

Chapter 2

Syndromes of Mineralocorticoid Excess

Eugen Melcescu and Christian A. Koch

Abstract In addition to obesity, diabetes type 2, and the metabolic syndrome, hypertension represents a major public and global health problem, most of which can be improved by lifestyle changes, including changing dietary habits with less consumption of processed and preserved foods, which generally contain higher amounts of salt than freshly prepared food items. Amongst causes for endocrine hypertension are syndromes of mineralocorticoid excess typically resulting from overactive amiloride-sensitive sodium channels located in the distal convoluted tubules and collecting ducts of the kidney, as well as other tissues, including vascular smooth muscle. The net effect of such an overactivation, which occurs mostly in primary aldosteronism is sodium and water retention with volume expansion and hypertension that is exacerbated by a diet high in salt. Biochemically, plasma renin activity is suppressed and hypokalemia may be present. Aldosterone mediates its action through the mineralocorticoid receptor (MR), which regulates salt homeostasis in the kidneys and plays a range of other roles in the vasculature, heart, brain, and adipose tissue.

Excessive MR activation can promote inflammation, fibrosis, and heart disease as well as psychiatric illness, including anxiety and depression, through key modulators, including the glucocorticoid receptor and the 11β -hydroxysteroid dehydrogenases.

Apart from aldosterone, the MR is also activated by products of abnormal adrenal steroid biosynthesis, dysregulated metabolism of cortisol in cells that are targets of mineralocorticoids, and activating mutations of the MR or of ion channels that are inducible by the MR. We provide here an overview of mineralocorticoid excess caused by congenital adrenal hyperplasia due to mutations of the 11β -hydroxylase and 17α -hydroxylase genes, by mutations of the 11β -hydroxysteroid dehydrogenase type 2 gene (apparent mineralocorticoid excess (AME)), mutations of the epithelial sodium channel genes (Liddle syndrome), mutations of the

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mineralocorticoid receptor gene (Geller syndrome), and pseudohypoaldosteronism type 2 or Gordon syndrome.

Most of these conditions are treated by restricted dietary salt intake. However, some require special therapies, including hydrocortisone (CAH), spironolactone/epplerenone, thiazide diuretics (Liddle and Gordon syndrome), while in others spironolactone and other MR antagonists may be contraindicated (Geller syndrome). Understanding the pathophysiology of these rare conditions may help designing future molecular-targeted therapies. Naturally, the mainstay of antihypertensive therapy continues to be reducing the overconsumption of salt in addition to increasing compliance and adherence of patients to currently available indicated therapies.

Keywords Mineralocorticoid excess • SME • Aldosterone • Endocrine hypertension • Congenital adrenal hyperplasia • Licorice-induced hypertension • Liddle syndrome • Pseudohypoaldosteronism type 2 • Geller syndrome

Introduction

Syndromes of mineralocorticoid excess (SME) typically result from overactive amiloride-sensitive sodium channels located in the distal convoluted tubule and collecting ducts of the kidney, as well as of other tissues, including vascular smooth muscle [1]. The effect of such an overactivation is sodium and water retention with volume expansion and hypertension (without hypernatremia) that is aggravated by a diet high in salt, as it is presently the case for many Americans, but also for people in other parts of the world where processed and preserved foods instead of freshly prepared meals are consumed. Biochemically, plasma renin activity is suppressed and hypokalemia may be present (Table 2.1).

Most frequently, the underlying condition for syndromes of mineralocorticoid excess is autonomous secretion of aldosterone or primary aldosteronism (see Chap. 1 in this book and ref. [2]). Aldosterone mediates its action through the mineralocorticoid receptor (MR) which regulates salt homeostasis in the kidneys and plays a range of other roles in the vasculature, heart, brain, and adipose tissue. To mediate transcription of target genes, the MR interacts with both mineralocorticoids and glucocorticoids (reviewed in [3]). The MR is able to exert tissue- and ligand-specific effects via its interactions with a range of binding partners. The MR also plays a major role in inducing glomerular podocyte injury and progression of chronic kidney disease which can be reduced by MR antagonists or selective MR inhibition [4].

Excessive MR activation can promote inflammation, fibrosis, and heart disease as well as psychiatric illness including anxiety and depression through key modulators including the glucocorticoid receptor (GR) and 11 β -hydroxysteroid dehydrogenases (11 β HSDs), which determine the amount of intracellular concentrations of active glucocorticoids [5, 6].

Table 2.1 Conditions with low renin concentrations

<i>Common conditions with low renin concentrations</i>		
Mineralocorticoid excess		
Primary aldosteronism (see Chap. 1)		
Cushing’s Syndrome (see Chap. 3)		
Glucocorticoid/cortisol resistance (see Chap. 4)		
Apparent mineralocorticoid excess syndrome		
Licorice or carbenoxolone in excess		
Congenital adrenal hyperplasia (11beta- and 17alpha-hydroxylase deficiencies)		
11-Deoxycorticosterone (DOC), 18-hydroxy-DOC excess		
Salt retention (Gordon and Liddle syndrome)		
Geller syndrome		
Salt loading (oral or intravenous)		
<i>Rare conditions leading to low renin levels</i>		
Increasing age		
Low renin essential hypertension		
Hyporeninemic hypoaldosteronism		
Hyperkalemia		
Therapy with beta-adrenergic blockers		
Autonomic dysfunction		
Decrease of renal tissue or being anephric		

Koch CA, Wofford MR, Ayala AR, Pacak K. Overview of endocrine hypertension (from Chapter 26) <http://www.endotext.org/adrenal/adrenal26/adrenalframe26.htm> In: Adrenal physiology and diseases (George Chrousos, section editor), In: [Endotext.org](http://www.endotext.org) (Leslie De Groot, editor)

Aldosterone secretion is stimulated by angiotensin II, high potassium, vasopressin, and ACTH (transient), and inhibited by high levels of natriuretic peptides. Apart from aldosterone the MR is also activated by products of abnormal adrenal steroid biosynthesis (Fig. 2.1), dysregulated metabolism of cortisol in cells that are targets of mineralocorticoids, and activating mutations of the MR or of ion channels that are inducible by the MR to mediate its action.

SME and its inherited forms of mineralocorticoid hypertension have helped our understanding of normal physiology and of the pathogenesis of hypertension called “essential” which represents a major public health problem [8].

