Endocrinology #1
Dr. Alex Pappas
Introduction to Endocrinology/Pituitary

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1. Introduction

2. The approach throughout the endocrine lecture series will be to correlate endocrine anatomy, histology, physiology, and pathology with the various clinicopathologic conditions.

3. What is the purpose of the endocrine system and how does it fulfill this purpose? The products of endocrine glands (hormones) control the function of other tissues by binding to cell surface receptors in those tissues.

4. The classical endocrine system is composed of the pituitary, thyroid, parathyroids, adrenals, the islets of Langerhans, and the gonads (ovaries/testes). Now included as part the of the endocrine system is the hypothalamus. There are scattered foci of various cells and tissues throughout the body that are "endocrine." Examples of such cells are found in the atrium of the heart. These atrial heart cells secrete natruretic peptide in response to vascular tone. In the kidney there are cells that secrete erythropoietin in response to anemia. We will not be discussing such tissues.

5. Hormones are blood chemical messengers. Hormones exert their respective effect on reproduction, growth and development, energy production, and the internal environment (homeostasis).

6. Endocrine hormone production is under very tight regulation. This is a schematic diagram of the typical negative feedback mechanism of the endocrine system (solid line = positive feedback; dotted line = negative feedback).

7. Normal hormonal regulation with the thyroid as an example (Robbins fig.20-1). Starting with decreased levels of triiodothyronine (T3) and thyroxine (T4), there is stimulation of the hypothalamus to secrete thyroid–releasing hormone (TRH). TRH stimulates the anterior pituitary to secrete thyroid stimulating hormone (TSH). TSH in turn increases production of T3 and T4 by the thyroid. Simultaneously and independently decreased levels of T3, T4 stimulate the secretion of TSH from the anterior pituitary. Subsequent increased secretion of T3 and T4 then suppresses the secretion of both TRH from the hypothalamus and TSH from the anterior pituitary. This suppression in turn leads to decreased production of T3 and T4. These interactions represent a negative feedback loop.

8. In normal hormonal regulation, in addition to feedback between the trophic hormone(s) and the endocrine gland product(s), there are many other complex pathways and interactions. Such interactions can include other tissue products and physiologic factors such as stress,

time of day, or physical activity. The adrenal glands, which will be discussed later, well illustrate these complex interactions.

9. Endocrine hormones can be broadly classified into three general chemical classes; steroids, peptides, & amino acids. Each class has differing mechanisms of receptor-effector mechanisms.

10. A single hormone can have multiple different actions. In this example, testosterone stimulates spermatogenesis, muscle growth, and prostatic hyperplasia.

11. A single action maybe under the control of multiple different hormones. For example, glucose is increased by glucagon (a peptide secreted by pancreatic islet cells), epinephrine (an amino acid secreted by the adrenal medulla), cortisol (a steroid secreted by the adrenal cortex), and growth hormone (a peptide secreted by the anterior pituitary). There is only one hormone that decreases glucose, and that is insulin (a peptide secreted by pancreatic islet cells).

12. Endocrine disease can be broadly classified into diseases of hyperfunction (e.g. Graves disease, Cushing's syndrome) or hypofunction in which there is either a deficiency of a hormone (e.g. Addison's disease), or peripheral resistance to a hormone (e.g. diabetes mellitus type II). In neoplasia (e.g. pituitary or thyroid adenoma) there may be normal function, increased function, or decreased function.

13. Diseases of hormonal deficiency **are more common** than diseases of hormone excess. The endocrine deficiency syndromes can be further subclassified as to etiology as listed on this slide.

14. The premier hormonal receptor defect/resistance syndrome is Type II diabetes or "adult onset diabetes."

15. The hypothalamus is now considered the master endocrine gland (so far). In days of yore, the pituitary gland was considered the "master gland."

16. The diagram shows the anatomy of the pituitary and its anatomic relation to the hypothalamus. The pituitary sits in a bony structure of the skull known as the sella turcica. The anterior pituitary arises from epithelial cells derived from the craniopharyngeal pouch. The posterior pituitary is nervous tissue which is an extension of hypothalamic axons and nuclei. The stalk consisting of hypothalamic axons connects the pituitary to the hypothalamus.

17. A brief review of pituitary anatomy and blood supply. This diagram further elucidates the blood supply and the anatomic relationships between the anterior pituitary (adenohypophysis), posterior pituitary (neurohypophysis) , and hypothalamus. The superior hypophyseal artery branches into a plexus surrounding the secretory cells of the anterior pituitary (pituicytes). The hormones secreted by the pituicytes are picked up by this venous plexus and carried into the general circulation by the efferent hypophyseal vein.

Likewise, another plexus superior to the anterior pituitary carries hormones secreted by the hypothalamus (hypothalamic nuclei) to the pituicytes.

18. This table lists in the first column the hypothalamic trophic (releasing) hormones, and in the second column, the corresponding anterior pituitary target cells (pituicytes) with the corresponding pituitary hormone secreted. In the third column, the respective target endocrine gland is given with its respective hormone. You do not need to memorize this table. I have provided it for you as a "snapshot" of the system and as a study aid.

