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Commentary

Glucocorticoid and mineralocorticoid action: Why should we consider influences by environmental chemicals?

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ABSTRACT

Treatment of so-called civilization diseases, including some forms of cancer, immune-related diseases and metabolic disorders, represent a major challenge in the industrialized world. In addition to genetic predisposition, behavior and exposure to xenobiotics contribute to these diseases. Here, we review existing evidence for an association of environmental chemicals with disturbed glucocorticoid- and mineralocorticoid-regulated physiological processes. Impaired activity of glucocorticoids and mineralocorticoids can contribute to several diseases, including neurological diseases, immune disorders and metabolic syndrome. Recent studies provide evidence for the existence of environmental chemicals that are able to disrupt the function of these hormones at different levels of their action. Therefore, potential interferences with these hormones should be considered for safety assessment of chemicals. Compared with the extensive knowledge on chemicals interfering with estrogen or androgen responses, the study of glucocorticoid and mineralocorticoid disruptors is an emerging field of research, and the identification of relevant xenobiotics and their underlying mechanisms of toxicity remains a major challenge.

1. Introduction

Corticosteroids are essential endocrine hormones involved in the regulation of nearly every physiological process. They can be divided into glucocorticoids (cortisol in human, corticosterone in rodents) and mineralocorticoids (aldosterone, deoxycorticosterone). Despite of their importance for the maintenance of physiological functions, only few studies addressed potential disturbances of corticosteroid action by xenobiotics [1]. Research on disruption of endocrine functions in wildlife and humans by environmental chemicals mainly focuses on sex steroid hormone receptor action. The focus on (anti)estrogenic and (anti)androgenic effects may be explained by early observations of altered sexual behavior, phenotype and reproduction in various species after exposure to high levels of chemicals from agriculture, sewage or paper pulp mills or contaminated water sources. This review focuses on the potential impact of environmental chemicals on corticosteroid-regulated biological processes and related diseases.

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Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase; ALL, acute lymphoblastic leukemia; AR, androgen receptor; ER, estrogen receptor; FAS, fetal alcohol syndrome; GR, glucocorticoid receptor; HPA, hypothalamus–pituitary–adrenal; IUGR, *in utero* growth retardation; MR, mineralocorticoid receptor; XIAP, X-linked inhibitor of apoptosis protein.

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Glucocorticoids and mineralocorticoids exert most of their effects through binding to glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). The importance of GR and MR is demonstrated by knock-out mice, which die shortly after birth [2,3]. GR-deficient mice have a number of abnormalities, including impaired activation of hepatic gluconeogenesis, hyper-activation of the hypothalamus–pituitary–adrenal (HPA)-axis, adrenal hyperplasia, impaired proliferation of erythroid progenitor cells, loss of glucocorticoid-dependent thymocyte apoptosis and impaired lung function. GR effects are mediated through direct regulation of gene transcription or via interaction with other proteins including AP-1 and NF-κB [4]. The active GR complex consists of several tissue-specifically regulated proteins and can be modulated by multiple post-translational modifications, making glucocorticoid responses highly dynamic. MR-deficient mice die about 2 weeks after birth from dehydration by renal sodium and water loss. They are hyperkalemic, hyponatremic and display highly elevated renin, angiotensin II and aldosterone levels. Moreover, abolishing corticosteroid production by adrenalectomy without appropriate hormonal supplementation causes death within a few days.

The maintenance of corticosteroid homeostasis is essential for the appropriate function of many cell types and for various physiological processes. Corticosteroid production is tightly regulated by the HPA-axis, and alterations in circulating corticosteroid levels usually lead to compensatory adaptation of the production rate and the rate of degradation and excretion. Environmental chemicals disrupting systemic or local corticosteroid hormone action are likely to contribute to metabolic disorders, cardiovascular disease, immune disease, mood disorders, impaired cognitive function, and cancer. Thus, disturbances of corticosteroid action are expected to contribute to complex diseases, which often are more difficult to detect than abnormal sexual phenotype observed after disruption of estrogen and androgen functions.

2. Potential disturbances of corticosteroid-regulated physiological processes by environmental chemicals

Corticosteroid responses are regulated at various levels, *i.e.* biosynthesis, binding to serum proteins, cellular uptake, intracellular binding and metabolism, receptor binding, cellular export, degradation and excretion from the organism (Fig. 1). Thereby, corticosteroid molecules are recognized by various proteins that belong to different protein families and share low primary sequence similarity. Xenobiotics can potentially disrupt each step of corticosteroid action or they may act on multiple targets by mimicking the corticosteroid molecule. Thus, depending on the target modified and cell