Hypertension is defined as a blood pressure exceeding 139/89 mmHg for adults aged 18 years or older based on the mean of two or more properly measured seated BP readings on each of two or more office visits. Hypertension affects approximately 31% of Americans; blood pressure control is suboptimal and is achieved in less than 1 in 3 [9, 10]. The prevalence of resistant hypertension varies from 34 to 53% in different large studies: ALLHAT (34%), NHANES (53%), or Framingham Heart Study (48%) [11]. The Joint National Committee (JNC VII) [12] classified hypertension for adults 18 years and older as follows:

Normal	<120 mmHg (systolic)	<80 mmHg (diastolic)
Pre-HTN	120–139	80–89
Stage 1 HTN	140–159	90–99
Stage 2 HTN	≥160	≥100

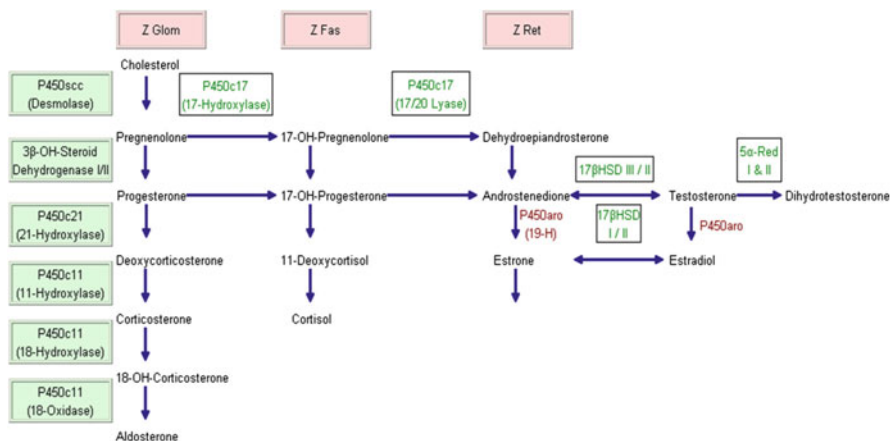


Fig. 2.1 Adrenal steroid synthesis. Modified from ref. [7]. *Z Glom* zona glomerulosa; *Z Fas* zona fasciculata; *Z Ret* zona reticularis; *19-H* 19-Hydroxylase; *HSD* Hydroxysteroid dehydrogenase; *P450aro* aromatase; *5α-Red* 5α-Reductase. The three adrenal cortex zones *Z Glom*, *Z Fas*, and *Z Ret* stand above the “column” of hormones that are produced in the respective zone. The steroidogenic enzymes on the *left* starting with *P450scc* (Desmolase) are listed in order for “vertical and horizontal reading,” i.e., Desmolase converts cholesterol to pregnenolone, 3β-OH-Steroid Dehydrogenase I/II convert pregnenolone to progesterone, 17-OH-Pregnenolone to 17-OH-Progesterone, and *P450c11* converts deoxycorticosterone to 18-OH-Corticosterone and 11-Deoxycortisol to cortisol, etc

Clinical Findings and Clues to Identify Patients with Endocrine Hypertension Caused by Mineralocorticoid Excess

Individuals homozygous for an inherited condition of SME may develop hypertension very early in life and become refractory to antihypertensive therapy (failing triple-drug treatment). However, the clinical phenotype varies and some patients may not be found to have SME before they reach adulthood (Table 2.2).

Pathogenesis

The pathophysiological mechanisms of mineralocorticoid excess syndromes are better understood at present with the advent of new techniques in molecular biology and genetics. The increasing availability of affordable genetic/molecular testing may elucidate further the pathogenesis of these rather rare genetic conditions and their implication in hypertension seen in the general public. Excessive production of aldosterone (primary: familial hypoaldosteronism, aldosterone-producing adenoma/carcinoma/hyperplasia [13–16] or secondary: reninoma [17–20]) and sometimes of

Table 2.2 Clinical findings in patients with mineralocorticoid excess

Condition	Clinical presentation
CAH: 11beta-hydroxylase deficiency	Early growth spurt initially, then short adult stature, advanced bone age, premature adrenarche, acne, precocious puberty in males, amenorrhea/hirsutism/virilism in females
CAH: 17alpha-hydroxylase deficiency	Pseudohermaphroditism (male), sexual infantilism (female)
Apparent mineralocorticoid excess	Growth retardation/short stature, nephrocalcinosis
Liddle syndrome	Severe hypertension, hypokalemia, and metabolic alkalosis, muscle weakness
Geller syndrome	Early onset hypertension (before age 20 year), exacerbated in pregnancy
Glucocorticoid remediable aldosteronism (GRA)	Early onset of hypertension, presence of family history of mortality or morbidity from early hemorrhagic stroke
Pseudohypoaldosteronism type 2	Short stature, hyperkalemic and hyperchlor-emic metabolic acidosis, borderline blood pressure
Glucocorticoid resistance (children) (Chrousos syndrome)	Ambiguous genitalia, precocious puberty. Women may have acne, excessive hair, oligo/anovulation, infertility

deoxycorticosterone (DOC) (primary: DOC-secreting adrenocortical adenoma/carcinoma [21–24] or secondary: 11beta-hydroxylase deficiency [25–27], 17alpha-hydroxylase deficiency [28–30], substances with high mineralocorticoid activity can lead to salt and water retention and consequently hypertension without causing hyponatremia.

11Beta-hydroxylase is responsible for the conversion of DOC to corticosterone (precursor of aldosterone) and 11-deoxycortisol to cortisol. In approximately 2/3 of individuals affected by a deficiency of this enzyme, monogenic low renin hypertension with low aldosterone levels ensues caused by accumulation of 11-deoxycortisol and DOC. Also, adrenal androgens are produced in excess in individuals with 11beta-hydroxylase deficiency compared with 17alpha-hydroxylase deficiency where they are deficient [25–30]. In patients with 17alpha-hydroxylase deficiency a persistent elevation of ACTH increases DOC and corticosterone levels and as a consequence affected patients will develop hypertension, hypokalemia, low aldosterone, and suppressed renin [28–30].

AME is caused by deficiency of the enzyme 11βHSD2) [31–33]. This enzyme is responsible for the conversion of cortisol to the inactive cortisone in renal tubular cells. Cortisol and aldosterone have equal affinity for the mineralocorticoid receptor but normal circulating concentrations of cortisol are 100–1,000-fold higher than those of aldosterone [34]. If 11βHSD2 is oversaturated or defective, more cortisol will be available to bind to the mineralocorticoid receptor [35]. Diminished

11 β HSD2 activity may be hereditary or acquired. Acquired deficiency of this enzyme may result from its inhibition by glycyrrhetic acid, the active metabolite generated when using licorice, certain brands of chewing tobacco, and carbenoxone. The mutations in the 11 β HSD2 gene are responsible for the reduced activity of the enzyme, which causes Na retention, low K, renin, and aldosterone.

In Liddle syndrome, “gain of function” mutations in the genes coding for the beta- or gamma-subunit of the renal epithelial sodium channel, located on chromosome 16p13, lead to constitutive activation of renal sodium and water resorption, hypertension, low renin, and aldosterone [36].

