Pharmacological Research 154 (2020) 104311

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Drug-induced endocrine blood pressure elevation

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ARTICLE INFO

Chemical compounds studied in this article:
Abiraterone
Carbenoxolone
Danazol
Etomidate
Itraconazole
Ketoconazole
Lisdexamphetamine
Metyrapone
Mifepristone
Posaconazole

Keywords:
Hypertension
Mineralocorticoid excess
Steroidogenesis
11beta-hydroxysteroid dehydrogenase
Catecholamine
Adverse drug reaction

ABSTRACT

Patients with uncontrolled hypertension are at risk for cardiovascular complications. The majority of them suffers from unidentified forms of hypertension and a fraction has so-called secondary hypertension with an identifiable cause. The patient's medications, its use of certain herbal supplements and over-the-counter agents represent potential causal factors for secondary hypertension that are often overlooked. The current review focuses on drugs that are likely to elevate blood pressure by affecting the human endocrine system at the level of steroid synthesis or metabolism, mineralocorticoid receptor activity, or by affecting the catecholaminergic system. Drugs with known adverse effects but where benefits outweigh their risks, drug candidates and market withdrawals are reviewed. Finally, potential therapeutic strategies are discussed.

1. Introduction

The majority of diagnosed hypertensive patients suffer from idiopathic hypertension. Secondary forms of hypertension due to an identifiable cause are less prevalent and found in approximately 10% of adult hypertensive patients and in up to 30% of patients with treatment-resistant hypertension [1–4]. However, a recent review described primary aldosteronism (PA) as a major public health problem, with inappropriate aldosterone secretion detected in up to 50% of patients with essential hypertension [5]. Other causes of secondary hypertension include obstructive sleep apnea (prevalence > 15%), renal parenchymal disease (1–8%), renal artery stenosis (1–8%), Cushing's syndrome (CS) (< 0.1%), hyper-/hypothyroidism (< 1%), pheochromocytoma (0.2-0.6%), and coarctation of the aorta (0.1%) [1,4,6]. Concomitant medications promoting hypertension or blunting the effects of anti-hypertensive therapy are frequently underrecognized by health care providers as contributors to secondary hypertension [7,8]. The patient's personal use of certain herbal supplements, over-the-counter agents or psychostimulants associated with blood pressure elevation renders individual assessments even more demanding. Importantly, a direct relationship between the degree of vascular disease and mortality risk over the normal range of blood pressure has been demonstrated [9]. Moreover, even a reduction of as little as 2 mm Hg of systolic blood pressure has been shown to lower mortality due to stroke

Abbreviations: 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; 11-DOC, 11-deoxycorticosterone; AAS, androgenic anabolic steroids; ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone; ADHD, attention deficit/hyperactivity disorder; AR, androgen receptor; COX, cyclooxygenase; CS, Cushing's syndrome; CYP, cytochrome P450; DHEA, dehydroepiandrosterone; MAO, monoamine oxidase; MR, mineralocorticoid receptor; NSAIDs, non-steroidal anti-inflammatory drugs; PA, primary aldosteronism; P-gp, P-glycoprotein; RAAS, renin-angiotensin-aldosterone system; SNRI, serotonin-noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants

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https://doi.org/10.1016/j.phrs.2019.104311
Received 7 March 2019; Received in revised form 8 June 2019; Accepted 10 June 2019
Available online 15 June 2019
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by 10% and due to ischemic heart disease by 7% [9]. This raises the question whether a slight increase of blood pressure, although still in the "normal" range, represents an unappreciated clinical issue. Therefore, it is crucial to consider the patient's medications as potential contributors to blood pressure elevation and to know the underlying pathways in order to apply an appropriate therapy. Three major mechanisms leading to blood pressure elevation can be distinguished: plasma volume expansion, increased sympathetic activity and direct vasoconstriction [10]. This review outlines mechanisms of drug-induced blood pressure elevation due to direct interference with the endocrine system, including the mimicking of endogenous hormones or disturbance of hormone synthesis, transport and metabolism.

2. Mineralocorticoid effects

2.1. Interference with adrenal steroidogenesis

The central role of the adrenal glands in stress responses makes them a particularly sensitive organ as seen in toxicological studies [11]. Despite this, the assessment of off-target effects on the adrenals in endocrine-related drug toxicity studies represents a neglected topic of investigation, although administration of drugs such as etomidate and aminoglutethimide caused the death of patients due to unrecognized interference with adrenocortical steroidogenesis [12]. The importance of evaluating drug candidates for their potential to interfere with steroidogenic enzymes has recently been addressed by the United States Food and Drug Administration guidance on non-clinical evaluation of endocrine-related drug toxicity [13]. It recommends the use of cytochrome P450 (CYP) isoenzyme assays during early drug development, including those for CYP11A1, CYP11B1, CYP11B2, CYP17A1 and CYP21A1 that are involved in adrenal androgen, mineralo- and glucocorticoid synthesis.

CYP11B1 (also known as 11β-hydroxylase) catalyzes the conversion of 11-deoxycortisol to the potent glucocorticoid cortisol, whereas CYP11B2 (also known as aldosterone synthase) converts 11-deoxycorticosterone (11-DOC) via corticosterone and 18-hydroxycorticosterone to the potent mineralocorticoid aldosterone [14]. Inhibition of CYP11B1 results in decreased cortisol production along with increased levels of 11-deoxycortisol and 11-DOC that possess mineralocorticoid activity and can result in low renin levels. Diminished CYP11B2 activity leads to decreased aldosterone production and accumulation of its substrate 11-DOC [15,16]. In the human circulation only about 6% of 11-DOC is not bound to plasma proteins, whereas > 30% of aldosterone is freely available [17], explaining the moderate mineralocorticoid activity of 11-DOC *in vivo*. However, supraphysiological 11-DOC levels can cause inappropriate activation of mineralocorticoid receptors (MR) and promote volume expansion and hypertension [16]. Moreover, decreased CYP11B1/2 activity results in elevated concentrations of adrenal androgens due to feedback regulation and increased adrenal steroidogenesis. In contrast, inhibition of CYP17A1 lowers cortisol and androgen production and, due to feedback and activation of steroidogenesis, promotes increased levels of 11-DOC, corticosterone and aldosterone. In both cases, the low cortisol levels cause an elevation of adrenocorticotropic hormone (ACTH) that further stimulates the adrenal glands and enhances the production of mineralocorticoids.

