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The science of steroids

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ABSTRACT

Steroids are complex lipophilic molecules that have many actions in the body to regulate cellular, tissue and organ functions across the life-span. Steroid hormones such as cortisol, aldosterone, estradiol and testosterone are synthesised from cholesterol in specialised endocrine cells in the adrenal gland, ovary and testis, and released into the circulation when required. Steroid hormones move freely into cells to activate intracellular nuclear receptors that function as multi-domain ligand-dependent transcriptional regulators in the cell nucleus. Activated nuclear receptors modify expression of hundreds to thousands of specific target genes in the genome. Steroid hormone actions in the fetus include developmental roles in the respiratory system, brain, and cardiovascular system. The synthetic glucocorticoid steroid betamethasone is used antenatally to reduce the complications of preterm birth. Development of novel selective partial glucocorticoid receptor agonists may provide improved therapies to treat the respiratory complications of preterm birth and spare the deleterious effects of postnatal glucocorticoids in other organs.

1. Introduction

Steroids are complex four-ringed organic molecules that serve many roles and functions in multicellular organisms. They are structural components of cell membranes exemplified by the important dietary steroid cholesterol and have many functional regulatory roles as modified structural forms of cholesterol to function as endogenous endocrine hormones. In all organisms, hormones *in vivo* play key regulatory roles in mediating communication and regulation of important functions and processes within and between cells, and across tissues, to connect all organs of the body [1]. Endocrine hormones circulate in the bloodstream and allow communication between cells and organs separated by relatively large distances. Hydrophilic or water-soluble hormones act primarily at the cell surface by binding to protein receptors embedded in the plasma membrane. In contrast, hydrophobic hormones circulate primarily bound to carrier plasma proteins and are able to freely defuse across cell membranes to activate specific intracellular hormone receptors [1].

This review will focus on the biology and actions of the lipophilic steroid hormones and some of the important synthetic steroid compounds, developed over the past 50 years to treat human disease, that act as specific agonists or antagonists to steroid hormone receptors *in vivo*. It will summarize current knowledge on the action of physiological steroid hormones in fetal development and the use of synthetic steroids to treat the postnatal complications associated with preterm birth.

2. Steroid biosynthesis and turnover

All steroids in the body are derived from cholesterol via a tightly regulated biosynthetic enzymatic pathway that operates predominantly in specific endocrine organs, including the adrenal gland, ovary, and testis. Further modifications of the steroid structure and resulting function can occur in many tissues and organs of the body such as in the liver, skin epidermis, brain and prostate [2].

In the steroidogenic cells of the adrenal gland, ovary and testis, cholesterol is first converted to pregnenolone by the cholesterol side-chain cleavage enzyme, $P450_{SSC}$, a cytochrome P450 enzyme, and this step represents the key regulatory point for synthesis of the majority of endogenous steroid hormones. Most of the enzymes in the steroid biosynthetic pathway are either cytochrome P450 enzymes or specialised hydroxysteroid dehydrogenase (HSD) enzymes, which belong to the short-chain alcohol dehydrogenase reductase (SDR) enzyme super family [3].

Adrenal steroid biosynthesis occurs in the outer cortex of the adrenal gland. The cortex is divided into three layers where specific

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steroids are produced, dependent on expression of specific biosynthetic enzymes. The outer zona glomerulosa specifically expresses the Cyp11B2 P450 enzyme aldosterone synthase to generate the cardiovascular steroid aldosterone. The centrally located zona fasciculata specifically expresses a closely related homologous Cyp11B1 P450 enzyme called 11β-hydroxylase to produce the glucocorticoid steroids cortisol and corticosterone. The inner zona reticularis produces the adrenal androgens, dihydroepiandrosterone (DHEA), DHEA-sulphate (DHEAS), androstenedione and testosterone, via the actions of the enzymes 3βHSD3, AKR1C3 and Sulfotransferase 2A1. These adrenal androgens circulate in the bloodstream and act as precursors for more biologically active reproductive steroids that are produced at higher levels in the gonads. There is some evidence, primarily at the RNA level, that some of these steroid biosynthetic enzymes are also expressed in other tissues and organs such as heart and brain, although it seems unlikely that these sites produce any significant levels of bioactive steroid [4].

