APUD SYSTEM: AN ANATOMICAL PERSPECTIVE

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INTRODUCTION

The endocrine system is the most wide-spread and segregated system in the body and classified as the diffuse and classic endocrine system. In the diffuse system the part receiving the prime focus as the APUD system (Amine Precursor Uptake and Decarboxylation). It is a collective term for a diffuse spectrum of endocrine cell types scattered throughout the body (Sternber, 2000). The individual cell of the APUD system is termed as apudocyte.

The clinical importance of these diffuse populations of cells from the fact that when these cells undergo unopposed proliferation they result in production of a number of neoplastic syndrome and tumors (Hassan and Safi, 2002).

APUD system includes the following diverse cells:

(Dellmann and Eurell, 1998)

- Endocrine cells in the mucosa of the gastrointestinal tract
- Endocrine cells (Kultchitsly cells) in the respiratory epithelium
- Thyroid parafollicular cells (C cells)
- Cells of the pancreatic islets
- Epinephrine and norepinephrine secreting cells in the adrenal medulla
- Chemoreceptors in the carotid body
- Juxtaglomerular cells

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- Corticotropes in pars distalis
- Melanotropes in the pars intermedia

ENDOCRINE CELLS IN THE GASTROINTESTINAL TRACT

The APUD system is the most wide spread in the gut specially stomach and small intestine and a part of the large intestine. In the stomach they are predominate in pyloric region and in the intestine they occur both in villi and crypts. Most frequently these cells are wedged between the basement membrane and the chief cells and do not reach the surface of the epithelium.

Origin

The APUD cells are considered to be of endodermal origin, while earlier they were thought to be neural crest derivatives. It was shown that the progenitor of the enterochromaffin cells are presumptive gut, before prospective neuroblast arrive. It is also shown that neuroblast is not necessary for the development of enterochromaffin cells. (Andrew, 1998; Harsh Mohan, 2005).

Histology, Histochemistry and Ultrastructure

The routine Haematoxylin and Eosin stain are ineffective for staining purpose (Hassan and Safi, 2002).

The cells become coloured when treated with osmic acid or with potassium dichromate, for that reason they are sometimes termed enterochromaffin cells. The granules of most of

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these cells precipitate silver when treated with ammonical silver nitrate, thus called argentaffin cells. A minority of the enterochromaffin cells are impregnated by silver only when reducer is employed, these are termed the argyrophil cells.

At least 12 different endocrine cells have been identified by electron microscopy in the gastrointestinal tract. On the basis of ultrastructure the well defined cells in the stomach and intestine are:

1. **Gastrin producing cell** - Present especially in the pyloric region of the stomach, extends from the basal lamina to the glandular lumen and has spherical membrane limited granules of variable density. Immuno histochernical method suggests that this cell produce gastrin (Grieder et al., 1972; Bloom and Fawcett, 1975).

2. **Serotonin secreting cell** - The predominant category of enterochromaffin cells found throughout the alimentary tract. The cells are pyramidal in shape with a narrow apical end covered with microvilli and granules are located near the cell base. These cells exhibit a chromaffin as well as argentaffin reaction. By immunohistochemical reaction they are known to contain 5- hydroxy tryptamie (Serotonin). It is very important for generation of peristaltic movement. They produce and contain about 90% of the body’s store serotonin (Thompson et al., 1990).

3. **Glucagon producing cell** - A third type of granulated cell bears striking resemblance to the alpha cells of the pancreatic islets and suspected of being the source of enteroglucagon. These cells do not reach the lumen. Granules are almost uniformly round and 500-700 nm in diameter. The position of the Golgi complex is variable but is often below the nucleus (Dellmann and Eurell, 1998).

### ENDOCRINE CELLS IN THE RESPIRATORY EPITHELIUM (KULTCHITSLY CELLS)

**Respiratory Epithelium Showing Kulchitsly Cells (K)**

The lining epithelium of the trachea and bronchial tree is respiratory epithelium, contains neuroendocrine cells are APUD cells. (Dellmann and Eurell, 1998). Scattered either singly or in small groups, throughout the epithelium of the conducting airways including the bronchioles. In terminal bronchioles the majority of neuroendocrine cells are close to or lining the bifurcation (Kwang, 1997). They are analogous to enteroedocrine cells of the GI tract. In comparative study it was found that they are common in the form of solitary cells in the bronchial tree of sheep but are much less in the yak and its inter breeding with the cattle (Gosny et al., 1998).

