolation of pancreatic cytoplasmic RNA is not yet technically feasible because of the high pancreatic ribonuclease activity [200 μg/g of tissue (90)], and present studies on translational control use total RNA of necessity. One should remember, though, that the results of these studies do not exclude possible regulation of nuclear transport of specific mRNAs. In addition to translational control, changes in protein stability can alter the apparent synthesis of a protein with no change in its mRNA or translational efficiency.

Evidence for translational control in dietary adaptation is limited. The discordant changes in the amylase mRNA level and its synthesis in response to HF (102) or protein-free (18) diets may result from translational control, but this remains to be determined. Evidence for hormonal regulation of translational efficiency in the pancreas exists for insulin, CCK, and its analog caerulein. Both CCK and insulin stimulate the synthesis of total protein, trypsinogen, chymotrypsinogen, lipase, and amylase in acini treated in vitro with actinomycin D, which inhibited the incorporation of [^{3}H] UTP into poly $(A)^+$ RNA (48a). Furthermore, infused caerulein increases the synthesis of trypsinogen (by 300%) and decreases the synthesis of amylase (by 75%) without changing the level of their mRNAs (90). The 5' noncoding regions of both mRNAs have a conserved 7-bp sequence that may form a stem-loop structure, which is proposed to affect translational control of these mRNAs (68a, 90).

Translational control mechanisms exist in the pancreas; however, no role of translational control has been demonstrated as yet in pancreatic adaptation to diet. Future studies must examine the role of translational control and, if possible, of nuclear transport in pancreatic adaptation.

Hormonal and Nutritional Mediators of Adaptation

PROTEASES CCK appears to mediate pancreatic adaptation to dietary protein through the feedback regulation of its secretion from the small intestine (Table 2) (33). Active luminal trypsin decreases the release of CCK by

Table 2 Proposed mediators of pancreatic adaptation to diet

Dietary stimulus	Proposed mediator		
	Hormonal	Nutritional	Stimulus
Protein	CCK	—	Luminal peptides and trypsin inhibitors
	—	None	
Carbohydrate	Insulin		Serum glucose
		Acinar glucose	Glucose and insulin
Triglyceride	Secretin		Luminal fatty acids
	—	Ketones	Serum triglycerides

degrading a CCK-releasing factor of pancreatic or mucosal origin. Either high levels of dietary protein or trypsin inhibitors block this degradation by substrate competition or enzyme inactivation, respectively, leading to large (threefold) but transient increases in plasma CCK levels. The transience of the elevation of the CCK level results from pancreatic adaptation of the proteases and resumed degradation of the CCK-releasing factor by the increased proteases.

This feedback regulation is dependent on adequate protein nutriture. In the presence of inadequate protein (5%), trypsin inhibitors cause prolonged increasing plasma CCK levels [fivefold at 7 days (33)]. Lack of available essential amino acids limits the pancreatic adaptation, leading to no increase in the level of the proteases and continued degradation of the CCK-releasing factor.

Other evidence supports CCK as the mediator of protease adaptation. Caerulein or CCK increases the protease content (77) and trypsinogen synthesis (90). Conflicting results have been reported for its effects on protease mRNA levels, however. Injected caerulein (77) increases chymotrypsinogen and trypsinogen mRNA levels, but infused caerulein (90) does not change the anionic trypsinogen mRNA levels. Why these results differ is unclear, but the cumulative daily dose of caerulein is twofold higher for the injected protocol (12 μg/kg/day) than for the infused protocol (6 μg/kg/day). Furthermore, the injected protocol represents long-term pulsatile exposure to CCK, whereas the infused protocol represents short-term exposure to constantly elevated hormone levels, which could result in receptor desensitization. Long-term pulsatile exposure to CCK may be more representative of pancreatic adaptation to dietary protein.

Despite the conflicting data on the effects of CCK on protease mRNA levels, several features of this feedback regulation make CCK an attractive candidate for the mediation of this adaptation. This model accounts for (*a*) the adaptation to only oral protein or oligopeptides, because oral amino acids would not spare the CCK-releasing factor from tryptic cleavage; (*b*) the failure of intravenous amino acids to alter proteases; and (*c*) the alterations of protease synthesis that occur with dietary protein. Although conclusive confirmation of this role of CCK is not yet available, CCK remains the likely mediator of pancreatic protease adaptation.