Pseudohypoaldosteronism type 2 or Gordon syndrome is an autosomal dominantly inherited disorder with genes mapping to chromosomes 1, 12, and 17 [37, 38]. Mutations have been identified in WNK kinases WNK1 and WNK4 on chromosomes 12 and 17, respectively. More recently, mutations in the KLHL3, CUL3, and SPAK genes have been linked to Gordon syndrome. Published families with this condition (hypertension, hyperkalemia, metabolic acidosis, normal renal function, low/normal aldosterone levels) are predominantly from Australia [38] or the United States (Lifton and coworkers at Yale University, CT). Hypertension in these patients may develop as a consequence of increased renal salt reabsorption; and hyperkalemia ensues as a result of reduced renal K excretion despite normal glomerular filtration and aldosterone secretion [39–41]. The reduced renal secretion of potassium makes this condition look like an aldosterone-deficient state, thus the term “pseudohypoaldosteronism.”

Activating mutations in the amiloride-sensitive sodium channel of the distal renal tubule may explain the pathogenesis of this condition. Overactivation of the NaCl cotransporter results in Na and water retention and increased blood pressure.

Glucocorticoid resistance or Chrousos syndrome (see Chap. 4 in this book) is caused by inactivating mutations of the glucocorticoid receptor gene [42–44]. Chronic elevation of ACTH can lead to stimulation of adrenal compounds with mineralocorticoid activity (corticosterone, DOC), and elevation of cortisol may lead to stimulation of the mineralocorticoid receptor, resulting in hypertension and increasing androgenic activity (androstenedione, DHEA, DHEAS) in women.

Constitutive activation of the MR is an autosomal-dominant condition determined by “gain of function” mutations in the MC gene on chromosome 4q31 [45].

Figure 2.2 provides an overview of these pathogenic mechanisms involved in mineralocorticoid excess syndromes Fig. 2.2.

Diagnosis

As is true for measuring any hormone, when analyzing steroids, it is important to obtain accurate information. The most sensitive and specific method to detect a defect in adrenal steroid biosynthesis is urinary steroid profiling [47]. Particularly robust appears to be measuring steroid precursor/product ratios which are independent of 24-h excretion and usually not determined by commercial laboratories.

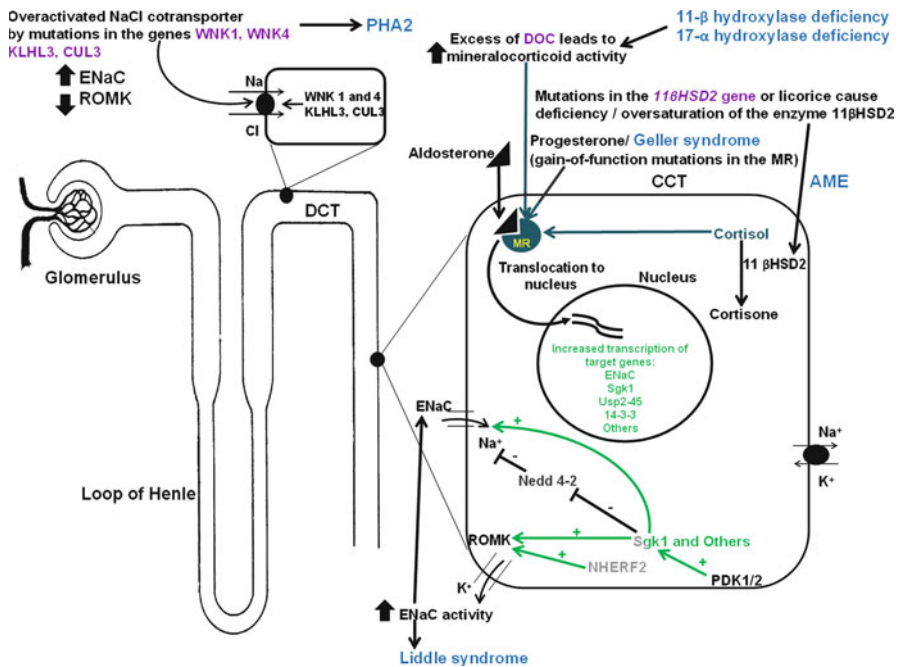


Fig. 2.2 Inherited endocrine conditions related to mineralocorticoid excess (modified after ref. [46, 47], and <http://home.comcast.net/~llpellegrini/urinarysystem.htm>). Shown are the molecular pathways involved in dysregulation of NaCl homeostasis located in the distal renal tubules. AME - Apparent mineralocorticoid excess, GRA - Glucocorticoid-remediable aldosteronism, PHA2 - Pseudohypoaldosteronism type 2; MR - mineralocorticoid receptor; WNK - with-nolysine (K) kinase 1, 4; ROMK- renal outer medullary potassium channel; ENaC - epithelial sodium channel; KLHL3 - kelch-like 3; CUL3 - cullin 3; Sgk1 - serum glucocorticoid kinase 1; Nedd4-2, ubiquitin-protein ligase; deubiquitylating enzyme Usp2-45; 14-3-3 proteins; NHERF2 - Na⁺/H⁺ exchange regulating factor 2; PDK1,2 - 3-phosphoinositide-dependent kinases 1 and 2; + activation; - inhibition

The diagnostic approach to syndromes of mineralocorticoid excess is based on the clinical presentation, laboratory, and genetic testing. The most important laboratory and genetic tests are described in Table 2.3.

Congenital Adrenal Hyperplasia: 17Alpha-Hydroxylase Deficiency

- This enzyme deficiency is rare and affects both adrenal and gonadal steroid production.
- Cytochrome P450c17 enzyme complex catalyzes both 17-hydroxylase and 17,20 lyase activity [25, 28–30].
- Clinical findings: pseudohermaphroditism (46, XY male), sexual infantilism (46, XX female), varying degrees of hypertension and hypokalemic alkalosis.

