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Corticosteroid-dependent hypertension: environmental influences

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Summary

Hypertension is a major disease of later life affecting 25% of the adult population in the industrialized world with most hypertensive individuals diagnosed as having essential hypertension. Approximately one third of these patients have elevated blood pressure due to increased sodium and water retention by the kidney resulting in suppressed plasma renin and aldosterone concentrations with high urinary potassium excretion and low plasma potassium levels. Monogenic forms of corticosteroid-dependent hypertension are rare. However, the discovery of these disorders has revealed genes whose proteins play a key role in the regulation of sodium homeostasis. The impaired function of these proteins, due to altered protein expression or the presence of inhibitors, contributes to the development of corticosteroid-dependent hypertension. This article focuses on the potential impact of environmental influences on corticosteroid-dependent regulation of sodium homeostasis and the development of hypertension.

Key words: aldosterone; cortisol; endocrine disruptor; environmental chemical; hypertension; sodium; 11beta-hydroxysteroid dehydrogenase

Introduction

Hypertension is a complex, multifactorial disease. Disturbed hormonal regulation at different stages during foetal development inducing irreversible changes, altered hormonal responses in the postnatal phase and a prolonged increase in blood pressure in later life essentially contribute to the development of cardiovascular and metabolic diseases. The combined effects of genetic predisposition, lifestyle and environmental influences may be responsible for most cases of these diseases. The present review addresses the potential negative impact of environmental influences that may contribute to corticosteroid-dependent hypertension. Exposure to chemicals that are not produced by our own organism including food ingredients and supply as well as medication were considered as environmental influences.

Regulation of sodium homeostasis

The average daily intake of sodium can be highly different among individuals. Whereas the African bushman consumes less than 0.5 g of sodium each day, an inhabitant of the industrialized countries consumes between 5 and 15 g. Despite these huge differences in sodium intake, plasma sodium concentration and blood pressure are maintained at near-constant levels in both individuals. Thus, a tight regulation of sodium homeostasis is required.

The main regulation of the water and electrolyte content occurs in the kidney (figure 1). Approximately 170 l of primary urine are produced

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Abbreviations

ACTH	adrenocorticotrophic hormone
AME	apparent mineralocorticoid excess
CRF	corticotrophin releasing factor
DTC	dithiocarbamate
ENaC	epithelial sodium channel
GR	glucocorticoid receptor
MR	mineralocorticoid receptor
Sgk	serum-glucocorticoid kinase
11β-HSD	11β-hydroxysteroid dehydrogenase
17β-HSD	17β-hydroxysteroid dehydrogenase

Figure 1

Sodium absorption by the renal tubular system. Upon filtration in the glomerulus, the epithelial cells along the renal tubular system reabsorb water and electrolytes. The amounts of sodium reabsorbed in each segment and the main transport proteins involved are indicated. The fine-tuning of sodium balance occurs in the cortical collecting duct by determining the amount of sodium excretion.

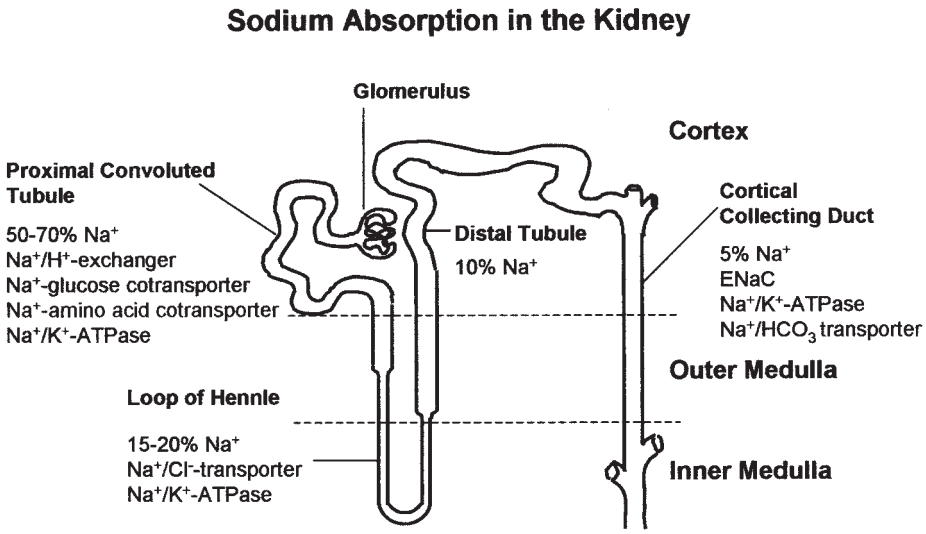
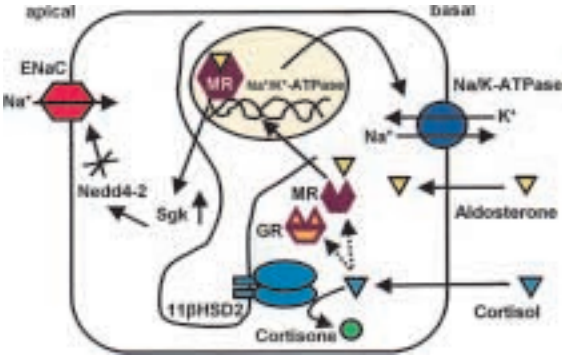


