ENDOCRINE HYPERTENSION

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Objectives:

1. Recognize hypertension as a major public health problem, and understand its classification.

2. Appreciate the current lack of specific knowledge regarding etiology of essential hypertension.

3. Identify possible endocrine mechanisms which have been implicated in essential hypertension.

4. Delineate the leading systemic causes of secondary hypertension and understand their rarity.

5. Recall the major endocrine causes of hypertension and the pathophysiologic mechanisms for elevation of blood pressure in these conditions.

OVERVIEW OF HYPERTENSION

Hypertension (elevated blood pressure, conventionally defined as a systolic blood pressure > 140 mm Hg, a diastolic blood pressure >90 mm Hg, or both) affects about 50 million Americans. It is important because it markedly **increases the risk of stroke, heart failure, myocardial infarction (heart attack)** and **renal failure**. High blood pressure itself causes **no symptoms**, except when extremely high. In more than 95% of patients, no underlying cause can be determined – they have **essential hypertension** ("essential' is a synonym for "idiopathic" and also means "we don't know the cause"), and are treated to lower blood pressure and risk of the diseases above. A small fraction (<5%) of patients with hypertension have diagnosable causes (**secondary hypertension**)**.** Essential hypertension is currently considered an incurable disorder that requires life-long medical management. **Prehypertension** is defined as a systolic BP of 120-139 mmHG and a diastolic BP of 80-89 mmHg. Persons with prehypertension progress to overt hypertension at a rate of >10% per year. Lifestyle modifications (salt reduction, fruits and vegetables, weight reduction, regular exercise) have been shown to reverse prehypertension back to normotension.

Endocrine Aspects of Essential hypertension

Although the underlying cause(s) of essential hypertension are unknown, there are definite alterations of endocrine systems in this condition. Many patients with essential

hypertension have demonstrable alterations of the renin-angiotensin-aldosterone system that permits them to be classified as having Low-, Normal-, or High-Renin Hypertension. The plasma renin activity is used for this classification. This subclassification of essential hypertension has therapeutic and prognostic implications. For instance, cardiovascular risk is markedly higher in high-renin patients than in low-renin patients. Also, the BP response to diuretics and calcium channel blockers is better in patients with low-renin hypertension compared with high-renin patients, whereas the latter respond better to angiotensin converting enzyme inhibitors. In addition to the renin-angiotensin-aldosterone system, alterations in catecholamines (sympathetic nervous system) have been noted in some patients with essential hypertension. In general, circulating levels of epinephrine and norepinephrine and urinary norepinephrine excretion tend to be higher in patients with essential hypertension than in normotensive subjects, although there is considerable overlap. The overlap is so large as to make this test not useful for diagnostic purposes. There may also be a defect in the vasodilatory kallikrein-bradykinin system in some familial forms of essential hypertension. Thus, although no single hormone or hormonal system appears to be the culprit, many patients with essential hypertension have some alterations in one or more endocrine systems.

Secondary hypertension

In the general populace, approximately <5% of patients with hypertension have an identifiable underlying cause; this form is referred to as "Secondary Hypertension". In the Hypertension Detection and Follow-Up Program conducted in the 1970's, 0.18% of 15,000 participants had secondary hypertension. Because secondary hypertension is extremely uncommon, current clinical practice discourages routine search or an elaborate work up for underlying causes in a typical patient with hypertension. The clinical importance of identifying cases of secondary hypertension is obvious, however. Unlike essential hypertension (which is an incurable, lifelong disorder) successful treatment of the underlying cause may provide a cure for patients with secondary hypertension.

Causes of secondary hypertension

- Renal parenchymal disease: e.g., acute nephritis, chronic glomerulonephritis, etc.
- Renovascular disease: e.g., renal artery stenosis, atherosclerosis, fibroplasia, etc.
- Endocrine causes

ENDOCRINE HYPERTENSION

Three endocrine diseases cause hypertension in the majority of patients who have them: **primary hyperaldosteronism, pheochromocytoma** and **Cushing's syndrome**. Each of these is a **rare** cause of hypertension, accounting for <1%. Renal artery stenosis also causes hypertension. Although increased angiotensin II and secondary hyperaldosteronism contribute to hypertension in patients with renal artery stenosis, this condition is not considered an endocrine cause of hypertension. On the other hand, there is a long list of endocrine conditions that have been associated with hypertension. The evidence for

causality is not equally strong across all of these conditions. A partial list of such conditions is presented, followed by a fuller discussion of the more characteristic (or more common) examples of endocrine hypertension.