Table 2.3 Laboratory testing protocols for some causes of mineralocorticoid excess syndromes

Disease	Laboratory testing	Genetic testing
CAH: 17 α -OH deficiency	\uparrow DOC, \downarrow 11-deoxycortisol $\downarrow\downarrow$ Aldosterone, \downarrow renin, \downarrow K \downarrow Plasma 17-hydroxyprogesterone \downarrow testosterone \uparrow Urinary 100*THDOC/(THE+THF+5 α THF) and (THA+THB+5 α THB)/(THE+THF+5 α TF)	<i>CYP17</i> gene
CAH: 11 β -OH deficiency	Potassium depletion (variable), \downarrow renin (The degree of hyporeninemia may vary widely) $\downarrow\downarrow$ Aldosterone \downarrow Cortisol, \uparrow ACTH \uparrow 11-Deoxycortisol, \uparrow DOC, \uparrow 17-OHP \uparrow 19-nor-DOC $\uparrow\uparrow$ Urinary 100*THS/(THE+THF+5 α THF) and 100*THDOC/(THE+THF+5 α THF)	<i>CYP11B1</i> gene
Apparent mineralocorticoid excess	Check the level of tritiated water in plasma samples when 11-tritiated cortisol is injected \uparrow 24 h Urinary free cortisol/cortisone and \uparrow urinary (THF+5 α THF)/THE	<i>11βHSD2</i> gene
Liddle syndrome	\downarrow Plasma K, \uparrow urinary K, \downarrow PRA and suppressed aldosterone secretion, metabolic alkalosis \downarrow Urinary THALDO (<2 μ g/24 h) Normal steroid profile (24-h urine cortisone/cortisol and other ratios)	<i>ENaC</i> gene
Pseudohypoaldosteronism type 2	$\uparrow\uparrow$ K, hyperchloremic metabolic acidosis \downarrow aldosterone, \downarrow renin \downarrow Serum HCO ₃ (variable in children) Hypercalciuria (occasionally) \downarrow Urinary THALDO	<i>WNK1 and 4</i> gene <i>KLHL3, CUL3, SPAK</i> gene
Geller syndrome	K, \downarrow aldosterone, \downarrow renin \downarrow Urinary THALDO	<i>MCR</i> gene

DOC - deoxycorticosterone; TH - tetrahydro; A - 11-dehydro-corticosterone; B - corticosterone; E - cortisone; F - cortisol; S - 11-deoxycortisol; ALDO - aldosterone, see also ref. [47, 48]

- Biochemical features: \uparrow DOC, \downarrow 11-deoxycortisol, $\downarrow\downarrow$ aldosterone, \downarrow renin, \downarrow K., \downarrow Plasma 17 α -hydroxyprogesterone, \downarrow testosterone, \uparrow urinary 100*THDOC/(THE+THF+5 α THF), and (THA+THB+5 α THB)/(THE+THF+5 α THF) ratios [47, 48].
- Diagnosis of this autosomal recessive condition is suggested by delayed puberty, absent secondary sexual characteristics or amenorrhea combined with typical biochemical findings described above.
- Genetic testing for mutations in the *CYP17*.
- Cortisol is the first-line therapy and sometimes mineralocorticoid replacement, especially in cases of bilateral and complete (adrenal rest tumors) adrenalectomy. Oral hydrocortisone is often preferred for children to maximize their growth potential while minimizing the risk for developing iatrogenic Cushing's syndrome.

Congenital Adrenal Hyperplasia: 11 β -Hydroxylase Deficiency

- 11 β -Hydroxylase deficiency is caused by several mutations in the CYP11B1 gene.
- The inherited enzymatic defect (autosomal recessive) results in elevated serum levels of DOC, the principal steroid index of 11 β -hydroxylase deficiency [49–53].
- Accounts for approx. 5–8% of all CAH cases, approx. 1 in 200,000 births.
- In Moroccan Jews, the prevalence is approx. 1 in 7,000 births [50, 51].
- Chronic elevation of ACTH due to a deficient cortisol production stimulates the biosynthesis of other mineralocorticoids: 11-deoxycortisol, DOC, and others.
- DOC is a weak mineralocorticoid, but at supraphysiologic levels promotes salt retention, volume expansion, and consequently hypertension.
- Short stature (adult males), hirsutism, advanced bone age, amenorrhea, infertility are some of the most common findings in patients affected by this condition. Males may develop pseudoprecocious puberty (boys are tall as children).
- Biochemical profile: potassium depletion (variable), \downarrow renin (variable), \downarrow aldosterone, \downarrow cortisol, \uparrow ACTH, \uparrow 11-deoxycortisol, \uparrow DOC, \uparrow 19-nor-DOC, \uparrow urinary 17-hydroxycorticosteroids and DOC, and \uparrow urinary 100*THS/(THE+THF+5 α THF) and 100*THDOC/(THE+THF+5 α THF) ratios [47, 48].
- Other laboratory abnormalities: elevated serum level of 17 α -hydroxy progesterone (17-OHP) and androstenedione and urinary pregnanetriol.
- Normalization of DOC is an indicator of adequate glucocorticoid therapy which represents the most important therapeutic indication for this condition. Hydrocortisone is frequently used in children to maximize their growth potential while minimizing their risk for developing Cushing's syndrome from overuse of glucocorticoid therapy (i.e., dexamethasone with its longer half-life and higher affinity for the glucocorticoid receptor) In selected patients, bilateral adrenalectomy may be safe and effective in managing blood pressure. In such cases, mineralocorticoid replacement (i.e., fludrocortisone) may be necessary.
- Mutations in the CYP11B1 gene may not always be found.

Apparent Mineralocorticoid Excess

- 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2) is highly expressed in the kidney where it metabolizes cortisol to cortisone. It is also expressed in all sodium-transporting epithelia.
- A reduced enzymatic activity of 11 β HSD2 caused by loss-of-function mutations explains the pathogenesis of the autosomal recessive syndrome of AME which was first described by Ulick et al. in 1979 [54–57].

- Diminished 11 β HSD2 activity may be hereditary or acquired.
- Acquired deficiency of this enzyme may result from inhibition by glycyrrhetic acid which may occur with use of licorice, chewing tobacco, carbenoxolone, and “asam boi” flavor (containing glycyrrhizic acid) if consumed on a daily basis in certain quantities [58].
- Impaired 11 β HSD2 activity alters the inactivation of cortisol in the target renal cell leading to above-normal cortisol activity, renal Na retention, and severe hypokalemia.
- The severity of hypertension in patients with AME syndrome seems to correlate with the degree of loss of 11 β HSD2 enzyme activity.
- The clinical presentation of AME can include: growth retardation/short stature, hypertension, hypokalemia, and occasional nephrocalcinosis [59, 60].
- A typical case of AME presents with: early hypertension (childhood), hypokalemia, suppressed renin, very low aldosterone levels, and metabolic alkalosis.
- There is a large spectrum of clinical and biochemical features in patients with homozygous mutations of the 11 β HSD2 gene; heterozygous individuals usually develop hypertension later in life, have milder biochemical profiles of AME and no phenotypic characteristics of AME [61].
- The biochemical diagnosis can be made by detecting \uparrow 24 h urinary-free cortisol/cortisone and \uparrow urinary (THF+5 α THF)/THE ratios [47, 48].
- Patients diagnosed with AME syndrome respond well to low sodium diet and spironolactone, which blocks binding of both cortisol and aldosterone to the MCR.
- Genetic testing for AME-associated loss-of-function mutations by DNA sequencing of the 11 β HSD2 gene may further elucidate the diagnosis.

