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GLUCOCORTICOSTEROIDS: THERAPEUTIC APPLICATION AND THE ADVERSE EFFECTS OF CHRONIC USE

Rutuja Dadasaheb Shriram*

DR. Shivajirao Kadam College of Pharmacy, Kasbe Digraj Sangli Maharashtra, India 416305.

***Corresponding Author: Rutuja Dadasaheb Shriram**

DR. Shivajirao Kadam College of Pharmacy, Kasbe Digraj Sangli Maharashtra, India 416305.

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ABSTRACT

Glucocorticosteroids (GCS) are steroid hormones synthesized primarily in the adrenal cortex and play a crucial role in regulating various physiological processes, including metabolism, immune response, and stress. Their synthesis involves several key enzymes, such as cholesterol desmolase (CYP11A1), 3β-hydroxysteroid dehydrogenase, and 21-hydroxylase, which are also involved in both adrenal and gonadal steroidogenesis pathways. Glucocorticosteroids are widely used in the treatment of inflammatory and autoimmune diseases, such as rheumatoid arthritis, asthma, and inflammatory bowel disease (IBD), due to their potent anti-inflammatory and immunosuppressive properties. Pharmaceutical glucocorticosteroids are designed to mimic endogenous cortisol and can be administered through various formulations (oral, intravenous, topical, etc.) depending on the clinical need. However, prolonged use of GCS is associated with several adverse effects, including osteoporosis, hypertension, hyperglycemia, and adrenal suppression. The availability of different GCS forms and doses aims to maximize therapeutic efficacy while minimizing side effects. This review focuses on the biochemical pathways of GCS synthesis, their therapeutic applications, and the adverse effects associated with long-term usage, along with strategies for mitigating these risks in clinical practice

KEYWORDS: Glucocorticosteroids (GCS), steroids, corticosteroids, enzymes, harmones.

INTRODUCTION

Since its discovery in 1935, steroids have been used for a variety of purposes. These isolates from the adrenal glands were first believed to be beneficial solely to Addison disease patients. These days, steroids have numerous therapeutic applications that stem from their strong anti-inflammatory and immune-suppressive characteristics. Steroids frequently cause side effects that are clinically significant and severe. These can range from mild acne to Cushing syndrome, which, if left untreated, can lead to diabetic mellitus and perhaps fatal cardiac disease.[1]

Numerous compounds with a variety of physiological effects are categorized as steroids. More particular, hormones produced naturally as well as those created in laboratories fall into the corticosteroids chemical class. Salt and water levels are regulated by mineralocorticoids, whereas glucosecorticoids generally control inflammation and metabolism. Steroid molecules are chosen according to how well they suit a certain treatment. Corticosteroids range in effects from solely glucocorticoid to exclusively mineralocorticoid. A chemical might, for instance, have strong anti-inflammatory effects but also have mineralocorticoid action, which lowers blood pressure.

The successful creation and maintenance of pregnancy, as well as the healthy development of the fetus, depend on the steroid hormones progestagens, estrogens, androgens, and glucocorticoids, together with their precursor cholesterol. The junction between the fetal and maternal circulation is where the human placenta forms. It is involved in the controlled exchange of steroids between the uterine and fetal compartments, as well as their biosynthesis and metabolism.[2]

ORIGIN OF STEROID HARMONES

Steroid hormones are synthesized through de novo steroidogenesis in the adrenal cortex, gonads, and placenta. Additionally, neurosteroids are produced in the brain, but these are not covered in this review. Steroidogenic tissues have the distinctive ability to use cholesterol as the starting material for the mitochondrial production of pregnenolone, the precursor for all steroid hormones. Cholesterol can be sourced in several ways, including being synthesized from acetate in the endoplasmic reticulum (ER), released from cholesteryl

esters stored in lipid droplets via cholesteryl ester hydrolases, or obtained from external cholesterol esters in lipoproteins through LDL receptor-mediated endocytosis or SR-BI-mediated uptake pathways. While all three main steroid-producing organs—the adrenal cortex, gonads, and placenta—can synthesize cholesterol de novo under the control of tropic hormones, plasma lipoproteins are generally considered the main source of cholesterol for steroid hormone production.[3,4,5]