Endocrine conditions associated with hypertension

- Pheochromocytoma
- Mineralocorticoid excess (e.g., primary hyperaldosteronism)
- Glucocorticoid excess (e.g., Cushing's syndrome)
- Acromegaly
- Diabetes mellitus
- Obesity
- Congenital adrenal hyperplasia
- Estrogen-induced hypertension
- Pregnancy-induced hypertension
- Renin-secreting tumors
- Hypothyroidism
- Hyperthyroidism
- Liddle syndrome

PHEOCHROMOCYTOMA

The sympathochromaffin (sympathoadrenal) system is the prototype neuroendocrine system. It has two components: 1) The sympathetic nervous system including its postganglionic neurons, the vast majority of which release **norepinephrine** (noadrenaline) among other neurotransmitters. 2) The chromaffin tissues including particularly the adrenal medullae (conceptually postganglionic neurons without axons), which are the major source of circulating epinephrine (adrenaline) among other hormones. Norepinephrine and epinephrine (along with dopamine) are **catecholamines**; their structures include a dihydroxyphenly ("catechol") nucleus and an amine side chain. The sympathochromaffin system and the parasympathetic nervous system comprise the **autonomic nervous system.**

Catecholamines: The catecholamines—dopamine (DA), norepinephrine (NE) and ephinephrine (E) are synthesized from tyrosine which is hydroxylated to dihydroxyphenylalamine (DOPA) in the presence of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis (figure 1). DOPA is decarboxylated by a nonspecific enzyme to form DA. Dopamine b-hydroxylase (DbH) converts DA to NE, phenylethanolamine-N-menthyl transferase (PNMT) NE to E. Some systems (e.g. most cells of the adrenal medullae) contain all of these enzymes, and release E. Others (e.g. most sympathetic postganglionic neurons) lack PNMT, and release NE. Still others (particularly in the brain) lack both DbH and PNMT and release DA.

The catecholamines are degraded by two principal enzyme systems, catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO). COMT converts NE and E to their O-methyl metabolites, **normetanephrine** and **metanephrine** respectively; after further metabolism these serve as substrates for MAO leading to formation of 3-methoxy 4-hydroxymandelic acid, better known as **vanillylmandelic acid (VMA)**, the major end product of catecholamine metabolism.

Catecholamines act through plasma membrane receptors of two broad types, a- and b-adrenergic receptors (adrenoceptors). Each type includes multiple subtypes (a_1 and a_2 and b_1, b_2 and b_3); cloning has revealed further divisions of these subtypes. NE and E are mixed agonists. They interact with both a-and b-adrenergic receptors although NE has a relatively low affinity for b_2 –adrenergic receptors including those that mediate vasodilation in skeletal muscles. This probably explains the differences in the hemodynamic responses to E (increased systolic, but not diastolic, blood pressure and increased heart rate) and NE (increased systolic and diastolic blood pressure with reflex restraint of the increase in heart rate).

Although extra-adrenal epinephrine secretion occurs, the adrenal medullae are the source of biologically effective plasma levels of E. Thus, E is a hormone in the traditional sense. In contrast, NE functions primarily as a neurotransmitter. Because most (~90%) of the NE released from sympathetic axon terminals is dissipated locally (by re-uptake or local metabolism) and does not enter the circulation, there is a steep NE concentration gradient from the synaptic clefts to the plasma when NE is released from the terminals in quantities sufficient to produce biologic effects (e.g. an increase in BP). This gradient must be reversed in order for circulating NE to raise blood pressure. Therefore, substantial increments over basal plasma NE levels are required to produce biological effects (e.g. hypertension) if the NE is released directly into the circulation (as from a pheochromocytoma).

PHEOCHROMOCYTOMA: Pheochromocytomas are catecholamine producing tumors, composed of chromaffin cells, that typically produce labile hypertension and paroxysmal symptoms. They are rare (perhaps 0.1% of hypertensive patient) but important to detect because: 1) The hypertension is usually curable. 2) The untreated patient is at risk for a lethal hypertensive paroxysm. 3) Some (perhaps 5-10%) are malignant. 4) They can be a clue to the presence of a familial, often autosomal dominant, syndrome. The latter include multiple endocrine neoplasia (type 2A with hyperparathyroidism and medullary carcinoma of the thyroid, and type 2B, with multiple mucosal neuromas and medullary carcinoma of the thyroid). Familial pheochromocytoma also occurs without associated disorders, in some kindred with von Hippel-Lindau disease and, uncommonly, in persons with neurofibromatosis.