2.1.1. Itraconazole and posaconazole

A number of recent case reports have described the occurrence of severe hypokalemia and hypertension together with low renin and aldosterone levels secondary to antifungal therapy with the azole antifungals posaconazole and itraconazole [18–26]. Boughton et al. [18] and Barton et al. [19] reported two cases of posaconazole-induced hypertension and hypokalemia with markedly elevated serum 11-DOC and 11-deoxycortisol concentrations that exceeded the upper limit of the normal range by 10–20 fold. These observations provided evidence for inhibition of CYP11B1 by posaconazole. Besides, both studies reported increased androstenedione and 17-hydroxyprogesterone levels, indicating that CYP17A1 was not compromised. The reported high serum 11-DOC and androgen concentrations differ from those found in a patient receiving posaconazole that showed normal 11-DOC and androgen levels, along with an increased cortisol/cortisone ratio [22]. However, the moderately elevated 11-deoxycortisol as well as 17-hydroxyprogesterone concentrations seemed to account at least for partial CYP11B1 inhibition. In addition, Wassermann et al. described a case with clearly elevated 11-deoxycortisol levels and an increased serum cortisol/cortisone ratio during posaconazole treatment [24], further supporting inhibition of both CYP11B1 and CYP11B2 by this azole. These reports did not or only partially assess the patient's plasma and urinary steroid profile, allowing only a limited insight into the mechanism of azole-induced hypertension and hypokalemia. However, a recent report on two cases of posaconazole-induced hypertension and hypokalemia that included detailed steroid metabolite analyses in blood and urine samples emphasized inter-individual differences in the mechanism underlying mineralocorticoid-dependent hypertension and hypokalemia, with predominant inhibition of CYP11B1 and CYP11B2 in one patient and predominant inhibition of 11β-HSD2 in the other [26].

Importantly, all cited case studies have reported serum drug concentrations that exceeded the therapeutic range. In three cases, a lowering of the dose resolved the mineralocorticoid symptoms [22–24]. Substitution of posaconazole or itraconazole with voriconazole or fluconazole also resolved the mineralocorticoid phenotype [21,22,25,26].

It is accepted knowledge that most azole antifungals are potent CYP3A4 inhibitors [27,28]. Therefore, care has to be taken when co-administering drugs that are metabolized by CYP3A4 (e.g. corticosteroids). For the same reason, a combined use of calcium channel blockers and itraconazole should be avoided as this can cause negative inotropic effects [29]. Moreover, ketoconazole and itraconazole are potent inhibitors of the efflux pump P-glycoprotein (P-gp) [30]. Therefore, doses of substrates of P-gp, such as corticosteroids or cyclosporin A, should be lowered when they are co-administered with these azoles.

In addition to CYP11B inhibition, certain azole fungicides have been shown to interfere with the cortisol-metabolizing enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (discussed in section 2.2.2).

2.1.2. Ketoconazole

Ketoconazole, the first orally active azole-type antifungal agent, was introduced in the early 1980s to treat systemic fungal infections [31,32]. Soon after its market launch, several studies reported low serum testosterone levels [33,34], the development of gynecomastia [35], and glucocorticoid suppression [36] upon long-term ketoconazole treatment. Inhibition of enzymes involved in adrenal and gonadal steroid synthesis, particularly CYP11A1, CYP17A1 and CYP11B1, was found to be responsible for this phenotype [37–39]. Therefore, ketoconazole has subsequently been used on an off-label basis to treat patients with endogenous hypercortisolism, *i.e.* Cushing's syndrome (CS). The therapeutic efficacy of long-term ketoconazole treatment of patients suffering from CS has been confirmed by several studies (reviewed by [40,41]). However, most of these studies included only a small number of patients, with the exception of a retrospective multicenter study involving 200 patients [42]. This study reported unresolved hypertension (50%) and hypokalemia (61.6%) in patients receiving ketoconazole as pre-surgical treatment (n = 40), and about 60% of patients receiving ketoconazole as primary or secondary treatment (n = 160) showed hypertension and hypokalemia. Generally, patients showed higher improvement rates for the endpoints 'clinical signs' and 'diabetes'. Unfortunately, no further results regarding improvement of hypertension and hypokalemia were shown, probably because the associated symptoms are barely distinguishable from the symptoms of CS itself. Two earlier studies reported sustained

hypertension with high-dose or long-term ketoconazole treatment in a minor subset of patients exhibiting increased plasma levels of 11-DOC and 11-deoxycortisol but markedly decreased cortisol and normal aldosterone concentrations [43,44], in line with potent inhibition of CYP11B1 but weak or moderate inhibition of CYP11B2. In 2013, the European Medicines Agency (EMA) and the Federal Drug Administration (FDA) restricted the use of ketoconazole for the treatment of fungal infections due to concerns of severe hepatotoxicity. This led to a change in the prescribing guidance in CS [40,45,46]. Nevertheless, the limited alternative options for the treatment of CS and the proven efficacy of ketoconazole contributed to its reapproval by the EMA for CS. In order to overcome the safety issue, levoketoconazole, the 2S,4R-enantiomer of ketoconazole, is currently under investigation, since it is claimed to provide higher specificity and thus safety than the racemic compound (reviewed in [47]).