(a) Bodian Silver Method; (b) Gomori’s Method; (c) Eosin and Methylene Blue (a,b,c) Reactions of Granules in Argentaffin Cells From Small Intestine of Pig
Origin

The evidence suggests that the APUD cells of the respiratory tract arise from the same precursor cells as the other epithelial cells (Sidhu, 1979). These cells develop early during morphogenesis and their amine/peptide content peak at the time of birth and decline postnatally. These cells are most abundant in young animals and are some times associated with nerve endings. A role in lung neoplasia is also suggested for endocrine cells (Kwang, 1997).

Histology, Histochemistry and Ultrastructure

These cells are more pyramidal than columnar and brush cells and produce granules that lie basally with in the cytoplasm (Samulson, 2007).

THYROID PARAFOLLICULAR CELLS (C CELLS)

The parafollicular (C) cells usually occurs as single cell enclosed within the basal lamina of the follicles but may also form groups in the same location or outside the follicles especially in dog. They do not border directly the lumen but are separated from it by overarching processes of neighboring follicular cells (Bloom and Fawcett, 1975; Dellmann and Eurell, 1998).

Parafollicular cells in the dog thyroid gland occurs as single cells (arrow head) but frequently form relatively large cluster (arrow) Trichome stain.

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form relatively large cluster (arrow) Trichome stain.

**NEURAL CREST CELLS MIGRATING INTO THE DEVELOPING THYROID GLAND**

**Origin**

The cells are derived from the neural crest (Dellmann and Eurell, 1998). In dogs they originate from the ultimobranchial bodies (Pearse and Carvalheira, 1967). They appear in small groups or a solitary cell between the follicular cells and the capillary wall. In early development they can be easily recognized as light cells localized among the follicular cells never reaching the follicular lumen. The number of parafollicular cells increases with age of animals and the increase is particularly pronounced in the early postnatal period (Nuzez and Gershan, 1976; Zebel, 1987).

Parafollicular cells develop and accumulate characteristic secretory granules prior to birth, at birth and during neonatal period but not in adult thyroids. The cells release their content by exocytosis, this indicates that the cells are more active at this time prior to birth, at birth and neonatal) than in early foetal and later adult life (Getty, 1975).

**Histology, Histochemistry and Ultrastructure**

The cells are also referred as C cells or clear cells because of their pale staining cytoplasm which surrounds a comparable large round nucleus. The cells often measure twice the diameter of that of follicular cells. They represent only a small fraction of the total parenchyma of the thyroid (Samulson, 2007).

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**Schematic Diagram of Exocytosis**

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**Transmission electron micrograph of parafollicular cells in the thyroid of cat**

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**Silver nitrate method of Cajals showing brown pigments in parafollicular cytoplasmic granules in dog thyroid**

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Secretory granules are from 100-200 nm in the rabbit and pig from 100-300 nm in the dog and sheep (Rost et al., 1975). The granules tend
to concentrate in the cytoplasmic areas closest to the follicular basement membrane.

Cytochemically they are distinguishable from the follicular cells by their high level of activity of the mitochondrial enzyme α-glycerophosphatase (Pearse, 1966; Bloom and Fawcett, 1975). The parafollicular cells elaborate and secrete the blood calcium lowering hormone calcitonin.

**CELLS OF THE PANCREATIC ISLETS**

Irregularly shaped patches of endocrine tissue located within the pancreas of most vertebrates.

**Origin**

The pancreatic islets originate from the same endoderm that gives rise to the rest of the exocrine pancreas (Samulson, 2007). Embryologically the islets tissue arise from the budding of the developing duct of the pancreas. The islets first appear as a single sprout from pancreatic ducts. Later in development they grow in complex masses which are spherical or ovoid or irregular in shape measuring from 40-200 mm in diameter (Getty, 1975).

Andrew (1979) after his experiment on chick embryo concluded that at least a and b cells are not derived from the neurectoderm. Their most likely origin remains the endoderm which is accepted source until recently. b cells increase a number by replication of preexisting cells and by ductal epithelium. Both mechanisms for adding new b cells (replication and neogenesis) are likely to be functional after birth in all species, but they make different contribution in different species (Susan and Sharma, 2006).