Figure 2

Regulation of sodium absorption by corticosteroids in the cortical collecting duct. Aldosterone binds to the MR; the receptor undergoes a conformational activation, translocates into the nucleus and regulates gene transcription. Activation of MR leads to increased expression of Sgk-1, which phosphorylates Nedd4-2. Phosphorylated Nedd4-2 no longer interacts with and internalises the ENaC, leading to increased expression of ENaC at the apical membrane. Activation of MR also leads to increased expression of Na^+/K^+-ATPase, thus causing a net increase in sodium uptake from the renal filtrate. The specificity of MR for aldosterone is provided by 11β-HSD2 by the rapid conversion of cortisol to cortisone in renal cortical collecting duct cells.



every day, whereby 98% or more of the water and sodium ions are reabsorbed by the renal tubular system. Between 50–70% of sodium ions are reabsorbed in the proximal convoluted tubule, corresponding to about 1.5 kg of salt per day. In this tubule segment, Na^+/H^+-exchanger, Na^+/glucose and Na^+/amino acid cotransporter play an essential role in sodium uptake from the renal filtrate. On the basolateral side of the epithelial cell, Na^+/K^+-ATPase acts as the driving force to transport sodium into the interstitial fluid. Between 15–20% of sodium is reabsorbed in the thick ascending limb of Henle and about 10% is reabsorbed in the distal tubule. Although only 5% of sodium is reabsorbed in the collecting duct, the fine-tuning of sodium balance occurs in this segment and most of the disorders due to an imbalance of sodium homeostasis are caused by defects in genes expressed in the distal tubule or in the cortical collecting duct.

The cortical collecting duct cell expresses a sodium channel (ENaC) on the lumenal cell surface and a Na^+/K^+-pump (Na^+/K^+-ATPase) on the basal cell membrane (figure 2). Upon opening of the ENaC, sodium enters the cell from the renal filtrate in the lumenal space. In order to keep intracellular concentrations constant, sodium is transported by the Na^+/K^+-ATPase into the interstitial fluid. Thus, the function of ENaC and Na^+/K^+-ATPase lead to a net flux of sodium from the renal filtrate into the interstitial fluid, resulting in sodium retention by the kidney. In order to cope with the huge differences in sodium intake, sodium homeostasis needs to be tightly controlled. Corticosteroid hormones, mainly aldosterone, control the regulation of sodium balance in the cortical collecting duct.

Corticosteroids are divided into glucocorticoids (cortisol in humans and corticosterone in rodents) and mineralocorticoids (aldosterone), both secreted from the adrenal cortex [1, 2]. Synthesis of the glucocorticoid cortisol is stimulated by corticotrophin releasing factor (CRF) and adrenocorticotrophic hormone (ACTH) from the hypothalamus and pituitary. In a given target cell, cortisol binds to the GR and under some circumstances to the MR. By a negative feedback mechanism, cortisol down regulates CRF and ACTH secretion. Cortisol secretion is up regulated by several physiological factors including hypoglycaemia, fever, pain and stress. In addition to the modulation of stress and inflammatory responses, cortisol regulates carbohydrate and amino acid metabolism and is important in blood pressure control [3].

In contrast, synthesis of the mineralocorticoid aldosterone is mainly controlled by angiotensin II in the renin-angiotensin system. Aldosterone exerts an essential role in sodium absorption and blood pressure control. In a target cell of the cortical collecting duct, aldosterone binds to the