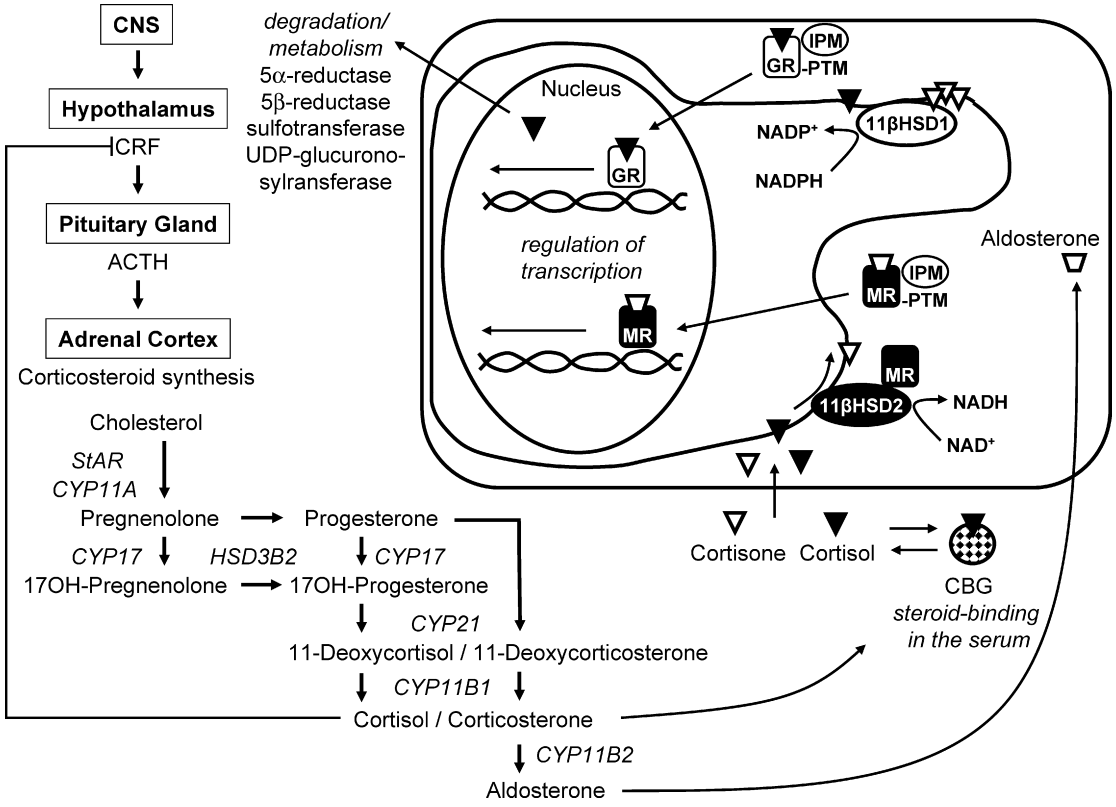

Fig. 1 – Proteins involved in mineralocorticoid and glucocorticoid homeostasis. In the regulation of corticosteroid hormone action, the hormone molecules are recognized by various proteins that belong to different families. Disturbances of the function of these proteins by compounds mimicking the corticosteroid molecule or by chemicals directly modifying a given target result in altered corticosteroid hormonal responses and can contribute to various diseases. CNS, central nervous system; CRF, corticotrophin releasing factor; ACTH, adrenocorticotrophic hormone; CBG, corticosteroid-binding globulin; IPM, interacting protein modification; PTM, post-translational modification.

Table 1 – Interference of xenobiotics with targets of the glucocorticoid and mineralocorticoid pathway