**DEVELOPMENT OF EXOCRINE AND ENDOCRINE PANCREAS**

**Histology, Histochemistry and Ultrastructure**

The islets are usually found within lobule parenchyma, a few in the interlobular connective tissue and a few attached to the exocrine ducts, the ducts however, receive no secretion from them (Getty, 1975).
In most domestic animals the cluster consists of 4 cell types based on a combination of a morphological and histochemical feature are A (α), B (β), D (δ) and C cells.

DEVELOPMENT OF EXOCRINE AND ENDOCRINE PANCREAS

A (α) cells - Form the second most numerous type of endocrine cell within the islet (Samulson, 2007). They possess secretory granules insoluble in alcohol that have a positive immuno-histochemical reaction for glucagon and stain brilliant red with Masson’s trichome and Gomori’s aldehyde fuchsin. The cells represent approximately 3-5% of the islet population. In horse the a cells are located in the centre whereas in cattle they tend to arrange at the periphery. The pancreatic islets of the uncinate process of dogs are devoid of a cells (Dellmann and Eurell, 1998).

Ultrastructurally these cells are typical protein secreting cells. The nucleus is generally deep indented or lobulated.

β cells - Are the most numerous cells in the pancreatic islets comprising approximately 60-80% of the total islet cell population (upto 98% in sheep). They predominate in the periphery of the islet of horse and in the centre in cattle. The β cells contain secretory granules soluble in alcohol and stain dark orange with Mallory's
trichome and deep purple with Gomori’s aldehyde fuchsin stain and have a positive immunohistochemical reaction for insulin (Dellmann and Eurell, 1998).

Fine structural characteristics are similar to those of α cells, but they have larger mitochondria and a prominent Golgi complex. The endoplasmic reticulum is less extensive than that of the α cells. The β cells show marked variation in the character of their granules. In all domestic animals except horse, the β granules have a very distinctive appearance because they contain one or more small dense crystals. The crystals are surrounded by a matrix. In electron micrographs, the dense crystals enclosed in a loose fitting membrane (Bloom and Fawcett, 1975). In dog δ cells granules often appear as rectangular crystallloid structure whereas in pig they are round shaped (Ham and Cormack, 1987).

δ cells - Are of relatively rare occurrence (approximately 5% in dogs) and are located mainly in the periphery of the islets. They synthesize somatostatin.

C cells - Are nongranulated or sparsely granulated cells that are considered to be (Dellmann and Eurell, 1998).

**EPINEPHRINE AND NOREPINEPHRINE SECRETING CELLS IN THE ADRENAL MEDULLA**

The endocrine cells of the adrenal medulla are modified postganglionic sympathetic neurons, the secretory activity of which is regulated by postganglionic sympathetic innervation. When treated with fixatives containing chromium salts, the large cells stain dark brown, consequently they are often referred to as chromaffin cells (Dellmann and Eurell, 1998). Their staining capacity in chromium solution is due to the presence of adrenalin (Jordan, 1952).

Photomicrograph of the junction of the zona reticularis (above) with the clusters of large pale cells of the adrenal medulla (below). Catecholamine granules ordinarily are not visible in the cells of the medulla with the light microscope.

In horse, cow, sheep and pigs the adrenal medulla is subdivided into 2 distinct zones, an outer zone made of large epinephrine cells and an inner zone of clusters of small polyhedral norepinephrine cells.

**Origin**

Certain cells which migrate ventrally from the neural crest at the time of the sympathetic
ganglia are formed, become gland cells (non nervous), active in the production of a specific hormone (Patten and Carlson, 1977). A continuous migration of cells from the developing celiac ganglia proceeds until approximately the time of birth so that substantial number of cells comes to occupy the central part of the adrenal gland to comprise its medulla. On migrating to the central region of the developing adrenal gland most of the neuroectodermally derived cells differentiate into secretory cells that are distributed along blood vessels.

**Histology, Histochemistry and Ultrastructure**

Two types of chromaffin cells are distinguished, epinephrine cells and norepinephrine cells. Approximately 80% of the cells are epinephrine cells. They have less affinity for chromium salts. The norepinephrine cells give a strong reaction and their secretory granules are more dense than those of epinephrine cells (Dellmann and Eurell, 1998).

A group of medullary cells along a vein in an adrenal gland fixed in formal – dischromate and then subjected to silver intensification before counterstaining with hematoxylin and eosin-azure.

The application of a group of histochemical methods to the chromaffin cells permit the identification of two types of cells, one containing norepinephrine and other epinephrine. The norepinephrine storing cells are autofluorescent, give argentaffin and potassium iodate reaction exhibit a low affinity for azocarmine and give a negative acid phosphatase reaction. The epinephrine storing cells have a high staining affinity for azocarmine and a positive acid phosphatase reaction and are not fluorescent or reactive with iodine or silver (Bloom and Fawcett, 1975).