2.1.3. Metyrapone

Besides ketoconazole, the most commonly used drug for CS therapy is metyrapone [40,48], an inhibitor of CYP11B1 and, to a lesser extent, of CYP11B2 and CYP17A1 [49] that was developed for this indication [50]. Oral administration of a dose of 750 mg of metyrapone to CS patients decreased serum cortisol concentrations within 2 h [51], whereby patients with reduced hepatic function and thereby decreased cortisol catabolism can display a delayed response [52]. The potent cortisol-lowering effect of metyrapone results in attenuation of negative feedback and thus causes an increase in ACTH, which stimulates steroidogenesis. The concomitant accumulation of androgens and 11-DOC [50,51,53] may cause adverse effects, such as hirsutism, worsening of acne, hypertension, hypokalemia and edema. Although the mineralocorticoid-dependent effects due to increased 11-DOC concentrations might be expected to occur frequently, hypertension, hypokalemia and edema have only rarely been described [51,54]. Metyrapone has initially been used for the differential diagnosis of ACTH-dependent forms of CS and to assess the functional integrity of the hypothalamo-pituitary-adrenal axis [55,56]. Caution has to be taken when interpreting results from immunoassays of metyrapone-increased concentrations of 11-deoxycortisol, as this steroid can cross-react with cortisol and therefore leading to apparently high cortisol levels and to potentially erroneous clinical decisions [57].

2.1.4. Osilodrostat

Osilodrostat (LCI699) is a novel aldosterone synthase (CYP11B2) inhibitor developed for the treatment of PA and essential hypertension [58–60]. However, an earlier proof-of concept study with patients suffering from PA reported 7- and 14-fold elevated 11-DOC levels after 0.5 mg and 1 mg of LCI699, respectively [59]. Moreover, plasma ACTH levels of these patients increased, whereas potassium concentrations decreased; but only a mild decrease (4 mm Hg) of systolic blood pressure was noted after 4 weeks of treatment. Plasma cortisol levels remained stable, whereas 11-deoxcortisol concentrations increased 4-fold above baseline. The increased ACTH together with maintained cortisol indicates CYP11B1 inhibition with a subsequent compensatory increase of adrenal steroidogenic output, explaining the rise in 11-DOC and 11-deoxycortisol. Osilodrostat is currently evaluated for its efficacy and safety in the treatment of CS in a phase III study [61]. In two phase II studies with CS patients, improved urinary cortisol levels were found, along with dramatically increased concentrations of 11-DOC and 11-deoxycortisol as well as mild hypokalemia [62,63]. One of these studies [62] found no blood pressure decrease, most likely as a result of the increased 11-DOC levels that may have reversed the blood pressure-lowering effect of CYP11B2 inhibition. The other study [63] observed a trend towards decreased blood pressure; however, as antihypertensive medication was not restricted, a medication bias cannot be excluded. Further, four phase II studies in patients with different forms of hypertension revealed astonishing results: Lower doses of LCI699 reduced and higher doses increased blood pressure [60]. The authors interpreted the latter result by the supra-physiological 11-DOC concentrations.

Several CYP11B2 inhibitors are currently assessed in preclinical studies and two of them entered phase I clinical trials [64,65]. A reduction of aldosterone levels in healthy subjects but an elevation of 11-DOC and 11-deoxycortisol levels was found with both compounds. Their effect on blood pressure in hypertensive patients will be assessed in subsequent phase II studies.

2.1.5. Abiraterone, orteronel and VT-464

The biosynthesis of the main androgen precursor dehydroepiandrosterone (DHEA) from pregnenolone includes only one enzyme, CYP17A1. In human, it catalyzes the 17α-hydroxylation of both, pregnenolone and progesterone with equal affinities, whereas the subsequent 17,20-lyase reaction preferably converts 17α-hydroxypregnenolone to DHEA rather than 17α-hydroxyprogesterone to androstenedione (reviewed in [66]). Abiraterone, a synthetic steroidal compound, significantly reduces androgen levels in castrate-resistant prostate cancer by equally inhibiting the 17α-hydroxylase and 17,20-lyase activities of CYP17A1 [67,68]. However, as a consequence of 17α-hydroxylase inhibition, the production of cortisol is also diminished, leading to an adaptive rise in ACTH levels, which in turn stimulates adrenal steroidogenesis and results in the accumulation of 11-DOC, corticosterone, and aldosterone. Due to the resulting mineralocorticoid excess, hypertension, hypokalemia and fluid retention are common adverse effects of abiraterone [69]. To counteract adrenal insufficiency and mineralocorticoid excess, and thus to overcome the drug-induced hypertension, patients undergoing abiraterone therapy are co- administered prednisone or methylprednisolone.

The combined use of abiraterone and the MR antagonist spironolactone should be avoided because spironolactone is also a partial agonist of the androgen receptor (AR) that can activate the AR in an androgen-depleted environment, thereby increasing prostate specific antigen levels [70,71]. The more specific MR antagonist eplerenone does not activate the wild-type AR but was found to activate a mutant form of this receptor that occurs in castrate-resistant prostate cancer [72]. Thus, if glucocorticoid supplementation is not sufficient to control mineralocorticoid symptoms, the application of amiloride (± hydrochlorothiazide) may be the preferred option [70].

To reduce the adverse mineralocorticoid effects, selective 17,20-lyase inhibitors represent an interesting option. In this regard, the nonsteroidal compound orteronel was developed. However, because overall survival rates were not improved in a clinical phase III study, further development of this compound was terminated [73]. Another nonsteroidal 17,20-lyase inhibitor, VT-464, is currently being tested in phase I/II trials and shows promising results without affecting downstream glucocorticoid levels [74,75].

