Endocrine Hypertension

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Perrin C. White

Abstract

Hypertension may be caused by abnormal synthesis of, or response to, various hormones. The proportion of pediatric hypertension cases resulting from such problems probably represents at most a few percent of cases overall but a higher fraction of cases of severe hypertension, those occurring in the very young, or cases clustering in families. Most endocrine hypertension involves the adrenal gland and its hormones. The adrenal gland is composed of two endocrine tissues: the medulla (secreting catecholamines) and the cortex (synthesizing cortisol and aldosterone). Pheochromocytoma is mainly a disease of the adrenal medulla, although extramedullary sites may be involved. Many different diseases affecting the adrenal cortex can cause hypertension. These include hypertensive forms of congenital adrenal hyperplasia, primary aldosteronism due to hyperplasia of the zona glomerulosa or to adenomas, and Cushing syndrome (excessive glucocorticoid exposure) due to iatrogenic etiologies, to pituitary or adrenal adenomas, or other tumors secreting excessive ACTH. Hypertension can also be caused by thyrotoxicosis due to Graves disease or to the thyrotoxic phase of Hashimoto's thyroiditis. It is important to accurately diagnose these disorders because the associated hypertension requires, and usually responds well to, specific treatment of the underlying condition.

Keywords

ACTH • Adrenal • Aldosterone • Catecholamines • Congenital adrenal hyperplasia • Cortisol • Cushing syndrome • Graves disease • Thyrotoxicosis • Thyroxine

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Hypertension may be caused by abnormal synthesis of, or response to, various hormones. The proportion of pediatric hypertension cases resulting from such problems is not known. It probably represents at most a few percent of cases overall but a higher fraction of cases of severe hypertension, those occurring in the very young, or cases clustering in families.

Pheochromocytoma

The vast majority of endocrine hypertension involves the adrenal gland and its hormones.

The adrenal gland is composed of two endocrine tissues: the medulla and the cortex. Pheochromocytoma is mainly a disease of the adrenal medulla although extramedullary sites may be involved.

Pathophysiology. The medulla consists mainly of neuroendocrine (chromaffin) cells and glial (sustentacular) cells with some connective tissue and vascular cells. The principal hormones of the adrenal medulla are the catecholamines dopamine, norepinephrine, and epinephrine (Fig. 25.1). Catecholamine synthesis also occurs in the brain, in sympathetic nerve endings, and in chromaffin tissue outside the adrenal medulla.

The effects of catecholamines are mediated through a series of G protein–coupled adrenergic receptors [1]. Both epinephrine and norepinephrine raise mean arterial blood pressure, but only epinephrine increases cardiac output. By increasing peripheral vascular resistance, norepinephrine increases systolic and diastolic blood pressures with only a slight reduction in the pulse rate. Epinephrine increases the pulse rate and, by decreasing the peripheral vascular resistance, decreases the diastolic pressure. The hyperglycemic and hypermetabolic effects of norepinephrine are much less pronounced than are those of epinephrine.

Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells. The most common site of origin (approximately 90 %) is the adrenal medulla; however, tumors may develop anywhere along the abdominal

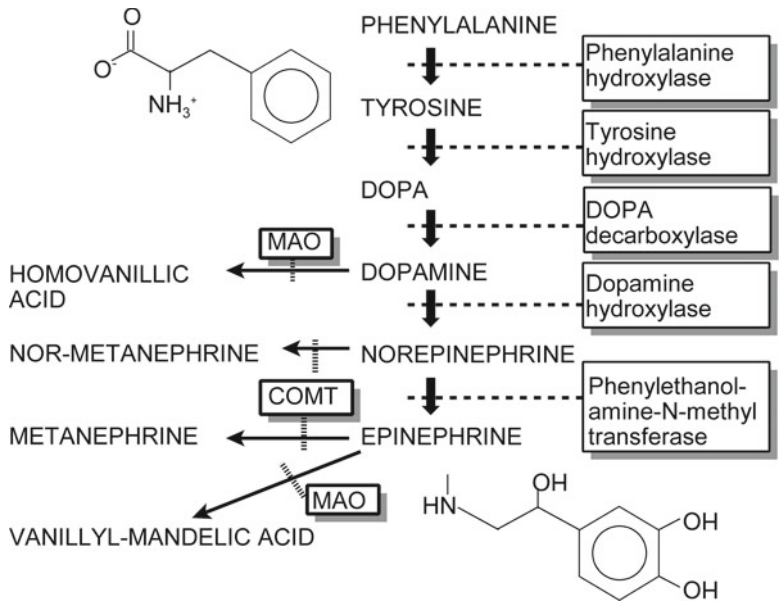

Fig. 25.1 Biosynthesis (*right side of figure*) and metabolism (*left side of figure*) of the catecholamines norepinephrine and epinephrine. COMT, catechol-*O*-methyltransferase; MAO monoamine oxidase. Planar structures of phenylalanine and epinephrine are shown at the top and bottom of the figure, respectively

sympathetic chain and are likely to be located near the aorta at the level of the inferior mesenteric artery or at its bifurcation. They also appear in the peri-adrenal area, urinary bladder or ureteral walls, thoracic cavity, and cervical region. They are rare in children, in whom they present most frequently between 6 and 14 years of age. Tumors vary from 1 to 10 cm in diameter; they are found more often on the right side than on the left. In more than 20 % of affected children, the adrenal tumors are bilateral; in 30–40 % of children, tumors are found in both adrenal and extra-adrenal areas or only in an extra-adrenal area [2].

Pheochromocytomas may be associated with genetic syndromes such as von Hippel–Lindau disease, as a component of multiple endocrine neoplasia (MEN) syndromes MEN 2A and MEN 2B, and more rarely in association with neurofibromatosis, tuberous sclerosis, Sturge–Weber syndrome, and ataxia-telangiectasia. Mutations in the SDHB, SDHD, and rarely the SDHC genes encoding subunits of the mitochondrial enzyme, succinate dehydrogenase, can cause pheochromocytomas and also paragangliomas, particularly at sites in the head and neck.

Somatic mutations of many of these genes, particularly *VHL*, have been found in some sporadic cases of pheochromocytoma [3–6].

