Physiology of the Gastrointestinal Tract

Volume 2

Editor-in-Chief
Leonard R. Johnson, Ph.D.

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Chapter 29

Structure-Function Relationships of the Pancreas

Frederick S. Gorelick and James D. Jamieson

The exocrine pancreas, with the acinar cell as its functional subunit, has served as the paradigm for the study of a protein-secreting gland. Although the relationship between the gross or morphologic features and the physiologic functions of this organ are still being elucidated, numerous investigations at the subcellular level have given us insight into basic structure-function relationships. This chapter is divided into four sections: The first is a general morphologic overview of the gland, in which we describe regional variations in cellular composition and the interrelationship of cells of the endocrine and exocrine gland to the surrounding connective tissue stroma and to each other. In addition, traditional neural pathways and paracrine interrelationships are discussed. The second section explores the role of tight junctions in delineating the internal and external environments of the gland and considers the function of communicating junctions in cell-cell interactions. The third and fourth sections focus on the subcellular organization of the acinar cell and conclude with a detailed review of the formation, storage, and release of secretory proteins.

GENERAL MORPHOLOGIC DESCRIPTION

The pancreas is a retroperitoneal organ with a mass of 85 ± 15 g in the human female and 90 ± 16 g in the male. It arises from two anlage of the primitive foregut: a dorsal portion coming from the dorsum of the duodenum, which forms a portion of the head and uncinate process and all of the body and tail, and a ventral portion derived from the primitive bile duct, which forms the remainder of the head and uncinate process. Generally, the ducts draining the dorsal and ventral pancreas fuse at about 6 weeks of gestation in humans, with the ventral duct providing the main conduit of drainage into the duodenum.

In the adult, different origins of the pancreas are reflected by the occasional persistance of separate dorsal and ventral ducts and a higher concentration of pancreatic polypeptide in the area derived from the ventral pancreatic bud (109,118). The functional meaning of the latter observation is unknown. The arterial supply arises from branches of the splenic artery, which forms

arcades with the pancreatic branches of the gastroduodenal and superior mesenteric arteries (99). The autonomic innervation is both parasympathetic and sympathetic through splenic subdivisions of the celiac plexus. The innervation of the pancreas is discussed later.

The pancreas is a mixed exocrine-endocrine gland, with the exocrine portion of the gland forming the greatest volume (84%). Ductular cells and blood vessels form about 4% of the gland volume, while endocrine cells comprise only 2%. The remainder (10%) is occupied by extracellular matrix.

The main pancreatic duct, in addition to serving as a conduit for secretory proteins, may contribute a portion of the fluid and electrolytes secreted by the pancreas (139), although micropuncture studies in the cat suggest that most fluid and electrolyte secretion arises from extralobular ducts (83). Although it has long been accepted that the exocrine pancreas is organized into true acinar units (79), and is referred to as such, several recent studies question this concept. Wax casts of dog pancreas demonstrate the final ductular subdivisions to be an anastomosing tubular arrangement rather than an acinar structure (13). Electrical coupling experiments in the mouse pancreas have shown the electrical subunit of the pancreas to be about 500 cells in size (57). These two studies suggest that the functional subunit of the pancreas is both electrically and morphologically larger than the traditional 20- to 50-cell acinus.

Acinus

The basic subunit of the exocrine pancreas is the acinus, which is bound by a connective tissue matrix, including the basal lamina, which does not course between the lateral areas of contiguous acinar cells (Fig. 1). This connective tissue layer is continuous with that surrounding the ductular epithelium. The majority of cells in the acinus consists of acinar cells, with a smaller number of centroacinar cells marking the beginning of the ductular system of the gland. The supporting matrix of the pancreas is a mixture of several different types of collagen. Preliminary investigations from this laboratory (D. E. Ingber, J. A. Madri, J. D. Jamieson) indicate that pancreatic basal lamina consists of type IV, collagen, laminin, and fibronectin, while types I and III are located in the adjacent extracellular space, ductular and vascular elements. Collagen types I and III are presumably produced by fibroblasts or other cell types in the intercellular space. Studies by Banerjee et al. (6) suggest that the basal lamina is produced by the epithelial cells. At the transmission electron microscope (TEM) level, the basal lamina, previously termed the basement membrane, is usually composed of three zones (157): (a) an electron lucent layer immediately adjacent to the plasma membrane, referred to as the lamina lucida or rara, (b) a central dense layer, the lamina densa, and (c) an outer (the lucent) layer—the lamina diffusa—which blends into the extracellular space. Since the electron lucent areas are often inconspicious or even absent, some authors have used the term basement membrane or basal lamina as synonomous with lamina densa. Further TEM studies of rat pancreas (68) reveal variations in the morphology of basal lamina according to the cell type.