AMYLASE Insulin is a proposed mediator of pancreatic adaptation to dietary carbohydrate because of the profound decrease in amylase content (7- to 32-fold) (1, 21a, 46, 65), synthesis (10-fold) (65), and mRNA levels (11-fold) (46, 62a) in rats with diabetes (alloxan or streptozotocin induced). Insulin restores the amylase content (1, 6, 46, 65), synthesis (65), and mRNA levels (46) in diabetic rats. Hyperinsulinemic diabetes (obese Zucker rat model) due to peripheral insulin resistance also decreases (5- to 6-fold) the

amylase content and synthesis; however, Ciglitazone treatment, which decreases insulin resistance and normalizes glucose metabolism, restores amylase content and synthesis (96). Further fasting in mice decreases the amylase content (21a) and synthesis (19), but glucose administration restores them. Concomitant injection of diazoxide, which inhibits glucose-induced insulin release, prevents this restoration (19). According to this mechanism, an increased plasma glucose level resulting from the digestion and absorption of starch stimulates the release of insulin, which regulates acinar amylase synthesis and mRNA levels. This proposed mediation by insulin accounts for the adaptation to orally or intravenously administered glucose and the increased amylase synthesis and mRNA levels in response to dietary carbohydrate.

Insulin, however, does not appear to be the sole mediator of this adaptation. Insulin administration to normal rats either decreases (89) or does not change (35, 65, 89) the amylase content. Furthermore, periinsular acini contain 50% less amylase than do teleinsular ones, even though they are exposed (presumably) to greater insulin levels (55). Restoration of the amylase content in diabetic animals treated with insulin is dependent on glucose availability (1). Diabetic rats fed a HF diet and treated with insulin exhibit a continued 10-fold decrease in amylase content. Finally, in vitro glucose starvation of the transformed acinar cell line (AR 42J cells) decreases amylase mRNA levels (92), as would be expected if acinar glucose availability is a mediator of amylase adaptation. In addition, insulin stimulates the uptake of glucose by pancreatic acinar cells (47), and HC diets cause a twofold increase in acinar glucose utilization by stimulating glucose transport (2). Together, these results suggest a role for glucose in the adaptation of amylase to carbohydrate.

Alternatively, increased plasma glucose resulting from HC diets stimulates insulin release, which then stimulates acinar glucose uptake, leading to increased intracellular glucose levels and metabolism. Intracellular glucose, alone or in conjunction with insulin, regulates amylase synthesis and mRNA levels (Table 2). This mechanism also accounts for adaptation to oral or intravenous glucose, the increased amylase synthesis and mRNA levels that occur with dietary carbohydrate, and the glucose dependence of insulin restoration of amylase in diabetic animals.

Amylase is also regulated by glucocorticoids. Adrenalectomy, independent of accompanying changes in insulin levels (59), decreases the amylase content (21, 53, 59), synthesis (59), and mRNA levels (53); however, corticosterone replacement restores amylase (53). Dexamethasone in vivo (62a) and in vitro (20, 52, 94) increases amylase content, synthesis, mRNA levels, and transcription rate (52). The 5'-flanking region of the pancreatic amylase gene contains a glucocorticoid-responsive element (36). Despite this clear regula-

tion of amylase, glucocorticoids do not mediate amylase adaptation to dietary carbohydrate, because adrenalectomized rats adapt fully to changes in carbohydrate levels (21).

Resolving the roles of insulin and glucose and their interaction in mediating the adaptation of amylase will be difficult until a long-term in vitro acinar system is available in which the acinar cells transcribe this tissue-specific mRNA. Presently, in vivo studies to answer this question are hampered by the rapid and complex multihormonal and metabolic responses. With an in vitro system, insulin, glucose, and their interaction can be evaluated without complicating in vivo homeostatic mechanisms.

LIPASE Secretin, a gastrointestinal hormone, and ketones, fatty acid metabolites, are proposed mediators of pancreatic adaptation to dietary fat (Table 2). Constant in vivo infusion of secretin increases the relative synthesis of lipase (1.8- to 2.5-fold) and decreases that of amylase (by 60%) (71–73). Infused secretin, however, does not alter lipase mRNA levels, which suggests a translational control mechanism (H. F. Kern and J. Heidtmeann, personal communication). Duodenally infused oleic acid increases plasma secretin levels [2-fold (25)]. Thus, the hydrolytic products of triglyceride are proposed to stimulate the release of secretin, which then regulates acinar synthesis of lipase (71). Although secretin mediation accounts for lipase adaptation to oral triglycerides or fatty acids, it does not account for adaptation to intravenous triglyceride, because the release of secretin requires luminal fatty acids.