2.1.6. Androgenic anabolic steroids

Androgenic anabolic steroids (AAS) are used by athletes and bodybuilders to enhance muscle strength and appearance. The increasing recreational application of AAS has become a considerable issue for public health [76], especially when doses are taken that cause serum concentrations to increase the therapeutic recommendations up to 100 fold [77–79]. AAS abuse is associated with dose-dependent cardiac pathologies, elevated blood pressure and edema (reviewed in [80–82]). Of note, the mechanisms by which AAS, testosterone itself or its derivatives contribute to or aggravate hypertension are multifactorial and incompletely understood [83].

The testosterone derivative danazol has been used since the 1960′s for the treatment of endometriosis and hereditary angioedema [84]. In spite of its efficacy, adverse effects limited its use and even led to market withdrawal in some countries. Vaginal administration may provide an improved profile, but its use in endometriosis is still only indicated if no other therapeutic option is available [85,86]. Nevertheless, recent reports have discussed danazol as a potential treatment

in telomere diseases or in autoimmune hemolytic disorders [87,88]. Swelling, edema and weight gain belong to the most common adverse effects of danazol [89]. An early case study described severe hypertension as an additional adverse effect [90]. Salt and water retention was suggested as main reason for this effect, presumably caused by weak mineralocorticoid properties of danazol. However, several other *in vitro* and *in vivo* studies have elucidated the effects of danazol on adrenal function [91–100] and indicated, though with partly contradictory results, inhibition of adrenal 3β-hydroxysteroid dehydrogenase, 21-hydroxylase, and 11β-hydroxylase [91,92,94–96]. Two of these studies used rat and guinea-pig as model species, and at least some of the contradictory results might be explained by species differences. Nevertheless, the majority of the *in vivo* studies demonstrated unchanged serum ACTH levels, a minor trend towards lower cortisol and increased 11-deoxycortisol and DHEAS levels, but decreased DHEA concentrations. Considerable cross-reactivity between danazol, its metabolites and androgens (DHEA, testosterone, androstenedione) in radioimmunoassays does not allow a conclusive evaluation [95]. None of the studies assessed all components of adrenal steroidogenesis. Thus, a direct interference of danazol with adrenal steroidogenesis, provoking an elevation of blood pressure, remains questionable and requires further research. Moreover, inhibition of the cortisol-metabolizing enzyme 11β-HSD2 by danazol has also been proposed (discussed in section 2.2) [101].

Whether other AAS interfere with adrenal steroidogenesis and are able to promote mineralocorticoid-driven hypertension remains to be elucidated. Interestingly, nandrolone, an AAS used for the treatment of osteoporosis in postmenopausal women is associated with hypertension [102], and was found to decrease corticosterone concentrations as well as adrenal Cyp11b1 mRNA expression in rats [103].

2.2. Inhibition of peripheral steroid metabolizing enzymes

Aldosterone and cortisol exhibit similar affinities for the MR, but normal circulating cortisol concentrations exceed those of aldosterone by 100-1000-fold [104,105]. In order to render specificity for aldosterone to the MR, the enzyme 11β-HSD2 inactivates cortisol to cortisone in mineralocorticoid target tissues, such as the renal cortical collecting duct, the distal tubules or the distal colon [106]. Patients suffering from a loss-of-function mutation in this enzyme display severe and early hypertension, hypokalemia, suppressed renin and low aldosterone levels [107–110]. This so-called apparent mineralocorticoid excess can be inherited or *de novo*.

However, the metabolic inactivation of cortisol might not be sufficient to protect the MR from activation by cortisol. Observations from enzyme activity measurements showed that 11β-HSD2 converts about 90% of supplied cortisol, suggesting that cortisol is still present at least at a 10-fold excess over aldosterone, likely occupying the majority of MR (own observations). Moreover, evidence from animal experiments indicated that in kidney and colon 11β-HSD2 is insufficient to exclude the physiologically active glucocorticoid from epithelial MR [111], suggesting that active glucocorticoids are bound to MR but the receptor exists in an inactive state.

To allow aldosterone to tune the activity of the MR, Funder [112] proposed that the high local levels of NADH, generated from NAD^+ by the 11β-HSD2-catalyzed oxidation of cortisol to cortisone in close proximity to the MR [113], allosterically keep cortisol-MR complexes in an inactive state. In support of that, it has been shown that the corepressor carboxyl-terminal binding protein serves as a metabolic sensor [114]. As a consequence of this regulation, inhibition of 11β-HSD2 and redox changes occurring under conditions of oxidative stress or tissue damage can decrease NADH levels and result in cortisol-induced MR activation.

2.2.1. Licorice and carbenoxolone

The most prominent example of acquired apparent mineralocorticoid excess is the licorice-dependent inhibition of 11β-HSD2 [115]. Licorice and its active component glycyrrhetinic acid are widely used as flavoring additives in dietary products, such as drinks and candies, or in cigarettes and chewing tobacco [116]. Moreover, licorice root has a long history as herbal remedy for a broad range of therapeutic applications and is still used, particularly in traditional Asian medicine, as yokukansan [117–119] or mumijo [120]. The exposure to licorice is particularly critical during pregnancy. The fetus is protected from the 5-10-fold increased maternal cortisol levels during pregnancy by highly expressed placental 11β-HSD2 [121–124]. Observational studies implicated shorter gestation times, poorer cognitive function and behavioral disturbances associated with an increased activity of the HPA axis after maternal consumption of large amounts of licorice [125–127]. Furthermore, although the underlying etiology is incompletely understood, reduced 11β-HSD2 activity has been reported to be involved in preeclampsia [128,129].

The structure of glycyrrhetinic acid served as a basis for the synthesis of carbenoxolone as a therapeutic agent for gastric and duodenal ulcers. Although clinical studies of carbenoxolone were successful in treating gastric ulcers, its mineralocorticoid-type adverse effects due to 11β-HSD2 inhibition and the discovery of *H. pylori* as major cause of peptic ulcers, along with specific antibiotic therapy, have limited its use [116,130].