Chemical	Target	Proposed effect and mechanism	References
1,1,1-Trichloro-2,2-bis (*p*-chlorophenyl)ethane (DDT)	Unknown	Altered glucocorticoid responses due to impaired adrenal steroidogenesis, increased human preterm parturition	[47,48]
2,3,7,8-Tetracholorodi-benzo-*p*-dioxin (TCDD); benzpyrene	GR	Impaired GR signaling, interference with imprinting, probably acting through indirect mechanisms by reducing transcriptional expression and/or altering the function of interacting proteins and post-translational modifications	[52]
3-Methylsulfonyl-2,5,6,2′,4′,5′-hexachlorobiphenyl; tolylfluanid; 4-substituted methyl-sulfonyl-PCBs	GR	Decreased GR activation, mechanism unclear	[20]
6-Hydroxyflavone; daidzein; genistein; biochanin A; formomonetin	3β-HSD2	Shift from glucocorticoid to androgen production, direct enzyme inhibition	[22]
Abietic acid, naringenin, gossypol, tea polyphenols	11β-HSD2, 11β-HSD1	Direct enzyme inhibition, weak inhibitors, physiological relevance unclear	[1,23,24]
Arsenite	GR, MR	Disruption of acclimation and decreased expression of stress-related genes in killifish, probably caused by indirect effects on post-translational modifications or receptor-associated proteins; biphasic inhibition of GR activation (stimulation at <1 μM, inhibition at >1 μM); involvement of DNA-binding domain; altered post-translational modifications	[17,27–31]
Cd^{2+}	11β-HSD2	Reproductive toxicity, exposure of fetus to maternal glucocorticoids, direct enzyme inhibition as well as indirect effect by decreasing transcriptional expression	[15,42]
Dithiocarbamates (thiram, disulfiram, maneb, zineb)	11β-HSD2	Irreversible inhibition, probably by covalent modification of cysteines, physiological effect unclear	[14]
Ethanol	HPA axis	Fetal alcohol syndrome, decreased GR expression, reduced GR-DNA-binding activity, altered HPA axis response	[49–51,57]
Flavanone, 2′-hydroxyflavanone, constituents in roasted coffee beans	11β-HSD1	Direct enzyme inhibition, reduced glucocorticoid activation	[23,24]
Genistein, daidzein	CYP21	Suppression of ACTH-stimulated corticosteroid synthesis, shift from glucocorticoid to androgen synthesis, protective effects on carbohydrate and lipid metabolism, direct enzyme inhibition	[21]
Glycyrrhetinic acid	11β-HSD2	Cortisol-induced MR activation, sodium retention, hypertension, altered vascular function, reproductive toxicity, enhanced exposure of fetus to glucocorticoids, direct enzyme inhibition	[1,10]
Hexachlorobenzene	GR	Impaired gluconeogenesis, decreased plasma glucocorticoid levels, reduced hepatic GR expression without altered receptor affinity, probably due to altered function of interacting proteins or post-translational modification	[18,19]
Tributyltin, dibutyltin, triphenyltin, diphenyltin	11β-HSD2	Reversible enzyme inhibition, physiological effect unclear	[13]
Trimethyltin	HPA axis	Neurotoxic, elevated expression of pro-inflammatory cytokines, mechanism unclear	[59]

type or organ involved, xenobiotics may affect different physiological processes that are regulated by corticosteroids. An overview of chemicals associated with disturbed corticosteroid responses is shown in Table 1 (for discussion see below).

2.1. *Disturbances of electrolyte control and cardiovascular function*

Impaired cardiovascular function is a major contributor to diseases in developed countries, with approximately 25% hypertensive individuals. In addition to genetic predisposition, lifestyle and exposure to environmental chemicals are likely contributors of cardiovascular diseases. Corticosteroids play a central role in blood pressure control by regulating electrolyte concentrations and vascular tone [5,6]. At low sodium, the mineralocorticoid aldosterone is produced and activates MR, leading to increased expression of proteins involved in renal sodium retention, such as the sodium channel ENaC and Na^+/K^+-ATPase.

Despite similar affinities of MR for aldosterone and cortisol, and 100–1000-fold higher circulating cortisol levels, renal MR activation is mainly controlled by aldosterone under normal conditions. This can be explained by the rapid conversion of active cortisol and corticosterone into inactive cortisone and 11-dehydrocorticosterone by 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) in cortical collecting ducts and distal tubules, rendering specificity of MR for aldosterone [7]. Loss-of-function mutations in *HSD11B2* result in cortisol-dependent MR activation with severe hypertension [8]. Moreover, recent studies with transgenic mice suggested that deficient 11β-HSD2 activity causes impaired vascular function with vasoconstriction and hypertension [9], and indicated a role for GR in vascular smooth muscle cells [6]. Thus, chemicals inappropriately inhibiting 11β-HSD2, or activating MR or GR, are expected to disturb vascular function.

Glycyrrhetinic acid, contained in licorice, is known to disrupt corticosteroid hormone action by inhibiting 11β-HSD2 [10]. Ingestion of high amounts of licorice (*e.g.* 50 g, containing approximately 100 mg of glycyrrhetinic acid) leads to sodium retention, hypokalemia, metabolic alkalosis and suppression of the renin–angiotensin–aldosterone system, as observed in patients with loss-of-function mutations in *HSD11B2*. Glycyrrhizin, the glucuronidated form of glycyrrhetinic acid, is used in a multitude of confection products, chewing gum, chewing tobacco and as casing material in cigarettes [11,12]. Consumption of high amounts of such products may contribute to cortisol-induced MR activation and hypertension. Other triterpenoid and flavonoid compounds reported to inhibit 11β-HSD2 include abietic acid, gossypol, naringenin and tea polyphenols, although they are weak inhibitors and it is unlikely that they reach relevant concentrations *in vivo* [1].