The acinar cell possesses a well-defined lamina lucida and lamina densa, while the lamina diffusa is indistinct. In contrast, the basal lamina adjacent to centroacinar cells consists of a more prominent lamina lucida and lamina densa and a distinct lamina diffusa. In addition, a sharp distinction is found between the two types of cells in the acinus when stained for acid substances. The lamina diffusa is exclusively stained under the acinar cell, while both the lamina diffusa and lucida stain beneath the centroacinar cell. Although the basement membrane probably functions as a molecular sieve in the kidney (38), its exact function in the pancreas is unknown. The staining characteristics found in the study by Katsuyama and Spicer (69) suggest the presence of abundant fixed anionic binding sites beneath the centroacinar cell which may be important in ion transport.

Acinar Cell

The majority of the pancreas (>80%) is comprised of acinar cells. By light microscopy, these cells are pyramidally shaped, with the apex facing the lumen of the acinus (Fig. 1). Areas of specialization are easily appreciated within acinar cells (1). Zymogen granules are restricted to the apical cytoplasm of the cell and vary in number, depending on the stage of development (65), supply of nutrients (114), and state of stimulation by neurohormonal agents (29). An area between the basally located nucleus and the apex is often paler staining by light microscopy. This represents the Golgi complex (discussed below). A third zone characterized by intense basophilia is located in the basal region of the cell and represents endoplasmic reticulum (ER). The acinar cells are generally uniform in their appearance throughout the pancreas, although a "halo" phenomenon is seen in the periinsular region. Acinar cells in this area have a larger cytoplasm and nucleus and an increased volume of zymogen granules compared to the remainder of the pancreas (49). The potential importance of this observation is discussed below.

Centroacinar Cell

The centroacinar cells are seen in the final subdivision of pancreatic ducts. They are smaller than the acinar cell (31), have a sparse cytoplasm devoid of zymogen granules, and contain a small Golgi complex and few ER cisternae. The mitochondria are large, abundant, and tend to be elongated. Occasionally, small smooth surface