Overview of steroidogenic enzyme

The production of all steroid hormones involves two main functional families of enzymes, namely hydroxysteroid dehydrogenase (HSD) and cytochrome P450 (CYP) enzymes. Making use of NADPH as an electron donor, the heme-containing CYP enzymes initiate molecular oxygen. While the other oxygen atom is reduced to water during catalysis, one oxygen atom gets incorporated into the substrate. Because of their capacity for catalysis, CYPs can catalyze a variety of processes. Two important reactions in the steroidogenesis process include hydroxylation and C-C bond cleavage. Based on where they are located inside cells and how they transport electrons, the CYP enzymes that are involved in steroidogenesis can be categorized into two classes. The inner mitochondrial membrane is home to CYP type I enzymes, which rely on ferredoxin and ferredoxin reductase to transport their electron from nadph. The flavoprotein ferredoxin reductase oxidizes NADPH and releases electrons to the tiny iron-sulfur protein ferredoxin. Ferredoxin then serves as a mobile electron carrier, sending the electrons to the cyclooxygenase enzyme. Adrenodoxin reductase (AdxR) and adrenodoxin (Adx), the terms for the enzyme ferredoxin reductase and ferredoxin, which are found in the adrenal glands, are frequently used interchangeably. The electron delivery system used by CYP type II enzymes, which are located in the ER, is mediated by cytochrome P450 oxidoreductase (POR), an electron donor enzyme. POR has two forms of flavones: flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), which enable the enzyme to oxidize NADPH and gradually decrease the CYP enzyme. A crucial component of CYP-catalyzed reactions is the availability of NADPH, and CYP activities are influenced differently by redox partner.[6,7,8]

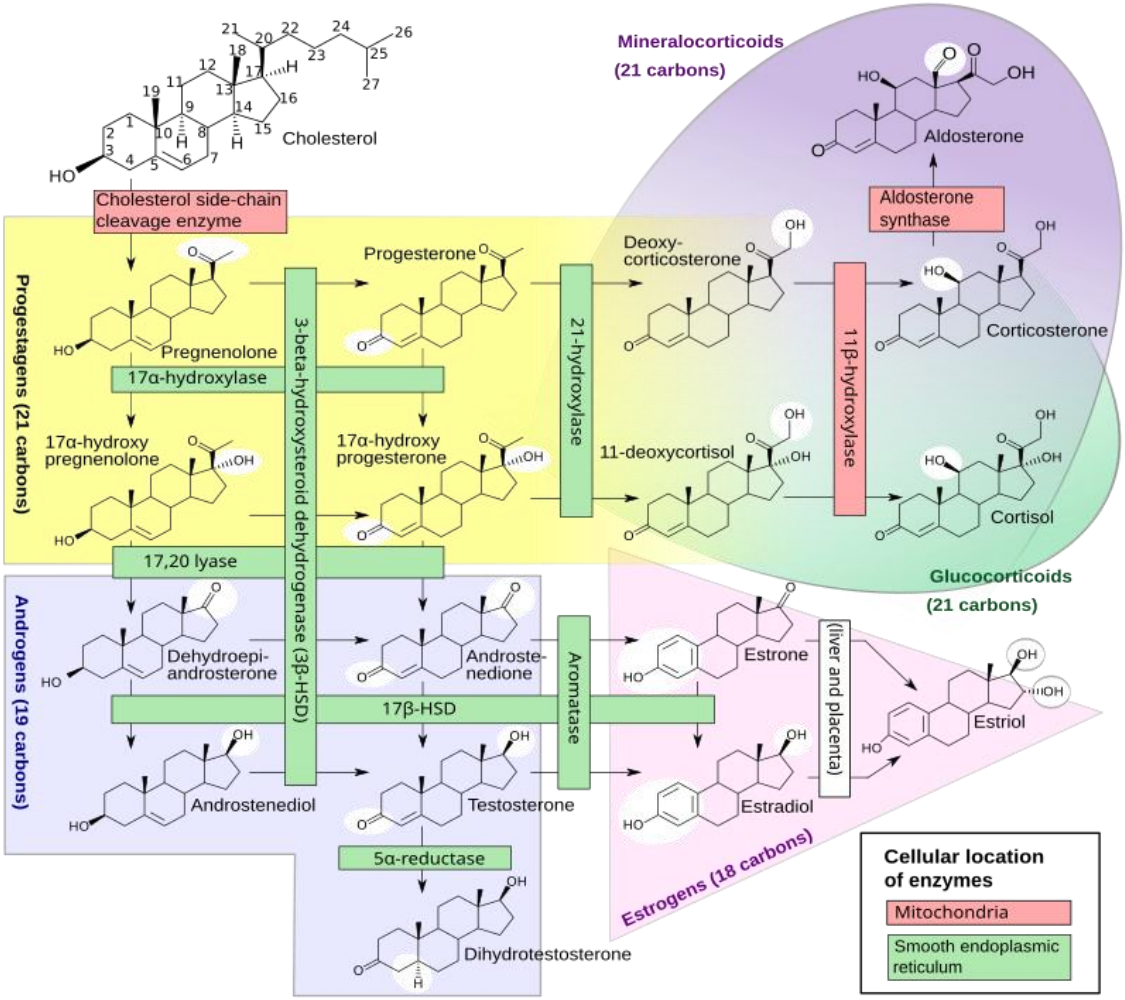
The another main functional category of enzymw involved in steroidogenesis are NAD(P)H and NAD(P)+ cofactors depends are the HSD enzyme, are devided into two different enzymes superfamilies based on their structural fold. AKR stands for aldo-keto reductases and short chain dehydrogenases. The purpose of the HSD enzymes from both families is to catalyze the conversion of a particular hydroxysteroid to its matching ketosteroid counterpart and vice versa, ultimately controlling the steroid's activity at particular steroid receptors. The majority of reactions catalyzed by HSD are reversible in their mechanism and exhibit bidirectional activity. However, in vivo, a significant directionality is noted due to co-factor affinity and cellular redox state.[9,10,11]