Human plasma and tissue extracts can contain a large number of different steroid compounds, many of which are biologically inactive. This is because many active steroids are continually modified by other enzymes, particularly in the liver, to produce inactive steroid metabolites. Most steroids are inactivated by hydroxylation or sulphation, which render the structure unable to activate receptors or downstream intracellular signalling pathways, and these modifications also increase the solubility of the steroid for renal excretion. Common hepatic modifications include 6β-hydroxylation, 5β-reduction of C_{21} and C_{19} steroids and 4-hydroxylation of estrogens.

The steroid sulfotransferases (SULT) enzymes are a large family of enzymes that transfer a sulphate moiety to the steroid ring from a donor molecule called 3′-phosphoadenine-5′-phosphosulphate [5]. Important SULT enzymes include SULT2A1 that converts DHEA to DHEAS in the adrenal cortex, and SULT1E1 that sulphonates and inactivates estradiol for excretion. The hydroxysteroid dehydrogenases (HSDs) are also a large and important family of enzymes that are involved in steroid biosynthesis and inactivation. The steroid cortisol can be modified by two related HSDs, 11βHSD1 and 11βHSD2, which interconvert the keto/hydroxy side-chain on the 11th carbon of the cortisol steroid ring. 11βHSD1 is a bidirectional enzyme but is predominantly a reductase with the production of active cortisol in many metabolic tissues, such as the liver, and also the brain, regions of the kidney, and white adipose, thereby amplifying glucocorticoid-mediated signalling in target cells [6]. 11βHSD2 is a unidirectional dehydrogenase and inactivates cortisol to cortisone in tissues and is the key enzyme protecting the mineralocorticoid receptor (MR) from inappropriate activation by cortisol [7]. Loss of function mutations in the human 11βHSD2 gene causes the condition of 'apparent mineralocorticoid excess' that is characterised by early-onset hypertension and cardiovascular complications in very young children [8]. 11βHSD1 antagonists have been explored recently as a potential treatment for metabolic syndrome by blunting or attenuating the metabolic effects of cortisol, although unwanted side-effect profiles have been an issue in early clinical trials [6].

3. Steroids as physiological hormones

Endogenous steroid hormones have been long recognised as physiological regulators of development, growth, reproduction and systemic homeostasis. The majority of physiological steroid hormones are derived from the precursor steroid cholesterol and synthesised in specialised endocrine cells within specific endocrine glands [2]. The key important physiological endogenous steroid hormones are listed in Table 1, and include the adrenal steroids cortisol and aldosterone, the adrenal androgen precursors DHEA and DHEAS, and the reproductive steroids estradiol, testosterone and dihydrotestosterone. The physiological sex steroids comprise estradiol, which is predominantly synthesised in the female ovary, and testosterone and dihydrotestosterone that are synthesised predominantly in the male testis. These endocrine glands are composed of steroid synthesising cells that contain complex steroid biosynthetic pathways that involve a large number of intracellular steroid intermediates some of which are now thought to potentially have physiological roles in abnormal states or in complex genetic disease [2,9]. The biosynthetic enzymes modify chemical groups and sidechains across the four-ringed structure giving each steroid intermediate or final product a specificity of interaction with other enzymes and with intracellular receptor proteins (Fig. 1A and B). Mutations in the genes encoding key biosynthetic enzymes, such as the enzyme 21α-Hydroxylase or 17α-Hydroxylase can cause common endocrine conditions such as congenital adrenal hyperplasia (CAH) [10]. Careful measurement of the levels of endogenous steroids and steroid metabolites in body fluids such as urine and blood by mass spectrometry is now the mainstay diagnostic technique to detect steroid abnormalities that may indicate the presence of disease [11].

3.1. The reproductive steroids

The estrogenic and androgenic classes of steroid hormones collectively control determination of secondary gender characteristics and the regulation of reproduction in males and females. Reproductive steroids are primarily synthesised in the adult gonads following puberty and are responsible for the majority of secondary sex characteristics, the physiological changes that occur during puberty and the regulation of the reproductive phases of gonadal function.