Licorice-Induced Hypertension

- Licorice has been used for medicinal purposes for many years.
- Licorice or its active component glycyrrhetic acid may cause hypertension and hypokalemia due to cortisol-mediated activation of the MR by decreasing 11 β HSD2 activity [62].
- A detailed dietary history has to be obtained in each patient in the presence of resistant hypertension with associated hypokalemia to exclude the acquired forms of AME.
- Various licorice containing foods, teas, or herbal products (like yokukansan) are available and their individual consumption varies considerably [63]. Possible adverse effects of yokukansan on blood pressure and electrolytes (low K) were reported recently [64]. A daily dose of 10 mg of glycyrrhetic acid is considered unharmed for most healthy individuals [64]. Glycyrrhizic acid (a component of licorice) is used as a sweetener and also can be found in chewing tobacco products [65, 66].

- Licorice seems to reduce serum testosterone by blocking 17-hydroxysteroid dehydrogenase and 17–20 lyase [67].
- Licorice as a medicinal plant contains not only glycyrrhetic acid but also compounds with estrogen-like or antiandrogen activity. PTH and calcium levels have been increased in healthy women after 2 months of licorice therapy reflecting its impact on calcium metabolism ([68], see Chap. 9 in this book on the topic Primary Hyperparathyroidism).
- The effects of administration of licorice may be observed after a few days and are reversible in weeks. In some cases, these effects last for months after licorice has been stopped [69, 70].
- Licorice-induced hypertension and hypokalemia are cortisol-dependent and are corrected by the administration of spironolactone [71]. In vitro studies have shown a similar inhibitory dose-dependent activity of both glycyrrhetic acid and carbenoxolone of the 11β HSD2 isoenzyme [70, 72].
- The wide variation of glycyrrhetic acid effects observed in various people may be due to individual variation to the effects of mineralocorticoids, bioavailability of glycyrrhetic acid, or sensitivity of 11β HSD2 [73, 74].

Liddle Syndrome

- Autosomal-dominant inherited form of mineralocorticoid hypertension described by Liddle in 1963 [36] in a patient who developed renal failure, underwent cadaveric renal transplant in 1989, and on salt restriction demonstrated normal aldosterone and renin values (previously suppressed).
- This disease is caused by the so-called gain of function mutations in the genes coding for the beta- or gamma-subunit of the renal epithelial sodium channel (expressed in cortical collecting ducts and distal tubule) located on chromosome 16p13.
- The epithelial Na (+) channel (ENaC) and the acid-sensitive ion channel (ASIC) branches of the ENaC/degenerin superfamily of cation channels, have a ubiquitous expression, and have been involved in a variety of disorders [75]. These mutations render a hyperactive renal ENaC due to increased intrinsic activity of ENaC and increasing the number of functioning channels by a lower rate of degradation. As a consequence, there is an increased renal sodium reabsorption with subsequent volume expansion and potassium wasting (through the ROMK K-channel) in the collecting duct.
- Clinical presentation: early severe hypertension (teens), hypokalemia, metabolic alkalosis.
- Commonly, children with this condition are asymptomatic and discovered incidentally at a routine check-up. On the other hand, hypertension resistant to treatment in children may suggest this diagnosis.
- A clinical phenotype with hypertension but without hypokalemia was reported in an Italian family with a β P617L mutation of the beta-subunit of the epithelial sodium channel suggesting the importance of suspecting Liddle syndrome in all cases of early onset hypertension irrespective of K concentrations [76].

- Typical biochemical profile: ↓plasma K, ↑urinary K, ↓plasma renin activity and suppressed aldosterone secretion, ↓urinary THALDO (<2 µg/24 h), normal steroid profile (24-h urine cortisone/cortisol and other ratios), and metabolic alkalosis [47, 48].
- The diagnosis may also be facilitated when hypertension is corrected with a combination of salt restriction (<100 mmol/day) and amiloride/ triamterene.
- Genetic testing (ENaC gene) can identify the disease mutations within 2 (β-subunit *SCNN1B* and γ-subunit *SCNN1G*) of the three subunits of the ENaC channel by direct sequencing (PCR).
- Various types of mutations have been described: missense mutations or deletions/insertions causing premature stop codons, frameshift mutations. Mutations in either beta- or gamma-subunit cause an increased channel number and activity of amiloride-sensitive sodium current by several-fold of this type of ENaC receptor [77–80].
- A heterozygous mutation c.C1852(p.Pro618Ser) in the *SCNN1B* gene was reported in a Serbian family (son, mother and uncle) in a 13-year-old asymptomatic boy with severe hypertension [81]. The familial history recollected over four generations seems to be concordant with this pathology.
- Another possible role in diagnosing Liddle syndrome may play the sequencing of the *Nedd4* gene essential for ENaC trafficking [82].
- Amiloride and triamterene are considered effective in the treatment of this disorder.
- A restricted dietary salt intake is necessary to maintain a good response to the therapy.
- Specific aldosterone antagonists like spironolactone and eplerenone play no role in the treatment of this condition because the accelerated rate of sodium transport is independent of the action of aldosterone [83].

Pseudohypoaldosteronism Type 2

- PHA-2 (Gordon syndrome or chloride shunt syndrome) is an autosomal-dominant condition caused by gain-of-function mutations in *WNK1* or *WNK4* (part of a family of serine–threonine protein kinases) which in turn increase the activity of NaCl cotransporter present in the distal tubule and consequently Na, Cl, and volume extension [84].
- Recently, mutations in the *KLHL3*, *CUL3*, and *SPAK* genes have also been implicated in Gordon syndrome.
- Patients with PHA-2 have short stature, intellectual dysfunction, muscle weakness, low fractional excretion of sodium, hyperchloremic metabolic acidosis, normal aldosterone, and symptoms of severe hypertension.
- Biochemical profile: ↑↑K, hyperchloremic metabolic acidosis, ↓aldosterone, ↓renin, ↓serum HCO₃ (variable in children), hypercalciuria (occasionally), and ↓urinary THALDO [47, 48].

- Genetic testing for WNK1, WNK4, KLHL3, CUL3, SPAK mutations.
- Administration of thiazide diuretics which inhibit salt reabsorption in the distal nephron is the treatment of choice.
- Gordon et al. found that all features could be reversed by very strict dietary salt restriction [38].

Constitutive Activation of the MR (Geller Syndrome)

- This is an autosomal-dominant condition caused by gain-of-function mutations in the MR located on chromosome 4q31.
- The onset of hypertension is before age 20.
- Pregnancy may exacerbate hypertension in patients with this condition because of elevated progesterone levels and altered specificity of the MR receptor with progesterone and traditional MR antagonists now acting as potent MR agonists [45].
- Biochemical profile: normal (!) K, ↓aldosterone, ↓renin, ↓urinary THALDO [47, 48].
- Genetic testing of the MR. A missense mutation S810L located in the hormone-binding domain of the MR has been found in a 15-year-old boy causing hypertension.
- Spironolactone is contraindicated in MR-L810 carriers.