Diagnosis. The diagnosis of pheochromocytoma is based upon clinical suspicion and biochemical confirmation and then (and generally only then) anatomical localization.
Clinical: Pheochromocytoma is suspected in a patient with paroxysmal symptoms (especially headache, diaphoresis and palpitations), labile (and sometimes truly paroxysmal) hypertension, a family history of pheochromocytoma or some combination of these. These paroxysms may be precipitated by a variety of stimuli: positional changes, emotional stress, abdominal pressure, direct pressure on tumor, medications, etc. Metabolic features of pheochromocytoma include signs of hypercatabolism: increased metabolic rate, profuse sweating, hyperglycemia, and weight loss (despite good appetite). The hyperglycemia may be accompanied by glycosuria, both being due to catecholamine stimulation of hepatic glucose production and inhibition of insulin secretion and action. Hematological manifestations

(attributable to catecholamine-induced vasoconstriction and plasma volume reduction) include orthostatic hypotension, which may also be due, in part, to blunted sympathetic reflexes. Patients with pheochromocytoma may have an elevated hematocrit, from plasma volume contraction and hemoconcentration. Rarely, true erythrocytosis (polycythemia) occurs from paraneoplastic production of erythropoietin by the tumor. Other clinical clues in some patients include orthostatic hypotension, hyperglycemia, and erythrocytosis. Routine testing for pheochromocytoma in patients with hypertension is both cost-inefficient and unwise – false positive tests would outweigh true positives by a large margin.

SYMPTOMS DURING PAROXYSMAL ATTACKS (% of Adults)

Headache	59
Sweating	52
Palpitations	49
Pallor	42
Nausea	34
Tremor	33
Anxiety	28
Abdominal pain	25
Chest pain	25
Weakness	19
Dyspnea	17
Weight loss	16
Flushing	14
Visual disturbance	12

adapted from Ross EJ, Griffith DNW. Quart J Med 1989;71(266): 485-496

Biochemical: Confirmation of the presence of a pheochromocytoma is traditionally accomplished with 24h urine catecholamine (NE and E). Although measurements of metabolites (preferably total metanephrines rather than VMA) can be used, specific measurements of catecholamines are preferable. These values are more than twice the upper limit of normal in >90% of patients with proven pheochromocytomas. Plasma catecholamine measurements (NE, E) can also be used. Recent data suggest a slight advantage to urinary catecholamine measurements (which provide information integrated over time), although plasma catecholamine measurements (which provide information only about a short time frame since the plasma half times are ~ 1-2 minutes) are effective and simpler for the patient.

Plasma samples should be obtained in the drug-free state if at all possible since many medications might elevate catecholamine levels producing false positive results. If hypertension must be treated, clonidine, which does not produce false positives, should be used. Samples should be obtained in the basal state (for which reference

values are well established and in which most affected patients have elevated levels) as well as during paroxysms.

Most patients with a pheochromocytoma have elevated plasma and urinary catecholamine (especially NE) values whenever sampled. Occasional patients have normal value when sampled when they are normotensive and asymptomatic. If clinical suspicion is high, plasma samples should be obtained during a paroxysm, if possible, and urinary NE should be measured. On the other hand, normal or slightly elevated catecholamine levels are good evidence against pheochromocytoma in a patient hypertensive at the time of sampling.

Localization: Although described in regions ranging from the carotid body to the pelvic floor, 90% of pheochromocytomas are in the adrenal medullae and 99% are in the abdomen. Most of the remainder are in the mediastinum. Pheochromocytomas are usually localized by computed tomography or magnetic resonance imaging. Iodobenzylguanidine scintigraphy is expensive, time consuming, less sensitive for intra-adrenal tumors and of somewhat limited availability, but has localized tumors not detected by CT (especially extra-adrenal, metastatic and recurrent pheochromocytomas). Although multiple tumors are found in less than 10% of patients with sporadic pheochromocytomas, bilateral adrenomedullary disease is the rule in familial pheochromocytoma.