Bioactive estradiol is produced from testosterone in the Granulosa cells of the ovary by the action of the P450 enzyme aromatase [12]. Ovarian theca cells also synthesise androstenedione and testosterone from cholesterol to provide androgenic precursors to the granulosa cell [2]. The enzyme aromatase is also expressed in other parts of the body including white adipose tissue and individuals with significant amounts of white fat can synthesise a high level of local estradiol that can contribute to higher systemic circulating estradiol levels. For example, this can lead to precocious puberty in very young girls that are overweight or obese [13]. Elevated aromatase expression in breast tissue can also drive breast tumour growth via increased local production of oestradiol that stimulates cell proliferation [12].

In the testis, Leydig cells produce androstenedione and testosterone from cholesterol via a five-step biosynthetic pathway. The more potent androgen dihydrotestosterone (DHT) is produced by the action of the enzyme 5α-Reductase that is predominantly expressed in peripheral tissues such as in the liver, brain, skin and the male prostate [14].

3.2. The cardiovascular steroids

The main role of the adrenal steroid aldosterone *in vivo* is the regulation of solute and fluid homeostasis primarily in the kidney and colon [15]. In the collecting duct of the kidney, aldosterone promotes the reabsorption of sodium, excretion of potassium, water uptake and therefore increased fluid volume, thereby maintaining systemic blood pressure. Synthesis and release of aldosterone from the adrenal gland is tightly regulated by the renin-angiotensin system. The renin secreting juxtaglomerular cells of the kidney sense volume, and low-volume (with low-sodium) stimulates secretion of renin, a protease enzyme, that cleaves circulating angiotensinogen to release angiotensin peptides thereby stimulating the adrenal zona glomerulosa to synthesise and secrete aldosterone [16]. Elevated plasma potassium is also able to directly stimulate aldosterone release from adrenal glomerulosa cells. The actions of aldosterone in collecting duct cells (and other epithelia) is mediated by the mineralocorticoid receptor (MR), a member of the nuclear receptor superfamily (described below).

A complication is that the MR is also activated by the related steroid cortisol that normally circulates at much higher concentrations in the bloodstream. However, inappropriate activation of the MR by cortisol in most MR expressing cells is prevented by the presence of the enzyme 11βHSD2 that converts cortisol to inactive cortisone thereby preventing

Table 1
List of the important physiological endogenous steroid hormones and synthetic steroid hormone agonists.

Steroid	Endogenous (E) or Synthetic (S)	Cell Receptor	Major functional roles in development or clinical importance
Cortisol/Corticosterone	E	GR, MR	Fetal organ development, metabolism, anti-stress and anti-immune responses
Aldosterone	E	MR	Postnatal renal function, fluid homeostasis and blood pressure control
Estradiol	E	ERα, ERβ	Puberty, female reproduction
Testosterone/Dihydrotestosterone	E	AR	Puberty, male reproduction
Progesterone	E	PR	Maintenance of pregnancy
DHEA/DHEAS	E	AR	Adrenal androgen precursor
Betamethasone	S	GR, MR	Prematurity, preterm birth
Dexamethasone	S	GR, MR	Prematurity, preterm birth, anti-inflammatory, lymphocyte apoptosis
Prednisolone	S	GR, MR	Anti-inflammatory; arthritis, autoimmune disease
Budesonide	S	GR, MR	Ant-inflammatory; asthma, COPD

DHEA, dihydroepiandrosterone; DHEAS, dihydroepiandrosterone-sulphate; GR; Glucocorticoid Receptor, MR, Mineralocorticoid Receptor, ER; Estrogen Receptor, AR; Androgen Receptor, PR; Progesterone Receptor. COPD; Chronic Obstructive Pulmonary Disease.