Conclusion

Syndromes of mineralocorticoid excess typically result from overactive amiloride-sensitive sodium channels located in the distal tubule and collecting ducts of the kidney. The effect of such an overactivation which mostly occurs in the condition primary aldosteronism is sodium and water retention with volume expansion and hypertension that is aggravated by a diet high in salt. Biochemically, plasma renin activity is suppressed and hypokalemia may be present. Aldosterone mediates its action through the mineralocorticoid receptor (MR), which regulates salt homeostasis in the kidneys and plays a range of other roles in the vasculature, heart, brain, and adipose tissue.

Apart from aldosterone, the MR is also activated by products of abnormal adrenal steroid biosynthesis, dysregulated metabolism of cortisol in cells that are targets of mineralocorticoids, and activating mutations of the MR or of ion channels that are inducible by the MR to mediate its action. Mineralocorticoid excess can be caused by congenital adrenal hyperplasia due to mutations of the 11 β -hydroxylase and 17 α -hydroxylase genes, by mutations of the 11 β HSD2 gene (AME), mutations of the epithelial sodium channel genes (Liddle syndrome), mutations of the mineralocorticoid receptor gene (Geller syndrome), and pseudohypoaldosteronism-type 2 or Gordon syndrome. Crousos syndrome (inactivation of the glucocorticoid

receptor) can also cause hypertension mediated by increased levels of DOC. Most of these conditions are treated by restricted dietary salt intake. However, some require special therapies including dexamethasone/hydrocortisone (CAH), spironolactone/eplerenone (AME), thiazide diuretics (Liddle and Gordon syndrome), while in others spironolactone and MR antagonists may be contraindicated (Geller syndrome). Understanding the pathophysiology of these rare conditions may help design future molecular targeted therapies, although the mainstay of anti-hypertensive therapy, reducing the overconsumption of salt in addition to increasing compliance and adherence of patients to therapy will remain [85].

Disclosure Statement

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References

1. Van Renterghem C, Lazdunski M. A new non-voltage-dependent, epithelial-like Na⁺ channel in vascular smooth muscle cells. *Pflugers Arch.* 1991;419(3–4):401–8.
2. Charmandari E, Sertedaki A, Kino T, Merakou C, Hoffman D, Hatch MM et al. A novel point mutation in the KCNJ5 gene causing familial primary hypoaldosteronism and early onset autosomal dominant hypertension. *J Clin Endocrinol Metab* 2012;24.
3. Yang J, Fuller PJ. Interactions of the mineralocorticoid receptor—within and without. *Mol Cell Endocrinol.* 2012;350(2):196–205.
4. Shibata S, Fujita T. Mineralocorticoid receptors in the pathophysiology of chronic kidney diseases and the metabolic syndrome. *Mol Cell Endocrinol.* 2012;350(2):273–8.
5. Odermatt A, Kratschmar DV. Tissue-specific modulation of mineralocorticoid receptor function by 11 β -hydroxysteroid dehydrogenases: an overview. *Mol Cell Endocrinol.* 2012;350(2):168–86.
6. Kolkhof P, Borden SA. Molecular pharmacology of the mineralocorticoid receptor: prospects for novel therapeutics. *Mol Cell Endocrinol.* 2012;350(2):310–7.
7. Koch CA. Adrenal cortex, physiology. In: Martini L, editor. *Encyclopedia of endocrinology and endocrine diseases.* San Diego: Academic; 2004.
8. Hassan-Smith Z, Stewart PM. Inherited forms of mineralocorticoid hypertension. *Curr Opin Endocrinol Diabetes Obes.* 2011;18(3):177–85.
9. Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension.* 2004;44(4):398–404.
10. Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment and control rates in United States adults between 1988–1994 and 1999–2004. *Hypertension.* 2008;52(5):818–27.
11. Calhoun DA, Jones CD, Textor S, Goff DC, Murphy TP, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension.* 2008;51:1403–19.

12. Chobanian AV, et al. The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *JAMA*. 2003;289:2560.
13. Young Jr WF. Endocrine hypertension: then and now. *Endocr Pract*. 2010;16(5):888–902.
14. Kratzsch J, Wende D, Thiery J, Koch CA. Basal aldosterone-renin-ratio and aldosterone levels in healthy adults during the saline load test. *Clin Chem Lab Med*. 2007;45–9:A114–5 (German dissertation, Diana Wende, 2008, Leipzig).
15. Mulatero P. A new form of hereditary primary aldosteronism: familial hypoaldosteronism type III. *J Clin Endocrinol Metab*. 2008;93(8):2972–4.
16. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93:3266–81.
17. Cho MJ, Sung EY, Park JA, Lee HD. Congestive heart failure as an initial manifestation of reninoma. *J Pediatr Endocrinol Metab*. 2011;24(11–12):1085–7.
18. Wong L, Hsu TH, Perlroth MG, Hofmann LV, Haynes CM, Katznelson L. Reninoma: case report and literature review. *J Hypertens*. 2008;26(2):368–73.
19. Shera AH, Baba AA, Bakshi IH, Lone IA. Recurrent malignant juxtaglomerular cell tumor: a rare cause of malignant hypertension in a child. *J Indian Assoc Pediatr Surg*. 2011;16(4):152–4.
20. Gottardo F, Cesari M, Morra A, Gardiman M, Fassina A, Dal Bianco M. A kidney tumor in an adolescent with severe hypertension and hypokalemia: an uncommon case—case report and review of the literature on reninoma. *Urol Int*. 2010;85(1):121–4.
21. Kondo K, Saruta T, Saito I, Yoshida R, Maruyama H, Matsuki S. Benign desoxycorticosterone-producing adrenal tumor. *JAMA*. 1976;236(9):1042–4.
22. Sone M, Shibata H, Homma K, Tamura N, Akahira J, Hamada S, et al. Close examination of steroidogenesis disorders in a DOC- and progesterone-producing adrenocortical carcinoma. *Endocrine*. 2009;35(1):25–33.
23. Kelly WF, O'Hare MJ, Loizou S, Davies D, Laing I. Hypermineralocorticism without excessive aldosterone secretion: an adrenal carcinoma producing deoxycorticosterone. *Clin Endocrinol (Oxf)*. 1982;17(4):353–61.
24. Müssig K, Wehrmann M, Horger M, Maser-Gluth C, Häring HU, Overkamp D. Adrenocortical carcinoma producing 11-deoxycorticosterone: a rare cause of mineralocorticoid hypertension. *J Endocrinol Invest*. 2005;28(1):61–5.
25. New MI, Geller DS, Fallo F, Wilson RC. Monogenic low rennin hypertension. *Trends Endocrinol Metab*. 2005;16:92–7.
26. Speiser PW, White PC. Congenital adrenal hyperplasia. *N Engl J Med*. 2003;349:776–88.
27. Zachmann M, Tassinari D, Prader A. Clinical and biochemical variability of congenital adrenal hyperplasia due to 11 β -hydroxylase deficiency. *J Endocrinol Metab*. 1983;56:222–9.
28. Ogawa K, Hara A, Tanabe S, Tamori S, Yoshida H, Pak CH, et al. A case of 17 α -hydroxylase deficiency syndrome associated with right adrenal tumor. *Clin Exp Hypertens A*. 1984;6(4):863–77.
29. Costa-Santos M, Kater CE, Auchus RJ, et al. Two prevalent CYP17 mutations and genotype-phenotype correlations in 24 Brazilian patients with 17-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2004;89:49–60.
30. Wong SL, Shu SG, Tsai CR. Seventeen α -hydroxylase deficiency. *J Formos Med Assoc*. 2006;105:177–81.
31. Ferrari P. The role of 11 β -hydroxysteroid dehydrogenase type 2 in human hypertension. *Biochim Biophys Acta*. 2010;1802(12):1178–87.
32. New MI, Levine LS, Biglieri EG, Paeira J, Ulick S. Evidence for an unidentified ACTH-induced steroid hormone causing hypertension. *J Clin Endocrinol Metab*. 1977;44:924–33.
33. Lin-Su K, Zhou P, Arora N, et al. In vitro expression studies of a novel mutation delta299 in a patient affected with apparent mineralocorticoid excess. *J Clin Endocrinol Metab*. 2004;89:2024–7.

