Commentary

Pathogenic Mechanisms of Endocrine Disease in Domestic and Laboratory Animals

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Introduction

The objective of this presentation is to summarize the major pathogenic mechanisms responsible for perturbations of endocrine function that result in important diseases in domestic and laboratory animals. For each major category, several specific disease problems have been selected to illustrate the functional and morphologic lesions that are characteristic for either a naturally occurring endocrinopathy or endocrine disturbances induced by the administration of xenobiotic chemicals. Disorders of the endocrine system are encountered in a wide variety of animal species and, as in human patients, often present challenging diagnostic problems. The examples to be discussed, by necessity, will be highly selective and include disease problems investigated by our laboratory as well as data from the literature.

Primary Hyperfunction

One of the most important mechanisms of endocrine disease is primary hyperfunction (Fig. 1). A lesion (most often a neoplasm derived from endocrine cells) synthesizes and secretes a hormone at an autonomous rate in excess of the body’s ability to utilize and subsequently degrade the hormone, thereby, resulting in functional disturbances of hormone-excess. A number of specific examples occur in different animal species.

Secondary Hyperfunction

In secondary hyperfunction a lesion in one organ secretes an excess of trophic hormone that leads to long-term stimulation and hypersecretion of a target organ (e.g. adrenal cortex) (Fig. 2). A classic example of this pathogenic mechanism in animals is the ACTH-secreting tumor derived from pituitary corticotrophs in dogs. The functional disturbances and lesions primarily are the result of elevated blood cortisol levels resulting from the ACTH-stimulated hypertrophy and hyperplasia of the zona fasciculata and reticularis of the adrenal cortex. In some aging dogs with similar marked adrenal cortical enlargement and functional disturbances of cortisol-excess, there is no gross or histopathologic evidence of a neoplasm in the pituitary gland. These animals may have a change in negative feedback control with a reduced inhibition of ACTH production by the pars intermedia of the pituitary gland due to an age-related increase in monoamine oxidase-β in the hypothalamus and increased metabolism of dopamine. The end result is severe corticotroph hyperplasia, elevated ACTH

Fig. 1.

Fig. 2.
levels in the blood, and long-term stimulation of the adrenal cortex resulting in the syndrome of cortisol-excess.

**Primary Hypofunction**

In primary hypofunction, hormone secretion either is subnormal due to excessive destruction of secretory cells by a disease process, the failure of an endocrine organ to develop properly (aplasia or hypoplasia), or the result of a specific biochemical defect in the synthetic pathway of a hormone (Fig. 3). Immune-mediated injury appears to be an important mechanism resulting in hypofunction of endocrine glands in animals including the parathyroid, adrenal cortex, thyroid gland, pancreatic islets, and hypothalamus.

**Secondary Hypofunction**

A destructive lesion in one organ (i.e. pituitary gland) interferes with the secretion of trophic hormones and results in subnormal function of target endocrine glands in secondary hypofunction (Fig. 4). Large, endocrinologically-inactive neoplasms may interfere with the secretion of multiple pituitary trophic hormones and result in clinically significant hypofunction of the adrenal cortex, follicular cells of the thyroid, and gonads. The disruption of growth hormone secretion has little effect on body stature because lesions of this type usually develop in adult to aged animals. Hypofunction of an endocrine organ also may be secondary to a lack of raw materials (e.g. iodine) necessary for the synthesis of hormone (T₄, T₃). Marginal deficiencies often are associated with the presence of goitrogenic chemicals in the diet that interfere with the process of hormone synthesis by thyroid follicular cells.

**Endocrine Hyperactivity Secondary to Other Conditions**

The best known example of endocrine hyperactivity secondary to diseases of other organs in animals is hyperparathyroidism that develops secondary to either chronic renal failure or nutritional imbalances (Fig. 5). In the renal form, the retention of phosphorus early and subsequent progressive destruction of cells in the proximal convoluted tubules interferes with the metabolic activation of vitamin D by 1α-hydroxylase in the kidney. This is the rate-limiting step in the metabolic activation of vitamin D and is tightly controlled by parathyroid hormone and several other factors including the serum phosphorus concentration and other hormones. The impaired intestinal absorption of calcium results in the development of progressive hypocalcemia that leads to long-term parathyroid stimulation and development of generalized demineralization of the skeleton. Nutritional hyperparathyroidism develops in animals fed abnormal diets that are either low in calcium, high in phosphorus, or deficient in cholecalciferol (e.g. new world nonhuman primates).

Hyperfunction of an endocrine organ also can be the result of hormonal imbalances induced by xenobiotic chemicals (Fig. 6). For example, hyperactivity of the pituitary gland in rodents during chronic toxicity testing often results in an increased development of tumors in the gonads or mammary glands. An excess production of
luteinizing hormone (LH) usually due to disruption of negative feedback control by estrogen or testosterone increases the incidence of tubulo-stromal adenomas and granulosal cell tumors in the ovary of mice and Leydig (interstitial) adenomas of the testes in rats.