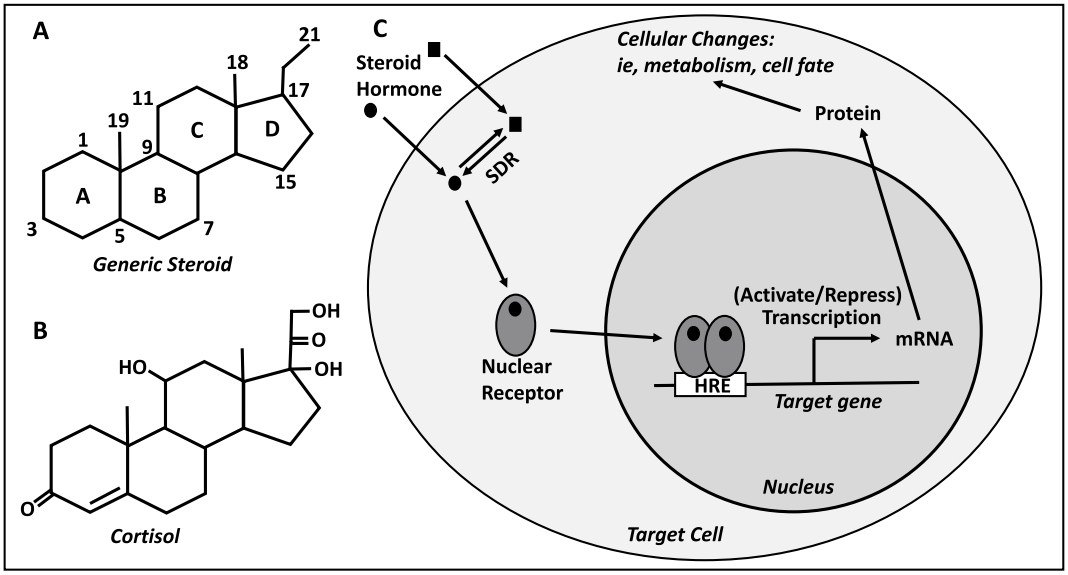

Fig. 1. The mechanism of action of intracellular nuclear receptors that mediate steroid signalling in cells. Nuclear receptors (NRs) bind lipophilic steroid hormones primarily in the cytosol of the cell, undergo a confirmation change, dimerise and translocate into the nucleus where they bind specific hormone response elements (HREs) close to specific target genes within the genome. The steroid hormone may require enzymatic modification by short-chain alcohol dehydrogenase reductase (SDR) enzymes to adopt their active confirmation. Activation or repression of gene expression alters cellular protein levels thereby initiating changes in cell function, such as metabolic activity and cell fate.

activation of inappropriate sodium and fluid uptake [17]. Very high levels of cortisol such as in conditions like Cushing's disease can overwhelm 11βHSD2 and cause in-appropriate hypertension. Treatments for hypertension have been developed that target the MR and this cardiovascular condition can now be well-controlled by specific MR antagonist drugs such as spironolactone and a newer drug eplerenone [18,19]. Aldosterone may also have other functional roles in tissues such as the brain where the MR is expressed in neural centres controlling thirst and appetite, but the mechanisms involved are not well understood [20].

3.3. The glucocorticoid steroids

The steroid cortisol is an essential mediator of the systemic stress response, yet plays major roles in many different physiological contexts and at different times during fetal and adult life [21]. Cortisol has a powerful effect on various arms of the immune system, and the development of strong synthetic glucocorticoid compounds such as dexamethasone and prednisolone more than 50 years ago have made them a mainstay for the clinical treatment of a range of inflammatory and autoimmune conditions [22]. Cortisol circulates in the bloodstream in a circadian fashion, with levels high in the morning and low in the evening, and release from the adrenal is tightly controlled by direct negative feedback to the hypothalamus and anterior pituitary where there is inhibition of corticotrophin-releasing hormone and adrenocorticotropic hormone, respectively.

Glucocorticoid steroids contribute to metabolic regulation as a catabolic hormone. They stimulate protein breakdown to release amino acids that can be utilised in hepatic gluconeogenesis to produce glucose, the breakdown of glycogen and the release of fatty acids from adipose depots. However, inappropriately elevated circulating cortisol (ie, in a 'Cushingoid' state) or synthetic glucocorticoids (eg, prednisolone) can stimulate excess hepatic glucose output leading to hyperglycemia and the development of diabetic states. These broad actions of glucocorticoids are mediated by the ubiquitous expression of its cognate receptor, the glucocorticoid receptor (GR) [23]. This is in contrast to the MR which has a much more restricted expression pattern in the body. Chronic high levels of cortisol can therefore lead to systemic effects that represent Cushing's disease, with remodelling of adipose depots, hyperglycemia, type-2 diabetes, high blood pressure, muscle wasting and bone remodelling leading to osteoporosis.