Clinical manifestations. Pheochromocytomas detected by surveillance of patients who are known carriers of mutations in tumor-suppressor genes may be asymptomatic [6, 7]. Otherwise, patients are detected due to hypertension, which results from excessive secretion of epinephrine and norepinephrine. Paroxysmal hypertension is characteristic of pheochromocytoma, but in contrast to adults, the hypertension in children is more often sustained rather than paroxysmal. When paroxysms of hypertension do occur, the attacks are usually infrequent at first but become progressively more frequent until continuous hypertension supervenes. Between attacks of hypertension, the patient may be free of symptoms. During attacks, the patient complains of headache, palpitations, abdominal pain, and dizziness; pallor, vomiting, and sweating also occur. Blood pressure may range from 180 to 260 mmHg systolic and from 120 to 210 mmHg diastolic. Convulsions and other manifestations of hypertensive encephalopathy may occur. Severely hypertensive patients may complain of precordial pain and may develop pulmonary edema and cardiac and hepatic enlargement. Symptoms may be exacerbated by exercise or with use of over-the-counter medications containing stimulants such as pseudoephedrine. Patients have a good appetite but because of the hypermetabolic state may not gain weight or grow well, and severe cachexia may develop. Polyuria and polydipsia can be sufficiently severe to suggest diabetes insipidus. Ophthalmoscopic examination may reveal papilledema, hemorrhages, exudate, and arterial constriction.

Laboratory findings. Pheochromocytomas produce norepinephrine and epinephrine. Normally, norepinephrine in plasma is derived from both the adrenal gland and adrenergic nerve endings, whereas epinephrine is derived primarily from the adrenal gland. In contrast to adults with pheochromocytoma in whom both norepinephrine and epinephrine are elevated, children with pheochromocytoma predominantly excrete norepinephrine in the urine. Total urinary catecholamine excretion usually exceeds 300 μg/24 h. Urinary excretion of metanephrines (particularly normetanephrine) is also increased [6, 8]. Daily urinary excretion of these compounds by unaffected children increases with age. Although urinary excretion of vanillylmandelic acid (VMA, 3-methoxy-4-hydroxymandelic acid), the major metabolite of epinephrine and norepinephrine, is increased, vanilla-containing foods and fruits can produce falsely elevated levels of this compound, which therefore is no longer routinely measured.

Elevated levels of free catecholamines and metanephrines can also be detected in plasma. In children, the best sensitivity and specificity are obtained by measuring plasma normetanephrine using gender-specific pediatric reference ranges, with plasma norepinephrine being next best [9]. Plasma metanephrine and epinephrine are not reliably elevated in children. Additionally, the patient should be instructed to abstain from caffeinated drinks and to avoid acetaminophen, which can interfere with plasma

normetanephrine assays. If possible, the blood sample should be obtained from an indwelling IV catheter, to avoid acute stress associated with venipuncture [10, 11].

Most tumors in the area of the adrenal gland are readily localized by CT or MRI, but extra-adrenal tumors may be difficult to detect. ^{131}I-metaiodobenzylguanidine (MIBG) is taken up by chromaffin tissue anywhere in the body and is useful for localizing small tumors [12, 13]. Venous catheterization with sampling of blood at different levels for catecholamine determinations is now only rarely necessary for localizing the tumor.

Differential diagnosis. Various causes of hypertension in children must be considered, such as renal or renovascular disease, coarctation of the aorta, other forms of endocrine discussed in this chapter, and primary hypertension. A nonfunctioning kidney may result from compression of a ureter or of a renal artery by a pheochromocytoma. Paroxysmal hypertension may be associated with porphyria or familial dysautonomia. Cerebral disorders, diabetes insipidus, diabetes mellitus, and hyperthyroidism must also be considered in the differential diagnosis. Hypertension in patients with neurofibromatosis may be caused by renal vascular involvement or by concurrent pheochromocytoma [14].

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma frequently produce catecholamines, but urinary levels of most catecholamines are higher in patients with pheochromocytoma, although levels of dopamine and homovanillic acid are usually higher in neuroblastoma. Secreting neurogenic tumors often cause hypertension, excessive sweating, flushing, pallor, rash, polyuria, polydipsia, and – particularly with ganglioneuroma – chronic diarrhea.

Treatment. Pheochromocytomas must be removed surgically [10, 11]. Because these tumors are often multiple in children, a thorough transabdominal exploration of all the usual sites offers the best opportunity to find them all. Manipulation and excision of these tumors result in marked increases in catecholamine secretion that increase blood pressure and heart rate. Therefore, preoperative α- and β-adrenergic blockade are required [6, 15]. The recommended approach is to produce complete alpha-blockade with either phenoxybenzamine or doxazosin before adding beta-blockade. Blood volume must be expanded with appropriate fluids before and during surgery to avoid a precipitous drop in blood pressure during the operation or within 48 h postoperatively.

Although these tumors often appear malignant histologically, the only accurate indicators of malignancy are the presence of metastatic disease, local invasiveness that precludes complete resection, or both [16]. Approximately 10 % of all adrenal pheochromocytomas are malignant, but such tumors are rare in childhood. Pediatric malignant pheochromocytomas occur more frequently in extra-adrenal sites and are often associated with mutations in the SDHB gene encoding a subunit of succinate dehydrogenase [4, 17].

Diseases of the Adrenal Cortex Causing Hypertension

Physiology. The adrenal cortex consists of three concentric zones: the zona glomerulosa outermost, then the zona fasciculata (which comprises around three-fourth of the cortex), and finally the zona reticularis, lying next to the adrenal medulla. The zona glomerulosa synthesizes aldosterone, the most potent mineralocorticoid. The zona fasciculata produces cortisol, and the zona fasciculata and zona reticularis synthesize adrenal androgens.

Adrenal steroidogenesis. Cholesterol is the starting substrate for all steroid biosynthesis (Fig. 25.2) [18]. In mitochondria, the side chain of cholesterol is cleaved to yield pregnenolone, which then diffuses out of the mitochondria and enters the endoplasmic reticulum. The subsequent reactions that occur depend on the zone of the adrenal cortex.