Among environmentally relevant industrial chemicals, dithiocarbamates, organotins and heavy metal ions inhibit 11β-HSD2 [13–15]. While triterpenoid and flavonoid compounds inhibit 11β-HSD2 by competing with substrate and cofactor binding, dithiocarbamates, organotins and heavy metal ions probably interfere with functional cysteines. Among several dithiocarbamates tested, thiram and disulfiram were most potent and inhibited 11β-HSD2 at nanomolar concentrations [14]. Thiram is used at high quantities in agriculture as fungicide and pesticide and in rubber production as accelerating agent. Disulfiram is famous as Antabuse to treat alcoholic patients. Interestingly, disulfiram has comparable IC_{50} values for 11β-HSD2 and the Antabuse target aldehyde dehydrogenase. Dithiocarbamates probably inactivate 11β-HSD2 by irreversible, covalent carbamoylation of sulfhydryl groups on catalytically essential cysteines. Glutathione protects 11β-HSD2 from dithiocarbamate-dependent inactivation, suggesting that dithiocarbamates are most critical in situations of oxidative stress and low intracellular glutathione levels.

In contrast, glutathione was unable to prevent organotin-dependent inhibition of 11β-HSD2 [13]. Measurements in intact cells revealed more efficient 11β-HSD2 inhibition by triorganotins compared with diorganotins, whereby triphenyltin was slightly more potent than tributyltin, suggesting lipophilicity as important parameter for the inhibitory potency of these chemicals. It has been proposed that organotins accumulate in the upper part of the phospholipid palisade near the lipid–water interface, thereby affecting the degree of hydration of the phospholipid carbonyl moiety [16]. Thus, organotins may reach high concentrations at the surface of membranes, including the endoplasmic reticulum membrane, where the hydrophobic ligand-binding pocket of 11β-HSD2 is located. To determine the relative contribution of 11β-HSD2 inhibition and disturbed corticosteroid action to organotin toxicity, animal studies assessing effects on appropriate marker genes and electrolyte concentrations are required.

A recent study by Shaw *et al.* suggested a role for arsenic in the disruption of acclimation of killifish (*Fundulus heteroclitus*) to seawater, a GR-dependent process [17]. Arsenic, a widespread environmental pollutant found in water and soil, accumulates in liver of killifish and reduces the expression of certain stress-related genes, without affecting plasma cortisol levels or hepatic GR mRNA expression. The DNA-binding domain of GR is formed by two zinc-fingers. Compared with mammalian GR, the killifish receptor contains nine additional amino acids between the two zinc-fingers, which may lead to a higher sensitivity to arsenic. Disruption of killifish GR function by arsenic seems to be indirect, involving altered post-translational modifications or impaired interaction with receptor-associated factors.

Thus, there are relevant environmental chemicals that might contribute to diseases related with disturbed electrolytes and cardiovascular function.

2.2. *Interference of xenobiotics with energy metabolism*

Xenobiotics interfering with glucocorticoid availability or GR function are expected to disturb the cellular energy status by altering the expression of genes involved in carbohydrate, lipid and protein metabolism. The fungicide hexachlorobenzene, a highly persistent environmental pollutant, has been associated with the development of a form of porphyria resembling human porphyria cutanea tarda due to inhibition of uroporphyrinogen decarboxylase [18]. In addition, impaired GR activity has been observed. In rats, hexachlorobenzene altered glucose metabolism by decreasing the expression of pyruvate carboxylase, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase. Hexachlorobenzene treatment led to reduced plasma insulin levels, probably by adaptive responses of the organism to stimulate gluconeogenesis rather than primary effects on pancreatic insulin secretion [19]. Hexachlorobenzene treated rats had significantly reduced plasma corticosterone levels and showed 50% lower hepatic GR expression without altered receptor affinity [18]. Furthermore, they displayed significantly reduced adrenal corticosterone production despite normal ACTH responses, indicating that hexachlorobenzene disrupts both adrenal glucocorticoid production and GR activity. Impairment of GR function seems to be indirect and may include altered post-translational modification, impaired protein stability and/or altered function of interacting proteins.

Diminished GR activation was also observed for 3-methylsulfonyl-2,5,6,2′,4′,5′-hexachlorobiphenyl, tolylfluanid and other 4-substituted methylsulfonyl-PCBs, with IC_{50} values of about 1 μM. These compounds inhibited glucocorticoid-induced activation of TAT-activity in H4IIE hepatoma cells in a dose-dependent and close to additive manner [20].

Some plant-derived chemicals may exert protective effects by modulating carbohydrate and lipid metabolism. Genistein and daidzein, the major isoflavones found in the circulation after ingestion of soy-rich food, were suggested to suppress ACTH-stimulated glucocorticoid synthesis by inhibiting 21-hydroxylase (CYP21) and stimulating androgen production [21]. Moreover, genistein, daidzein, 6-hydroxyflavone, biochanin A and formomonetin inhibit 3β-HSD2 activity (IC_{50} values around 1 μM), thereby shifting glucocorticoid to androgen production [22]. Natural compounds may also ameliorate adverse glucocorticoid effects by decreasing 11β-HSD1-dependent conversion of cortisone to cortisol. Several compounds including glycyrrhetinic acid, abietic acid, flavanone and constituents in roasted coffee beans were found to inhibit 11β-HSD1 [23,24].