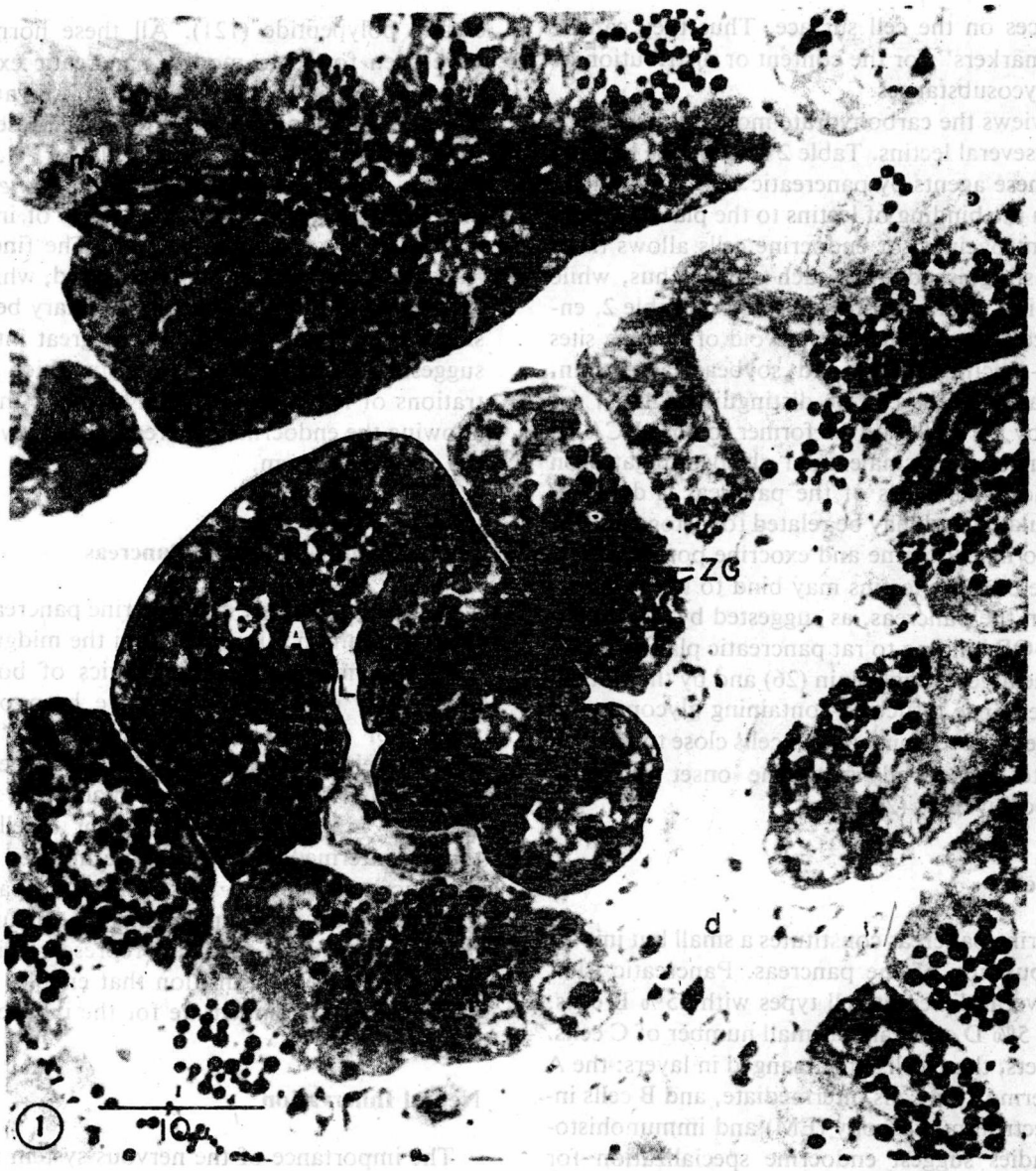

FIG. 1. Light photomicrograph of a guinea pig pancreas. The heavy line denotes an acinus. *Region A,* apical cytoplasm, rich in zymogen granules (ZG). *Region B,* basal, basophilic staining region representing ER. *Region C,* pale, epinuclear region representing the Golgi complex. L, lumen of the acinus; N, acinar cell nucleus; n, nucleolus; M, mitochondria; d, intralobular duct.

vesicles are seen in the cytoplasm. Both the acinar and centroacinar cell have microvillous processes. Supporting the contention that centroacinar cells are responsible for fluid and electrolyte secretion is the histochemical localization of carbonic anhydrase to this cell type (20). In addition, Katsuyama and Spicer (69) found that silver, when used as a marker for anions, precipitates predominantly on the luminal surface of centroacinar cells and not on acinar cells. The capacity of nitric acid to reduce the staining of centroacinar cells suggests that the anion present is not Cl^- and most likely is bicarbonate (102). Both of these findings distinguish the acinar from the centroacinar cell on a functional basis and indicate the role of the latter in electrolyte secretion.

The acinar and centroacinar cells can also be distinguished by sparse staining of sialomucins on the basolateral membrane of the former compared to the latter (69). Since it has been suggested that the sialic acid-rich proteins may act as a cation filter in other systems (89), this difference may also reflect specialization of the centroacinar cell in electrolyte transport.

Lectin Binding

Differences between the centroacinar and acinar cells have been demonstrated by specific binding patterns for lectins (92). These substances are usually derived from plants and bind reversibly to certain carbohydrates or

glycosubstances on the cell surface. Thus they can be utilized as "markers" for the content or distribution of membrane glycosubstances.