34. Arriza JL, Weinberger C, Cerelli G, Glaser TM, et al. Cloning of the human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor. *Science*. 1987;237:268–75.
35. Funder JW, Pearce PT, Smith R, Smith AI. Mineralocorticoid action: target tissue specificity is enzyme, not receptor mediated. *Science*. 1988;242:583–5.
36. Liddle GW, Bledsoe T, Coppage Jr WS. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. *Trans Assoc Am Physicians*. 1963;76:199–213.
37. Wilson FH, Disse-Nicodeme S, Choate KA, et al. Human hypertension caused by mutations in WNK kinases. *Science*. 2001;293:11–4.
38. Gordon RD, Geddes RA, Pawsey CG, O'Halloran MW. Hypertension and severe hyperkalemia associated with suppression of renin and aldosterone and completely reversed by dietary sodium restriction. *Australas Ann Med*. 1970;19:287–94.
39. Mansfield TA, Simon DB, Farfel Z, et al. Multilocus linkage of familial hyperkalemia and hypertension, pseudohypoaldosteronism type II, to chromosomes 1q31-42 and 17p-q21. *Nat Genet*. 1997;16:202–5.
40. Kahle KT, Wilson FH, Leng Q, et al. WNK4 regulates the balance between renal NaCl reabsorption and K secretion. *Nat Genet*. 2003;35:372–6.
41. Klemm SA, Gordon RD, Tunny TJ, Thompson RE. The syndrome of hypertension and hyperkalemia with normal GFR (Gordon's syndrome): is there increased proximal sodium reabsorption? *Clin Invest Med*. 1991;14:551–8.
42. Chrousos GP, Vingerhoeds A, Brandon D, et al. Primary cortisol resistance. *J Clin Invest*. 1982;69:1261–9.
43. Charmandari E, Kino T, Ichijo T, Chrousos GP. Generalized glucocorticoid resistance: clinical aspects, molecular mechanisms, and implications of a rare genetic disorder. *J Clin Endocrinol Metab*. 2008;93:1563–72.
44. Charmandari E, Kino T. Chrousos syndrome: a seminal report, a phylogenetic enigma and the clinical implications of glucocorticoid signalling changes. *Eur J Clin Invest*. 2010;40(10):932–42.
45. Geller DS, Farhi A, Pinkerton N, Fradley M, Moritz M, Spitzer A, et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science*. 2000;289:119–23.
46. Matthew KA, Manish PP, Thomas HH. Renal and electrolyte disorders : Disorders of the renin-angiotensin-aldosterone system 2010;8:251–271.
47. Ferrari P, Bianchetti MG. Diagnostic investigations in inherited endocrine disorders of sodium regulation. In: Ranke MB, Mullis PE, editors. *Diagnostics of endocrine function in children and adolescents*. 4th ed. Basel: Karger; 2011. p. 210–34.
48. Shackleton CH. Profiling steroid hormones and urinary steroids. *J Chromatogr*. 1986;379:91–156.
49. Parsa AA, New MI. Low-renin hypertension of childhood. *Endocrinol Metab Clin North Am*. 2011;40(2):369–77.
50. White PC, Dupont J, New MI, Leiberman E, Hochberg Z, Rösler A. A mutation in CYP11B1 (Arg-448—His) associated with steroid 11 beta-hydroxylase deficiency in Jews of Moroccan origin. *J Clin Invest*. 1991;87(5):1664–7.
51. Paperna T, et al. Mutations in CYP11B1 and congenital adrenal hyperplasia in Moroccan Jews. *J Clin Endocrinol Metab*. 2005;90(9):5463–5.
52. Ben Charfeddine I, Riepe FG, Kahloul N, Kulle AE, Adala L, Mamaï O, et al. Two novel CYP11B1 mutations in congenital adrenal hyperplasia due to steroid 11 β hydroxylase deficiency in a Tunisian family. *Gen Comp Endocrinol*. 2012;175(3):514–8.
53. Melcescu E, Phillips JW, Moll G, Subauste JS, Koch CA. 11-beta-hydroxylase deficiency and other syndromes of mineralocorticoid excess as a rare cause of endocrine hypertension. *Horm Metab Res*. 2012;44:1–12.
54. Ulick S, et al. A syndrome of apparent mineralocorticoid excess associated with defects in the peripheral metabolism of cortisol. *J Clin Endocrinol Metab*. 1979;49:757–64.