**Hypersecretion of Hormones by Nonendocrine Tumors**

Certain neoplasms of nonendocrine tissues in both animals and man either secrete new humoral substances or hormones that share chemical and/or biologic characteristics with the “native” hormones secreted by an endocrine gland (Fig. 7). Most of the recently discovered humoral substances secreted by nonendocrine tumors are peptides rather than steroids, iodothyronines or catecholamines, which require more complex biosynthetic pathways. Humoral hypercalcemia of malignancy (“pseudohyperparathyroidism”) is a clinical syndrome produced primarily by the autonomous hypersecretion of parathyroid hormone-related peptide (PTH-rP) by cancer cells. PTH-rP is able to interact with the parathyroid hormone receptor in target cells (e.g. bone and kidney) and result in persistent, often life-threatening, hypercalcemia. A well characterized example of this disease mechanism in animals is the adenocarcinoma derived from the apocrine glands of the anal sac in dogs. These tumors produced PTH-rP that results in an accelerated mobilization of calcium from bone by osteoclasts and leads to the development of persistent hypercalcemia. Serum PTH levels are lower in dogs with apocrine carcinomas than in controls and PTH levels are undetectable in tumor tissue.

**Failure of Target Cells to Respond to Hormone**

This mechanism of endocrine disease has been appreciated coincident with the more complete understanding of how hormones interact with target cells to convey their biologic message. A failure of target cells to respond to hormone may be due either to a lack of adenylate cyclase in the cell membrane or to an alteration in hormone receptors on the cell surface (Fig. 8). Hormone is secreted in normal or increased amounts by the cells of the endocrine gland. For example, insulin-resistance associated with obesity in both animals and humans can result from a decrease or “down regulation” of receptors on the surface of target cells. This develops in response to the chronic increased insulin secretion stimulated by the hyperglycemia resulting from the excessive food intake. Secretory cells in the corresponding endocrine gland (i.e. pancreatic islets) undergo compensatory hypertrophy and hyperplasia in an attempt to secrete additional hormone.

An interesting form of hypoparathyroidism has been reported in human patients in which the inability of target cells to respond is due to a defect in the cAMP-mediated signal transduction resulting from a lack of specific nucleotide regulatory protein in the cell membrane. Patients with “pseudohypoparathyroidism” develop hypocalcemia and hyperphosphatemia in spite of hyperplastic parathyroids and elevated blood levels of PTH.
Failure of Fetal Endocrine Function

Subnormal activity of the fetal endocrine system, especially in ruminants, may disrupt normal fetal development and result in prolongation of the gestation period (Fig. 9). In Guernsey and Jersey cattle, there is a genetically determined failure of development (aplasia) of the adenohypophysis. This results in a lack of fetal pituitary trophic hormone secretion during the last trimester and hypoplastic development of target endocrine organs. Fetal development is normal up to approximately seven months gestation but subsequently fetal growth ceases irrespective of how long the viable fetus is retained in utero. The concepts that have emerged from the study of these naturally occurring diseases are; first, fetal hormones are necessary for final growth and development in utero in certain animals; and second, normal parturition at term in these species requires an intact fetal hypothalamic-adenohypophyseal-adrenal cortical axis working in concert with trophoblasts of the placenta.

Abnormal Degradation of Hormone

Increased degradation

In laboratory rodents, the long-term administration of various xenobiotics (i.e. phenobarbital and others) results in the induction of liver enzymes (e.g. T₄–UDP glucuronyl transferase) that increase the degradation of thyroxine (Fig. 10). This chronic disruption of the thyroid-pituitary axis and augmented TSH secretion in rodents, especially male rats, often increases the development of thyroid follicular cell tumors in chronic toxicity and oncogenicity studies with certain drugs and chemicals (Fig. 11).

Decreased degradation

The rate of secretion of hormone by an endocrine gland may be normal with this mechanism but blood levels are persistently elevated, thereby simulating a syndrome of hypersecretion, due to a decreased rate of degradation (Fig. 10). The classic example of this pathogenic mechanism is the syndrome of feminization due to hyperestrogenism associated with cirrhosis and decreased hepatic degradation of estrogens. Chronic renal disease in dogs occasionally is associated with hypercalcemia due, in part, to decreased degradation of PTH (along with decreased urinary excretion of calcium) by the diseased kidney.

Iatrogenic Syndromes of Hormone-Excess

The administration of hormone, either directly or indirectly, influences the activity of target cells with this mechanism and results in important functional disturbances (Fig. 12). It is well recognized that the administration of potent preparations of adrenal cortical steroids at inappropriately high daily doses for prolonged intervals in the symptomatic treatment of various diseases can produce most of the functional disturbances associated with an
endogenous hypersecretion of cortisol. Similarly, the administration of excessively large doses of insulin can result in hypoglycemia and an excess T₄/T₃ may result in hyperthyroidism, especially in certain species (e.g. cats) that have limited capacity to conjugate T₄ with glucuronic acid and enhance biliary excretion.

The administration of progestogens to dogs indirectly results in a syndrome of growth hormone-excess. The injection of medroxyprogesterone acetate for the prevention of estrus in dogs stimulates the expression of the growth hormone gene in the mammary gland and results in many of the clinical manifestations of acromegaly due to elevated circulating growth hormone levels.

References


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