Physical characteristics of human genes encoding steroidogenic enzymes

Enzyme	Gene	Gene size (kb)	Chromosomal location	Exons (n)	mRNA size (kb)
StAR	*STAR*	8	8p11.2	8	1.6
P450scc	*CYP11A1*	30	15q23-q24	9	2.0
P450c11β	*CYP11B1*	9.5	8q21-22	9	4.2
P450c11AS	*CYP11B2*	9.5	8q21-22	9	4.2
P450c17	*CYP17A1*	6.6	10q24.3	8	1.9
P450c21	*CYP21A2*	3.4	6p 21.1	10	2.0
P450aro	*CYP19A1*	130	15q21.1	10	1.5–4.5
3βHSD1	*HSD3B1*	8	1p13.1	4	1.7
3βHSD2	*HSD3B2*	8	1p13.1	4	1.7
11βHSD1	*HSD11B1*	7	1q32-q41	6	1.6
11βHSD2	*HSD11B2*	6.2	16q22	5	1.6
17βHSD1	*HSD17B1*	3.3	17q11-q21	6	1.4, 2.4
17βHSD2	*HSD17B2*	63	16q24.1-q24.2	5	1.5
17βHSD3	*HSD17B3*	67	9q22	11	1.2
17βHSD6 (RODH)	*HSD17B6*	24.5	12q13	5	1.6
AKR1C1	*AKR1C1*	14.3	10p14-p15	9	1.2
AKR1C2	*AKR1C2*	13.8	10p14-p15	9	1.3
AKR1C3	*AKR1C3*	13.0	10p14-p15	9	1.2
AKR1C4	*AKR1C4*	22.1	10p14-p15	9	1.2
5α-Reductase 1	*SRD5A1*	36	5p15	5	2.4
5α-Reductase 2	*SRD5A2*	56	2p23	5	2.4
SULT2A1	*SULT2A1*	17	19q13.3	6	2.0
PAPSS2	*PAPSS2*	85	10q24	13	3.9
P450-oxidoreductase	*POR*	69	7q11.2	16	2.5
Ferredoxin	*FDX1*	35	11q22	5	1.0, 1.4, 1.7, 3.2

Ferredoxin reductase	*FDXR*	11	17q24-q25	12	2.0
Cytochrome b_5	*CYB5A*	32	18q23	5	0.9
H6PDH	*H6PD*	36.5	1p36	5	9.1

HSD3Bisoforms, HSD3B1atio.