Table 1 reviews the carbohydrate moieties thought to be bound by several lectins. Table 2 reviews the binding patterns of these agents by pancreatic cells. Qualitative differences in the binding of lectins to the plasmalemma of acinar, centroacinar, or endocrine cells allows these cells to be distinguished from each other. Thus, while acinar cells bind all the lectins indicated in Table 2, endocrine and centroacinar cells are devoid of binding sites for L-fucose-specific lectins and soybean agglutinin, while centroacinar cells can be distinguished from endocrine cells by the ability of the former to bind RCA II. The appearance of plasmalemmal glycoconjugates on endocrine and acinar cells of the pancreas is developmentally regulated and may be related to histogenesis of the gland into its endocrine and exocrine portions (91). Finally, some of these lectins may bind to hormone receptor sites in the pancreas, as suggested by the inhibition of CCK-OP binding to rat pancreatic plasma membranes by wheat germ agglutinin (26) and by the finding that the appearance L-fucosyl-containing glycoproteins on the surface of developing acinar cells close to parturition correlates temporally with the onset of secretogogue responsiveness (29).

Endocrine Cells

The endocrine pancreas constitutes a small but important cell population of the pancreas. Pancreatic islets consist of several different cell types with 75% B cells, 20% A cells, 5% D cells, and a small number of C cells. In human islets, these cells are arranged in layers: the A cells are outermost, D cells intermediate, and B cells innermost. Electron microscopy (EM) and immunohistochemical studies suggest endocrine specialization for each of these cell types. B cells produce insulin, A cells glucagon, and D cells somatostatin, gastrin, and pancreatic polypeptide (121). All these hormonal agents have been found to modify pancreatic exocrine secretion (28,45,66,105,158). Recent observations in this laboratory and by others confirm the presence of an insulin receptor on the acinar cell (8, L. J. Miller, V. Iwanij, and J. D. Jamieson, *unpublished*). Whether pharmacologic or physiologic effects of insulin are being observed remains to be seen. The finding that the islets are supplied with a capillary bed, which has its efferents connecting to a second capillary bed encompassing the exocrine pancreas, is of great interest (40). It suggests an insuloacinar system in which high concentrations of islet hormones may contact the acinar cell, allowing the endocrine pancreas to directly interact with the exocrine system.

TABLE 1. *Carbohydrate moieties bound by various lectins*[a]

Lectin[b]	Hapten sugar
Con. A	Glucose, mannose
Lotus lectin	Fucose
RCA I	Galactose
RCA II	*N*-acetylgalactosamine, galactose
SBA	*N*-acetylgalactosamine, galactose
WGA	*N*-acetylglucosamine
Limulin	*N*-acetylneuraminic acid

[a] From ref. 92.
[b] ConA, concanavalin A; Lotus lectin, lotus tetragonolobus; RCA, ricinus communis agglutinin; SBA, soybean agglutinin; WGA, wheat germ agglutinin.

Intermediate Cells of the Pancreas

Both the endocrine and exocrine pancreas are derived from a common outpouch from the midgut endoderm. Cells that maintain characteristics of both endocrine and acinar pancreatic cells have been observed in a variety of animals and are designated "intermediate cells". Melmed (97) suggests that these cell types show characteristics of acinar cells, in addition to containing secretory granules of the α, β, or δ cell variety. Although intermediate cells can be induced in iatrogenic diabetic states or in rats following partial pancreatectomy (90), their importance is not understood. It has been suggested that they represent acinar cells that have undergone a transition that enables them to produce insulin to compensate for the induced diabetes.

Neural Innervation

The importance of the nervous system in the control of pancreatic secretion is not fully understood, but a role for the cholinergic, adrenergic, and paracrine path-

TABLE 2. *Summary of lectin binding to various cells of the pancreas*[a]

Lectin[b]	Acinar cell[c]	Centroacinar	Endocine
Con. A	II	II	II
Lotus	III	—	—
RCA I	III	III	III
RCA II	III	III	—
SBA	III	—	—
WGA	III	III	III
Limulin	III	III	III

[a] From ref. 92.
[b] See Table 1 for abbreviations.
[c] —, no binding; II, moderate binding; III, heavy binding.

ways has been implicated in physiologic studies (145). Morphologic studies also suggest that neural controls are active in exocrine pancreatic function. In humans and dogs (156,165), both vagal and sympathetic nerves innervate the pancreas. The supply tends to be richer in the head of the pancreas than in the tail. The head and isthmus tend to be innervated by the right celiac, hepatic, and superior mesenteric plexus, while the tail and body are mainly innervated by the celiac plexus and the splanchnic neurologic network.