As part of the response to stress, cortisol has a profound effect on the brain. Stress from a range of causes (trauma, infection, fear, pain etc.) triggers the hypothalamus-pituitary-adrenal axis to release cortisol [21]. Elevated circulating cortisol seems to play two major roles: 1) promoting or preparing permissive effects to respond to the stressor,

such as producing glucose, increasing heart rate and neural awareness and acuity; and 2) suppressive effects, including activating defence mechanisms to prevent overshoot or damage to the body, such as anti-immune and anti-inflammatory responses. The mechanisms at play here are not entirely clear and are under active study.

Finally, cortisol has an important developmental role in the fetus, promoting maturation of the major organs in late gestation, including the respiratory system, kidney, gastrointestinal tract and the brain [24,25]. Cortisol levels from the fetal adrenal rise dramatically five to six weeks prior to birth and play a crucial role in the later stages of organogenesis. As described below, preterm babies miss this window of glucocorticoid stimulation and are born with a number of maturation abnormalities that require immediate treatment postnatally in the neonatal intensive care unit.

4. The mechanism of action of steroids in cells via intracellular nuclear receptors

Steroid hormones exert the majority of their physiological effects in cells by binding to and activating specific intracellular proteins called nuclear receptors. Each steroid hormone is only able to bind and activate a very restricted number of receptors, and in many cases only one specific nuclear receptor protein. The human nuclear receptor superfamily is composed of 48 receptors that includes the GR, MR, Progesterone receptor (PR), Androgen receptor (AR), Estrogen receptors (ER), Retinoic Acid receptor and Thyroid Hormone receptor. Nuclear receptors are ligand-dependent transcription factors and exert their effects by binding directly to specific sites near genes in genomic DNA [26]. They therefore have essential roles in various physiological process including development, behaviour, metabolism and growth. All nuclear receptors share a common structure consisting of an N-terminal domain (termed A-B domain) that contains at least one gene co-activation region, a conserved DNA binding domain containing a highly conserved DNA binding motif composed of two zinc-fingers, and a hinge region that is the least conserved and provides the receptor with domain flexibility [26]. The largest domain is the C-terminal ligand-binding domain (LBD) that binds in a hydrophobic pocket its cognate steroid ligand, and this domain is moderately conserved across the steroid receptors. The most C-terminal end of the LBD contains another activation/repression domain whose conformation is altered by ligand binding and this determines specific interaction with either coactivator and corepressor proteins in the nucleus to mediate increased and decreased transcription rates of specific target genes [26].

Nuclear receptors can be divided into two subgroups based on their mechanism of action, Type I nuclear receptors include the AR, ER, GR and PR and in an inactive state are located in the cytosol. They are maintained in an inactive complex with heat shock proteins [27]. When a steroid ligand diffuses across the cell membrane and binds to the receptor, the receptor translocates to the nucleus and homodimerizes. The homodimer then binds to specific palindromic sites near genes in genomic DNA leading to transrepression or transactivation of gene expression (shown in Fig. 1C). Type II nuclear receptors include the thyroid hormone receptors and the retinoic acid receptors. The type II nuclear receptors are nearly always localised in the nucleus bound to sequence-specific binding sites in genomic DNA and in the absence of ligand the receptor is mostly bound by a repressor protein [28]. When the ligand binds to the nuclear receptor the repressor protein dissociates leading to interaction with coactivator proteins that initiate transactivation of gene expression. An interesting subgroup of the nuclear receptors are the so-called orphan nuclear receptors. These receptors share the conserved structure of the classical steroid hormone receptors but unlike the classical members that were discovered with specific ligands the orphan receptors were identified without ligands and many of their roles and mechanisms of action in the nucleus are completely unknown [29].

5. The actions of steroid hormones in the developing fetus

There are now a large number of reports demonstrating the action of steroid metabolites and physiological steroid hormones during fetal development in various animal models. The actions of glucocorticoid steroids during development will be discussed below; however, there are now reports that androgens, estradiol and DHEA may have hitherto unknown developmental roles during mammalian fetal development.

It has been recently demonstrated that the adrenal androgen steroid metabolites DHEA and DHEAS may be important neuroactive neurosteroids in the developing fetal brain [30]. Levels of these steroids are known to be relatively high in late gestation and these levels drop following birth. The specific developmental roles of DHEA are currently unknown. Deficiency of DHEA has, however, been linked to the development of mental illnesses such as early-onset dementia and schizophrenia, and it has been reported that administration of DHEA improved schizophrenia symptoms, although this remains controversial [31]. It is therefore possible that DHEA may have neuroprotective roles in the neonate.