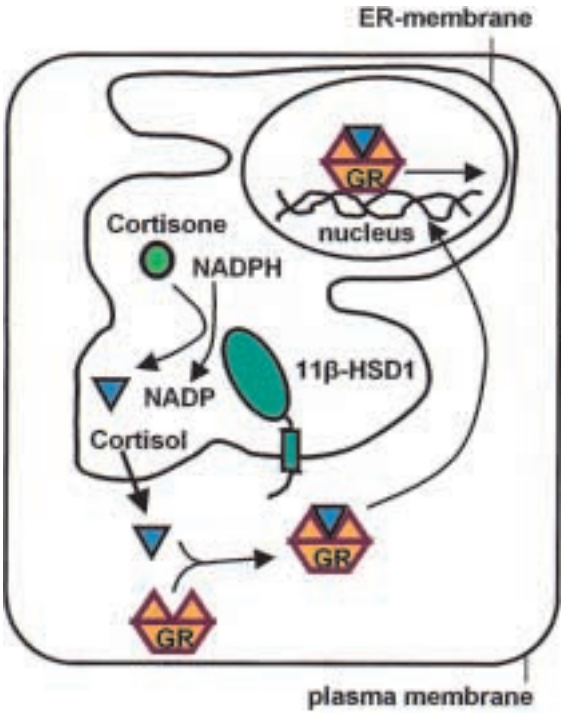


Figure 3

Local activation of the glucocorticoid receptor. 11β-HSD1 converts the inactive 11-ketoglucocorticoid cortisone to the active 11β-hydroxyglucocorticoid cortisol and controls the local activation of the GR. Upon binding of cortisol, the GR translocates into the nucleus where it regulates the transcription of a variety of genes.

MR and induces a conformational activation of the receptor followed by its translocation into the nucleus and regulation of gene transcription (figure 2). At low sodium intake, the renin angiotensin system stimulates aldosterone secretion. The activation of MR leads to an increased expression of Na^+/K^+-ATPase and, indirectly by stimulating serum-glucocorticoid dependent kinase 1 (Sgk-1) and phosphorylating Nedd4-2, to an increased number of active ENaC, thus enhancing sodium uptake from the renal filtrate [4]. The inappropriate activation of MR is associated with renal salt retention with hypertension, hypokalaemia and heart failure [1, 2]. Therefore, a tight control of corticosteroid homeostasis is essential for health.

Cortisol and aldosterone have similar affinities to bind and activate the MR [5]. Although the plasma cortisol concentration is between 100–1000 times higher than that of aldosterone, the latter hormone regulates the activation of the MR under normal conditions. This can be explained by the expression of 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2 which is preferentially found in mineralocorticoid target tissues such as renal cortical collecting ducts [1, 2]. By oxidizing 11β-hydroxyglucocorticoids 11β-HSD2 protects the MR from inappropriate activation by cortisol and renders specificity of the receptor for aldosterone.

In contrast, 11β-HSD1 is expressed in most tissues with the highest expression in liver and adipose tissue. This enzyme converts biologically inactive 11-ketoglucocorticoids into active 11β-hydroxyglucocorticoids and is essential for the local activation of GR (figure 3).

Monogenic forms of corticosteroid-dependent hypertension

There are at least four main levels where defects can affect sodium homeostasis, the hormone production (figure 4), the pre-receptor control (figures 2 and 3), the hormone receptor and the sodium transport (figure 1). For all of these four levels, genetic defects, although rare, have been described.

In glucocorticoid-remediable aldosteronism, a crossover of the gene encoding 11β-hydroxylase (CYP11B1) and the gene encoding aldosterone synthase (CYP11B2) results in a fusion gene, which is under the control of ACTH, thus explaining the seemingly paradoxical glucocorticoid suppressibility of the phenotype. A hallmark of glucocorticoid-remediable aldosteronism is the unusual production of 18-hydroxy- and 18-oxocortisol as well as high amounts of aldosterone, mimicking primary aldosteronism [6].

Congenital adrenal hyperplasia and 17α-hydroxylase deficiency are caused by genetic defects in the CYP11B1 gene and in the CYP17 gene respectively, with loss-of-function mutations leading to enhanced concentrations of the potent mineralocorticoid deoxycorticosterone [7, 8]. The in-