Ketones, another proposed family of mediators of lipase, are strongly correlated with pancreatic lipase. A HF diet containing either triglyceride or fatty acids increases lipase and blood ketone levels (3). Importantly, constant infusion of β-hydroxybutyrate increases the lipase content and decreases the amylase content comparably to the effects of a 40% fat diet (3). Additionally, two metabolic states (fasting and diabetes) increase the lipase content and blood ketone levels in parallel. Both lipase and ketone levels are reversed in diabetic rats treated with insulin and fed a HC diet, but are increased further (1.7- and 4-fold, respectively) in diabetic rats treated with insulin and fed a HF diet (1). The effects of ketones on lipase synthesis and mRNA levels have not been assessed, but they should be. The effect of ketones on lipase content supports their role in mediating lipase adaptation to fat and accounts for lipase adaptation to oral and intravenous triglycerides and oral fatty acids, all of which increase levels of ketones.

It is not yet possible to eliminate either secretin, ketones, or their interaction as mediators of lipase adaptation. Whatever the mediator(s), it must affect lipase synthesis and mRNA in parallel and allow for adaptation to both oral and systemic triglycerides.

SUMMARY

Pancreatic adaptation represents dietary regulation of gene expression; dietary substrates alter the synthesis and mRNA levels of their respective digestive enzymes. The mechanisms whereby mRNA levels change are not understood, but they must be elucidated. Although the changes in synthesis of proteases, amylase, and lipase parallel the changes in their mRNA levels in response to respective substrates, the concomitant changes in the synthesis of the other enzymes can be discordant with mRNA levels. The evidence supports a pretranslational mechanism of the adaptation of proteases, amylase, and lipase to their respective substrates and suggests potential translational mechanisms of other enzymes in these adaptations. Changes in synthesis occur within hours after a dietary change, but whether mRNA levels also change so early is unknown. Rapid, adaptive changes may occur by a different mechanism from later adaptation, possibly by translational control or nuclear transport. The differential effects of acute and chronic caerulein administration support the possibility of multiple mechanisms of regulation by a single effector. The mediators of pancreatic adaptations have not yet been identified, except for adaptation to dietary protein. CCK appears to mediate protease adaptation through the feedback regulation of its release by dietary protein. Available evidence supports a role of insulin and glucose in the adaptation to carbohydrate and a role of secretin and ketones in the adaptation to dietary fat. Elucidation of the mediators of pancreatic adaptation to carbohydrate and fat and their mechanisms is needed.

ACKNOWLEDGMENTS

I thank Drs. H. F. Kern and W. Steinhilber for their helpful comments in the preparation of this manuscript. This work was supported in part by Public Health Service grant AM32690 from the National Institutes of Health and by the Pew Charitable Trusts.

Literature Cited

1. Bazin, R., Lavau, M. 1979. Diet composition and insulin effect on amylase to lipase ratio in pancreas of diabetic rats. *Digestion* 19:386–91
2. Bazin, R., Lavau, M. 1982. Effects of high-fat diet on glucose metabolism in isolated pancreatic acini of rats. *Am. J. Physiol.* 243:G448–54
3. Bazin, R., Lavau, M., Herzog, J. 1978. Pancreatic lipase and ketogenic conditions. *Biomedicine* 28:160–65
4. Behrman, H. R., Kare, M. R. 1969. Adaptation of canine pancreatic enzymes to diet composition. *J. Physiol.* 205:667–76
5. Ben Abdeljlil, A., Desnuelle, P. 1964. Sur l'adaptation des enzymes exocrines du pancreas a la composition du regime. *Biochim. Biophys. Acta* 81:136–49
6. Ben Abdeljlil, A., Palla, J. C., Desnuelle, P. 1965. Effect of insulin on pancreatic amylase and chymotrypsinogen. *Biochem. Biophys. Res. Commun.* 18:71–75
7. Ben Abdeljlil, A., Visani, A. M., Desnuelle, P. 1963. Adaptation of the exocrine secretion of rat pancreas to the composition of the diet. *Biochem. Biophys. Res. Commun.* 10:112–16
8. Borgström, B., Erlanson, C. 1973. Pan-

