The Rat Adrenal Medulla\footnote{Address correspondence to: Dr. Arthur S. Tischler, Department of Pathology, Tufts University School of Medicine, 136 Harris Avenue, Boston, Massachusetts 02111.}

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ABSTRACT

Adult adrenal medullary cells, in many strains of rats, develop diffuse and nodular hyperplasia and neoplasia under a variety of conditions. Both endogenous and exogenous factors affect the development of these proliferative changes. The former include the animals' strain, age, and sex. The latter include drugs and other environmental agents, diet, and perhaps stress. Adrenal medullary neoplasms which arise under diverse circumstances often closely resemble each other both morphologically and functionally, and exhibit characteristics of immature chromaffin cells. Recent data indicate that normal, mature-appearing epinephrine- and norepinephrine-type chromaffin cells are able to divide, and suggest that signals which regulate chromaffin cell function also regulate cell proliferation. Prolongation of these signals or superimposed abnormalities might initiate pathological proliferative states. It remains to be determined whether the mechanisms which promote or prevent cell proliferation in the adult adrenal are related to those involved in normal development.

Keywords: Chromaffin cells; development; morphology; plasticity; hyperplasia; pheochromocytoma

The embryology, morphology, physiology and pathology of the rat adrenal medulla have recently been reviewed in detail (9, 10), and are summarized and updated here. Chromaffin cell development proceeds through 3 developmental stages (15). The first (through embryonic day 17) is characterized by norepinephrine (NE) and a small amount of dopamine (DA) in all cells, without epinephrine (E). The second (through postnatal day 3) is characterized by both E and NE in all cells. The final stage, beginning thereafter, is marked by the appearance of separate cell populations producing predominantly E or NE, an increase in total catecholamine stores, and an increase in E/NE ratio to the young adult level. The initial stages of maturation occur concurrently with the onset of functional splanchnic innervation after the first postnatal week (6, 7). The ratios of E/NE-type cells and of stored E/NE in young adult rats are each about 4/1 (13). A third cell type, the small granule containing (SGC) cell, comprises less than 1% of the total chromaffin cell population. This cell type is morphologically intermediate between chromaffin cells and neurons (9). The adrenal medulla also contains a small number of intrinsic neurons.

In addition to catecholamines, adrenal chromaffin cells produce a variety of neuropeptides, which are stored in the same secretory granules. Neurotensin and NPY, for example, are present in NE-type cells, while enkephalins are present in cells of both types. Serotonin and histamine may also be present, but it is not clear whether their presence reflects uptake or synthesis (9). Chromaffin cells have been utilized extensively as models for the study of cellular organization and function in the neuroendocrine system, and are discussed in detail in that context elsewhere in this symposium (8).

Microenvironmental signals are believed to play a role in specifying the lineage of adrenal medullary cells during development, and in regulating their function both during development and in adult life. Current evidence suggests that the commitment of adrenal medullary cells to chromaffin cell or neuronal lineages is determined by a balance of hormones and neuronotrophic factors. For example, in cell cultures derived from immature adrenal glands, nerve growth factor (NGF) causes a sizable subpopulation of adrenal medullary cells to differentiate in a neuronal direction by extending neurites, whereas corticosteroids both antagonize the effects of NGF and increase catecholamine storage. NGF also shifts the norepinephrine/epinephrine ratio of immature chromaffin cells toward norepinephrine, whereas glucocorticoids increase epinephrine production (1, 3, 14). On the other hand, the persistence of separate lineages of E-, NE-, and SGC-type chromaffin cells in the same hormonal microenvironment in adults...
suggests that certain commitments, once made, are irreversible.

The regulation of adrenal medullary cells by adrenal cortical hormones is permitted by the adrenal glands' centripetal pattern of blood flow. Multiple, small branches of the aorta and its major derivatives penetrate the capsule of the gland and give rise to a network of capillaries that begin in the cortex and ultimately drain into a single central vein in the medulla. In addition, small arteries or arterioles traverse the cortex and directly give rise to a medullary capillary plexus, thus providing the medulla with a dual blood supply. Most of the steroid-rich blood which reaches the cells in the adrenal medulla probably does so via small peripheral branches of the central vein, since the adrenal does not appear to have a true portal circulation (5). In contrast to the arterial blood supply, a single major adrenal vein drains each gland, entering the inferior vena cava on the right and the inferior phrenic vein or renal vein on the left.