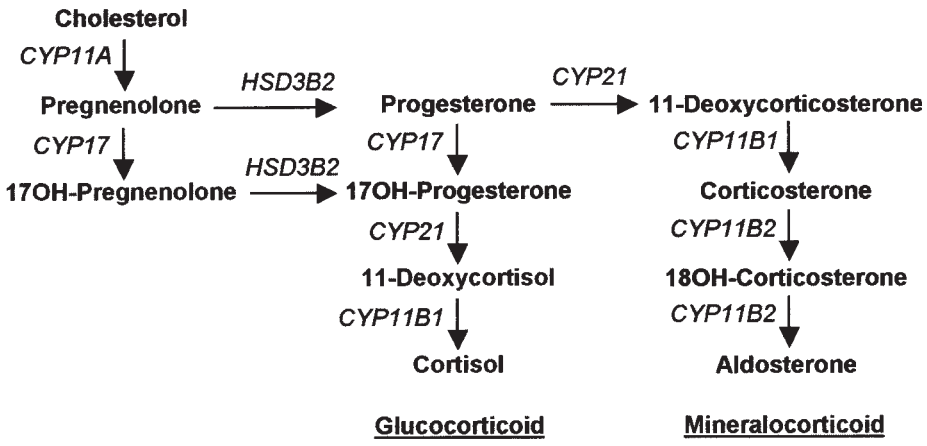


Figure 4

Biosynthetic pathway for corticosteroids in the adrenal gland. Genes are in italic. HSD3B2 codes for 3β-hydroxysteroid dehydrogenase, CYP21 for 21-hydroxylase and CYP17 encodes an enzyme with 17α-hydroxylase and 17,20-desmolase activities. CYP11B1 encodes 11β-hydroxylase and CYP11B2 codes for aldosterone synthase, an enzyme with 18-hydroxylase and 18-hydroxysteroid dehyrogenase activities.

creased concentration of systemic MR ligands causes hypokalaemia, low plasma renin concentrations and hypertension.

Under normal conditions, 11β-HSD2 exerts a pre-receptor mechanism by protecting the MR from inappropriate activation by cortisol and renders specificity of the receptor for aldosterone (figure 2). However, in patients with genetic defects resulting in a loss of 11β-HSD2 activity, excessive cortisol-dependent activation of the MR causes severe hypertension [9–11]. The disorder, known as apparent mineralocorticoid excess (AME), is characterized by low birth weight, low plasma renin and aldosterone concentrations, hypokalaemia and severe hypertension [12]. An increased ratio of urinary free cortisol to cortisone and an increased ratio of their metabolites tetrahydrocortisol plus 5α-tetrahydrocortisol to tetrahydrocortisone reflect the lack of conversion of cortisol to cortisone. In AME patients, concentrations of free cortisone and of tetrahydrocortisone in the urine are very low, due to an intact negative feedback mechanism.

Recently another form of MR-dependent hypertension was reported [13]. In two women with pregnancy-induced hypertension, a genetic defect in the gene encoding MR was found, leading to an increased basal activity as well as to a change in ligand specificity, whereby the mutated receptor is also activated by progesterone, a natural MR antagonist. In addition, cortisone is also able to activate the mutant receptor, although the activation seems to be less pronounced than with progesterone. In the affected family members, arterial hypertension was markedly exacerbated in pregnancy. The affected family members had an increased mineralocorticoid activity, including reduced serum potassium concentration and arterial hypertension but low serum and urinary aldosterone concentrations.

Liddle syndrome is caused by gain-of-function mutations in the β- or γ-subunit of the epithelial sodium channel (ENaC) [14–16]. Interaction of the mutant ENaC with Nedd4-2 is abolished, leading to a reduced internalisation and degradation of the sodium channels from the plasma membrane on the apical surface of the epithelial cell [17]. The resulting increase in the number of active channels at the plasma membrane causes an enhanced uptake of sodium from the renal tubular lumen. As a result of the feedback regulation, these hypertensive patients have low plasma renin and aldosterone concentrations. The opposite is the case in patients with loss-of-function mutations in the α- or β-subunits of ENaC, causing pseudohypoaldosteronism type 1 which is characterized by salt wasting, hyperkalaemic acidosis and hypotension [18].

Environmental influences

Environmental chemicals: occurrence, route of uptake and interference with corticosteroid hormone action

Environmental chemicals such as herbicides, fungicides, pesticides, plasticizers and polychlorated biphenyl compounds as well as food ingredients, including phyto-hormones that mimic endogenous hormone action disturb the endocrine regulation of various biological processes. Environmental chemicals are taken up orally from contaminated food and drinking water, by breathing from polluted air or via the skin from dust and soil. Other potential sources for the exposure to environmental compounds are body lotions and vanishing creams, clothes and medical drugs.

Endocrine disruptors interfere with mechanisms regulated by sex steroid hormone receptors, mainly oestrogen and androgen receptors [19, 20]. However, such chemicals can also act on the biosynthesis of a steroid hormone, its catabolism or its intracellular distribution. Recent evidence indicated that disturbances of hormone receptor-mediated responses by some environmental chemicals could be due to the interference with intracellular hormone concentrations by inhibition of pre-receptor enzymes that control the ratio of biologically active to inactive hormones. For example, 17β-hydroxysteroid dehydrogenases (17β-HSD), interconverting the physiologically potent oestrogen, oestradiol and the less active oestrone, are inhibited by various environmental chemicals, which may result in critical alterations in intracellular oestrogen concentrations and subsequent oestrogen receptor mediated action [21, 22].

There is a fast growing literature on environmental compounds with effects on sex steroid hormone action [19, 20]. In contrast, relatively little is known about the interference of environmental chemicals and food ingredients with corticosteroid-mediated responses, the focus of the present review.