In electron micrographs the most prominent feature of these cells is the presence of large number of membrane bounded dense granules 100-300 nm in diameter.

**JUXTAGLOMERULAR CELLS (GRANULAR CELLS)**

The juxtaglomerular cells (JG) form the juxtaglomerular apparatus along with the macula densa and extraglomerular mesengial
cells. The JG cells are a group of modified smooth muscle cells located at the distal end of the arteriole, close to the macula densa of the distal straight tubule (Dellmann and Eeurell, 1998).

**Origin**

Sequeria *et al.* (2001) observed in his experiment on mice that JG cells originate from the metanephric mesenchyme rather than from an external source and also proposed that these cells are less differentiated than (and have capability to give rise ) smooth muscle cells of the renal arteriole. In other experiment the Sequeria *et al.* (2010) concluded that the juxtaglomerular cells are highly specialized myoepitheloid granulated cells located in the glomerular afferent arteriole.

**Histology, Histochemistry and Ultrastructure**

The juxtaglomerular cells are described as myoepitheloid because they appear to be highly modified smooth muscle cells. They have a slightly basophilic cytoplasm and their specific granules are mostly clearly demonstrated by the PAS reaction (Bloom and Fawcett, 1975).

In electron micrographs, they have a moderately abundant granular endoplasmic reticulum and a well developed Golgi complex. The granules are of variable shape and have a crystalline internal structure with a periodicity of 50 to 100 Å. These cells are the site of the production of renin.

**CHEMORECEPTORS IN THE CAROTID BODY**

The carotid bodies are inconspicuous flattened structure at the bifurcation of each common carotid artery. This body is a highly vascular structure, with a high blood flow in relation to
By electron micrographs in which the two cell types are more clearly distinguished. The type-I (glomus cell) contain very small, dense-cored vesicles resembling secretory granules. The cells occur in small clustures that are surrounded by type II cells which are devoid of cytoplasmic granules. The type I cells are the chemoreceptors The Type II cells are supportive cells. The granules in the glomus cell contain catecholamine and 5- hydroxytryptamine.

COTICOTROPES IN PARS DISTALIS

They are dispersed throughout the pars distalis and are usually difficult to identify. The cells may be spherical, ovoid or stellate depending on the species.

Origin

The ventral neural ridge gives rise to the adenohypophysis, thus the adenohypophysis is of neuroectodermal but not stomodeal origin (Arey, 1974). Corticotropes are the first immunopositive cells to appear on ontogenesis of the pituitary gland (Taniguchi et al., 2000)

Histology, Histochemistry and Ultrastructure

These cells are included in basophilic cells of the pars distalis, because many of these cells have faintly PAS positive granules owing to the presence of a non-hormonal glycoprotein. Their granules stain immunohistochemically for ACTH and β-LPH, they average 150-200 nm in diameter and frequently are located peripherally (Dellmann and Eurell, 1998). The peripheral location of the cells and the irregular shape of the cells are the valuable identifying criteria (Siperstein and Miller, 1970). Cells with characteristics attributed to corticotropes are stained with peroxidase-labeled antibody against corticotropin.

MELANOTROPES IN PARS INTERMEDIA

Melanotropes are present in the pars
intermedia of pituitary gland. The pars intermedia is well developed in domestic mammalian species enveloping the neural lobe of the neurohypophysis in many instances including the carnivores, the pig and the horse. The parenchyma of the pars intermedia is arranged in clusters, cords and small follicles (Samulson, 2007).

**Origin**
The cells are ectodermal in origin.

**Histology, Histochemistry and Ultrastructure**
These cells are polygonal or prismatic in shape and are basophilic in their staining properties. In light microscope they resemble with the basophils of the pars distalis but clearly seen in electron micrographs. Light and dark cells have been distinguished by light microscopy (on the basis of their staining affinity for PAS). The only hormone known to be secreted is melanocyte stimulating hormone (MSH), a simple polypeptide having structural affinity to adrenocorticotropic ACTH (Bloom and Fawcett, 1975).

By transmission electron microscopy there are more light cells than dark ones. Light cells have ovoid nucleus. Their cytoplasm contains many clear vesicles that are round and measure 200-300 nm.

**REFERENCES**

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