In summary, the diagnosis of pheochromocytoma is based upon suggestive clinical findings, measurement of urinary and/or plasma catecholamines, followed by localization by CT or MRI scans.

Treatment: Briefly, the treatment of pheochromocytoma is surgical excision by an experienced surgeon working with a vigilant anesthesiologist. Pre-operative control of blood pressure with an alpha-adrenergic antagonist (e.g. phenoxybenzamine, prazosin) helps prevent catastrophic rise in blood pressure during surgical handling of the tumor. The prompt resolution of hypertension following successful resection of a pheochromocytoma is one of the most gratifying clinical experiences.

MINERALOCORTICOID EXCESS

MINERALOCORTICOIDS stimulate the distal renal tubules to **reabsorb sodium** from tubular fluid (ie,excrete less sodium) and **excrete more potassium** and **hydrogen ions (acid).** They increase open sodium and potassium channels in the luminal membrane of tubular cells and increase synthesis of basolateral membrane Na+/K+ ATPase, which generates the gradients that drive ion movement.

Mineralocorticoids **expand extracellular fluid (ECF) volume** by increasing the amount of sodium in the body, and **increase blood pressure** due to greater intravascular volume and increased arteriolar resistance. They **lower plasma potassium** levels and increase plasma pH. There is some evidence that effects on the brain contribute to hypertension.

The **mineralocorticoid receptor** is activated by both cortisol and aldosterone. Aldosterone is the primary mineralocorticoid because an enzyme **(11 – beta hydroxysteroid dehydrogenase)** coexists with this receptor in the renal tubule and coverts cortisol to inactive cortisone. Hereditary defects or drug inhibition of this enzyme produces a syndrome of apparent mineralocorticoid excess, due to receptor activation by normal levels of cortisol. **Licorice** contained in some candies and tobacco products has a metabolite (glycyrrhetinic acid) that produces mineralocorticoid excess by inhibiting 11-beta hydroxysteroid dehydrogenase. Severe cortisol excess causes mineralocorticoid effects, including hypertension and hypokalemia.

Aldosterone is the primary mineralocorticoid in man. Cortisol has mineralocorticoid activity that is clinically important at high concentrations. 11-deoxycorticosterone, an aldosterone precursor, is also a mineralocorticoid.

• **Mineralocorticoid excess** causes **hypertension** and **hypokalemic alkalosis.** Two things you might expect, hypernatremia and edema (excess fluid in subcutaneous tissue, producing swelling of the feet and ankles) don't occur. Plasma sodium increases only slightly (and usually remains normal) because it is regulated by antidiuretic hormone and thirst that control water balance. ECF expansion stops before edema develops, in part because atrial natriuretic hormone levels rise and limit sodium retention.

Aldosterone secretion is regulated by the **volume of the extracellular fluid (ECF) (**Fig 3a and 3b). This is sensed by receptors in the juxtaglomerular apparatus of the kidney, through changes in renal arteriolar blood pressure and sodium concentration of renal tubular fluid. ECF volume contraction ("dehydration") stimulates secretion of the enzyme **renin.** Renin cleaves the circulating protein angiotensinogen to release angiotensin 1, which is converted to **angiotensin II** by **angiotensin converting enzyme (ACE)** on endothelial cells. **Angiotensin II stimulates aldosterone secretion,** which then decreases sodium excretion, tending to increase ECF volume and suppress renin secretion, forming a **negative feedback loop.** Conversely expansion of ECF volume by high salt intake or intravenous infusion of saline suppresses renin and aldosterone secretion, increasing sodium excretion and tending to correct ECF volume expansion.

Angiotensin ll is also a **potent vasoconstrictor**, and increases blood pressure directly. In summary, the regulatory steps in aldosterone secretion are:

$$\text{angiotensinogen} \xrightarrow{\text{Renin}} \text{angiotensin I} \xrightarrow{\text{ACE}} \text{angiotensin II} \longrightarrow \text{stimulation of aldosterone}$$

The renin-angiotensin-aldosterone system maintains ECF volume by responding to decreased salt intake or increased salt loss (eg sweating) to limit further sodium loss in the urine. Pathological causes of sodium loss (vomiting, diarrhea), diuretic therapy and other conditions in which renal blood flow is decreased hypotension, renal artery stenosis, heart failure) increase renin and aldosterone secretion.