Interference with biological processes may occur during foetal development through exposure to maternal nutrients and hormones, in the postnatal phase during breast-feeding and in the pubertal phase or in adult life through exposure to chemicals present in food, water and air. Environmental chemicals may disturb biosynthesis of corticosteroid hormones (figure 4), intracellular availability and hormone receptor response (figures 2 and 3) or catabolism of steroid hormones. The inappropriate regulation of corticosteroid concentrations induces an array of GR-mediated effects including osteoporosis, weight gain, diabetes, and cataracts, as well as MR-mediated effects including renal salt retention with hypertension, hypokalaemia and heart failure [1, 2, 23]. All these disease states show an age-dependent increasing

frequency and the accumulation of inappropriate GR and MR effects, due to receptor response modulation by endocrine disruptor compounds throughout life, might contribute to these pathological processes.

Prenatal influences: programming

A strong association was found between low birth weight and the development of diabetes type 2, hypertension and ischaemic heart disease in both prepubertal children and adults [24, 25]. Barker and co-workers provided evidence that following a prenatal insult the incidence of these diseases is significantly increased, independent of adult lifestyle influences [26], implying that the nutritional and hormonal intrauterine environment is important in determining foetal growth and development [27, 28].

In addition to their role in the regulation of carbohydrate and amino acid metabolism, glucocorticoids play an essential role in growth and development and in the regulation of bone metabolism. In humans, maternal undernourishment causes increased cortisol plasma concentrations in both the mother and the growth-retarded foetus [29, 30]. Maternal undernourishment affects up to 20% of the whole population so that the overexposure of the foetus to cortisol and growth retardation is a critical issue. Babies with reduced birth weight have lower activity of 11β-HSD2 [31]. In the placenta, 11β-HSD2 plays a crucial protective role by converting physiologically active cortisol into inactive cortisone, thus protecting the foetus from the high levels of maternal serum cortisol. Therefore, reduced placental 11β-HSD2 activity, resulting in enhanced exposure of the foetus to high maternal glucocorticoids, could lead to disturbances in the intrauterine development.

The exposure of rats in utero to high concentrations of the synthetic glucocorticoid, dexamethasone leads to reduced birth weight and a higher risk for cardiovascular and metabolic disorders such as hypertension and diabetes type 2 in the adult offspring [32, 33]. Lesage et al. [34] have shown in experiments with rats that maternal undernourishment during late gestation induces foetal overexposure to glucocorticoids and intrauterine growth retardation with disturbances in the hypothalamus-pituitary adrenal axis. Food restriction led to a decrease at term of both the maternal plasma corticosteroid-binding globulin level and placental 11β-HSD2 expression. In the litter, maternal food restriction reduced body and adrenal weights, reduced GR and MR expressions in the hippocampus and plasma ACTH levels. In line with these findings, Bertram et al. [35] have shown that mild protein restriction during pregnancy leads not only to increased expression of GR in offspring during foetal and neonatal life but also in juvenile and adult life. In addition, protein restriction reduced 11β-HSD2 expression in the placentas of the mothers in late gestation and in offspring in the kidney and in adrenals during foetal and postnatal life. The programmed decline in 11β-HSD2 activity may explain the marked increases in glucocorticoid action in these tissues and potentiates both GR- and MR-mediated induction of raised blood pressure.

Maternal malnutrition can also disturb foetal corticosteroid-dependent responses if chemicals are present that lead to an inhibition of 11β-HSD2 and cause an increased foetal exposure to cortisol (see below).

Postnatal influences

After birth babies are potentially exposed to environmental chemicals present in breast milk or to chemicals in milk formulas produced during processing. An extensively discussed issue is the widespread use of soy-based formula for babies [36]. Infants fed soy formula consume up to 11 mg/kg per day of isoflavones, representing an approximately ten-fold higher amount compared with adults eating moderate amounts of soy. The main isoflavones found in the circulation are genistein and daidzein. Soy isoflavones can function as oestrogen agonists, antagonists or selective oestrogen receptor modulators. The isoflavones genistein and daidzein also alter adrenocortical function by suppression of glucocorticoid and stimulation of androgen production [37]. Whether the postnatal exposure to isoflavones has negative effects on health in later life remains unclear [38].

The presence of xenobiotics in the food chain and in polluted air is especially critical for babies and children. The food intake per kg body weight and the relative lung volume and respiratory capacity is significantly higher in babies and children compared with adults. In addition, children are more exposed to dust and soil and their absorption of chemicals through the skin is more efficient.

Influences in adult life

In the prenatal phase a single exposure to a chemical disrupting corticosteroid action can affect programming. In contrast, during adult life disturbances in corticosteroid receptor-mediated action are likely to be caused by the long-term exposure to industrial chemicals released into the environment and chemicals present in clothes and cosmetics or taken up from the diet or through medication.