creatic lipase and colipase: Interactions and effects of bile salts and other detergents. *Eur. J. Biochem.* 37:60–68
9. Borgström, B., Erlanson-Albertsson, C. 1984. Pancreatic colipase. In *Lipases*, ed. B. Borgström, H. L. Brockman, pp. 152–83. Amsterdam: Elsevier
10. Boulet, A. M., Erwin, C. R., Rutter, W. J. 1986. Cell-specific enhancers in the rat exocrine pancreas. *Proc. Natl. Acad. Sci. USA* 83:3599–03
11. Brannon, P. M., Demarest, A. S., Sabb, J. E., Korc, M. 1986. Dietary modulation of epidermal growth factor action in cultured pancreatic acinar cells of the rat. *J. Nutr.* 116:1306–15
12. Chapus, C., Rovery, M., Sarda, L., Verger, R. 1988. Minireview on pancreatic lipase and colipase. *Biochimie* 70:1223–34
13. Connolly, T., Gilmore, R. 1989. The signal recognition particle receptor mediates the GTP-dependent displacement of SRP from the signal sequence of the nascent polypeptide. *Cell* 57:599–10
14. Corring, T., Calmes, R., Rérat, A., Geugneau, A. M. 1984. Effects de l'alimentation protéiprive à court terme sur la sécrétion d'azote endogène: sécrétion pancréatique exocrine chez le porc. *Reprod. Nutr. Dev.* 24:495–506
15. Corring, T., Saucier, R. 1972. Sécrétion pancréatique sur porc fistulé. Adaptation a la teneur en protéines du régime. *Ann. Biol. Anim. Biochim. Biophys.* 12:223–41
16. Craik, C. S., Choo, Q. L., Swift, G. H., Quinto, C., MacDonald, R. J., Rutter, W. J. 1984. Structure of two related rat pancreatic trypsin genes. *J. Biol. Chem.* 259:14255–64
17. Dagorn, J. C., Lahaie, R. G. 1981. Dietary regulation of pancreatic protein synthesis. I. Rapid and specific modulation of enzyme synthesis by changes in dietary composition. *Biochim. Biophys. Acta* 654:111–18
18. Dakka, N., Wicker, C., Puigserver, A. 1988. Specific response of serine protease mRNA to a protein-free diet in the rat pancreas. *Eur. J. Biochem.* 176:231–36
19. Danielsson, A., Marklund, S., Stigbrand, T. 1974. Effects of starvation and islet hormones on the synthesis of amylase in isolated exocrine pancreas of the mouse. *Acta Hepato-Gastroenterol.* 21:289–97
20. Darlington, G. J., Tsai, C. C., Samuelson, L. C., Gumucio, D. L., Meisler, M. H. 1986. Simultaneous expression of salivary and pancreatic amylase genes in cultured mouse hepatoma cells. *Mol. Cell. Biol.* 6:969–75
21. Deschodt-Lanckman, M., Robberecht, P., Camus, J., Baya, C., Christophe, J. 1974. Hormonal and dietary adaptation of rat pancreatic hydrolases before and after weaning. *Am. J. Physiol.* 226:39–44
21a. Deschodt-Lanckman, M., Robberecht, P., Camus, J., Christophe, J. 1971. Short-term adaptation of pancreatic hydrolases to nutritional and physiological stimuli in adult rats. *Biochimie* 53:789–96
22. Devillers-Thiery, A., Kindt, T., Scheele, G., Blobel, G. 1975. Homology in amino-terminal sequence of precursors to pancreatic secretory proteins. *Proc. Natl. Acad. Sci. USA* 72:5016–20
23. DiMagno, E. P., Go, V. L. W., Summerskill, W. H. J. 1973. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *New Engl. J. Med.* 288: 813–15
24. Erlanson-Albertsson, C., Larsson, A., Duan, R. 1987. Secretion of pancreatic lipase and colipase from rat pancreas. *Pancreas* 2:531–35
25. Faichney, A., Chey, W. Y., Kim, Y, C., Lee, K. Y., Kim, M. S., Chang, T. M. 1981. Effect of sodium oleate on plasma secretin concentration and pancreatic secretion in dog. *Gastroenterology* 81:458–62
26. Flores, C. A., Brannon, P. M., Bustamante, S. A., Bezerra, J., Butler, K. T., et al. 1988. Effect of diet on intestinal and pancreatic enzyme activities in the pig. *J. Pediatr. Gastroenterol. Nutr.* 7:914–21
27. Fölsch, U. R., Grieb, N., Caspary, W. F., Creutzfeldt, W. 1981. Influence of short and long term feeding of an α-amylase inhibitor (Bay e 4609) on the exocrine pancreas of the rat. *Digestion* 21:74–82
28. Gardner, J. D., Jensen, R. T. 1986. Receptors mediating the actions of secretagogues on pancreatic acinar cells. See Ref. 32a, pp. 109–22
29. Gidez, L. I. 1973. Effect of dietary fat on pancreatic lipase levels in the rat. *J. Lipid Res.* 14:169–77
30. Giorgi, D., Bernard, J. P., Lapointe, R., Dagorn, J. C. 1984. Regulation of amylase messenger RNA concentration in rat pancreas by food content. *EMBO J.* 3:1521–24
31. Giorgi, D., Renaud, W., Bernard, J. P., Dagorn, J. C. 1985. Regulation of proteolytic enzyme activities and mRNA concentrations in rat pancreas by food