Renin secretion is also stimulated by the **sympathetic nervous system,** via beta-adrenergic receptors. This increases renin and aldosterone levels on standing, and contributes to the response to hypotension. Hyperkalemia stimulates aldosterone secretion and hypokalemia suppresses it, but this regulatory mechanism is less important than ECF volume. **ACTH is not part of the physiologic control of aldosterone,** so patients with ACTH deficiency lack cortisol, but aldosterone secretion is intact.

• **Mineralocorticoid excess** may be due to autonomous aldosterone secretion, eg by an adrenal adenoma (**primary hyperaldosteronism**), in which case plasma renin and angiotensin are suppressed by negative feedback. It may also be due to increased renin secretion (**secondary hyperaldosteronism**). Secondary hyperaldosteronism may be an adaptive physiologic response to ECF volume depletion, or cause some symptoms of disorders in which renal perfusion is decreased (eg congestive heart failure).

Plasma levels of renin and aldosterone vary widely due to differences in salt intake, and whether patients were standing before samples were drawn. This means that random plasma levels of either one alone are seldom helpful. The **ratio of plasma aldosterone** to **plasma renin activity** is used to diagnose primary hyperaldosteronism. During physiologic increases in aldosterone secretion due to increased renin secretion, the ratio remains unchanged. In primary hyperaldosteronism, plasma aldosterone increases while renin is suppressed by negative feedback, so the aldosterone to renin ratio is much higher than normal. Manipulation of ECF volume is also used for diagnosis – intravenous infusion of saline suppresses normal secretion of renin and aldosterone.

PRIMARY HYPERALDOSTERONISM

Primary hyperaldosteronism is excessive production of aldosterone due to an adrenal disorder, and **not** due to excess renin secretion. It results in ECF expansion, hypertension and marked suppression of renin secretion.

Secondary hyperaldosteronism is increased secretion of both renin and aldosterone. It is a normal response to deficient salt intake, and is a compensatory mechanism in diseases that decrease ECF volume (eg, vomiting, diarrhea) or reduce perfusion of the kidneys (eg, cirrhosis, heart failure, renal artery stenosis). It contributes to clinical findings such as edema in the latter diseases, and the aldosterone antagonist spironalactone is sometimes used to treat them.

ETIOLOGY OF PRIMARY HYPERALDOSTERONISM: About 2/3 of cases are due to an **aldosterone-secreting adrenal adenoma.** These tumors tend to be small – average diameter <2 cm. Remaining cases are due to bilateral adrenal hyperplasia of unknown cause (idiopathic hyperaldosteronism).

CLINICAL FINDINGS in primary hyperaldosteronism are **hypertension**, and **hypokalemia**. Hypertension in this disorder is due to increased body sodium, which

increases ECF volume and vascular resistance. Patients rarely have symptoms, although severe hypokalemia may cause muscle weakness, cramps, and polyuria. Edema does not occur, since compensatory mechanisms limit the degree of ECF expansion. Plasma sodium concentration is usually normal, not increased.

DIAGNOSIS: This disorder is suspected in a patient with **hypertension and spontaneous hypokalemia**. Since diuretics used to treat hypertension (eg thiazides) are a much more common cause of hypokalemia than primary hyperaldosteronism, serum potassium should be measured while the patient is not taking diuretics (or after they have been stopped for several weeks).

In a patient with hypertension and hypokalemia not due to diuretics, urine potassium is measured to be sure hypokalemia is due to excess renal potassium excretion (rather than to excess gastrointestinal loss, eg in diarrhea or laxative abuse). Urine potassium >30 mmo1/24 hr indicates renal potassium wasting.

Tests for primary hyperaldosteronism are based on the fact that excess aldosterone secretion is not under normal control by renin. Plasma renin activity (PRA) is low, and the **ratio of plasma aldosterone to PRA** is increased. Measuring the ratio minimizes diagnostic problems caused by normal variation of these two hormones with body position (supine vs standing), salt intake and other factors that affect ECF volume. In essential hypertension, renin and aldosterone tend to change in parallel, and the ratio between them remains fairly constant. Likewise, the ratio is not elevated in secondary hyperaldosteronism.

