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Histochemistry and Cell Biology of Autonomic Neurons and Paraganglia

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Distribution of the Ca^{++} Binding Protein Chromagranin A in the Pancreatic Islets

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Introduction

More than 20 years ago, experimental data suggested that proteins are released together with catecholamines from the adrenal medulla upon stimulation (Banks and Helle 1965). Co-storage and co-release of these proteins, named chromogranins, with catecholamines is now well established (cf. Winkler et al. 1986). Chromogranin A is the most abundant member of this acidic group of proteins, which has also been detected in many other endocrine cells secreting by exocytosis (cf. Winkler et al. 1986). Previous investigations differed in the precise cellular location of the antigen in the pancreatic islet (O'Connor et al. 1983; Cohn et al. 1984; Wilson and Lloyd 1984; Varndell et al. 1985). The present contribution summarizes recent data on the cellular and subcellular distributions of chromogranin A in the bovine pancreatic islet (Ehrhart et al. 1986) and relates them to the Ca^{++} binding function of chromogranin A (Reiffen and Gratzl 1986a,b).

Immunocytochemical Observations

Four peptides constitute the established islet hormones within the mammalian endocrine pancreas: insulin, glucagon, somatostatin and pancreatic polypeptide. Appropriately diluted antisera against these hormones were used to identify the different endocrine cells (PAP-technique). A polyclonal antibody directed against bovine chromogranin A was applied to consecutive sections. It was observed by this procedure that the cells which reacted with antibodies against insulin, glucagon or somatostatin also displayed immunoreactivity against chromogranin A.

At the ultrastructural level (protein A-gold technique), chromogranin A was confined exclusively to the secretory vesicles of the pancreatic endocrine cells. As an example, immunostaining of the insulin containing secretory vesicles of pancreatic B cells is shown in Fig. 1. The topography of the gold particles after staining with the antibody against insulin was different from that observed with the anti-chromogranin A antibody. Approximately 70% of the insulin immunoreactivity was located in the center of the electron dense core of the vesicles. Whereas 64% of the gold particles indicating chromogranin A immunoreactivity were observed overlying the clear halo and the outer layer of the electron dense core. Similar results were obtained in the glucagon containing vesicles. This subvesicular distribution of chromogranin A is very much reminiscent of the distribution of Ca^{++} in the vesicles as revealed by the pyroantimonate technique (cf. Lenzen and Klöppel 1984).

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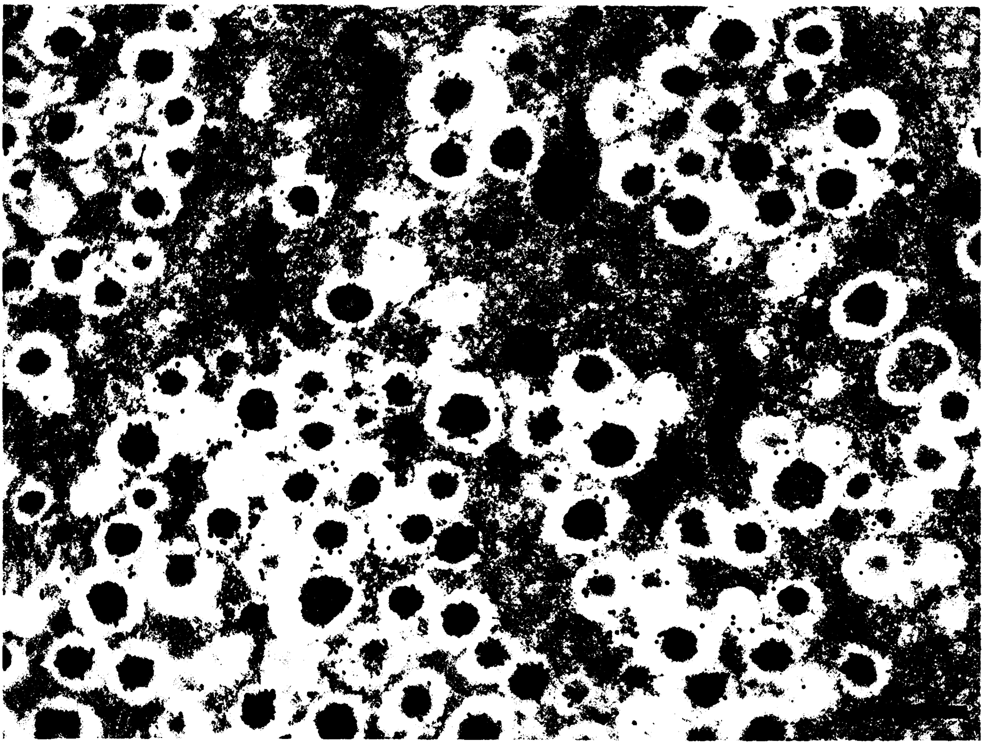

Fig. 1. Photomicrograph of an ultrathin section of a pancreatic B cell immunostained for chromogranin A by the protein A-gold technique. Bar = 0.5 um.
(Courtesy of M. Ehrhart, Abteilung Klinische Morphologie, Universität Ulm)

Functional Considerations

Low intracellular free Ca^{++} concentrations are maintained in mammalian cells by Ca^{++} transport systems present in the plasma membrane, endoplasmic reticulum and mitochondria. In endocrine cells, cytoplasmic Ca^{++} plays a strategic role in the regulation of secretion by exocytosis and in these cells, secretory vesicles constitute an additional Ca^{++} sequestration system. Secretory vesicles of practically all endocrine cells contain large amounts of Ca^{++}, and, in some cases, the transport system for this divalent cation across the membrane has been characterized in some detail (cf. Krieger-Brauer and Gratzl 1983; Saermark et al. 1983).

Ca^{++} transported into the vesicles is largely bound to intravesicular substances (Bulenda and Gratzl 1985). Among the proteins present within chromaffin secretory vesicles, only chromogranin A binds Ca^{++} (Reiffen and Gratzl 1986a,b). The presence of this protein within almost all endocrine cells, including the pancreatic islet cells may indicate that processes similar to those found in chromaffin vesicles work in many endocrine cells secreting by exocytosis. In this conjunction, the cytochemical observation that Ca^{++} and chromogranin A exist together in the submembrane space of the secretory vesicle of the pancreatic islet cells is of particular interest (see previous chapters).

Markers for Endocrine Cells

A certain division of endocrine cells within the body have been described as "endocrine epithelial organs" (Feyrter 1938). The endocrine cells belonging to this division can be identified by cytochemical characteristics, by ultrastructural criteria (Pearse 1968) and by their properties related to the process of stimulus-secretion coupling (Fujita 1976).

During the investigation of the molecular events of exocytosis and its regulation, more and more constituents of these specialized endocrine cells have been identified. Besides chromogranin A, a variety of additional markers, all of which exhibit a very similar pattern of distribution in the body, have been detected in polypeptide secreting endocrine cells. Obviously, these components are linked to the function or the specific metabolic requirements of endocrine cells.

A Ca^{++} binding membrane protein with a molecular weight of 38,000 is among these cellular constituents (cf. Navone et al. 1986) as well as neuron specific enolase (Schmechel et al. 1978). Thus, a new generation of biochemical markers for the polypeptide secreting endocrine cells is available. They can be used to find out whether certain endocrine cells belong to the "endocrine epithelial organs" first described by Feyrter (1938).

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