content. *Biochem. Biophys. Res. Commun.* 127:937–42
32. Girard-Globa, A., Simond-Cote, E. 1977. Nutritional and circadian variations in lipase activity and colipase saturation in rat pancreas. *Ann. Biol. Anim. Biochim. Biophys.* 17:539–42
32a. Go, V. L., Gardner, J. W., Brooks, F. P., Lebenthal, E., DiMagno, E., Scheele, G. A., eds. 1986. *The Exocrine Pancreas: Biology, Pathobiology and Diseases.* New York: Raven. 920 pp.
33. Green, G. M., Levan, V. H., Liddle, R. A. 1986. Interaction of dietary protein and trypsin inhibitor on plasma cholecystokinin and pancreatic growth in rats. *Adv. Exp. Med. Biol.* 199:123–32
34. Grossman, M. I., Greengard, H., Ivy, A. C. 1942. The effect of dietary composition on pancreatic enzymes. *Am. J. Physiol.* 138:676–82
35. Grossman, M. I., Greengard, H., Ivy, A. C. 1943. On the mechanism of the adaptation of pancreatic enzymes to dietary composition. *Am. J. Physiol.* 141: 38–41
36. Gumucio, D. L., Wiebauer, K., Caldwell, R. M., Samuelson, L. C., Meisler, M. H. 1988. Concerted evolution of human amylase genes. *Mol. Cell. Biol.* 8:1197–1205
37. Guy, O., Lombardo, D., Bartelt, D. C., Amic, J., Figarella, C. 1978. Two human trypsinogens. Purification, molecular properties and *N*-terminal sequences. *Biochemistry* 17:1669–75
38. Hellman, B., Wallgren, A., Petersson, B. 1962. Cytological characteristics of the exocrine pancreatic cells with regard to their position in relation to the islets of Langerhans. *Acta Endocrinol. (Copenhagen)* 39:465–73
39. Houghton, M. R., Morgan, R. G. H., Gracey, M. 1983. Effects of long-term dietary modifications on pancreatic enzyme activity. *J. Pediatr. Gastroenterol. Nutr.* 2:548–54
40. Howard, F., Yudkin, J. 1963. Effect of dietary change upon amylase and trypsin activities of the rat pancreas. *Br. J. Nutr.* 17:281–94
41. Imondi, A. R., Bird, F. H. 1967. Effects of dietary protein level on growth and proteolytic activity of the avian pancreas. *J. Nutr.* 91:421–28
42. Jensen, R. T., Gardner, J. D. 1978. Cyclic nucleotide-dependent protein kinase activity in acinar cells from guinea pig pancreas. *Gastroenterology* 75:806–16
43. Johnson, A., Hurwitz, R., Kretchmer, N. 1977. Adaptation of rat pancreatic amylase and chymotrypsinogen to changes in diet. *J. Nutr.* 107:87–96
44. Kanazawa, Y., Kuzuya, T., Ide, T. 1968. Insulin output via the pancreatic vein and plasma insulin response to glucose in dogs. *Am. J. Physiol.* 215:620–26
45. Kern, H. F. 1986. Fine structure of human exocrine pancreas. See Ref. 32a, pp. 9–19
46. Korc, M., Owerbach, D., Quinto, C., Rutter, W. J. 1981. Pancreatic islet–acinar cell interaction: Amylase messenger RNA levels are determined by insulin. *Science* 213:351–53
47. Korc, M., Sankaran, H., Wong, K. Y., Williams, J. A., Goldfine, I. D. 1978. Insulin receptors in isolated mouse pancreatic acini. *Biochem. Biophys. Res. Commun.* 84:293–99
48. Lahaie, R. G. 1984. Dietary regulation of protein synthesis in the exocrine pancreas. *J. Pediatr. Gastroenterol. Nutr.* 3:S43–50
48a. Lahaie, R. G. 1986. Translational control of protein synthesis by isolated pancreatic acini: Role of CCK_8, carbachol, and insulin. *Pancreas* 1:403–10
49. Lahaie, R. G., Dagorn, J. C. 1981. Dietary regulation of pancreatic protein synthesis. II. Kinetics of adaptation of protein synthesis and its effect on enzyme content. *Biochim. Biophys. Acta* 654:119–23
50. Lavau, M., Bazin, R., Herzog, J. 1974. Comparative effects of oral and parenteral feeding on pancreatic enzymes in the rat. *J. Nutr.* 104:1432–37
51. Lee, S. S., Nitsan, Z., Liener, I. E. 1984. Growth, protein utilization and secretion of pancreatic enzymes by rats in response to elevated levels of dietary protein. *Nutr. Res.* 4:867–76
52. Logsdon, C. D., Perot, K. J., McDonald, A. R. 1987. Mechanism of glucocorticoid-induced increase in pancreatic amylase gene transcription. *J. Biol. Chem.* 262:15765–69
53. Logsdon, C. D., Akana, S. F., Meyer, C., Dallman, M. F., Williams, J. A. 1987. Pancreatic acinar cell amylase gene expression: Selective effects of adrenalectomy and corticosterone replacement. *Endocrinology* 121:1242–50
54. MacDonald, R. J. 1987. Expression of the pancreatic elastase I gene in transgenic mice. *Hepatology* 7:42S–51S.
54a. MacDonald, R. J., Crerar, M. M., Swain, W. F., Pictet, R. L., Thomas, G., Rutter, W. J. 1980. Structure of a

