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INTRODUCTION IN ENDOCRINOLOGY

Introduction

The traditional and still major part of clinical endocrinology deals with the glands that produce hormones and in particular with the circulating concentrations of hormones to which cells expressing specific receptors for hormones are exposed. The capacity to form hormones is not limited to endo-crine glands. In recent years the traditional view of the endocrine system's glandular nature has broadened to include production of hormones in specialized endocrine cells scattered in organs whose primary function is not endocrine, such as the stomach, the small intestine, the heart, the kidney and adipose tissue. Hormones may also be activated outside the endocrine organs, by proteolytic cleavage of protein prohormones (e.g., in the vascular bed). Others, such as dihydrotes-tosterone, triiodothyronine, and estradiol, are in part secreted by endocrine glands and in part formed in peripheral tissues from circulating precursors.

Endocrinology also includes messengers that circulate primarily in restricted compartments such as the hypothalamic-pituitary portal system, as well as messengers that act on adjacent cells (paracrine), on the cell of origin (autocrine), and within the secretory cell (intracrine). Many hormones, of which insulin and dihydrotestosterone are examples, have both paracrine actions in the tissues in which they are formed and classical endocrine actions at peripheral sites. Other forms of intercellular communication studied by endocrinologists include exocrine secretion (e.g., in milk and semen) and the release of pheromones (in air or water).

There are strong similarities in signaling mechanisms between the endocrine and nervous systems. The same molecule can be both a hormone and a neurotransmitter. For example, catecholamines are hormones when released by the adrenal medulla and neurotransmitters when released by nerve terminals. Thyrotropin-releasing hormone (TRH) is a hormone when produced by the hypothalamus, but has several neurotransmitter actions in the central nervous system.

Endocrine disorders

Endocrine disorders occurring in the dog and the cat can be divided into the following six broad categories, most of which can be further subdivided:

1. *Deficient hormone production*. Endocrine glands may be injured or destroyed by autoimmune disorders or by neoplasia and theoretically also by infection or hemorrhage, and the resulting hypofunction is said to be **primary**. Primary hypofunction may also be due to agnesia of an endocrine gland or it may be iatrogenic (e.g., due to castration). Hypofunction can also be due to inadequate stimulation of the gland and is then said to be **secondary**.
2. *Excessive hormone production*. The most frequent cause of hormone excess syndromes is hypersecretion of hormones by a tumor of the endocrine gland (**primary** hyperfunction) and hyper-secretion due to hyperstimulation of the endocrine gland, of which there may be several causes (**secondary** hyperfunction). Excessive hormone production may also be traced to cells that are not normally the primary source of circulating hormone (ectopic hormone production). Rarely, hormone hypersecretion is the result of expression or activation of receptors in an endocrine gland that does not normally harbor functional receptors of this type. For example, the adrenal cortex may express aberrant receptors such as luteinizing hormone receptors. When hormones are used to treat nonendocrine diseases or when hormone replacement for an endocrine deficiency is excessive, the resulting syndrome of hormone excess is said to be iatrogenic.
3. *Defective hormone synthesis*. Genetic defects can cause abnormalities in hormone synthesis. Sometimes this leads not only to hormone deficiency but also to manifestations of a compensatory adaptation, such as goiter resulting from defective thyroid hormone synthesis.
4. *Resistance to hormone action*. Hormone resistance is defined as a defect in the capacity of normal target tissues to respond to the hormone. It may be an inherited disorder involving one or more molecular abnormalities, including defects in receptors and in postreceptor mechanisms. Hormone resistance may also be acquired, as is insulin resistance in some forms of diabetes mellitus. A common feature of hormone resistance is an elevated concentration of the hormone in the circulation in the presence of diminished or absent hormone action.

5. *Abnormalities in hormone transport*. Feedback control of hormone production and release is mediated by the concentration of free hormone. Thus a change in the concentration of transport or carrier proteins in the plasma usually affects only the total hormone concentration in plasma but not hormone action.
6. Finally, endocrine glands may be affected by *abnormalities not impairing function*. These include tumors, cysts, and infiltrative diseases not leading to significant impairment of hormone secretion.

Clinical assessment

History and physical examination.
The diagnostic process is hampered by the inaccessibility for physical examination of all of the endocrine glands except the thyroids, parathyroids, and testes. However, deranged hormone secretion has consequences for the function of other organ systems, usually leading to multiple abnormalities which often have a characteristic pattern. The diagnosis of an endocrine disease thus often begins with the recognition of a pattern of characteristics in the medical history and in the findings by physical examination.

Many syndromes of hormone excess or deficiency lead to manifestations that are readily apparent at the time of the initial presentation of the patient for examination. Especially now that the definitive diagnosis can often be secured by laboratory data, veterinary clinicians have learned to recognize the patterns of physical characteristics of endocrine syndromes. Nevertheless, in some cases the changes are very subtle and it is necessary to rely completely on laboratory testing. This is especially true when endocrine disease is being considered in the differential diagnosis of common problems such as weakness, lethargy, and weight loss or gain.