19. In addition to stimulatory hypothalamic hormones, there are the inhibitory or suppressor hypothalamic hormones, somatostatin, and dopamine.

20. This figure by the noted medical illustrator, Dr. Frank Netter, shows the structures adjacent to the pituitary. The pituitary is located inferiorly to the optic chaism.
Lesions of the pituitary can cause various visual field defects, impingement of cranial nerves, and ischemia of major cranial vessels.

21. The normal pituitary shows a colorful spectrum of cells ranging from acidophilic (red/orange) or Alpha Cells, to deeply basophilic (blue) or Beta Cells. Cytoplasmic color reflects the hormonal content of the cell. Some cells do not stain and are know as chromophobes or C-cells. The staining characteristics are not particularly specific, but were relied upon before the advent of immunostains to make a pathologic diagnosis.

22. Robbins Fig 20-2. There is a colorful array of polygonal cells with abundant cytoplasm and a distinct, centrally placed nucleus. The cells are arranged in nests. The nests of cells are separated by the rich sinusoidal plexus (see image 19 above). The variability of cytoplasmic staining reflects the different content of the pituitary trophic hormones.

23. Pituitary disease can be broadly classified into either hyperpituitarism (increased pituitary hormone secretion) or hypopituitarism (decreased pituitary hormone secretion). Adenomas are a major cause of hyperpituitarism and can cause the clinical effects as listed on this slide. Destructive processes are a major cause of hypopituitarism.

24. Pituitary adenomas-some general associations.

25. Pituitary adenomas can further categorized as to whether they are **functioning** (hormonally **active** with clinical manifestations) or **non-functioning** (hormonally **inactive** with no detectable clinical effects). Microadenomas tend to be hormonally active and detected early. Macroadenomas tend to be hormonally inactive and are usually detected later.

26. Pituitary adenomas can manifest clinically by their hormonal effect or "mass" effect. The most common hormone secreted by a functioning pituitary adenoma is prolactin, followed by growth hormone, and ACTH. Mass effects are usually associated with non-functioning adenomas but can be seen in functioning adenomas as well.

27. Pituitary adenoma-nonfunctioning with distortion of the brain. (Robbins fig 20-3). This lesion would be expected to have "mass" effects. This large pituitary adenoma was detected late when the patient developed seizures. Note the distortion of the brain and the foci of hemorrhage due to the neoplasm outgrowing its blood supply.

28. Pituitary adenoma-Microscopic. (Robbins fig 20-4) Note the monomorphic cell population and lack of vascularity. Compare this image with image #21 and #22 above. Blood hormone levels and specific immunostains would be used to exactly identify the cell type.

29. The hormonal and mass effects of pituitary adenoma are summarized.

30. MRI-Normal. Arrows point to the anterior and posterior pituitary.

31. MRI-Abnormal. The pituitary adenoma is an irregular, large, white area anterior and superior to the cerebellum

32. Visual field defects (bitemporal hemianopsia) in pituitary adenoma. The dark areas represent areas of blindness due to impingement on the optical nerves by the pituitary adenoma.

33. The distinct hormonal syndrome associated with a pituitary adenoma depends upon the respective hormone(s) secreted by the adenoma. The more common syndromes are listed.

34. Prolactinomas-clinicopathologic correlates. The prolactinoma is the most common type of pituitary adenoma. Prolactinomas tend to be microadenomas, are usually chromophobic or weakly acidophilic. The diagnosis depends upon the clinical findings, a blood prolactin level of greater than 200, and specific immunostaining of the neoplasm. Because prolactinomas tend to be hormonally active, they are detected earlier.

35. Hormonal actions of prolactin.

36. MRI of pituitary adenoma -- dense irregular white area.

37. There are causes of prolactin increase other than pituitary adenoma that must be kept in mind when evaluating a patient with amenorrhea, galactorrhea, infertility, and libido loss.

38. Chemotherapeutic treatment of prolactinoma. Normally, dopamine is secreted by the hypothalamus and inhibits prolactin secretion by the pituitary. A dopamine receptor agonist such as bromocriptine will similarly and markedly inhibit the secretion of prolactin. Most patients will respond to bromocriptine and not require surgery or radiation.

39. Growth Hormone (somatotroph) adenomas-Essential facts.

40. Growth Hormone Adenomas-Gigantism vs. Acromegaly. The stigmata of growth hormone excess is dependent on whether the epiphyses have closed. In children, gigantism occurs, whereas in adults there is acromegaly.

41. In growth hormone excess there are other metabolic consequences. Growth hormone is anabolic and leads to diabetes, hypertension, arthritis, osteoporosis and finally congestive heart failure.

42. Sequential photographs of the disfigurement in a patient with untreated acromegaly. In the final panel the prognathism and elongated sausage like fingers are obvious. In the intermediate panels, the subtle changes can be appreciated, retrospectively.

43. Pituitary adenomas secreting adrenocorticotrophin hormone (ACTH) are known as corticotroph cell adenomas. Corticotroph cell adenomas tend to be microadenomas, basophilic, and immunostain positive for ACTH.