In the zona glomerulosa, pregnenolone is successively converted to progesterone and deoxycorticosterone. Deoxycorticosterone then reenters mitochondria and is converted to

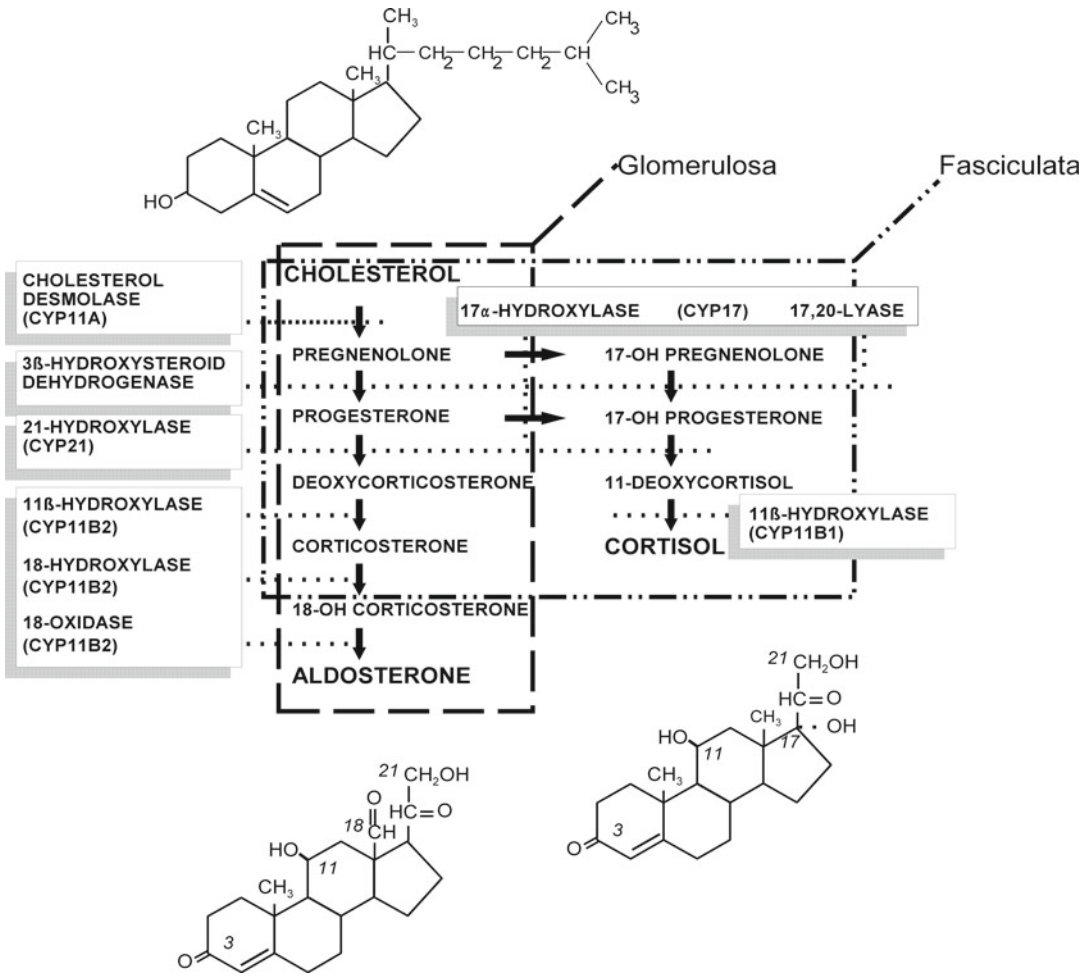

Fig. 25.2 Adrenal steroid biosynthesis. Reactions occurring in the zonae glomerulosa and fasciculata are enclosed by labeled dotted lines; several reactions take place in both zones. Many of the involved enzymes are cytochromes P450 (CYP). CYP11B2 mediates successive 11β-hydroxylase, 18-hydroxylase, and 18-oxidase reactions in the zona glomerulosa for the conversion of deoxycorticosterone to aldosterone. Planar structures of cholesterol, aldosterone, and cortisol are illustrated; relevant carbon positions on the latter two molecules are marked

aldosterone by aldosterone synthase (P450aldo, CYP11B2), a P450 enzyme which carries out three successive oxidations: 11β-hydroxylation, 18-hydroxylation, and further oxidation of the 18-methyl carbon to an aldehyde [19].

In the endoplasmic reticulum of the zona fasciculata, pregnenolone is converted by 17α-hydroxylase (P450c17, CYP17) to 17-hydroxypregnenolone. This enzyme is not expressed in the zona glomerulosa, which consequently cannot synthesize 17-hydroxylated steroids. 17-hydroxypregnenolone is converted to 17-hydroxyprogesterone and then 11-deoxycortisol which finally 11-deoxycortisol reenters mitochondria and is converted to cortisol by steroid 11β-hydroxylase (P450c11, CYP11B1). This enzyme is closely related to aldosterone synthase but has low 18-hydroxylase and nonexistent 18-oxidase activity [19]. Thus, under normal circumstances, the zona fasciculata cannot synthesize aldosterone.

Regulation of cortisol secretion. Glucocorticoid secretion is regulated mainly by adrenocorticotropic hormone (corticotropin, ACTH), which is

secreted by the anterior pituitary gland in pulses which vary diurnally in amplitude. Pulses of ACTH and cortisol are highest at about the time of waking, are low in late afternoon and evening, and reach their lowest point 1 or 2 h after sleep begins.

ACTH acts through a specific G protein–coupled receptor (also termed the melanocortin receptor 2, encoded by the *MCR2* gene) to activate adenylate cyclase and increase levels of cyclic adenosine monophosphate (cAMP) [20]. Cyclic AMP has short-term (minutes to hours) effects on cholesterol transport into mitochondria by increasing expression of steroidogenesis acute regulatory (StAR) protein [21]. The long-term effects (hours to days) of ACTH stimulation are to increase the uptake of cholesterol and the expression of genes encoding the enzymes required to synthesize cortisol.