family of rat amylase genes. *Nature* 287:117–22
55. Malaisse-Lagae, F., Ravazzola, M., Robberecht, P., Vandermeers, A., Malaisse, W. J., Orci, L. 1976. Hydrolases content in peri-insular and teleinsular exocrine pancreas. In *Endocrine Gut and Pancreas*, ed. T. Fujita, pp. 313–20. Amsterdam: Elsevier
56. Marchis-Mouren, G., Paséro, L., Desnuelle, P. 1963. Further studies on amylase biosynthesis by pancreas of rats fed on a starch-rich or casein-rich diet. *Biochem. Biophys. Res. Commun.* 13: 262–66
57. Meda, P., Bruzzone, R., Knodel, S., Orci, L. 1986. Blockage of cell-to-cell communication within pancreatic acini is associated with increased basal release of amylase. *J. Cell Biol.* 103:475–83
58. Mickel, F. S., Weidenbach, F., Swarovsky, B., LaForge, K. S., Scheele, G. A. 1989. Structure of the canine pancreatic lipase gene. *J. Biol. Chem.* 264:12895–901
59. Mössner, J., Böhm, S., Fischbach, W. 1989. Role of glucocorticosteroids in the regulation of pancreatic amylase synthesis. *Pancreas* 4:194–203
60. Muorot, J., Corring, T. 1979. Adaptation of the lipase–colipase system to dietary lipid content in pig pancreatic tissue. *Ann. Biol. Anim. Biochim. Biophys.* 19:119–24
61. Niemann, C. 1964. Alpha-chymotrypsin and the nature of enzyme catalysis: The problem of catalysis is considered in terms of the behavior of a single hydrolytic enzyme. *Science* 143:1287–96
62. Orchard, J. L., Davis, J. S., Larson, R. E., Farese, R. V. 1984. Effects of carbachol and pancreozymin (cholecystokinin-octapeptide) on polyphosphoinositide metabolism in the rat pancreas *in vitro*. *Biochem. J.* 217:281–87
62a. Osborn, L., Rosenberg, M. P., Keller, S. A., Meisler, M. H. 1987. Tissue-specific and insulin-dependent expression of a pancreatic amylase gene in transgenic mice. *Mol. Cell. Biol.* 7:326–34
63. Ouagued, M., Saraux, B., Girard-Globa, A., Bourdel, G. 1980. Differential regulation of lipase and colipase in the rat pancreas by dietary fat and proteins. *J. Nutr.* 110:2302–09
64. Palade, G. E. 1975. Intracellular aspects of the process of protein synthesis. *Science* 189:347–58
65. Palla, J. C., Ben Abdeljlil, A., Desnuelle, P. 1968. Action de l'insuline sur la biosynthèse de l'amylase et de quelques autres enzymes du pancréas de rat. *Biochim. Biophys. Acta* 158:25–35
66. Pavlov, J. P. 1902. *The Work of the Digestive Glands*. London: Griffin
67. Peiken, S. R., Rottman, A. J., Batzri, S., Gardner, J. D. 1978. Kinetics of amylase release by dispersed acini prepared from guinea pig pancreas. *Am. J. Physiol.* 235:E743–49
68. Pfeffer, S. R., Rothman, J. E. 1987. Biosynthetic protein transport and sorting by the endoplasmic reticulum and Golgi. *Annu. Rev. Biochem.* 56:829–52
68a. Pinsky, S. D., LaForge, K. S., Scheele, G. 1985. Differential regulation of trypsinogen mRNA translation: Full-length mRNA sequences encoding two oppositely charged trypsinogen isoenzymes in the dog pancreas. *Mol. Cell. Biol.* 5:2669–76
69. Poort, S. R., Poort, C. 1981. Effect of feeding diets of different composition on the protein synthetic pattern of the rat pancreas. *J. Nutr.* 111:1475–79
70. Puigserver, A., Wicker, C., Gaucher, C. 1985. Aspects moléculaires de l'adaptation des enzymes pancréatiques et intestinales au régime alimentaire. *Reprod. Nutr. Dev.* 25:787–802
71. Rausch, U., Rüdiger, K., Vasiloudes, P., Kern, H., Scheele, G. 1986. Lipase synthesis in the rat pancreas is regulated by secretin. *Pancreas* 6:522–28
72. Rausch, U., Vasiloudes, P., Rüdiger, K., Kern, H. F. 1985. In-vivo stimulation of rat pancreatic acinar cells by infusion of secretin. I. Changes in enzyme content, pancreatic fine structure and total rate of protein synthesis. *Cell Tissue Res.* 242:633–39
73. Rausch, U., Vasiloudes, P., Rüdiger, K., Kern, H. F. 1985. In-vivo stimulation of rat pancreatic acinar cells by infusion of secretin. *Cell Tissue Res.* 242:641–44
74. Reboud, J. P., Ben Abdeljlil, A., Desnuelle, P. 1962. Variations de la teneur en enzymes du pancreas de rat en fonction de la composition des régimes. *Biochim. Biophys. Acta* 58:326–37
75. Reboud, J. P., Marchis-Mouren, G., Cozzone, A., Desnuelle, P. 1966. Variations in the biosynthesis rate of pancreatic amylase and chymotrypsinogen in response to a starch-rich or protein-rich diet. *Biochem. Biophys. Res. Commun.* 22:94–99
76. Reboud, J. P., Marchis-Mouren, G., Paséro, L., Cozzone, A., Desnuelle, P. 1966. Adaptation de la vitesse de biosynthèse de l'amylase pancréatique et