55. Stewart PM, et al. Syndrome of apparent mineralocorticoid excess: a defect in the cortisol-cortisone shuttle. *J Clin Invest.* 1988;82:340–9.
56. Knops NB, Monnens LA, Lenders JW, Levchenko EN. Apparent mineralocorticoid excess: time of manifestation and complications despite treatment. *Pediatrics.* 2011;127(6):e1610–4.
57. Bailey MA, Paterson JM, Hadoko PW, Wrobel N, Bellamy CO, Brownstein DG, et al. A switch in the mechanism of hypertension in the syndrome of apparent mineralocorticoid excess. *J Am Soc Nephrol.* 2008;19(1):47–58.
58. Hamidon BB, Jeyabalan V. Exogenously-induced apparent hypermineralocorticoidism associated with ingestion of “asam boi”. *Singapore Med J.* 2006;47(2):156–8.
59. Moudgil A, Rodich G, Jordan SC, Kamil ES. Nephrocalcinosis and renal cysts associated with apparent mineralocorticoid excess syndrome. *Pediatr Nephrol.* 2000;15(1–2):60–2.
60. Lin-Su K, Zhou P, Arora N, Betensky BP, New MI, Wilson RC. In vitro expression studies of a novel mutation delta299 in a patient affected with apparent mineralocorticoid excess. *J Clin Endocrinol Metab.* 2004;89(5):2024–7.
61. Morineau G, Sulmont V, Salomon R, Fiquet-Kempf B, Jeunemaitre X, Nicod J, et al. Apparent mineralocorticoid excess: report of six new cases and extensive personal experience. *J Am Soc Nephrol.* 2006;17:3176–84.
62. Epstein MT, Espiner EA, Donald RA, Hughes H. Liquorice toxicity and the renin–angiotensin–aldosterone axis in man. *Br Med J.* 1977;1:209–10.
63. Sontia B, Mooney J, Gaudet L, Touyz RM. Pseudohypoaldosteronism, liquorice, and hypertension. *J Clin Hypertens (Greenwich).* 2008;10(2):153–7.
64. Nishiyama N, Takeshita M, Tanaka K, Miyao M, Mizuno Y. A case of severe hypokalemia caused by a Chinese herbal remedy (Yokukansan) in an 81-year-old woman with dementia. *Nihon Ronen Igakkai Zasshi.* 2011;48(5):553–7.
65. Stormer FC, Reistad R, Alexander J. Glycyrrhizic acid in liquorice—evaluation of health hazard. *Food Chem Toxicol.* 1993;31:303–12.
66. Ploeger B, Mensinga T, Sips A, Deerenberg C, Meulenbelt J, DeJongh J. A population physiologically based pharmacokinetic/pharmacodynamic model for the inhibition of 11 β -hydroxysteroid dehydrogenase activity by glycyrrhetic acid. *Toxicol Appl Pharmacol.* 2001;170(1):46–55.
67. Armanini D, Mattarello MJ, Fiore C, Bonanni G, Scaroni C, Sartorato P, et al. Licorice reduces serum testosterone in healthy women. *Steroids.* 2004;69(11–12):763–6.
68. Mattarello MJ, Benedini S, Fiore C, Camozzi V, Sartorato P, Luisetto G, et al. Effect of licorice on PTH levels in healthy women. *Steroids.* 2006;71(5):403–8.
69. Farese Jr RV, Biglieri EG, Shackleton CH, Irony I, Gomez Fontes R. Licorice-induced hypermineralocorticoidism. *N Engl J Med.* 1991;325:1223–7.
70. Van Uum SHM, Hermus ARMM, Smits P, Thien T, Lenders JWM. The role of 11 β -hydroxysteroid dehydrogenase in the pathogenesis of hypertension. *Cardiovasc Res.* 1998;38:16–24.
71. Kageyama Y, Suzuki H, Saruta T. Role of glucocorticoid in the development of glycyrrhizin-induced hypertension. *Clin Exp Hypertens.* 1994;16:761–78.
72. Stewart PM, Wallace AM, Atherden SM, Shearing CH, Edwards CR. Mineralocorticoid activity of carbenoxolone: contrasting effects of carbenoxolone and liquorice on 11 β -hydroxysteroid dehydrogenase activity in man. *Clin Sci.* 1990;78:49–54.
73. Nicholls MG, Ramsay LE, Boddy K, Fraser R, Morton JJ, Robertson JJ. Mineralocorticoid-induced blood pressure, electrolyte, and hormone changes, and reversal with spironolactone, in healthy men. *Metabolism.* 1979;28:584–93.
74. Kageyama Y, Suzuki H, Saruta T. Glycyrrhizin induces mineralocorticoid activity through alterations in cortisol metabolism in the human kidney. *J Endocrinol.* 1992;135:147–52.
75. Qadri YJ, Rooj AK, Fuller CM. ENaCs and ASICs as therapeutic targets. *Am J Physiol Cell Physiol.* 2012;302(7):C943–65.
76. Rossi E, Farnetti E, Nicoli D, Sazzini M, Perazzoli F, Regolisti G, et al. A clinical phenotype mimicking essential hypertension in a newly discovered family with Liddle’s syndrome. *Am J Hypertens.* 2011;24(8):930–5.

77. Firsov D, Schild L, Gautschi I, Merillat A-M, Schneeberger E, Rossier BC. Cell surface expression of the epithelial Na channel and a mutant causing Liddle syndrome: a quantitative approach. *Proc Natl Acad Sci USA*. 1996;93:15370–5.
78. Furuhashi M, Kitamura K, Adachi M, Miyoshi T, Wakida N, Ura N, et al. Liddle's syndrome caused by a novel mutation in the proline-rich PY motif of the epithelial sodium channel β -subunit. *J Clin Endocrinol Metab*. 2005;90:340–4.
79. Hansson JH, Nelson-Williams C, Suzuki H, Schild L, Shimkets R, Lu Y, et al. Hypertension caused by a truncated epithelial sodium channel γ subunit: genetic heterogeneity of Liddle syndrome. *Nat Genet*. 1995;11:76–82.
80. Inoue J, Iwaoka T, Tokunaga H, Takamune K, Naomi S, Araki M, et al. A family with Liddle's syndrome caused by a new missense mutation in the β subunit of the epithelial sodium channel. *J Clin Endocrinol Metab*. 1998;83:2210–3.
81. Bogdanović R, Kuburović V, Stajić N, Mughal SS, Hilger A, Ninić S, et al. Liddle syndrome in a Serbian family and literature review of underlying mutations. *Eur J Pediatr*. 2012;171(3):471–8.
82. Abriel H, Loffing J, Rebhun JF, Pratt JH, Schild L, Horisberger J-D, et al. Defective regulation of the epithelial Na(+) channel by Nedd4 in Liddle's syndrome. *J Clin Invest*. 1993;103:667–73.
83. Warnock DG. Liddle syndrome: an autosomal dominant form of human hypertension. *Kidney Int*. 1998;53:18–24.
84. Yang CL, Angell J, Mitchell R, Ellison DH:WNK kinases regulate thiazide-sensitive NaCl cotransport. *J Clin Invest*. 2003;111:1039–45.
85. Suckling RJ, He FJ, Macgregor GA. Altered dietary salt intake for preventing and treating diabetic kidney disease. *Cochrane Database Syst Rev*. 2010;8(12):CD006763.



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