2.2.2. Itraconazole and posaconazole (see also 2.1.1)

Despite its important physiological role, 11β-HSD2 is not included in current preclinical off-target screening approaches. Thus, a recent study evaluated possible inhibitory effects of approved drugs on 11β-HSD2 [131] and identified itraconazole, its active metabolite hydroxy-itraconazole and posaconazole as potent 11β-HSD2-inhibitiors *in vitro*. Interestingly, important species-specific differences between human and rodent 11β-HSD2 were found, potentially leading to biased results. As discussed in section 2.1.1, these compounds might inhibit CYP11B1 and CYP11B2 but also 11β-HSD2 activity *in vivo*. Two case studies reported occurrence of hypertension and hypokalemia, as well as lowered renin and aldosterone levels following itraconazole treatment [20,21]. In both studies, patients had serum itraconazole and hydroxy-itraconazole concentrations above the therapeutic range, whereas cortisol, ACTH and 11-DOC levels were unaltered. These observations resemble the syndrome of apparent mineralocorticoid excess. The patient described by Hoffmann et al. [21] showed slightly elevated 11-deoxycortisol levels, indicating a partial inhibition of CYP11B1. Based on the available reports describing pseudohyperaldosteronism secondary to itraconazole or posaconazole treatment, it is difficult to fully assign the relative contributions of CYP11B and 11β-HSD2 inhibition. While itraconazole appears to preferably inhibit 11β-HSD2, leading to cortisol-dependent MR activation, posaconazole shows a dual mechanism with more pronounced effects towards CYP11B1, resulting in 11-DOC-mediated MR activation.

2.3. Mineralocorticoid receptor activation

2.3.1. Corticosteroids

Direct stimulation of the MR as is the case for aldosterone, results in increased renal sodium retention and potassium excretion, causing hypokalemia and hypernatremia, volume expansion and increased blood pressure. The synthetic mineralocorticoid fludrocortisone (also known as 9α-fluorocortisol) is used, usually in combination with a GR agonist, as replacement therapy in adrenal insufficiency, particularly in patients suffering from Addison's disease [132]. The potency of fludrocortisone to activate MR is 200–400 times greater than that of cortisol, although both steroids exhibit similar receptor biding affinities [133–136]. Moreover, because of its fluoro substituent, fludrocortisone was hypothesized to be protected from metabolism by 11β-HSD2 [137]; however, whether the 11-keto form is indeed produced and is active at the corticosteroid receptors, as is the case for the fluorinated

glucocorticoid dexamethasone [138], remains to be determined.

As mentioned, cortisol possesses considerable potency to activate MR and can therefore disrupt the electrolyte balance, leading to edema formation and hypertension. Studies addressing the role of the MR in cortisol-induced hypertension showed diminished mineralocorticoid effects upon co-administration of spironolactone, but no effect on blood pressure, suggesting that the mineralocorticoid effects are not solely responsible for cortisol-induced hypertension [139,140]. Increasing evidence even speaks against a major role of the MR in glucocorticoid-dependent hypertension but implicates other targets, such as altered nitric oxide synthase activity or increased expression of AT1 receptors (reviewed by [141–143]). These observations are further supported by the fact that dexamethasone, which has negligible MR activity [138], can also cause hypertension. Thus, antihypertensive treatment of glucocorticoid-induced hypertension with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists might represent the best option.

2.3.2. Mifepristone

Mifepristone is an antagonist at progesterone receptors and thus can induce abortion in first-trimester pregnancies. However, mifepristone is also a potent GR antagonist and has been approved in 2012 by the US FDA for the treatment of hyperglycemia associated with CS [144]. Paradoxically, prolonged administration of this GR antagonist causes HPA axis activation and leads to increased ACTH and cortisol levels [145,146]. As a result of the disrupted negative HPA feedback, the elevated cortisol (and corticosterone) concentrations can activate MRs and promote hypokalemia, hypertension and edema [147–150].

2.4. Renin–angiotensin–aldosterone system

Indirect activation of the renin–angiotensin–aldosterone system (RAAS) represents a mechanism by which several drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), estrogens, cyclosporine A and erythropoietin, and also alcohol, can promote hypertension, often in combination with other mechanisms (reviewed by [7,10,151,152]). A detailed discussion of the numerous mechanisms that activate the RAAS exceeds the scope of the current review that focuses on the most frequently used medications.

2.4.1. NSAIDs

Both selective cyclooxygenase type 2 (COX-2) and nonselective cyclooxygenase inhibitors have been reported to induce blood pressure elevation, particularly in patients with pre-existing hypertension [153–156]. The prostaglandins PGE_2 and PGI_2 are involved in the regulation of renal vasodilatation and renin synthesis, thereby controlling renal perfusion and salt homeostasis. By inhibiting the COX-mediated generation of prostaglandins, NSAIDs can impair renal function and lead to sodium retention, hyperkalemia and hyporeninemic hypoaldosteronism [155,157]. The nonselective NSAIDs indomethacin, naproxen and piroxicam have been associated with the highest risk to promote hypertension [155]. Rofecoxib, which has been withdrawn from the market, was shown among COX-2 inhibitors in earlier studies more likely to induce hypertension than celecoxib [158,159].

The blood pressure increasing effect of the different NSAIDs depends on their dose, treatment duration, patient's age, co-morbidities, co-medications, and dietary salt intake. Thus, particularly in high risk patients, dose and duration of therapy with NSAIDs should be reduced to a minimum and blood pressure should be monitored.