In adult life, the function of adrenal medullary cells is regulated by neurogenic as well as hormonal signals. The adrenal medulla is richly innervated by cholinergic preganglionic sympathetic endings which synapse on chromaffin cells and stimulate hormone synthesis and secretion. Some recent evidence suggests that E-type and NE-type cells might receive their innervation from different sources (6). The roles of neurogenic signals in regulating certain functions, for example the synthesis of enkephalins (4), is controversial because of the complexity of the adrenal nerve supply. Although the innervation of the adrenal medulla is to a large extent derived from the splanchnic nerve, significant contributions are also made by small fibers from the celiac and superior mesenteric ganglia. Surgical denervation for experimental purposes is therefore difficult to achieve, and the effects of different procedures are difficult to interpret (4). Completeness of denervation is usually assessed by choline acetyltransferase assay.

Recent evidence suggests that neurogenic signals stimulate proliferation in addition to function of adult chromaffin cells (12). This effect probably serves normally to increase functional reserve of the adrenal medulla in response to increased physiological demands, and might be mediated by oncogene-activation, which occurs as a consequence of cholinergic stimulation (2). Electron microscopy and immunocytochemical studies which utilize antibodies against catecholamine biosynthetic enzymes to discriminate between E- and NE-type cells indicate that mature-appearing cells of both types are able to proliferate throughout life (12). There is little or no proliferation of SGC cells.

The adrenal medulla in many strains of rats develops diffuse and nodular hyperplasia and, in some instances, neoplasia, either spontaneously in the course of aging, or after prolonged exposure to a variety of hormones, drugs, and other agents (10). These agents include hormones or drugs which affect the hypothalamic-endocrine axis or the autonomic nervous system, dietary factors, miscellaneous drugs and toxins, and radiation. Their diversity suggests that they might, in some instances, affect the adrenal medulla indirectly, by acting as systemic stressors. Within any given strain of rat, adrenal medullary hyperplasia and neoplasia occur most frequently in older animals and in males.

The evolution of adrenal medullary proliferative changes from diffuse hyperplasia through diffuse and nodular hyperplasia and neoplasia is accompanied by increased production of NE and decreased E/NE ratios. Adrenal medullary neoplasms arising under diverse circumstances appear to produce almost exclusively NE. At least some are also able to produce immunoreactive neurotensin and neuropeptide-Y (10, 11). Further, the cells which comprise the neoplasms contain secretory granules which are smaller than those in normal chromaffin cells, and they show varying degrees of spontaneous or NGF-induced neurite outgrowth in vitro (11). These findings initially suggested that proliferative capacity in the adult rat adrenal might be restricted to morphologically and functionally distinctive stem cells, possibly the SGC cells (11). Since both E- and NE-type cells divide in normal adult rats, however, it now seems likely that sustained proliferation in response to various stimuli accounts for the mixed cell population in diffuse adrenal medullary hyperplasia, and that superimposed events both initiate the development of tumors and account for the distinctive characteristics of those tumors. Such events might be specific mutations, facilitated by an increased rate of cell proliferation. It has not been ruled out that mitogenic stimuli might elicit greater numbers of proliferating NE-type cells in rat strains prone to develop tumors than in other strains (12), or that SGC cells might begin to proliferate only after prolonged stimulation.

There has been considerable debate over the relevance of rat adrenal medullary tumors to human pheochromocytomas (10). Although the rat tumors contain less abundant catecholamine stores than many of their human counterparts, their morphology and hormone content are comparable to those of sparsely granulated NE-producing human pheochromocytomas. The principal difference between rat and human lesions is in their clinical context. While most human pheochromocytomas are solitary and sporadic, the rat tumors are often multifocal and bilateral, and associated with proliferative
lesions in other endocrine glands. This situation closely resembles human mixed-type multiple endocrine neoplasia syndromes, which are extremely rare.

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REFERENCES