Based on these recent observations, we hypothesize that the modulation of glucocorticoid responses by environmental chemicals may allow an organism to coordinate its physiological processes and adapt to changes in the environment, such as food availability and composition.

2.3. *Impaired glucocorticoid-mediated control of cell proliferation*

A tightly controlled balance between cell proliferation and differentiation is essential during development of an organism and to adapt to a changing environment. Glucocorticoids promote cell cycle arrest in the G1-phase by regulating the transcription of cyclin-dependent kinases and their corresponding inhibitors [25]. Reduced expression of cyclin-dependent kinase inhibitors has been associated with pituitary tumors [26]. For cell cycle control both GR-mediated regulation of gene transcription and transrepression of NF-κB signalling are important. In addition, a switch from 11β-HSD1 to 11β-HSD2 in GR-rich tissues may represent a pro-proliferative and potentially neoplastic stimulus to cell growth, and the chronic exposure to chemicals disrupting glucocorticoid-mediated cell cycle control and/or apoptosis constitutes a potential risk factor for cancer.

Arsenic has been associated with impaired GR function and it is also recognized as a potent carcinogen [27,28]. Humans are mainly exposed to arsenic through uptake from food and drinking water. Chronic exposure to low doses has been associated with cardiovascular diseases (hypertension, blackfoot disease), neurological disorders (peripheral neuropathy, encephalopathy), type 2 diabetes, bone marrow depression, developmental problems and cancer. The mechanisms underlying arsenic-induced toxicity are not well understood. Trivalent arsenite and pentavalent arsenate are of major importance from a toxicological point of view. Arsenate can mimic the phosphate group, thereby disrupting phosphorylation reactions or causing ATP depletion. Arsenite interacts with sulfhydryl groups and disrupts the function of various proteins. Recent studies indicated that arsenic disrupts GR action, providing an explanation for some of its toxicity. Early studies with purified GR showed that arsenite but not arsenate inhibits ligand binding with an IC_{50} of about 7 μM, probably by binding of arsenite to functional sulfhydryl groups on the receptor [27]. Experiments in intact cells suggested that arsenite interacts with GR complexes and selectively inhibits GR-mediated transcription by a mechanism involving altered nuclear function rather than reduced hormone-induced GR activation or nuclear translocation [29]. A biphasic response of GR activity was found with stimulation of activity at low doses of arsenite (<1 μM) and inhibition at higher doses (>1 μM) [30]. Furthermore, arsenite blocked GR-mediated transcriptional activity but not transrepression of AP1 and NF-κB, and involvement of the DNA-binding domain of GR was suggested. Arsenite similarly affected other steroid hormone receptors (ER, MR, AR and PR), indicating modulation of the conserved DNA-binding domain of these receptors.

Surprisingly, the use of arsenic trioxide in combination with glucocorticoids was suggested for treatment of glucocorticoid-resistant acute lymphoblastic leukemia (ALL) [31]. Low-dose arsenic trioxide restored the response to glucocorticoid treatment in ALL cells isolated from T-cell and precursor B-cell ALL patients. Simultaneous incubation with arsenic trioxide and dexamethasone led to enhanced expression of the proapoptotic factor Bad and down-regulation of the X-linked inhibitor of apoptosis protein (XIAP), probably by inhibition of Akt. The sensitizing effect of arsenic trioxide was abolished by expression of dominant-active Akt, reduction of Bad expression by RNA interference, or overexpression of XIAP. However, possible therapeutic applications of arsenic compounds have to consider the association of chronic exposure to low doses of arsenic with the development of various diseases, including neurological disorders.

2.4. *Impact of glucocorticoid disrupting chemicals for the regulation of reproduction and development*

Appropriate function of glucocorticoids is especially important in a critical window during pregnancy for the regulation of gestation and birth. Impaired glucocorticoid production, HPA axis regulation and 11β-HSD2 activity have been associated with altered gestation length and timing of birth [32]. Undernourishment of the pregnant mother and prenatal stressful insults lead to elevated circulating glucocorticoids with a subsequently increased risk for retarded fetal growth, low birth weight and development of metabolic and cardiovascular diseases later in life, independent of adult lifestyle [33]. Similarly, exposure of pregnant rats to dexamethasone caused reduced birth weight and an increased risk for metabolic and cardiovascular diseases in the adult offspring [34,35]. Unlike the endogenous glucocorticoid pair of active cortisol and inactive cortisone, dexamethasone and its reduced form 11-dehydrodexamethasone are both potent GR agonists [36], thus circumventing inactivation by 11β-HSD2 in the placenta and leading to excessive exposure of the fetus to glucocorticoids.