The optimum ratio for separating primary hyperaldosteronism from essential hypertension is debated, but if the ratio is >30, primary hyperaldosteronism is very likely; if the ratio is >50, it is almost certain. The ratio may be affected by many antihypertensive drugs, which should be stopped several weeks before testing. If the aldosterone/renin ratio is elevated, the diagnosis of primary hyperaldosteronism is confirmed by demonstrating that **plasma aldosterone cannot be normally suppressed by ECF volume expansion.** IV infusion of saline is usually used for this purpose.

DIAGNOSTIC TESTS FOR PRIMARY HYPERALDOSTERONISM

Screening:

- plasma potassium (while not treated with diuretics)

Definitive:

- plasma aldosterone (ng/dl) / plasma renin activity (ng/ml/hr) ratio:

  <30: probably not primary hyperaldosteronism

  >50: almost certainly primary hyperaldosteronism

- aldosterone suppression: 2 liters 0.9% (normal) saline IV over 4 hrs with patient supine. Normal: plasma aldosterone <4 ng/dl

DIFFERENTIAL DIAGNOSIS: Although small, adrenal adenomas are usually seen on CT scans, remember that non-functioning, **incidental adrenal nodules are common.** Primary hyperaldosteronism is diagnosed by endocrine testing, not radiology. There are some differences in regulation of aldosterone secretion by adenomas and idiopathic hyperaldosteronism that may help in differential diagnosis. Occasionally, adrenal venous aldosterone measurements are necessary.

TREATMENT: Resection of an aldosterone-secreting adenoma cures hypokalemia and, in most cases, hypertension. In idiopathic hyperaldosteronism, even bilateral adrenalectomy doesn't cure hypertension, so it is treated with the aldosterone antagonist spironolactone, and other antihypertensives as needed to control blood pressure.

GLUCOCORTICOID EXCESS

GLUCOCORTICOIDS have multiple actions, including effects on glucose metabolism (hence their name). In high concentrations, they cause profound **catabolic effects** on protein metabolism, especially in skeletal muscle and connective tissue, and **suppress immunity and inflammation.** They are necessary for normal **cardiovascular function.** They have effects on the brain, including increased appetite. **Cortisol** is the primary glucocorticoid in man. Synthetic glucocorticoids are widely used to treat allergic and inflammatory disorders, and to suppress autoimmune diseases and rejection of organ transplants. When physicians say "steroids'< they mean this pharmacologic use of glucocorticoid drugs. **Prednisone** is the most commonly used glucocorticoid. **Dexamethasone** is a potent synthetic glucocorticoid used to produce negative feedback in diagnostic tests because it interferes very little with measurement of cortisol. Treatment with excessive doses of prednisone or dexamethasone or other glucocorticoid agent produces a syndrome that is clinically similar to that produced by endogenous cortisol excess.

• **Glucocorticoid excess** (known as Cushing's syndrome after the neurosurgeon who described it) causes a variety of clinical effects, some of which can be explained by known actions of cortisol. Obesity is due mainly to stimulation of appetite, while catabolic effects cause weakness of skeletal muscle and connective tissue of the skin. Bone mass decreases and fractures are common.

Glucocorticoid excess and Hypertension

General information on Cushing's syndrome is discussed more fully elsewhere. Up to 80% of patients with Cushing's syndrome have hypertension (high blood pressure occurs less frequently in drug-induced cases of the syndrome). The exact mechanism of hypertension in Cushing's syndrome is unknown. Some suggested pathways include

direct effects of excess cortisol, acting via three mechanisms: 1) angiotensin, 2) mineralocorticoid, and 3) vascular reactivity.

Angiotensin mechanism: Glucocorticoids stimulate hepatic synthesis of angiotensinogen, wich is acted upon by renin and angiotensin converting enzyme to the potent vasoconstrictor angiotensin II. This mechanism probably operates in some but not all patients with Cushing's syndrome.

Mineralocorticoid: High concentrations of cortisol can bind to and cross-activate mineralocorticoid receptors, resulting in typical mineralocortocid effects–hypertension and hypokalemia. The sodium and fluid retention from this mechanism also will suppress plasma renin. However, most patients with Cushing's disease (from pituitary tumor) or syndrome from adrenal adenoma do not have hypokalemia or suppressed renin. Interestingly, when the Cushing's syndrome results from ectopic paraneoplastic production of ACTH, hypokalemia and renin become more prominent features. One possible explanation may the effect of high levels of ACTH on the biosynthesis of cortisol precursors with enhanced mineralocorticoid activity (e.g. 11-deoxycortisol). Furthermore, the renal enzyme 11 beta-hydroxysteroid dehydrogenase (which breaks down cortisol) has been found deficient in some patients with paraneoplastc (ectopic) ACTH syndromes. Deficiency in 11 beta-HSD allows high intrarenal levels of cortisol to activate the mineralocorticoid receptor, resulting is hypertension and hypokalemia.