Regulation of aldosterone secretion. The rate of aldosterone synthesis, which is normally 100- to 1,000-fold less than that of cortisol synthesis, is regulated mainly by the renin–angiotensin–aldosterone system (RAAS) and by potassium levels, with ACTH having only a short-term effect. In response to decreased intravascular volume, renin is secreted by the juxtaglomerular apparatus of the kidney. Renin is a proteolytic enzyme that cleaves angiotensinogen (renin substrate), an α_2-globulin produced by the liver, to yield the inactive decapeptide angiotensin I. Angiotensin-converting enzyme in the lungs and other tissues rapidly cleaves angiotensin I to the biologically active octapeptide angiotensin II. Cleavage of angiotensin II produces the heptapeptide angiotensin III. Angiotensin II and III are potent stimulators of aldosterone secretion; angiotensin II is a more potent vasopressor agent. Angiotensin II and III occupy a G protein–coupled receptor activating phospholipase C [22]. The latter protein hydrolyzes phosphatidylinositol bisphosphate to produce inositol triphosphate and diacylglycerol, which raise intracellular calcium levels and activate protein kinase C and calmodulin-activated (CaM) kinases [23]. Similarly, increased levels of extracellular potassium depolarize the cell membrane and increase calcium influx through voltage-gated L-type calcium channels. Phosphorylation of transcriptional regulatory factors by CaM kinases increases transcription of the aldosterone synthase (CYP11B2) enzyme required for aldosterone synthesis [24, 25].

Adrenal steroid hormone actions. Aldosterone and cortisol act through distinct receptors that belong to a larger superfamily of nuclear transcriptional factors. Hormone molecules diffuse through the cell membrane and bind to these receptors, changing their conformation and causing them to bind DNA at specific hormone response elements. Bound receptors may recruit other transcriptional co-regulatory factors to DNA.

The responses to each hormone are determined by the different genes that are regulated by the hormone in different tissues. Additionally, different combinations of co-regulators are expressed in different tissues, allowing each steroid hormone to have many different effects. Moreover, enzymes may increase or decrease the affinity of steroids for their receptors and thus modulate their activity. For example, 11β-hydroxysteroid dehydrogenase type 1 (HSD11B1) converts cortisone, which is not a ligand for the glucocorticoid receptor, to cortisol, which is an active glucocorticoid [26]. This increases local glucocorticoid concentrations in several tissues, especially the liver. Conversely, 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2) oxidizes cortisol to cortisone, particularly in the kidney, preventing mineralocorticoid receptors from being occupied by high levels of cortisol [27, 28] (see Chap. 6, and below).

Actions of glucocorticoids. The term glucocorticoid refers to the glucose-regulating properties of these hormones. However, glucocorticoids such as cortisol have many other effects, including actions on circulatory and renal function, that may contribute to the development of hypertension.

Glucocorticoids have a positive inotropic influence on the heart, increasing the left ventricular work index [1]. Moreover, they have a permissive effect on the actions of epinephrine and norepinephrine on both the heart and the blood

vessels [29]. In the absence of glucocorticoids, decreased cardiac output and shock may develop; in states of glucocorticoid excess, hypertension is frequently observed. This may be due in part to the activation of the mineralocorticoid receptor (see later), which occurs when renal 11β-hydroxysteroid dehydrogenase is saturated by excessive levels of glucocorticoids.

Actions of mineralocorticoids. The most important mineralocorticoids are aldosterone and, to a lesser degree, deoxycorticosterone; corticosterone and cortisol are normally not important as mineralocorticoids unless secreted in excess. Mineralocorticoids maintain intravascular volume by conserving sodium and eliminating potassium and hydrogen ions. They exert these actions in the kidney, gut, and salivary, and sweat glands [30]. Aldosterone may have distinct effects in other tissues. Mineralocorticoid receptors are found in the heart and vascular endothelium, and aldosterone increases myocardial fibrosis in heart failure [31].

Mineralocorticoids have their most important actions in the distal convoluted tubules and cortical collecting ducts of the kidney, where they induce reabsorption of sodium and secretion of potassium. In the medullary collecting duct, they act in a permissive fashion to allow vasopressin to increase osmotic water flux [30]. Thus, patients with mineralocorticoid excess may develop hypertension, hypokalemia, and metabolic alkalosis.

The mechanisms by which aldosterone affects sodium excretion are incompletely understood. Most effects of aldosterone are presumably due to changes in gene expression mediated by the mineralocorticoid receptor, and indeed levels of subunits of both the Na^+, K^+-ATPase and the epithelial sodium channel (ENaC) increase in response to aldosterone. Additionally, aldosterone increases expression of the serum and glucocorticoid-regulated kinase (SGK), which indirectly reduces turnover of ENaC subunits and thus increases the number of open sodium channels [32] (see also Chap. 6).

The mineralocorticoid receptor has similar affinities in vitro for cortisol and aldosterone, yet cortisol is a weak mineralocorticoid in vivo. This discrepancy results from the action of 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to cortisone. Cortisone is not a ligand for the receptor, whereas aldosterone is not a substrate for the enzyme. Pharmacologic inhibition or genetic deficiency of this enzyme allows cortisol to occupy renal mineralocorticoid receptors and produce sodium retention and hypertension. Pharmacologic inhibition is most often caused by excessive licorice ingestion (the active compounds are glycyrrhizic acid and glycyrrhetinic acid) or licorice-flavored chewing tobacco; the genetic condition is termed apparent mineralocorticoid excess syndrome [27, 28] (see Chap. 6).

Hypertensive Forms of Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia due to 11β-hydroxylase deficiency. Deficiency of 11β-hydroxylase is caused by mutations in the *CYP11B1* gene located on chromosome 8q24 [33, 34]. Its incidence has been estimated to be 1/250,000 to 1/100,000. *CYP11B1* mediates 11-hydroxylation of 11-deoxycortisol to cortisol. Because 11-deoxycortisol is not converted to cortisol, levels of corticotropin are high. In consequence, precursors accumulate and are shunted into androgen biosynthesis, so that females may be born with ambiguous genitalia. However, the adjacent *CYP11B2* gene encoding aldosterone synthase is generally unaffected in this disorder, so patients are able to synthesize aldosterone normally. Plasma levels of 11-deoxycortisol and deoxycorticosterone are elevated. Because deoxycorticosterone and metabolites have mineralocorticoid activity, plasma renin activity is suppressed. Consequently, aldosterone levels are low, even though the ability to synthesize aldosterone is intact. Approximately two-thirds of patients become hypertensive, although this can take several years to develop. Hypokalemic alkalosis occasionally occurs.