Immediately after birth, circulating glucocorticoid levels are low and the feedback regulation by the HPA axis is not fully developed. Exposure to glucocorticoids during this period has been associated with impaired development and function of the brain [37]. Deficits in learning and memory and in behavior have also been observed in adrenalectomized animals, indicating that the maintenance of adequate glucocorticoid concentrations is essential for brain development and function. Furthermore, rats treated post-natal with adrenocorticotrophic hormone (ACTH) showed delayed sexual maturation

and deficits in female sexual behavior, suggesting a role for glucocorticoids in the regulation of reproduction and behavior [38].

Due to its localization to the syncytiotrophoblast layer of the human placenta, the site of maternal–fetal exchange, 11β-HSD2 has a key function in controlling fetal development [39]. Inhibition or down-regulation of placental 11β-HSD2 ultimately leads to enhanced fetal exposure to cortisol. Patients with genetic mutations in *HSD11B2* and transgenic mice lacking 11β-HSD2 have a high incidence of miscarriages, preterm birth, low birth weight and metabolic and cardiovascular diseases in later life of the offspring [40]. Similar observations were made in pregnant rats treated with glycyrrhetinic acid. Despite the importance of glucocorticoids for reproductive health and the fact that fetal growth restriction is a leading cause of perinatal morbidity and mortality, affecting 5–10% of all pregnancies, there are only few studies on chemicals interfering with glucocorticoid action.

Recently, Yang *et al.* suggested placental 11β-HSD2 as a molecular target for the reproductive toxicity of Cd^{2+} [15]. They observed a time- and dose-dependent inhibition of 11β-HSD2 mRNA expression Cd^{2+} in cultured human placental trophoblast cells and suggested activation of ERK and estrogen receptor as possible mechanisms for the down-regulation of 11β-HSD2. In contrast to Cd^{2+}, no effect on 11β-HSD2 was observed for Zn^{2+}, Mg^{2+}, Mn^{2+}, nicotine and cotinine.

The primary exposure of humans to Cd^{2+} is tobacco smoke [41]. Maternal exposure to Cd^{2+} during pregnancy enhances the risk for fetal growth restriction, spontaneous abortion and premature delivery [42]. Cd^{2+} accumulates in placenta and reduces progesterone production in human trophoblast cells. Progesterone levels inversely correlated with Cd^{2+} levels in placenta from women who were smoking during pregnancy [43]. The findings by Yang *et al.* suggest detrimental effects of Cd^{2+} on fetal development by inhibition of 11β-HSD2 and causing excessive exposure to glucocorticoids. In epidemiological studies in the US, maternal smoking has been associated with 20–30% low birth weight infants, approximately 10% infant death and the sudden death syndrome [44].

Furthermore, there is evidence for an association of a nicotine-induced increase of glucocorticoids and reduced birth weight of babies from actively or passively smoking pregnant mothers [45]. Chronic exposure of pregnant rats to nicotine led to increased circulating glucocorticoid levels in maternal blood and reduced placental 11β-HSD2 activity. The reduced placental inactivation of maternal glucocorticoids results in an enhanced fetal exposure, which contributes to *in utero* growth retardation (IUGR) and permanently alters glucocorticoid homeostasis later in life. Moreover, nicotine readily crosses the placenta and can thus directly interfere with fetal glucocorticoid production. Interestingly, serum cortisol levels were higher in smokers than non-smokers, probably due to elevated pituitary ACTH secretion [46].

Other chemicals associated with impaired gestation length and timing of birth include metabolites of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT), which is still used in many tropical regions to combat malaria. DDT metabolites were suggested to disrupt adrenal steroidogenesis in some mammalians, including humans, thus leading to altered glucocorticoid responses [47]. Furthermore, a significant increase in human preterm parturition was linked to the use of DDT [48].

Probably the most relevant chemical interfering with endocrine function is ethanol. Exposure to ethanol during pregnancy is linked with fetal alcohol syndrome (FAS), IUGR, insulin resistance, hyperlipidemia, glucose intolerance and elevated glucocorticoids throughout life [49]. FAS comprises symptoms associated with abnormal HPA axis development, including dysfunction of the central nervous system, craniofacial dysmorphology and growth restriction [50]. Exposure to ethanol stimulates the HPA axis, with subsequent increases in plasma CRH, ACTH and glucocorticoid levels both in rodents and humans. Overexposure to glucocorticoids during development can permanently alter the programming of the HPA axis. Repetitive administration of low doses of glucocorticoids during gestation was shown to cause hippocampal neuronal degeneration and decreased brain weight in the offspring [50]. Thus, appropriate fetal brain development depends on adequate glucocorticoid concentrations. Moreover, enhanced local glucocorticoid activation by 11β-HSD1 was observed in offspring of rats exposed to ethanol during pregnancy [51].