In addition to their own blood pressure increasing effect, NSAIDs may blunt the effectiveness of antihypertensive agents that reduce the activity of the RAAS. This includes inhibitors of renin and ACE, angiotensin receptor antagonists, diuretics and β-blockers. In contrast, calcium channel blockers maintain their antihypertensive properties with concurrent NSAID administration and may therefore be the preferred antihypertensive therapy in such cases [153,160–163].

2.4.2. Oral contraceptives

A moderately increased risk of hypertension in women using oral contraceptives was reported in a prospective cohort study lasting 4 years [164]. The increased risk diminished rapidly with cessation of contraceptives. This risk was associated with high doses of proestrogens ($\geq$ 50 µg of daily ethinyl estradiol) and less with lower doses ($\leq$ 30 µg of daily ethinyl estradiol; reviewed in [165]). Progesterone-only agents ("mini-pills") were devoid of a blood pressure rising activity [166]. Thus, these drugs are the favorable contraceptive option for hypertensive women. Drospirenone, a progestogen structurally related to spironolactone possessing about eight times the antimineralocorticoid activity of the latter [167], was shown to lower blood pressure [168,169]. However, increasing evidence suggests a higher risk of drospirenone-containing contraceptives causing deep vein thrombosis and pulmonary embolism [170–174]. In a recent small study, it was shown that vaginal rings releasing daily 15 µg of ethinyl estradiol and 120 µg of etonogestrel slightly increased 24 h diastolic (2.75 ± 5.13 mm Hg) and mean (2.69 ± 5.35 mm Hg) 24 h ambulatory blood pressure [175].

Estrogens participate in blood pressure elevation by a number of mechanisms that have not been fully elucidated. It was suggested that estrogens can modulate the RAAS-system by increasing expression levels of angiotensinogen and of AT1 receptors [165,176–178].

3. Catecholamines

The three catecholaminergic neurotransmitters dopamine, noradrenaline (norepinephrine) and adrenaline (epinephrine) are derived from the amino acid tyrosine. Their agonistic ("sympathomimetic") activity on adrenergic receptors affects many metabolic and cardiovascular processes, including blood pressure, myocardial contractility and heart rate. Catecholamine-secreting tumors, so-called pheochromocytoma (including adrenal and extra-adrenal paraganglioma), belong to the less prevalent causes of secondary (paroxysmal) hypertension. For diagnosis, it is crucial to consider drugs that share the same mechanism and may lead to an increase of catecholamines and their metabolites, the metanephrines, thereby causing symptoms of pheochromocytoma, including endocrine hypertension [2,179]. Moreover, it is important to consider medications that can precipitate a hypertensive crisis in patients with pheochromocytoma. In particular, the following drug classes should be taken into account [2,6]: β-adrenergic receptor blockers (nonselective ones such as propranolol and timolol or high doses of β_1-blockers such as sotalol, nadolol and labetalol), dopamine D_2 receptor antagonists (metoclopramide, sulpiride, amisulpride, tiapride, chlorpromazine, prochlorperazine, droperidol), sympathomimetics (discussed in the following section), noradrenaline reuptake inhibitors (including tricyclic antidepressants (TCA)), monoamine oxidase (MAO) inhibitors, opioid analgesics (morphine, pethidine, tramadol), corticosteroids, ACTH, glucagon or neuromuscular blocking agents (succinylcholine, tubocurarine and atracurium).

3.1. Sympathomimetic amines

Noradrenaline increases vasoconstriction and therefore blood pressure via α-adrenergic receptors. It is used for reanimation in emergency medicine, acute hypotensive conditions or after cardiac arrest [180]. Adrenaline that activates α- and β-adrenergic receptors is used for emergency cases of severe anaphylactic reactions and for resuscitation.

3.1.1. Decongestants

Nasal and oral decongestants like xylometazoline, oxymetazoline, phenylephrine and pseudoephedrine are among the most frequently used non-prescription drugs. They cause vasoconstriction by stimulating α_1-adrenergic receptors. Their oral formulations can lead to blood pressure elevation as has been described for oral phenylpropanolamine [181] and pseudoephedrine [182] although no effect on blood pressure of patients with well-controlled hypertension and

standard pseudoephedrine doses was found [183,184]. Thus, short-term oral decongestant treatment with α_1-adrenergic agonists can be regarded as safe.

Phenylephrine is often co-administered with acetaminophen, which has been reported to increase the bioavailability of phenylephrine. Doses of 650–1000 mg of acetaminophen nearly quadrupled the C_{max} and doubled the AUC of 10 mg phenylephrine, and this was not associated with changes in blood pressure in healthy volunteers [185–187]. Nevertheless, the combination treatment of acetaminophen with phenylephrine has the potential to increase blood pressure compared to phenylephrine alone in patients with underlying hypertension [187]. Furthermore, combination therapies of sympathomimetic amines with MAO inhibitors, TCA or ergot alkaloids are contraindicated, since these drugs can amplify sympathomimetic effects.

3.1.2. Anti-obesity drugs

Obesity is associated with many comorbidities including hypertension [188]. Early drugs were often derivatives of amphetamine that inhibit reuptake of catecholamines and suppress appetite; many had considerable cardiovascular safety issues, leading to their market withdrawal [189]. As a result, the EMA revised the safety requirements [190] and released a new guideline for medical products used in weight control in 2016 [191].

An example is sibutramine. It inhibits noradrenaline and serotonin reuptake and was initially developed as an antidepressant and later established as an anorexiant [192]. The blood pressure reduction attributable to the patient's weight loss was found to be attenuated or even slightly increased due to the sympathomimetic effect of sibutramine; this was considered a therapeutic dilemma early after its market launch [193]. Since additional adverse cardiovascular events were reported in sibutramine-treated patients, a long-term large-scale prospective trial was carried out to evaluate its efficacy/safety ratio (reviewed in [194]). The benefits of the drug as a weight-reducing agent did not outweigh its cardiovascular risks, and therefore, the EMA and FDA suspended its market authorization [195,196].