Vascular reactivity: Administration of cortisol to normal subjects enhances vascular reactivity to pressors, resulting in vasocontriction, increased peripheral resistance, and elevation in BP. This is likely to be a more general mechanism than the alterations of specific hormone pathways discussed earlier.

Diagnosis The diagnosis of Cushing's syndrome is covered elsewhere in this syllabus.

Treatment In patients without a family history of hypertension, blood pressure often returns promptly to normal, or becomes easier to control with few drugs, once the underlying cause of Cushing;s syndrome has been localized and removed.

Natriuretic Peptides, Hypertension and Heart Failure

Increased wall stretch due to volume and pressure overload in patients with heart failure triggers the release of natriuretic peptides (ANP and BNP and their N-terminal fragments NT-proANP and NT-proBNP) by atrial and ventricular myocytes. Other natriuretic peptides include guanylin and uroguanylin. Normal BNP levels are <20 pg/ml.In clinical practice, a plasma BNP plasma concentration of >100 pg/ml indicates a diagnosis of heart failure. Also, urine uroguanylin levels are elevated in patients with heart failure.

Recent evidence suggests that lower levels of increases in plasma BNP and other natriuretic peptides may indicate increased risks of cardiovascular diseases other than heart failure. In patients without HF, a history of hypertension is associated with higher median BNP levels (38 pg/ml vs 21 pg/ml in normotensive subjects). Similarly, plasma levels of proguanylin and prouroguanylin (precursors of natriuretic hormones guanylin and uroguanylin) are increased in patients with hypertension, renal impairment as well as heart failure. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, and spironolactone have been shown to decrease circulating natriuretic peptide levels (e.g., BNP and NT-proBNP) simultaneously with clinical and hemodynamic improvement.

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ENDOCRINE HYPERTENSION CASE # 1

A 47 year old woman is referred because of poorly controlled hypertension. She has leg Cramps and polyuria, but no episodes of headache, sweating or palpitations. There is no family history of hypertension.

She is not obese. HR is 78/min and BP 160/98 mm; the exam is otherwise normal.

Plasma potassium: 2.5 mM

1) What symptoms are caused by hypertension? By severe hypokalemia?

2) What are the three major endocrine causes of hypertension (ie, disorders in which the majority of patients have high blood pressure)? How common are they in patients with hypertension?

3) Which endocrine cause of hypertension is most likely in this patient? What test should be done now?

A blood sample is drawn with the patient seated:

Plasma aldosterone: 25 ng/dl plasma renin activity: <0.5 ng/ml/hr

After these results are available, another test is performed. With the patient supine, 2 liters of normal Saline (0.9% NaCl) is infused IV over 4 hr. Plasma aldosterone at the end of the infusion is 20 ng/dl.

4) Do these results establish a diagnosis? Why were aldosterone and renin activity measured simultaneously? Can a diagnosis be made by measuring either hormone level alone?

5) What is the purpose of saline infusion?

6) What are the major causes of this syndrome? Why is it important to distinguish between them, and how can this be done?

abdominal CT shows a 2 cm mass in the right adrenal

ENDOCRINE HYPERTENSION CASE #2

A 34 year old man complains of episodes of palpitations and severe, pounding headache, usually lasting less than 30 minutes. He has no history of hypertension or other medical problems.

BP is 160/95 and HR 78/min; otherwise the exam is normal.

Plasma potassium is 4.4 mM

1) What endocrine disorder can cause this man's symptoms? Excessive secretion of what compound causes hypertension in this disorder?

2) What diagnostic tests can be done to confirm this diagnosis?

_____
_____
_____

24 hr urine norepinephrine: 280 μg (normal 15-80) epinephrine: 5 μg (normal <15)

_____
_____
_____

3) What are the pathologic features of this disorder?

4) Should all patients with hypertension be tested for this disorder?