Hormonal imprinting has been proposed as an important mechanism for the control of physiological processes, assuring an appropriate maturation of the receptor-signal transduction system [52]. The exposure to steroid hormones in the perinatal period can cause life-long changes in the density and affinity of the cognate receptors. A single neonatal treatment of rats with low doses of dexamethasone decreased the number of thymic GR in the adulthood and also slightly enhanced receptor affinity [53]. Among the compounds interfering with imprinting of GR and causing life-long alterations in GR signalling are vitamins (K1, E, D3 and retinoic acid), steroid hormones (testosterone, dexamethasone and thyroid hormones) and xenobiotics (benzpyrene and 2,3,7,8-tetracholorodibenzo-*p*-dioxin (TCDD)) [52]. Importantly, benzpyrene was able to affect imprinting of GR through lactational exposure and its effects were transgenerational, lasting up to the third generation. Whether the transgenerational effects of benzpyrene on GR imprinting are caused by altered epigenetic regulation, as recently suggested for the anti-androgenic endocrine disruptor vinclozolin [54], remains to be investigated.

2.5. *Disturbances of glucocorticoid action in the brain*

Elevated circulating cortisol concentrations and cognitive impairments including memory deficits are commonly found in patients with major depression, posttraumatic stress disorder or Cushing's syndrome. McIntyre *et al.* proposed to reclassify depressive syndromes as metabolic syndrome type 2, since disturbances in metabolic networks (insulin–glucose homeostasis, immune-inflammatory pathways) are implicated in brain pathophysiology of depressive disorders [55]. Experiments in transgenic mice indicated a role for impaired GR activity in the forebrain and altered HPA axis regulation in the development of major depressive disorders [56]. Other psychiatric diseases linked with enhanced endogenous glucocorticoids include anxiety, excitability, hypomania and psychosis. These processes involve the neocortex, the amygdala and the hippocampus. After withdrawal of glucocorticoids,

the psychiatric symptoms usually disappear with normalization of cortisol levels.

Regular, high alcohol consumption leads to decreased GR expression and reduced GR–DNA-binding activity in some areas of the brain [57]. Chronic prenatal ethanol exposure results in reduced hippocampal volume and altered glucocorticoid signalling in the hippocampus with disrupted hippocampal GR expression [50]. Several other chemicals have been associated with disturbed glucocorticoid action in the brain and altered HPA axis responses. Elevated glucocorticoid levels modulate the neurotoxicity of lead, possibly by interaction of glucocorticoids with the mesocorticolimbic dopamine system [58]. Glucocorticoids also influence the neurotoxicity of the organotin trimethyltin (TMT). Treatment of rats with TMT containing food resulted in a loss of pyramidal neurons in the hippocampal CA3 region, with elevated expression of the cytokines IL-1α and IL-1β [59]. TMT-induced toxicity and cytokine production was abolished upon administration of glucocorticoids but aggravated in adrenalectomized rats. It was suggested that altered HPA axis responses are involved in TMT neurotoxicity. Impaired HPA axis responses and suppressed basal and stimulated glucocorticoid levels were also observed in rats exposed to PCBs in early development. The perinatal exposure to PCBs caused neurobehavioral changes with impaired memory functions [60]. In fish, exposure to PCBs abrogated the fasting-induced elevation of circulating cortisol and the upregulation of GR expression in the brain [61]. Furthermore, a link between AhR activation by polycyclic aromatic hydrocarbons (PAHs) and an impaired glucocorticoid response to stress by disruption of the rate-limiting steps in steroidogenesis has been proposed. Thus, exogenous chemicals disrupting corticosteroid action in the brain by direct or indirect mechanisms can contribute to metabolic disturbances and psychiatric disorders.

2.6. *Interference with glucocorticoid-mediated immune responses*

Chronically elevated glucocorticoid levels, as a result of chronic stress or due to long-term therapeutic treatment, are associated with an increased susceptibility to infectious diseases. A higher frequency of infectious complications is observed in alcohol-addicted individuals. Alcohol-induced elevation of circulating glucocorticoid and cathecholamine concentrations inhibit the mobilization of granulocytes in humans and reduce the number and activity of natural killer cells in mice [62]. Neutrophile accumulation at the site of infection is also impaired by ethanol, possibly due to decreased TNFα-production by macrophages as a result of elevated glucocorticoids. Alternatively, the acute intake of high doses of alcohol (model for binge drinking) may cause a loss of splenic and thymic immune cells and inhibit TNFα-production *in vivo* [62,63]. Moreover, ethanol seems to directly inhibit NF-κB activation in monocytes with concomitantly increased nuclear translocation of GR but reduced GR–DNA-binding activity [64].