3.2. Psychostimulants

3.2.1. Methylphenidate

Over the past 20–30 years, concerns have been raised regarding the cardiac safety of psychostimulants used for the treatment of children and adolescents with Attention Deficit/Hyperactivity Disorder (ADHD) [197]. Systematic reviews and meta-analyses assessing cardiovascular outcomes of methylphenidate, which inhibits noradrenaline and dopamine reuptake, reported a small but significant increase of systolic blood pressure in children/adolescents and adults with ADHD [198,199]. This led to an assessment of the benefit/risk ratio of methylphenidate-containing medicines by the regulatory bodies [200,201]. The EMA's Committee for Medicinal Products for Human Use and the American Heart Association concluded that the benefits of methylphenidate continue to outweigh its risks and therefore reported no urgent need to restrict its use [197,200]. However, family history analyses, cardiovascular pre-treatment and regular blood pressure and heart rate monitoring were recommended. Data on long-term cardiovascular effects of methylphenidate are not available; to continue methylphenidate therapy, a one-year drug-free program is recommended before methylphenidate treatment is resumed [200]. The α_2-adrenoreceptor agonist guanfacine can be used as an antidote for methylphenidate-induced hypertension.

3.2.2. Lisdexamphetamine

Due to the considerable misuse potential of d-amphetamine, lisdexamphetamine, a prodrug consisting of covalently linked d-amphetamine to L-lysine, was approved for the treatment of ADHD (reviewed in [202,203]). After oral administration, lisdexamphetamine is hydrolyzed to its active component d-amphetamine [204]. Although amphetamine is not a catecholamine, it acts as an "indirect sympathomimetic amine" by inhibiting noradrenaline and dopamine reuptake. As for the parent drug, a dose-related blood pressure increase has been reported for lisdexamphetamine [205]. The conversion of this prodrug was thought to occur gradually, leading to low d-amphetamine plasma concentrations, prolonged action, and therefore a safer profile [203,205]. Such a prolonged pharmacokinetic profile was linked with delayed dopamine release, decreased euphoric effects and a possibly lower risk of abuse [202,205].

However, no industry-independent studies were available and neither were comparative pharmacokinetic data of d-amphetamine and lisdexamphetamine. A recent study addressing this gap found a short lag time of amphetamine plasma concentrations after administering lisdexamphetamine but no difference in C_{max} and AUC between the two treatments [206]. Moreover, both drugs after a single dose caused similar peak increases in systolic (from 120 to 160 mm Hg) and diastolic blood pressure (from 75 to 90 mm Hg). Additionally, ACTH, glucocorticoid, androgen and 11-DOC levels were similarly enhanced but no changes of aldosterone concentrations with lisdexamphetamine and d-amphetamine treatment were noted [207]. Single and high-dose treatments are the major limitations of this study. Whether activation of the HPA axis may further enhance blood pressure or whether repeated administration of lisdexamphetamine (or d-amphetamine) may lead to tolerance, remain to be addressed. Interestingly, among the adverse effects listed in the prescribing information, children and adolescents are reported to occasionally ($\geq$1:1000 to < 1:100) develop increased blood pressure, whereas adults seem to be affected more frequently ($\geq$1:100 to < 1:10) [208].

3.2.3. Atomoxetine

Atomoxetine is a selective noradrenaline uptake inhibitor used for the treatment of ADHD. Hypertension was reported as a highly variable adverse effect already during its market authorization studies [209]. Thus, it is recommended to assess the patient's blood pressure prior to and during therapy.

3.3. Antidepressants

3.3.1. Serotonin-noradrenaline reuptake inhibitors (SNRIs)

SNRIs inhibit the neuronal reuptake of noradrenaline and serotonin. Venlafaxine is approximately 30 times more selective for serotonin than noradrenaline reuptake, whereas duloxetine is ˜10 times more selective [210]. In contrast to selective serotonin reuptake inhibitors (SSRIs), which display a constant adverse effect profile throughout their dose range, adverse effects of SNRIs increase with increasing dosage [211,212]. In this regard, the adverse effects due to noradrenaline reuptake inhibition, such as tachycardia, tremor and mild but sustained hypertension occur at higher doses of both duloxetine and venlafaxine [211]. The latter and its major active metabolite desvenlafaxine have been reported to lead to a mildly raised blood pressure with increasing doses [209,213–216]. The same is the case for duloxetine, although no consistent dose-relationship has been demonstrated [217]. Therefore, patients with preexisting hypertension should be carefully monitored or administered a SSRI, if possible.

3.3.2. Bupropion

Bupropion, a noradrenaline-dopamine reuptake inhibitor, is approved for the treatment of major depressive disorders and for smoking cessation, but also to treat ADHD on an off-label basis. In spite of reports of spontaneous hypertension and package label warnings for use in hypertensive patients, data regarding blood pressure effects are conflicting [10,209,218].

3.3.3. MAO inhibitors

MAO blockers inhibit the oxidative inactivation of monoamines, such as serotonin, noradrenaline and dopamine, causing their levels to

increase. There are two isoforms, MAO-A and MAO-B. Selective MAO-A inhibitors, such as moclobemide, are used to treat depression and anxiety, whereas MAO-B inhibitors, such as selegilin and rasagilin, are used in Parkinson's disease due to their relative specificity to inhibit dopamine oxidation. The pharmacodynamic interaction of MAO inhibitors with the foodborne biogenic amine tyramine is considered as a rare but serious interaction, potentially leading to a hypertensive crisis [219]. This interaction particularly affects non-selective and irreversible MAO inhibitors (e.g. tranylcypromine). Adaptations of food production technology led to lower levels of tyramine and only patients receiving non-selective or irreversible MAO inhibitors need to pay attention on their diet. A common misconception is that MAO inhibitors increase the blood pressure and should be avoided in patients with hypertension. Indeed, MAO inhibitors were applied in the early 1960s to treat hypertension [220,221]. However, MAO inhibitors should not be prescribed for patients with pheochromocytoma or ADHD therapy with methylphenidate, lisdexamphetamine or amoxetine due to the risk of a hypertensive crisis. A recent study of three pheochromocytoma patients, reported symptoms of severe depression and anxiety disorders [222]. After surgical resection, these disorders disappeared, emphasizing to include pheochromocytoma in the differential diagnosis of long-term panic disorders refractory to medication.