An inappropriate diet combined with the lack of physical exercise is responsible for obesity-induced hypertension. Obesity is an increasingly prevalent condition associated with a large number of diseases with enormous socio-economical consequences. Patients with obesity-induced hypertension are at increased risk of developing left ventricular hypertrophy and kidney damage. So far, the most effective and safe treatment for these patients is calorie restriction and a reduction of salt intake [39].

Glucocorticoids play an important role in the regulation of gluconeogenesis, carbohydrate metabolism and adipose tissue differentiation,

function and distribution. Inappropriately high concentrations of glucocorticoids cause central obesity [40]. By converting inactive 11-ketoglucocorticoids (cortisone) to active 11β-hydroxyglucocorticoids (cortisol), 11β-HSD1 essentially controls the local activation of GR. In obese individuals, adipose 11β-HSD1 activity positively correlates to body mass index, percentage of body fat, waist circumference, as well as fasting glucose, insulin and insulin resistance [41]. Transgenic mice over expressing 11β-HSD1 selectively in adipose tissue have elevated adipose corticosterone concentrations. On a high fat diet, they develop visceral obesity with insulin-resistant diabetes and hyperlipidaemia [42]. These transgenic mice have high arterial blood pressure and increased sensitivity to dietary salt and increased plasma levels of angiotensinogen, angiotensin II and aldosterone [43], indicating activation of the circulating renin-angiotensin system. The increased regeneration of cortisol in adipose tissue contributes to the development of obesity, metabolic syndrome and salt-sensitive hypertension mediated by an activated renin-angiotensin system.

Biological mechanisms of altered corticosteroid action

Suppression of glucocorticoid biosynthesis

The isoflavones genistein and daidzein were shown to decrease ACTH-stimulated cortisol production [37]. Both phytohormone compounds did not affect the expression of steroid-metabolising enzymes, but specifically inhibited the activity of 21-hydroxylase (CYP21) (figure 4). It was suggested that genistein and daidzein reduce cortisol synthesis by suppressing 21-hydroxylase activity and, as a consequence, increase dehydroepiandrosterone production by shunting metabolites away from the glucocorticoid synthetic pathway [37]. Evidence was also provided for an inhibition of 3β-hydroxysteroid dehydrogenase by genistein and daidzein, which would result in a shift from glucocorticoid to androgen production. The reduced glucocorticoid action may explain at least part of the positive effects of genistein and daidzein in obese individuals and in the delay of onset of diabetes type 2 [44].

Inhibition of 11β-HSD1

Recently, we have shown that flavanone and some monohydroxylated flavanone derivatives selectively inhibit the reductase activity of 11β-HSD1 [45]. Inhibition of 11β-HSD1 activity may be beneficial in obese individuals since the local activation of GR, which is enhanced in obese individuals, is reduced. Inhibitors of 11β-HSD1 have been suggested as potential drugs to control blood glucose levels and to improve insulin sensitivity [46].

Inhibition of 11β-HSD2

Glycyrrhetinic acid

Liquorice is prepared from the liquorice root *succus liquiritiae* or from the liquorice plant *glycyrrhizia glabra*, and it was used for the treatment of patients with gastric ulcers [47]. Carbenoxolone, a hemisuccinate derivative of 18β-glycyrrhetinic acid was developed as an anti-ulcer drug. However, mineralocorticoid side effects such as oedema and increased blood pressure were described for both glycyrrhetinic acid [48, 49] and carbenoxolone [50]. Liquorice-induced hypertension is characterized by sodium retention, hypokalaemia, metabolic alkalosis and suppression of the renin-angiotensin-aldosterone system. It is induced by consumption of 50 g or more of liquorice per day, corresponding to 100 mg or more of glycyrrhetinic acid [51, 52]. Glycyrrhizin, the glucuronidated form of glycyrrhetinic acid, is widely used in confectioneries and also as a sweetener in chewing gums and chewing tobacco [53, 54]. Liquorice is also present in low and high level cigarettes (0.11% and 0.16%, respectively), where it is added as a casing material [55]. Whether the long-term exposure to glycyrrhetinic acid in smokers contributes to the development of hypertension remains to be investigated.

It has been demonstrated that glycyrrhetinic acid is a potent inhibitor of 11β-HSD2 [56–58], thus explaining the subsequent cortisol-induced nuclear translocation and activation of the MR [59] causing sodium retention and hypertension.

Women, especially those taking oral contraceptives, seem to be more susceptible to glycyrrhetinic acid-induced hypertension [60]. It was shown that progesterone and its metabolites are potent inhibitors of 11β-HSD2 [61]. Therefore, in women mineralocorticoid hypertension may be caused by direct effects of progesterone or oestrogen metabolites on the MR or by inhibition of 11β-HSD2 and subsequent cortisol-dependent MR activation.