2.7. *Glucocorticoids and metabolism of xenobiotics*

Glucocorticoids are important for the regulation of the metabolism of endogenous hormones, toxic endogenous metabolites and xenobiotics. The synthetic glucocorticoid dexamethasone activates the pregnane-X receptor (PXR) [65], which has a major role in the hepatic detoxification of many endogenous and exogenous chemicals. In addition, dexamethasone induces the expression of PXR, its corresponding coreceptor RXR, glutathione-S-transferase, xenobiotics transporters and several cytochrome P450 enzymes [66,67]. Thus, altered glucocorticoid levels due to stress or upon medication may significantly influence the detoxification of chemicals.

Recent evidence indicates that CYP3A4 induction by phthalates is dependent on glucocorticoid-induced PXR expression [68]. Treatment of human hepatocytes and rat liver-derived cells with the plasticizer di-2-ethylhexyl phthalate (DHEP) or its primary metabolite MHEP resulted in a PXR-dependent CYP3A4 induction, which was potentiated by glucocorticoids. The blockade of GR by siRNA or antagonist RU486 abrogated phthalate-dependent CYP3A4 induction, suggesting that exposure to these plasticizers in situations of stress or upon clinical treatment with glucocorticoids may affect drug therapy.

Importantly, corticosteroid action itself is influenced by activation of xenobiotics metabolism. Genetic or pharmacological activation of PXR results in significantly increased plasma glucocorticoid and mineralocorticoid concentrations [69]. Transgenic mice with liver-specific expression of an activated human PXR construct had approximately eightfold higher circulating corticosterone levels than wild-type mice. The transgenic mice showed significantly increased adrenal weights with elevated mRNA expression of the key steroidogenic enzymes CYP11A1, CYP11B1, CYP11B2 and 3β-HSD. In addition, normal circadian rhythms as well as stress responses were impaired in transgenic mice, but HPA axis function was intact. Similarly, elevated levels of circulating corticosterone and aldosterone with a concomitant increase in the expression of adrenal steroidogenic enzymes were observed after treatment of wild-type mice with the PXR agonist rifampicin. Rifampicin treated tuberculosis patients showed increased urinary excretion of steroid metabolites [70], and administration of rifampicin has been associated with enhanced urinary excretion of cortisol metabolites [71]. Thus, activation of PXR by xenobiotics may disrupt adrenal steroid homeostasis, and the prolonged exposure to environmental chemicals or drugs activating PXR may cause a form of chemical stress, with adverse effects due to elevated glucocorticoids.

Another link between glucocorticoids and xenobiotics metabolism is indicated by the ability of 11β-HSD1 to catalyze the reactivation of glucocorticoids and the conversion of several carbonyl-containing chemicals into their hydroxyl forms. The tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [72], which is found in high amounts in tobacco products and plays a role in lung cancer induction in smokers, the anti-cancer drug oracin [73], the 11β-hydroxylase inhibitor metyrapone, the major cholesterol oxidation product 7-ketocholesterol [74] and the potential neurosteroids 7-ketodehydroepiandrosterone and 7-ketopregnenolone were identified as alternative substrates of 11β-HSD1 [75]. Moreover, a recent study by Marcolongo *et al.* showed that metyrapone, which is reduced by 11β-HSD1 [76], causes a depletion of NADPH in the ER lumen and induces a

shift from 11β-HSD1 reductase to oxidase activity [77]. Thus, 11β-HSD1 has a relatively low substrate specificity, which might allow a coupling of detoxification reactions and glucocorticoid generation in the liver.

3. Conclusions

There is increasing evidence for the existence of environmental chemicals disturbing glucocorticoid- and mineralocorticoid-dependent physiological processes, with potential relevance for diseases including brain disorders, metabolic and cardiovascular dysfunctions, developmental disorders, immune diseases and cancer. Glucocorticoids play an important role in coordinating metabolic functions and detoxification reactions. By modulating glucocorticoid-mediated responses in the presence of certain xenobiotics, the organism may be able to adapt to changes in the environment, which represents a protective mechanism. Compared with the extensive field of research on chemicals disrupting estrogen and androgen action, limited information exists on potential corticosteroid hormone disruptors. For safety assessment of chemicals, the development of suitable biological *in vitro* and *in vivo* tests is required that allow to detect disturbances at various levels of hormone action, including HPA axis regulation, steroidogenesis, transport protein activity, the activity of metabolizing enzymes and receptor function. The development of *in silico* prediction tools and systemic approaches, including analyses of effects of xenobiotics on the transcriptome and proteome, are necessary to facilitate the identification of chemicals disrupting corticosteroid hormone action and to understand their mechanism of action.

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