Congenital adrenal hyperplasia due to 17-hydroxylase deficiency. This is a very rare disorder caused by mutations in the *CYP17* gene

[35]. The encoded enzyme catalyzes two distinct reactions: 17-hydroxylation of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, and the 17, 20-lyase reaction mediating conversion of 17-hydroxypregnenolone to dehydroepiandrosterone. The enzyme is expressed in both the adrenal cortex and the gonads. Most mutations affect both the hydroxylase and lyase activities.

Patients with 17-hydroxylase deficiency cannot synthesize cortisol, but their ability to synthesize corticosterone is intact. Because corticosterone is an active glucocorticoid, patients do not develop adrenal insufficiency. Deoxycorticosterone, the immediate precursor of corticosterone, is synthesized in excess. This can cause hypertension, hypokalemia, and suppression of renin and aldosterone secretion, as occurs in 11-hydroxylase deficiency. However, in contrast to 11-hydroxylase deficiency, patients with 17-hydroxylase deficiency are unable to synthesize sex hormones. Affected males are incompletely virilized and present as phenotypic females (but gonads are usually palpable in the inguinal region or the labia) or with sexual ambiguity. Affected females usually present with failure of sexual development at the expected time of puberty.

Treatment. Patients are treated with hydrocortisone in doses of 15–20 mg/M^2/d. Hypertension often resolves with glucocorticoid treatment but may require additional therapy if it has been long standing. Calcium channel blockers may be beneficial under these circumstances. Additionally, females with 17-hydroxylase deficiency require estrogen replacement at puberty, whereas genetic males with this condition may require either estrogen or androgen supplementation depending on the sex of rearing.

Primary Aldosteronism

Clinical manifestations. Primary aldosteronism encompasses disorders caused by excessive aldosterone secretion independent of the RAAS. These disorders are characterized by hypertension, hypokalemia, and suppression of the RAAS. The three main etiologies are aldosterone-secreting adenomas, bilateral micronodular adrenocortical hyperplasia, and glucocorticoid-suppressible (or remediable) aldosteronism.

Aldosterone-secreting adenomas are usually unilateral and have been reported in children as young as 3 1/2 years of age. Bilateral micronodular adrenocortical hyperplasia tends to occur in older children. Primary aldosteronism due to unilateral adrenal hyperplasia may also occur.

Glucocorticoid-suppressible aldosteronism (also discussed in Chap. 6) is an autosomal dominant form of low-renin hypertension in which aldosterone secretion is rapidly suppressed by glucocorticoid administration, suggesting that it is regulated by ACTH instead of by the RAAS. The disorder is caused by unequal meiotic crossing over events between the adjacent *CYP11B1* (11β-hydroxylase) and *CYP11B2* (aldosterone synthase) genes, which produces a third chimeric gene with regulatory sequences of *CYP11B1* juxtaposed with coding sequences of *CYP11B2* [36, 37]. This results in the inappropriate expression of a *CYP11B2*-like enzyme with aldosterone synthase activity in the adrenal fasciculata.

These conditions are thought to be rare in children, but they may account for 5–10 % of cases of hypertension in adults. Although adenomas and bilateral hyperplasia are usually sporadic, kindreds with several affected members have been reported. Genetic linkage to chromosome 7p22 has been identified in some of these kindreds, but the involved gene has not yet been identified. Mutations in the KCNJ5 gene on chromosome 11q24 have been identified in several kindreds; these mutations (G151R and G151E) altered channel selectivity, producing increased Na^+ conductance and membrane depolarization, which increases aldosterone production and proliferation of adrenal glomerulosa cells [38]. Moreover, such mutations have been identified in a subset of sporadic aldosterone-producing adenomas [39].

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension. Others may have severe hypertension (up to 240/150 mmHg), with headache, dizziness, and visual disturbances.

Laboratory findings. Hypokalemia occurs often but not invariably; it is exacerbated by thiazide diuretics. Chronic hypokalemia may lead to polyuria, nocturia, enuresis, and polydipsia. Muscle weakness and discomfort, intermittent paralysis, fatigue, and growth failure affect children with severe hypokalemia.

Serum pH and the carbon dioxide and sodium concentrations may be elevated and the serum chloride and magnesium levels decreased. Serum levels of calcium are normal. Plasma levels of aldosterone may be normal or elevated. Aldosterone concentrations in 24 h urine collections are always increased. Plasma levels of renin are consistently low. The ratio of plasma aldosterone concentration to renin activity is always high, and this represents a cost-effective screening test for primary aldosteronism [40]. However, both renin and aldosterone levels may vary by time of day, posture, and sodium intake, making it difficult to establish consistent reference ranges. Therefore, a consistent sampling protocol should be used, for example, midmorning after the patient has been sitting for 15 min. If possible, antihypertensive drugs or other medications that can affect aldosterone or renin secretion should be avoided for several weeks prior to testing, including diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, clonidine, and nonsteroidal anti-inflammatory agents. Calcium channel blockers have smaller effects on the biochemical measurements.

Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol – 17-hydroxylated homologs of aldosterone and 18-hydroxycorticosterone, respectively – are markedly increased in glucocorticoid-suppressible aldosteronism and to a lesser extent in other forms of primary aldosteronism.

Primary aldosteronism should be distinguished from glucocorticoid-suppressible hyperaldosteronism, which is specifically treated with glucocorticoids. An autosomal dominant pattern of inheritance should raise suspicion for the latter disorder. Glucocorticoid-suppressible aldosteronism is diagnosed by dexamethasone suppression tests or by specific genetic testing (see Chap. 6).

Provocative testing may increase the accuracy of diagnosis of primary aldosteronism; aldosterone will not decrease with administration of saline solution or fludrocortisone. Selective adrenal vein sampling may establish whether the abnormal aldosterone secretion is originating from one or both adrenals and thus distinguish between adenomas and bilateral hyperplasia. MRI may detect an adenoma but should be interpreted cautiously (particularly in adults) because adrenal incidentalomas are not uncommon (in adults) and can confuse the diagnosis [41, 42].