The reproductive actions of estradiol are mediated by the ERα nuclear receptor but the functional roles of estradiol signalling through the related ERβ receptor are less well understood. Interestingly, it has been recently reported that as in adult mice, fetal mice only expresses ERβ in the developing lung [32]. The functional role and significance, if any, of estradiol signalling in the fetal lung is unclear. There are also reports of the expression of the androgen receptor in developing fetal lung tissue and in lung cells, together with the expression of enzymes involved in the peripheral metabolism of androgens, such as hydroxysteroid-17β-dehydrogenase, 2 and 5, steroid-5α-reductase 1, and 3αHSD, which is suggested to modulate and switch off AR activation [33,34]. Finally, very curiously, other studies report intra-fetal lung synthesis of glucocorticoid steroids via an adrenal-like steroid biosynthetic pathway, although it is not clear if this would produce a significant amount of steroid hormone to further modulate fetal developmental programs [35].

6. The action of glucocorticoids in the developing fetus

The main role of the late gestational surge in endogenous fetal cortisol is to drive appropriate maturation of a large number of fetal organs [24]. The most important fetal organ in terms of immediate survival at birth is the lung, where glucocorticoids promote thinning of the mesenchymal tissue to reduce blood vessel to airway distances to allow appropriate gas exchange. Glucocorticoid signalling thins the mesenchymal tissue by decreasing cell proliferation rates rather than increasing interstitial cell apoptosis. Glucocorticoids also promote surfactant production and mature the pulmonary mechanisms for clearing airway liquid from the lung at birth [36].

Glucocorticoids exert the majority of their effects by binding to the GR, a member of the nuclear receptor family of intracellular receptors that is expressed in virtually every nucleated cell of the body [37]. The GR functions in cells as a ligand-activated transcriptional regulator. Cortisol enters the cell by passive diffusion and binds to the GR in the cytoplasm where it exists in an inactive complex together with chaperone proteins. Binding of cortisol to the LBD of the GR causes a conformational change that allows dimerization of the receptor followed by translocation through the nuclear pores into the nucleus. The activated GR homodimer then binds to specific DNA response-elements in genomic DNA close to a large number of specific target genes. This initiates further interactions with nuclear coactivator or corepressor proteins to either increase or decrease the transcription rate of target genes and thereby drive functional changes in the cell [37]. Cortisol can regulate many hundreds of different target genes in individual cells that collectively change metabolic pathways, cell proliferation rates and cell architecture [37]. Indeed, both cortisol and betamethasone regulate over 300 specific nuclear target genes in rat fetal lung mesenchymal

fibroblasts, with betamethasone causing a much greater effect on transcription rates [38]. This may explain its greater efficacy and potential to accelerate cellular and tissue changes antenatally in the fetal lung.

These transcriptional responses and outcomes most likely differ in different cell types and organs of the fetus. As a result, antenatal glucocorticoids are able to have complex regulatory affects in most organs in the fetus. For example, glucocorticoids increase liver glycogen by increasing the activity of hepatic gluconeogenic enzymes, stimulate perinatal renal function such as sodium resorption by stimulating the Na+/K + ATPase and maturation of the gut enteric system [39,40]. In the fetal adrenal gland, glucocorticoids have been shown to promote normal development of adrenal architecture and induce factors such as the chromaffin cell enzyme phenylethanolamine N-methyltransferase, cytochrome P450s and ACTH receptors which have important roles in catecholamine and steroid hormone synthesis and metabolism. Antenatal synthetic glucocorticoids therefore have the capacity to accelerate many of these developmental processes; and some of these changes have also been observed to persist postnatally in animal studies [41].

6.1. Effects of synthetic glucocorticoids on the fetal lung

Antenatally, the synthetic glucocorticoids used clinically are dexamethasone and betamethasone. These two compounds are fluoridated steroids with very similar chemical structures and almost identical tissue and cellular effects *in vivo* [42]. In 1972, Liggins and Howie demonstrated that administration of betamethasone prior to birth reduced morbidity and mortality in preterm infants, especially risk of respiratory distress syndrome (RDS) [43]. This ground-breaking study led to the routine use of betamethasone to promote fetal lung maturation in women at risk of preterm delivery [44–46].