An altered progesterone metabolism in the kidney could also contribute to the pathogenesis of pre-eclampsia, which is characterized by enhanced sodium retention, hypertension, oedema and proteinuria in the third trimester of pregnancy. Patients with pre-eclampsia have an increased urinary free cortisol to cortisone ratio compared with women with normal pregnancy [62]. This may explain the observed down regulation of MR with reduced plasma renin and aldosterone concentrations in pre-eclamptic patients [63–65].

The consumption of glycyrrhetinic acid containing products is especially critical for pregnant women since it may contribute to pregnancy-induced hypertension and it would cause an enhanced exposure of the foetus to glucocorticoids with long-term effects on the cardiovascular system. Therefore, the use of glycyrrhetinic acid-

containing products should be strictly controlled to both prevent and treat hypertension.

Grapefruit juice

A clinical study on two men drinking 1–2 l of grapefruit juice daily indicated an increased cortisol to cortisone ratio [66]. Grapefruit juice contains various flavanoids from among which naringenin has been shown to inhibit 11β-HSD2 with an IC_{50} value of 336 μM [67]. Naringenin is a relatively weak inhibitor of 11β-HSD2 with a high IC_{50} concentration and it is not clear whether such high concentrations can be reached *in vivo*. Plasma concentrations of flavanoids typically reached in individuals consuming a soy-based diet range from 2–5 μM [68, 69]. This leaves open the question whether the combination of various flavanoids inhibiting 11β-HSD2 or an as yet unidentified potent inhibitor is responsible for the observed increase in cortisol to cortisone ratio. In addition, naringenin was also shown to be a weak inhibitor of 11β-HSD1 with an IC_{50} value between 300–500 μM [45, 70] and its effect on systemic glucocorticoid concentrations remains to be analysed.

Furosemide

Using guinea pig kidney cortex microsomes, an inhibitory effect on 11β-HSD activity was shown for the three loop diuretics furosemide (IC_{50} 59 μM), ethacrynic acid (IC_{50} 450 μM) and bumetanide (IC_{50} 2 mM) [67]. In line with an expected inhibition of 11β-HSD2 and cortisol-induced MR activation, furosemide caused a more pronounced urinary potassium loss than bumetanide for equal sodium excretion. Experiments with recombinant 11β-HSD1 and 11β-HSD2 expressed in COS-1 cells suggested competitive inhibition for the oxidation of corticosterone for both enzymes by furosemide with Ki values of 17 μM and 30 μM, respectively [71, 72]. Upon i.p. administration of furosemide to rats, an increased ratio of tetrahydrocorticosterone plus 5α-tetrahydrocorticosterone to 11-dehydrotetrahydrocorticosterone was detected in the urine, indicating reduced activity of 11β-HSD2 [72]. In addition, an increased ratio of the 11β-hydroxyglucocorticoid prednisolone to its 11-keto metabolite prednisone was measured upon administration of furosemide [71].

Dithiocarbamates

Dithiocarbamates (DTCs) are widely used in cosmetics, in agricultural products as pesticides, herbicides and fungicides and in the manufacture of rubber products as accelerating agents. The DTC disulfiram is also known as Antabuse and is used as aversion therapy in severe alcoholic patients. Pyrrolidine dithiocarbamate is applied in chelation therapy for metal intoxication.

Widespread use of these compounds as well as the large quantities released into the environment has led to an increased exposure of humans to DTCs. These compounds belong to the most potent allergens in rubber products [73]. Various toxic effects of DTCs have been described both in humans and in animal model systems, including effects in liver, kidney, testis and placenta [74–78]. For example, excessive exposure to the DTCs maneb and zineb caused acute renal failure and nephrotic syndrome in agricultural workers [79] and led to kidney damage and reduced body weights in the offspring of exposed pregnant rats [78].

DTCs interfere with the control of local glucocorticoid concentrations by irreversibly inhibiting 11β-HSD2 through sulfhydryl modification. 11β-HSD1 activity is not affected by DTCs and 17β-HSD1 and 17β-HSD2 are only inhibited at very high concentrations (IC_{50} >100 μM; [80]).

The inhibition of 11β-HSD2 may contribute to some of the observed toxic effects of DTCs in the kidney and on blood pressure, as well as those on placenta and on foetal development. DTCs pass the blood-brain barrier [81], which explains the neurotoxic effects of these compounds. They also pass the foetal-placental barrier, explaining the toxic effects on foetal life [78]. Inhibition of placental 11β-HSD2 is especially critical since inappropriately increased cortisol concentrations would disturb foetal programming and pose a risk to the foetus for the development of hypertension, diabetes and cardiovascular disease in later life [57, 82–84]. The present evidence suggests caution in the use of these compounds in clinical applications and in exposure of the general population to cosmetics and other products containing DTCs.