du chymotrypsinogène a régimes riches en amidon ou en protéines. *Biochim. Biophys. Acta* 117:351–67
77. Renaud, W., Giorgi, D., Iovanna, J., Dagorn, J. C. 1986. Regulation of concentrations of mRNA for amylase, trypsinogen I and chymotrypsinogen B in rat pancreas by secretagogues. *Biochem. J.* 235:305–8
78. Rinderknecht, H. 1986. Pancreatic secretory enzymes. See Ref. 32a, pp. 163–83
79. Robberecht, P., Deschodt-Lanckman, M., Camus, J., Bruylands, J., Christophe, J. 1971. Rat pancreatic hydrolases from birth to weaning and dietary adaptation after weaning. *Am. J. Physiol.* 221:376–81
80. Roberts, P. J. P., Whelan, W. J. 1960. The mechanism of carbohydrase action. 5. Action of human salivary α-amylase on amylopectin and glycogen. *Biochem. J.* 76:246–53
81. Robyt, J. F., French, D. 1970. The action pattern of porcine pancreatic alpha-amylase in relationship to the substrate binding site of the enzyme. *J. Biol. Chem.* 245:3917–27
82. Sabb, J. E., Godfrey, P. M., Brannon, P. M. 1986. Adaptive response of rat pancreatic lipase to dietary fat: Effects of amount and type of fat. *J. Nutr.* 116: 892–99
83. Saraux, B., Girard-Globa, A., Ouagued, M., Vacher, D. 1982. Response of the exocrine pancreas to quantitative and qualitative variations in dietary lipids. *Am. J. Physiol.* 243:G10–15
84. Schick, J., Verspohl, R., Kern, H., Scheele, G. 1984. Two distinct adaptive responses in the synthesis of exocrine pancreatic enzymes to inverse changes in protein and carbohydrate in the diet. *Am. J. Physiol.* 247:G611–16
85. Schotton, D. M., Hartley, B. S. 1970. Amino-acid sequence of porcine pancreatic elastase and its homologies with other serine proteinases. *Nature* 225: 802–6
86. Simoes Nunes, C. 1986. Adaptation of pancreatic lipase to the amount and nature of dietary lipids in the growing pig. *Reprod. Nutr. Dév.* 26:1273–80
87. Snook, J. T. 1965. Dietary regulation of pancreatic enzyme synthesis, secretion and inactivation in the rat. *J. Nutr.* 87:297–305
88. Snook, J. T. 1969. Factors in whole-egg protein influencing dietary induction of increases in enzyme and RNA levels in rat pancreas. *J. Nutr.* 97:286–94
89. Snook, J. T. 1971. Dietary regulation of pancreatic enzymes in the rat with emphasis on carbohydrate. *Am. J. Physiol.* 221:1383–87
90. Steinhilber, W., Poensgen, J., Rausch, U., Kern, H. F., Scheele, G. A. 1988. Translational control of anionic trypsinogen and amylase synthesis in rat pancreas in response to caerulein stimulation. *Proc. Natl. Acad. Sci. USA* 85: 6597–6601