Laboratory testing.
The development of techniques for the measurement of hormones in biological fluids has made it possible to assess endocrine function in quantitative terms by the following approaches:

Hormone concentrations in plasma. The total concentration of steroid and thyroid hormones in plasma ranges between 1 and 1000 nmol/l, while that of peptide hormones is generally between 1 and 500 **p**mol/l. The application of radioimmunoassay, radioreceptorassay, chromatography, mass spectrometry, and more recently molecular biological techniques has transformed endocrinology from a largely descriptive discipline to a more quantitative one. Yet there are only a few situations in which a single measurement of the concentration of a hormone in plasma provides a reliable assessment of hormone production. There are several reasons for caution in assessing isolated measurements of hormone concentration in plasma:

- Several hormones are secreted in a pulsatile manner and/or their concentrations may vary in a diurnal rhythmicity, as well as with the sexual cycle, and pregnancy.
- Steroid and thyroid hormones are transported in plasma largely bound to proteins. The small percentage (<1-10 per cent of the total) of unbound hormone exerts the biological effect. The total hormone level reflects the amount of free hormone only if the amount and the affinity of binding protein remain constant or fluctuate within narrow limits.
- The range of reference values for most hormones is fairly broad. Thus it is possible for the level in an individual animal to double or to decrease by half and yet still be in the reference range. For this reason it is sometimes useful to measure the concentrations of a related pair of hormones simultaneously (e.g. cortisol and ACTH).
- Some messengers circulate only in restricted compartments, such as the hypothalamic-pituitary portal system, and do not reach the systemic circulation in appreciable quantities.
- Paracrine and autocrine effects of hormones are usually not reflected by hormone concentrations in plasma.
- Exocrine secretion of hormones and the release of pheromones cannot be determined by measuring the hormone concentration in plasma.

Urinary excretion. Measurements of urinary excretion of hormones have the advantage of reflecting average concentrations in plasma and hence average production rates over the time interval between collections. Certain limitations must be kept in mind:

– Collection of urine during a 24-hour period is a cumbersome procedure in most animals. It can be circumvented by relating the hormone concentration to the urinary creatinine concentration.
– The concentration of a hormone in urine is less meaningful if the hormone, such as thyroxine, is excreted in intact or conjugated form predominantly via the bile and only in very small amounts in the urine.
– There is considerable individual variation in the metabolism, and hence urinary excretion, of some of the peptide hormones.
– Changes in renal function may influence the rates of hormone excretion in the urine.

Production and secretion rates. These techniques can circumvent many of the problems associated with isolated measurements of hormones in plasma or urine, but they are difficult to perform and often require administration of radionuclides, for which reason they are not generally available.

Dynamic endocrine tests. Dynamic testing provides additional information. It involves either stimulation or suppression of endogenous hormone production. Stimulation tests are utilized most often when hypofunction of an endocrine organ is suspected. In the most commonly employed stimulation tests a tropic hormone is administered to test the capacity of a target gland to increase hormone production. The tropic hormone can be a hypothalamic releasing hormone such as corticotropin releasing hormone (CRH), in which case the target gland is the pituitary and the measured response is the increment in the plasma concentration of ACTH, or a pituitary hormone such as ACTH, with the adrenal cortex as the target gland being assessed by the measurement of the increment in the plasma concentration of cortisol. Suppression tests are utilized when endocrine hyperfunction is suspected. They are designed to determine whether negative feedback control is intact. A hormone or other regulatory substance is administered and the inhibition of endogenous hor-mone secretion is assessed. Dynamic tests continue to be of importance in the diagnosis of certain disorders but in circumstances in which hormone pairs can be measured accurately (e.g., thyrotropin (TSH) and thyroxine) they are re-quired less often.

Hormone receptors and antibodies. The measurement of hormone receptors in biopsy material from target tissues may become increasingly useful in companion animal endocrinology, especially in the diagnosis of hormone resistance. Measurement of antibodies to hormones or antigens in endocrine tissues may also be essential in order to characterize certain endocrine abnormalities as autoimmune phenomena. Antibodies against hormones may also interfere with diagnostic procedures such as radioimmunoassays.

Diagnostic imaging.
The inaccessibility of most of the endocrine glands for direct physical examination has been progressively overcome during the past two decades by the use of diagnostic imaging techniques such as ultrasonography, scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI). The first technique is relatively inexpensive but requires extensive operator experience, whereas the latter three may be easier to perform but require expensive equipment as well as immobilization which necessitates anesthesia.

Further reading

– Rijnberk A, Kooistra HS. Clinical Endocrinology of Dogs and Cats, Hannover: Schlütersche; 2010.