Abietic acid

Abietic acid is found in cosmetics such as foundations, concealers, sunscreens, mascaras, eyeliners, lipsticks, creams and colour pencils that contain colophony. An inhibitory effect of abietic acid on gastric secretions was observed, suggesting its application in ulcer treatment [85]. Since abietic acid inhibits 11β-HSD1 with an IC_{50} value in the low micromolar range [45], its effect in ulcer treatment may be similar than that of carbenoxolone. In addition, abietic acid efficiently inhibits the oxidation of cortisol by 11β-HSD2 (IC_{50} 12 μM) [45]. There is evidence indicating anti-inflammatory activity of abietic acid after oral or topical administration [86]. This effect may be explained, at least partially, by the local inhibition of 11β-HSD2 causing enhanced local concentrations of cortisol.

Gossypol

In a clinical trial, gossypol, a polyphenolic compound extracted from the cotton plant, was tested as a potential antifertility agent for males. Gossypol eliminates sperm motility, thereby abolishing sperm count and causing azoospermia [87, 88] Some of the participants of this trial became hypokalaemic due to excessive potassium excretion. Experiments using guinea pig kidney cortex microsomes revealed a competitive inhibition of 11β-HSD2 by gossypol with a Ki of 67 μM [89]. Gossypol had an IC_{50} of 147 μM for the oxidation of cortisol by 11β-HSD2 when human kidney mi-

crosomes were used [90]. Polyphenols in tea also inhibited 11β-HSD2 activity, whereby this effect was additive to that of gossypol [91].

Outlook

Although monogenic forms of corticosteroid-dependent hypertension are rare, the identification of the genes underlying these disorders represent the first step in the understanding of the molecular mechanisms involved in the development of hypertension. Polymorphisms in these genes may lead to a predisposition of these individuals to the development of hypertension, which may be induced depending on lifestyle and exposure to environmental chemicals. The exposure to endocrine disruptors is most critical in the prenatal phase but also plays a role in postnatal and adult life. In the last part, lifestyle becomes more important, indicated by the increasing number of individuals with obesity-induced hypertension.

In contrast to xenoestrogens, little is known on the molecular mechanisms of action of environmental chemicals and their relevance to the development of corticosteroid-dependent hypertension. Environmental influences may lead to altered gene expression or impaired activity due to the presence of inhibitors or receptor ant/agonists. A role for environmental influences has been demonstrated and these have been shown to affect biosynthesis of glucocorticoids as well as pre-receptor control. Inhibitors of 11β-HSD2 lead to inappropriate activation of MR and GR by cortisol and can be regarded as "bad" environmental chemicals. In contrast, inhibitors of 11β-HSD1 reduce the local activation of GR, which is beneficial in obese individuals and may delay onset of diabetes type 2. Thus, such inhibitors may be regarded as "good" environmental chemicals. Similar positive effects were observed for isoflavones suppressing glucocorticoid synthesis. However, their multiple effects on various enzymes are not well understood.

The recently emerging evidence indicates that environmental influences should be considered in the treatment and prevention of corticosteroid-dependent hypertension. Potential mechanisms by which environmental chemicals may directly disturb corticosteroid binding in serum, hormone receptor function or sodium transport remain to be uncovered.

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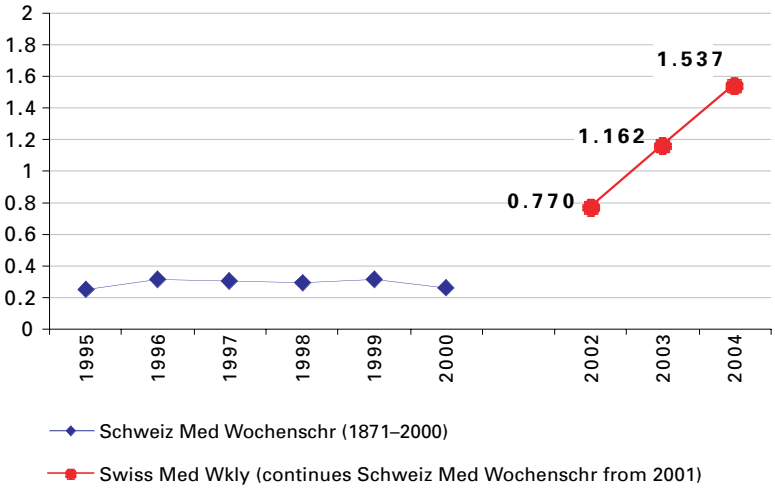

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