Treatment. The treatment of an aldosterone-producing adenoma is surgical removal. Aldosteronism due to bilateral adrenal hyperplasia is treated with the mineralocorticoid antagonists spironolactone or eplerenone, often normalizing blood pressure and serum potassium levels. There is greater experience with spironolactone, but this agent has antiandrogenic properties that may be unacceptable in pubertal males. Eplerenone is a more specific antimineralocorticoid that is safe and effective in children with hypertension, but has not been examined specifically in those with aldosteronism [43]. As an alternative, an epithelial sodium channel blocker such as amiloride may be used and other antihypertensive agents, such as calcium channel blockers, added as necessary [41, 42, 44].

Glucocorticoid-suppressible aldosteronism is managed by daily administration of a glucocorticoid, usually dexamethasone, 25 μg/kg/day in divided doses. Hypertension resolves in patients in whom the hypertension is not severe or of long standing. If necessary, additional antihypertensive medications may be used, such as spironolactone or eplerenone.

Cushing Syndrome

Pathophysiology. Cushing syndrome is the result of abnormally high blood levels of cortisol or other glucocorticoids. This can be iatrogenic or the result of endogenous cortisol secretion, due either to an adrenal tumor or to hypersecretion of corticotropin (adrenocorticotropic hormone

[ACTH]) by the pituitary (Cushing disease) or by a tumor.

The most common cause of Cushing syndrome is prolonged exogenous administration of glucocorticoid hormones, especially at the high doses used to treat lymphoproliferative disorders. Endogenous Cushing syndrome is most often caused in infants by a functioning adrenocortical tumor. Patients with these tumors often exhibit signs of hypercortisolism along with signs of hypersecretion of other steroids such as androgens, estrogens, and aldosterone.

Although extremely rare in infants, the most common etiology of endogenous Cushing syndrome in children older than 7 years of age is Cushing disease, in which excessive ACTH secreted by a pituitary adenoma causes bilateral adrenal hyperplasia. Such adenomas are often too small to detect by imaging techniques and are termed microadenomas. ACTH-dependent Cushing syndrome may also result from ectopic production of ACTH, although this is uncommon in children. Ectopic ACTH secretion in children has been associated with islet cell carcinoma of the pancreas, neuroblastoma or ganglioneuroblastoma, hemangiopericytoma, Wilms tumor, and thymic carcinoid. Hypertension is more common in the ectopic ACTH syndrome than in other forms of Cushing syndrome because very high cortisol levels may overwhelm 11β-hydroxysteroid dehydrogenase type 2 in the kidney and thus have an enhanced mineralocorticoid (salt-retaining) effect.

Several syndromes are associated with the development of multiple autonomously hyperfunctioning nodules of adrenocortical tissue, rather than single adenomas or carcinomas. Primary pigmented nodular adrenocortical disease (PPNAD) is a distinctive form of ACTH-independent Cushing syndrome. It may occur as an isolated event or, more commonly, as a familial disorder with other manifestations. The adrenal glands have characteristic multiple, small (<4 mm in diameter), pigmented nodules containing large cells with cytoplasm and lipofuscin; there is cortical atrophy between the nodules. This adrenal disorder occurs as a component of Carney complex, an autosomal dominant disorder also consisting of centrofacial lentigines and blue nevi; cardiac and cutaneous myxomas; pituitary, thyroid, and testicular tumors; and pigmented melanotic schwannomas. Carney complex is inherited in an autosomal dominant manner, although sporadic cases occur. Genetic loci for Carney complex have been mapped to the gene for the type 1α regulatory subunit of protein kinase A (PRKAR1A) on chromosome 17q22–24 [45] and less frequently to chromosome 2p16. Patients with Carney complex and PRKAR1A mutations generally develop PPNAD as adults, and those with the disorder mapping to chromosome 2 (and most sporadic cases) develop PPNAD less frequently and later. Conversely, children presenting with PPNAD as an isolated finding rarely have mutations in PRKAR1A or subsequently develop other manifestations of Carney complex. Some patients with isolated PPNAD have mutations in the PDE8B [46] or PDE11A [47]genes encoding different phosphodiesterase isozymes.

ACTH-independent Cushing syndrome with nodular hyperplasia and adenoma formation occurs rarely in cases of McCune–Albright syndrome, with symptoms beginning in infancy or childhood. McCune–Albright syndrome is caused by a somatic mutation of the GNAS gene encoding the G protein, $G_s\alpha$, through which the ACTH receptor (MCR2) normally signals. This results in inhibition of guanosine triphosphatase activity and constitutive activation of adenylate cyclase, thus increasing levels of cyclic adenosine monophosphate (cAMP). When the mutation is present in adrenal tissue, cortisol and cell division are stimulated independently of ACTH. Other tissues in which activating mutations may occur are bone (producing fibrous dysplasia), gonads, thyroid, and pituitary. Clinical manifestations depend on which tissues are affected.

In summary, where the genes causing nodular adrenocortical hyperplasia have been identified, they all produce overactivity of the ACTH signaling pathway either by constitutively activating $G_s\alpha$ (McCune-Albright syndrome), by reducing the breakdown of cAMP and thus increasing its intracellular levels (mutations of PDE8B or PDE11A), or by disrupting the regulation of the cAMP-dependent enzyme, protein kinase A (PRKAR1A mutations).

Additionally, adrenocortical lesions including diffuse hyperplasia, nodular hyperplasia, adenoma, and rarely carcinoma may occur as part of the multiple endocrine neoplasia type 1 syndrome, an autosomal dominant disorder, in which there is homozygous inactivation of the menin (MEN1) tumor-suppressor gene on chromosome 11q13. Adrenocortical carcinomas can occur in infancy or later in childhood in patients with Li-Fraumeni syndrome, which is caused by heterozygous mutations in the TP53 tumor-suppressor gene on chromosome 17p13.1.