44. Corticotroph adenoma-Effect on the hypothalamic-pituitary-adrenal axis. The excess of ACTH leads to cortisol excess which is known clinically as Cushing's disease.

45. Microscopic appearance of a basophilic corticotroph microadenoma in a patient with Cushing's disease.

46. Corticotroph adenoma (Cushing's Disease)-Clinicopathologic correlates. Cortisol causes hyperglycemia, leading to diabetes. Cortisol also causes hypertension, muscle wasting, and truncal obesity.

47. A patient with Cushing's disease showing truncal obesity and striae. There is also a moon facies and proximal muscle atrophy.

48. Nelson's Syndrome-clinicopathologic correlates.

49. Pituitary adenomas- The "Others." Essential findings.

50. Pituitary Carcinoma-rare, rare, rare-forget about it.

51. Hypopituitarism is defined as the loss or absence of 75% or more of the pituitary. A very common cause of hypopituitarism is a nonsecretory (nonfunctioning) pituitary adenoma. Various destructive causes can cause hypopituitarism.

52. Less common, but important causes of hypopituitarism are listed.

53. Nonsecretory (null cell) anterior pituitary adenoma with necrosis and hemorrhage causing anterior hypopituitarism.

54. There is an evolutionary pattern of pituitary hormone loss in hypopituitarism. Growth hormone is lost first and ultimately TSH and ACTH are lost. Loss of TSH and ACTH can be life threatening.

55. Ischemic necrosis of the pituitary, or Sheehan's syndrome can occur in the immediate postpartum period. In Sheehan's, there is a sudden loss of maternal blood pressure leading to decreased blood flow to the already hypertrophied anterior pituitary causing ischemic necrosis.

56. Photomicrograph of infarcted anterior pituitary. The cells infarcted anterior pituitary on the right have a "ghostly" outline.

57. Posterior Pituitary- extension of hypothalamic nuclei and axons.

58. This diagram illustrates the neural connections between the supraoptic and paraventricular nuclei of the hypothalamus and the posterior pituitary (neurohypophysis).

59. This 10x magnification of the pituitary shows the histologic difference between the anterior and posterior pituitary.

60. The two hormones secreted by the posterior pituitary are (1) vasopressin, also known as antidiuretic hormone (ADH), and (2) oxytocin. ADH maintains osmotic pressure and blood volume by reabsorbing renal tubular free water (RT-H_20). Reabsorption of rental tubular free water causes a low volume and very concentrated urine to be excreted. In plasma, free water is increased, and serum sodium (S-Na+) is decreased, and this results in decreased serum osmolality. Oxytocin causes smooth muscle contraction, particularly of the uterus in the immediate postpartum period and the lactiferous ducts during suckling.

61. The normal physiologic response to ADH. ADH is secreted when the hypothalamic nuclei sense an increase in osmolality ($\downarrow H_20$ or $\uparrow$Na) or a decrease in blood pressure. ADH causes renal tubular reabsorption of water (RT-H_20). With increased reabsorption of renal tubular water, there is decreased urine volume and increased in urine sodium (U-Na+) concentration. Concomitantly, in the intravascular system, serum water increases and helps to raise blood pressure. The increase in serum water and decrease in serum sodium causes a decrease in serum osmolality.

62. ADH deficiency is also known as diabetes insipidus. A patient with ADH deficiency produces large volumes (polyuria) of dilute (low Na+) urine. The findings in diabetes insipidus are summarized in this slide. In diabetes insipidus, the glucose is normal.

63. The causes of ADH deficiency include autoimmune, trauma, neoplasia, idiopathic, and hypothalamic lesions. In trauma-induced ADH deficiency there is usually resolution with time. Treatment of diabetes insipidus includes water deprivation or administration of a synthetic ADH known as desmopressin or DDAVP.

64. The **inappropriate hypersecretion** of ADH is known as the Syndrome of Inappropriate ADH (SIADH). This inappropriate or autonomous secretion of ADH is not responsive to the normal negative feedback mechanisms of hypoosmolality. Life threatening hyponatremia and hypoosmolality develop. With SIADH, a low volume of urine that is extremely concentrated is produced but serum sodium is decreased. The "inappropriate" findings of a "dilute" serum with a "concentrated" urine defines SIADH.

65. SIADH is commonly associated with a paraneoplastic syndrome of which small cell (oat cell) carcinoma is the most common. SIADH can occur with other pulmonary malignancies, and in stroke, trauma or with the same medications.

    The classic laboratory findings in SIADH are:

	Urine	**Serum**
Osmolality	↑↑	↓↓
Sodium (Na)	↑↑	↓↓

66. In SIADH, although total body water increases, edema does not develop. As body water is retained, serum sodium is diluted, leading to hyponatremia. Untreated SIADH progressively leads to confusion, convulsion, and finally coma and death.

67. Treatment of SIADH includes removal of the primary cause, if possible, fluid restriction and use of an ADH antagonist.

68. This is a patient with SIADH who has a normal pituitary on MRI.

69. Chest X-Ray (CXR) in this patient shows an rounded opacity in the left hilar area.

70. Small cell (oat cell) carcinoma of the lung in this patient caused the SIADH.