91. Stöckmann, F., Soling, H. D. 1981. Regulation of biosynthesis of trypsinogen and chymotrypsinogen by nutritional and hormonal factors in the rat. *Eur. J. Clin. Invest.* 11:121–32
92. Stratowa, C., Rutter, W. J. 1986. Selective regulation of trypsin gene expression by calcium and by glucose starvation in a rat exocrine pancreas cell line. *Proc. Natl. Acad. Sci. USA* 83:4292–96
93. Streb, H., Irvine, R. F., Berridge, M. J., Schulz, I. 1983. Release of Ca^{+2} from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-triphosphate. *Nature* 306: 67–69
94. Swarovsky, B., Steinhilber, W., Scheele, G. A., Kern, H. F. 1988. Coupled induction of exocrine proteins and intracellular compartments involved in the secretory pathway in AR4-2J cells by glucocorticoids. *Eur. J. Cell Biol.* 47: 101–11
95. Temler, R. S., Dormond, C. A., Simon, E., Morel, B., Mettraux, C. 1984. Response of rat pancreatic proteases to dietary proteins, their hydrolysates and soybean trypsin inhibitor. *J. Nutr.* 114:270–78
96. Trimble, E. R., Rausch, U., Kern, H. F. 1987. Changes in individual rates of pancreatic enzyme and isoenzyme biosynthesis in the obese Zucker rat. *Biochem. J.* 248:771–77
97. Vandermeers-Piret, M. C., Vandermeers, A., Wijns, W., Rathe, J., Christophe, J. 1977. Lack of adaptation of pancreatic colipase in rats and mice. *Am. J. Physiol.* 232:E131–35
98. Walter, P., Lingappa, V. R. 1986. Mechanism of protein translocation across the endoplasmic reticulum membrane. *Annu. Rev. Cell Biol.* 2:499–516
99. Wicker, C., Puigserver, A. 1987. Effects of inverse changes in dietary lipid and carbohydrate on the synthesis of some pancreatic secretory proteins. *Eur. J. Biochem.* 162:25–30
100. Wicker, C., Puigserver, A. 1989.

Changes in mRNA levels of rat pancreatic lipase in the early days of consumption of a high lipid diet. *Eur. J. Biochem.* 180:563–67
101. Wicker, C., Puigserver, A., Scheele, G. 1984. Dietary regulation of levels of active mRNA coding for amylase and serine protease zymogens in the rat pancreas. *Eur. J. Biochem.* 139:381–87
102. Wicker, C., Scheele, G. A., Puigserver, A. 1988. Pancreatic adaptation to dietary lipids is mediated by changes in lipase mRNA. *Biochimie* 70:1277–83
103. Williams, J. A., Goldfine, I. D. 1985. The insulin–pancreatic acinar axis. *Diabetes* 34:980–86
104. Williams, J. A., Hootman, S. R. 1986. Stimulation-secretion coupling in pancreatic acinar cells. See Ref. 32a, pp. 123–39