Clinical manifestations. The disorder appears to be more severe and the clinical findings are more flagrant in infants than in older children. The face is rounded, with prominent cheeks and a flushed appearance (moon facies). Generalized obesity is common in younger children. Hypertension is common (occurring in approximately half of affected children) [48] and may occasionally lead to heart failure. In children with adrenal tumors, signs of abnormal masculinization occur frequently; accordingly, there may be hirsutism on the face and trunk, pubic hair, acne, deepening of the voice, and enlargement of the clitoris in girls. Growth is impaired, with length falling below the third percentile, except when significant virilization produces normal or even accelerated growth.

In older children, in addition to obesity, short stature is a common presenting feature. Gradual onset of obesity and deceleration or cessation of growth may be the only early manifestations. Older children most often have more severe obesity of the face and trunk compared with the extremities. Purplish striae on the hips, abdomen, and thighs are common. Hypertension and hyperglycemia usually occur; hyperglycemia may progress to frank diabetes. Pubertal development may be delayed, or secondary amenorrhea may occur in girls past menarche. Weakness, headache, and emotional lability may be prominent. Osteoporosis is common and may cause pathologic fractures.

Laboratory findings. Cortisol levels in blood are normally elevated at 8 a.m. and decrease to less than 50 % by midnight except in infants and young children in whom a diurnal rhythm is not always established. In patients with Cushing syndrome, this circadian rhythm is lost; midnight cortisol levels >4.4 mcg/dl strongly suggest the diagnosis. It is difficult to obtain diurnal blood samples as part of an outpatient evaluation, but cortisol can be measured in saliva samples, which can be obtained at home at the appropriate times of day. Elevated nighttime salivary cortisol levels raise suspicion for Cushing syndrome [49, 50].

Excretion of free cortisol is increased. This is best measured in a 24 h urine sample and is expressed as a ratio of micrograms of cortisol excreted per gram of creatinine. This ratio is independent of body size and completeness of the urine collection.

A single-dose dexamethasone suppression test is often helpful; a dose of 25 μg/kg (maximum of 2 mg) given at 11 p.m. results in a plasma cortisol level of less than 5 μg/dL at 8 a.m. the next morning in normal individuals but not in patients with Cushing syndrome. It is prudent to measure the dexamethasone level in the same blood sample to ensure adequacy of dosing [49, 50].

A glucose tolerance test is often abnormal. Levels of serum electrolytes are usually normal, but potassium may be decreased, especially in patients with tumors that secrete ACTH ectopically.

After the diagnosis of Cushing syndrome has been established, it is necessary to determine whether it is caused by a pituitary adenoma, an ectopic ACTH-secreting tumor, or a cortisol-secreting adrenal tumor. ACTH concentrations are usually suppressed in patients with cortisol-secreting tumors, are very high in patients with ectopic ACTH-secreting tumors, but may be normal in patients with ACTH-secreting pituitary adenomas. After an intravenous bolus of corticotropin-releasing hormone (CRH), patients with ACTH-dependent Cushing syndrome have an exaggerated ACTH and cortisol response, whereas those with adrenal tumors show no increase in ACTH and cortisol. The two-step dexamethasone suppression test consists of administration of dexamethasone, 30 and 120 μg/kg/24 h in four divided doses, on consecutive days. In children with pituitary Cushing syndrome, the larger dose, but not the smaller dose, suppresses serum levels of cortisol. Typically, patients with ACTH-independent Cushing

syndrome do not show suppressed cortisol levels with dexamethasone.

CT detects virtually all adrenal tumors larger than 1.5 cm in diameter. MRI may detect ACTH-secreting pituitary adenomas, but many are too small to be seen; the addition of gadolinium contrast increases the sensitivity of detection. Bilateral inferior petrosal blood sampling to measure concentrations of ACTH before and after CRH administration may be required to localize the tumor when a pituitary adenoma is not visualized; this is not routinely available in many centers.

Differential diagnosis. Cushing syndrome is frequently suspected in children with obesity, particularly when striae and hypertension are present. Children with simple obesity are usually tall, whereas those with Cushing syndrome are short or have a decelerating growth rate. Although urinary excretion of cortisol is often elevated in simple obesity, salivary nighttime levels of cortisol are normal and cortisol secretion is suppressed by oral administration of low doses of dexamethasone.

Elevated levels of cortisol and ACTH without clinical evidence of Cushing syndrome occur in patients with generalized glucocorticoid resistance [51]. Affected patients may be asymptomatic or exhibit hypertension, hypokalemia, and precocious pseudopuberty; these manifestations are caused by increased mineralocorticoid and adrenal androgen secretion in response to elevated ACTH levels. Mutations in the glucocorticoid receptor have been identified.

Treatment. Transsphenoidal pituitary microsurgery is the treatment of choice in pituitary Cushing disease in children [52, 53]. The overall success rate with follow-up of less than 10 years is 60–80 %. Low postoperative serum or urinary cortisol concentrations predict long-term remission in the majority of cases. Relapses are treated with reoperation or pituitary irradiation.

Cyproheptadine, a centrally acting serotonin antagonist that blocks ACTH release, has been used to treat Cushing disease in adults; remissions are usually not sustained after discontinuation of therapy. Experience with this agent is limited in children [54], given that surgical cure is attempted whenever possible. Inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, aminoglutethimide, etomidate) have been used preoperatively to normalize circulating cortisol levels and reduce perioperative morbidity and mortality.

If a pituitary adenoma does not respond to treatment or if ACTH is secreted by an ectopic metastatic tumor, the adrenal glands may need to be removed. This can often be accomplished laparoscopically. Adrenalectomy may lead to increased ACTH secretion by an unresected pituitary adenoma, evidenced mainly by marked hyperpigmentation; this condition is termed Nelson syndrome.

Management of patients undergoing adrenalectomy requires adequate preoperative and postoperative replacement therapy with a corticosteroid. Tumors that produce corticosteroids usually lead to atrophy of the normal adrenal tissue, and replacement with cortisol (10 mg/M^2/24 h in three divided doses after the immediate postoperative period) is required until there is recovery of the hypothalamic–pituitary–adrenal axis.