It is often assumed that antenatal glucocorticoids exert their beneficial actions through stimulating type-II cell differentiation and increased surfactant production. However, gene-targeted ablation of GR expression in a mouse ‘gene knockout’ model has been shown to increases both type-II cell, and the undifferentiated cell phenotype, numbers while reducing type-I cell numbers [47]. In addition, GR knockout increased both the proportion of tissue to airspace and air/blood tissue barriers, which was consistent with much higher mesenchymal cell proliferation rates in the distal lung. Cell-type specific GR knockouts has confirmed that the primary effect of GR activation in the developing lung is mediated through mesenchymal cells, leading to major changes in distal lung tissue architecture [48].

The synthetic glucocorticoid dexamethasone is also often given to preterm infants postnatally to treat lung inflammation, reduce ventilator dependence and reduce the incidence and/or severity of bronchopulmonary dysplasia (BPD). Postnatally, dexamethasone has strong anti-inflammatory effects in the neonatal lung, including direct suppression of pro-inflammatory cytokine gene expression, inhibition of cytokine production in lymphocytes and macrophages, and driving apoptotic cell death of lymphocytes to further promote immune suppression [37].

6.2. Deleterious effects of synthetic glucocorticoids in other organs

Of greatest concern is the potential for deleterious effects of antenatal betamethasone and postnatal dexamethasone on the developing fetal brain and gastrointestinal system, together with increased risk of hyperglycaemia and hypertension [49]. A recent retrospective study of 214 infants born < 28 weeks assessed postnatal steroid use and showed improved respiratory but inferior neurodevelopmental outcomes [50].

Although synthetic antenatal glucocorticoids mature the lung more rapidly, there have been concerns about longer term adverse effects on lung development. Animal studies have shown that synthetic antenatal glucocorticoids improve survival, primarily by thinning the mesenchyme and reducing the airway to blood vessel distance for gas exchange, but can also impair continuing alveolar development, a key feature of BPD [25]. However, in humans exposure to antenatal betamethasone was not associated with altered lung function or the prevalence of wheeze and asthma at early adulthood [51].

7. Conclusion

Steroid hormones are important systemic endocrine regulators of many key physiological processes throughout all stages of life. They contribute to the regulation of cell and organ growth, changes in adolescence, regulation of reproduction, maintenance of homeostasis, the control of cardiovascular health, and help mediate and protect cognition. Steroid hormone biosynthesis is carefully regulated in specific endocrine glands and steroid hormones such as cortisol, aldosterone and estradiol are only secreted when required. Many steroid-related endocrine diseases can arise from mutations in genes encoding steroid biosynthetic enzymes, such as in CAH, the steroid modifying enzymes, such as with AME, and from overproduction of steroids such as cortisol in Cushing's disease. Their intracellular nuclear receptors are complex multi-domain signalling proteins that together with a large number of cytosolic and nuclear binding partners modulate many cellular targets both in the nucleus and in the cytoplasm of cells.

A better understanding of the detailed mechanisms of action of steroid hormones in cells will potentially lead to the development of better targeted therapies to treat endocrine and steroid-related dysfunction and disease. Nuclear receptor antagonists have the capacity to block inappropriate steroid receptor activation in common conditions such as cancer, hypertension and diabetes. Alternatively the development of selective, tissue-selective agonist compounds that activate specific steroid receptors is another avenue for the creation of new approaches to treat, in particular, perinatal deficits that arise from preterm and very preterm birth. Partial glucocorticoid receptor agonists as antenatal steroid treatments may have the ability in the future to promote better overall long-term outcomes from preterm birth.

7.1. Practice points

- Steroid hormones are key regulators of fetal development, particularly glucocorticoids, that have a profound role in the maturation of most of the major organs, especially the fetal respiratory system.
- The synthetic glucocorticoid steroid betamethasone remains the mainstay of antenatal treatment for preterm birth.

7.2. Gaps in knowledge

- The detailed mechanisms of action of steroids such as cortisol in fetal cells and organs, where they regulate large numbers of target genes in the nucleus and alter cellular pathways and programs, are not fully understood and require more investigation.
- Development of novel selective partial glucocorticoid receptor agonists may provide better therapies to treat the respiratory complications of preterm birth and reduce deleterious effects in other organs.

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