Nerve Terminals

The ultrastructure of pancreatic innervation has been studied in several animals. Myelinated fibers are generally not found in the parenchyma, and ganglion cells are seen in the interlobular tissue.

The site of nerve termination varies from species to species but can be divided generally into four terminal areas: (a) blood vessels, (b) pancreatic acinar cells, (c) duct cells, and (d) islet cells.

In the bat, dove, or domestic fowl, pancreas nerve endings can be observed in direct contact with the acinar cell surface (164,165). In contrast, in the monkey, dog, or guinea pig, nerve endings do not directly contact the cell surface but rather terminate near the base of the acinar cell separated from the plasmalemma by a layer of basal lamina (165). In the rat, the minimum separation between the nerve terminals and the acinar cell plasma membrane is 1,000 Å (141).

Nerve terminals about blood vessels generally possess a prominent gap (500 Å), with a thin band of connective tissue intervening. Nerve termination is usually on or near the basement membrane of ductular cells. Innervation of islets is generally richer than that of the acini, and nerve terminals directly abut on islet cell plasmalemma; in some species, however, differences have been noted (165).

Nerve terminals have been subdivided according to the morphology of their synaptic vesicles (164). Four types of endings have been described, based on the presence of small clear vesicles and/or large dense core vesicles. Several studies suggest that each type of nerve ending differs in the type of neurosecretory material that it contains. In addition, there is a tendency for specific nerve endings to be associated with one of the regional subunits of the pancreas; e.g., nerve endings with large and small dense core vesicles are found only in association with pancreatic blood vessels in fowl (164).

Cholinergic Nerves and the Pancreas

Numerous *in vivo* studies have implicated the importance of cholinergic input on pancreatic secretion, although its role is still controversial (128). Debas and Yamagishi (25) showed a reflex arc connecting the antrum of the stomach and the pancreas. Antral distention with acid or alkali results in secretion of protein and bicarbonate by the dog pancreas. The observation that truncal vagotomy diminished and atropine abolished this phenomenon suggests that this is mediated by a cholinergic reflex arc. In the dog, Solomon and Grossman (148) examined secretory capacity from a transplanted denervated pancreas in response to exogenous cerulein or food stimulation. They observed that: (a) protein secretion in response to exogenous cerulein is the same for the intact and transplanted pancreas; (b) the transplanted pancreas is significantly less sensitive to intestinal fat or amino acid perfusion than is the intact pancreas; (c) neither atropine nor vagotomy alters the response of the transplanted pancreas to intestinal stimulation. In addition, Singer et al. (144) have demonstrated that amylase secretion occurs more rapidly after intestinal food stimulation, compared to direct stimulation with cholecystokinin (CCK). Atropine or vagotomy increased the latency period for enteric stimulation. These findings support the presence of an enteropancreatic reflex.

Supportive of the importance of the parasympathetic nervous system in pancreatic function is the localization of a muscarinic receptor on the acinar cell. Acetylcholine or its analogs administered to pancreatic lobules or isolated acinar cells results in release of secretory proteins (2). This receptor is different from that for CCK, since it alone is blocked by atropine (19) and not by dibutyryl-cyclic GMP (120). In addition, the simultaneous administration of CCK and a cholinergic agonist at their ED_{50} results in an additive release of secretory proteins (170), supporting the presence of two different receptor populations.

Other Neural Pathways Involving the Exocrine Pancreas

Sympathetic.

In addition to the cholinergic nervous system, several other neural pathways have been implicated in controlling exocrine pancreatic function. In the dog pancreas, norepinephine causes a decrease in cerulein-induced protein and fluid secretion, which is reversed by phenoxybenzamine (160). Pancreatic blood flow studies show that this effect is mediated by vasoconstriction. This study is consistent with histochemical observations (32) demonstrating that adrenergic terminals are predominantly associated with vascular structures in the pancreas.

Several studies suggest that dopaminergic agents are active in stimulating pancreatic fluid and electrolyte secretion. Although one study suggests that they also pro-