Hyperthyroidism

Pathophysiology

Synthesis, regulation, and actions of thyroid hormones. Thyroid hormones are synthesized in follicular cells. Adjacent tyrosine residues on thyroglobulin (which has around 120 tyrosines) are iodinated by thyroid peroxidase; the adjacent phenolic rings are conjugated and the hormones released by proteolysis. There are two active hormones, thyroxine (T4) and triiodothyronine (T3); the latter is approximately four times as active as, but has a much shorter half-life than, thyroxine. Both are synthesized de novo; additionally, a deiodinase enzyme can convert T4 to T3 [55].

Synthesis is regulated at the hypothalamic and pituitary levels by thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH), respectively. Thus, TSH levels are high in patients with primary hypothyroidism and suppressed in patients with hyperthyroidism. TSH signals via a G protein–coupled receptor on the surface of

follicular cells to increase thyroid hormone synthesis [56, 57].

Thyroid hormones act via thyroid hormone receptors that are members of the nuclear hormone receptor superfamily. There are two distinct genes, THRA and THRB, encoding receptors that are expressed in different tissues; each can bind DNA as monomers, homodimers, or as heterodimers with the retinoid X receptor (RXR). Thyroid hormones have important permissive effects on neural development, skeletal maturation, and somatic growth, and they increase rates of cellular metabolism [58]. Most importantly in the context of this chapter, they regulate sensitivity to catecholamines in both the cardiovascular and nervous systems [59]. Thus, hyperthyroidism (if symptomatic, termed thyrotoxicosis) causes signs and symptoms very similar to those of catecholamine excess as might be seen in pheochromocytoma.

Thyrotoxicosis. Two autoimmune diseases can cause thyrotoxicosis. Graves disease is caused by antibodies to the thyroid-stimulating hormone (TSH) receptor that interact with the receptor to activate it in the same way that would occur by occupation by its physiologic ligand (TSH). These are termed thyroid-stimulating antibodies (TSI). Chronic lymphocytic (Hashimoto's) thyroiditis is more often associated with hypothyroidism, but it can present with a thyrotoxic phase, in which autoimmune destruction of thyroid cells by cytotoxic lymphocytes causes them to release their contents of thyroxine (T4) and triiodothyronine (T3). Finally, hyperfunctioning ("hot") thyroid nodules can cause thyrotoxicosis; these are rare in children.

Clinical manifestations. Patients have typically lost weight. They have tachycardia and hypertension (mainly systolic) with wide pulse pressure. Hyperpyrexia is present only in very severe cases and is an indication for hospitalization to stabilize the patient. Thyroid enlargement is highly variable and need not be present. The gland may have a firm or micronodular consistency; a single palpable nodule should raise suspicion for a hyperfunctioning nodule and prompt a thyroid scan (see below). There is often a bruit or thrill over the thyroid. The precordium is hyperdynamic. Patients appear nervous and often give a history of poor school performance with inability to pay attention in class. They are usually tremulous, with tremors most easily elicited by having the patient extend the hands or the tongue, and they have brisk reflexes, often with a mild to moderate degree of clonus.

A lid lag can often be elicited by having the patient look rapidly downward (the lids do not immediately drop as they would normally). Other ocular findings are pathognomonic for Graves disease, including conjunctival injection, puffy eyelids, and proptosis.

Laboratory findings. TSH levels are usually undetectably low. Total and free T4 levels are elevated. Total T3 levels are also elevated, and because T3 has a much shorter half-life than T4, it is particularly useful for monitoring the short-term response to treatment. Levels of antibodies to thyroid proteins – antithyroid peroxidase and antithyroglobulin – are usually elevated in both Graves disease and Hashimoto's thyroiditis, but thyroid-stimulating antibodies are elevated only in Graves disease and are useful for distinguishing the two conditions. Radioactive iodine (I-123) uptake is increased in Graves disease but decreased in Hashimoto's thyroiditis, even in the thyrotoxic phase. A thyroid scan after I-123 administration may detect a hot nodule.

Treatment. The hypertension, tachycardia, and tremulousness may all be treated by beta-blockade, typically with 25–50 mg per day of atenolol. This is continued until thyroid hormone levels have returned to normal with specific treatment. There are three long-term treatments for thyrotoxicosis [60]. Thioamide drugs can suppress thyroid hormone synthesis and are useful for both Graves disease and the thyrotoxic phase of Hashimoto's thyroiditis. In the United States, methimazole is the main agent used (initially ~0.5 mg/kg/d in two divided doses); propylthiouracil was extensively used in the past but is no longer recommended, particularly in children, because of the risk of liver failure [61]. Methimazole frequently causes rashes or other allergic reactions and may rarely cause agranulocytosis or liver failure; thus, complete blood

counts and transaminases should be monitored. The dose of medication can usually be decreased after the patient is euthyroid, and approximately one quarter of patients with Graves disease eventually remit and can be completely weaned off medication. Patients with Hashimoto's thyroiditis typically "burn out" after a few months and must be weaned off methimazole and usually require thyroid replacement with levothyroxine.

The two other approaches are relevant mainly to Graves disease; their relative merits are somewhat controversial. Radioactive iodine (I-131) is specifically taken up by the thyroid gland and can ablate thyroid cells with relatively limited whole-body radiation exposure. Rarely used in children 20 years ago, it is becoming increasingly accepted in teenagers and older schoolchildren, even as initial treatment [62]. Risks of causing a thyroid adenoma may be minimized by aiming to completely ablate thyroid function rather than trying to render the patient euthyroid. Nevertheless, the author believes that a risk of subsequent thyroid tumors may exist before 8 years of age (based on data from atomic bombs and Chernobyl) and that it is more prudent in a young child to temporize with methimazole until the patient is older, as long as the drug is well tolerated. Alternatively, the thyroid may be removed surgically [63]. This has a low risk of long-term complications but requires an experienced surgeon to avoid hypoparathyroidism or damage to the recurrent laryngeal nerve. Hemithyroidectomy is the treatment of choice for a hyperfunctioning nodule.

Conclusion

Endocrine disorders such as pheochromocytoma, congenital adrenal hyperplasia, Cushing syndrome, primary aldosteronism, and hyperthyroidism collectively account for a small proportion of cases of hypertension in children, but the hypertension is often relatively severe. It is important to accurately diagnose these disorders because the associated hypertension usually requires, and responds well to, specific treatment of the underlying condition.

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