3.3.4. Tricyclic antidepressants (TCA)

The introduction of SSRIs reduced the use of TCAs, which inhibit noradrenaline and serotonin reuptake with variable selectivity depending on their structure. TCAs are sometimes suspected to lead to hypertension, although therapeutic doses are correlated with postural hypotension and tachycardia [223].

This "hypertensinogenic hypothesis" is based on an early report of patients with panic disorders or major depression undergoing TCA therapy [224] and found the development of hypertension in 6 out of 114 patients - all suffering from panic disorders but none with major depression alone - suggesting a probable reporting bias [209,225]. However, TCA-induced hypertension reactions should be considered in patients with pheochromocytoma or in co-medicated patients receiving sympathomimetics or MAO inhibitors [226]. Furthermore, evaluation of risk of hyper- or hypotension associated with psychiatric medications needs to differentiate between sedative (amitriptyline, doxepin) and non-sedative (desipramine) TCAs, since sedative TCAs show an even stronger association with (orthostatic) hypotension [209].

3.4. Mirabegron

Mirabegron is the first registered β_3-adrenoreceptor agonist used to treat overactive bladder syndrome. β_3-adrenergic receptors are expressed in the urinary bladder and mediate detrusor muscle relaxation (reviewed in [227]). In phase III trials, hypertension was the most common adverse effect of mirabegron [228]. Off-target stimulation of β_1-adrenoreceptors at high mirabegron doses are the likely causes of these cardiovascular effects, because the mirabegron-induced increase in blood pressure and heart rate was attenuated by the nonselective $\beta_{1/2}$-adrenoreceptor antagonist propranolol and the selective β_1-adrenoreceptor antagonist bisoprolol [229].

4. General diagnostic and therapeutic strategies

Suspicion of secondary hypertension should be raised if a patient shows one of the following characteristics [230]: Acute worsening of hypertension in previously normotensive or chronically stable patients, treatment-resistant hypertension, young hypertensive patients, or clinico-biochemical features suggesting an endocrine cause. In order to distinguish a drug-induced from an endogenous cause, a detailed assessment of the patient's medication, the use of over-the-counter drugs or herbal supplements, and the dietary behavior should be conducted.

In order to avoid artifacts of analytical results, precautions are necessary. This is particularly important for the diagnosis of pheochromocytoma and paraganglioma [231]. When a substance is suspected to interfere with the hormonal system or directly with the biochemical test, the test should be repeated after elimination of potentially interfering agents and additional diagnostic tests should be performed.

The majority of the blood pressure changes induced by the drugs described above are comparatively minor and many of them are transient. However, the degree of the hypertensive effect may vary between subgroups of the population, with elderly or patients already suffering from hypertension or renal failure at a higher risk [8]. Such patients should be advised to measure their blood pressure at home, on occasion under surveillance by healthcare providers [232]. A recent review suggested home blood pressure monitoring as a prognostic indicator that is better than office blood pressure measurement [233].

Despite the different mechanisms by which drugs can elevate blood pressure, a few general considerations should be addressed:

- Polymedicated patients and their diets, such as consumption of grapefruit juice, should be assessed to rule out potential drug-drug and drug-food interactions, provoking adverse effects.
- It should be routinely reassessed whether continuation of treatment is still required. Should this be the case, substitution, dose de-escalation or limitation of drug exposure should be considered.
- Depending on the underlying mechanism, an alternative antihypertensive therapy should be introduced [10].
- For first-line treatment of mineralocorticoid excess, a MR antagonist, i.e. spironolactone or eplerenone (potentially finrenone in the near future), together with potassium supplementation should be the treatment of choice. Exceptions: a) In prostate cancer patients receiving abiraterone, the partial agonist effect of spironolactone might promote tumor growth. b) As eplerenone is metabolized by CYP3A4, it should not be used in combination with CYP3A4 inhibitors, such as azole fungicides.
- To address volume retention and edema, potassium-sparing diuretics might be indicated, particularly in situations of hypokalemia.
- The most appropriate method to circumvent adverse effects is often to lower the drug exposure. This is particularly the case for non-prescription drugs, including most NSAIDs, decongestants, herbal remedies or licorice-containing products. Thus, to avoid unnecessary long drug administration, patients should be informed about the optimal dosage and duration of treatment.
- ACE inhibitors and AT1 receptor antagonists are associated with hyperkalemia, especially in patients with chronic renal insufficiency [234,235]. To avoid dose de-escalation or even therapy discontinuation and thereby compromising blood pressure control, administration of a recently authorized potassium lowering agent, sodium zirconium cyclosilicate, might allow treatment continuation [236].

In conclusion, drugs associated with blood pressure elevation should be critically considered as treatment option, except in patients suffering from uncontrolled hypertension. Routinely monitoring blood pressure is recommended for early identification of hypertension followed by an appropriate therapeutic strategy.

Declaration of competing interest

None.

Author contribution statement

All authors were involved in the literature search, interpretation and writing of the manuscript.

Funding source statement

AO was supported by the Swiss Centre for Applied Human Toxicology.

Acknowledgements

We thank Urs T. Ruegg, University of Geneva, for comments and editing of the manuscript.

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