Overview of adrenal steroidogenesis

Higher primates alone are able to produce adrenal androgen precursors and androgens, as well as mineralocorticoids and glucocorticoids, through the cortex of the adrenal gland.[19,20] Because steroidogenic enzymes express differently in each of the three functional zones that make up the cortex, each zone is in charge of producing a certain class of steroids. The adrenal's outer region, known as the zona glomerulosa, expresses enzymes that catalyze the main mineralocorticoid, aldosterone synthesis, which is regulated by the renin-angiotensin-aldosterone pathway. Production of cortisol, the principal glucocorticoid, takes place in the zona fasciculata, the middle zone. Last but not least, the zona reticularis, the innermost zone, aids in the synthesis of C19 androgen precursors, such as dehydroepiandrosterone (DHEA] and its sulfate (DHEAS), 11β-hydroxyandrostenedione (11OHA4), androstenedione (A4) (Fig. 1). The generation of glucocorticoids and adrenal androgen precursors by the adrenal gland is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. In summary, corticotrope cells in the anterior pituitary are stimulated to produce and release adrenocorticotropic hormone (ACTH) by the hypothalamus through the production of corticotropin-releasing hormone (CRH). This, in turn, stimulates the adrenal gland to produce steroid hormones,. notably cortisol and DHEA Since glucocorticoids have a negative feedback impact on the pituitary, hypothalamus, and hippocampus, they complete the system, unlike adrenal androgen precursors which do not inhibit the HPA axis in a feedback manner.[12,13,14]

Overview of gonadal steroidogenesis

The gonads are specialized for producing androgens and estrogens through steroidogenesis, and the corpus luteum also plays a significant role in producing progesterone, the primary endogenous progestogen. Similar to the classification, DHEA and cortisol in particular In contrast to adrenal androgen precursors, which do not block the HPA axis in a feedback manner, glucocorticoids complete the system by having a

negative feedback impact on the pituitary, hypothalamus, and hippocampus. of the adrenal, the amount of steroids generated is determined by the specific expression pattern of steroidogenic enzymes inside each cell type. During puberty, the hypothalamic-pituitary-gonadal axis develops, which sets off gonadal steroidogenesis. Gonadotropin-releasing hormone (GnRH) is pulsatilely produced and secreted by the hypothalamus. This increases the pituitary's production and secretion of luteinizing hormone (LH). In males and women, respectively, androgens and estrogens supply the hypothalamus and pituitary gland negative feedback to decrease LH. Additionally, gonadal steroidogenesis is active during "minipuberty," a brief period of newborn activation of the hypothalamic-pituitary-gonadal axis.[15]

USE OF STEROIDS IN VARIOUS DISEASE TREATMENT

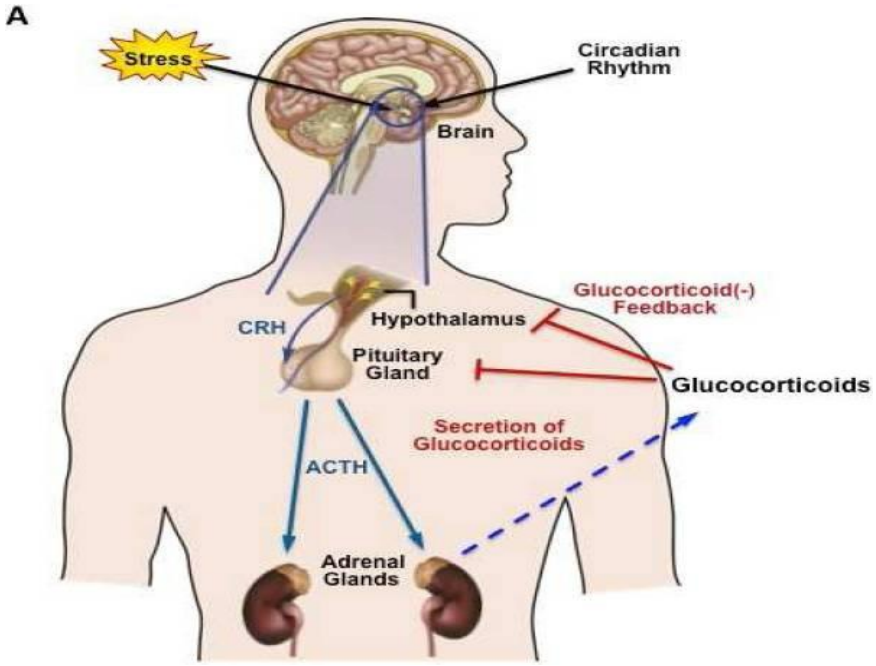
Important medicinal drugs called corticosteroids are used to treat inflammatory and allergic diseases as well as to inhibit the immune system's improper or undesired responses. In the clinical context, drugs having glucocorticoid action are referred to as corticosteroids. The endogenous glucocorticoid cortisol is called for its effects on glucose metabolism, but it also carries out the other corticosteroid-mediated immune functions. The adrenal gland uses cholesterol metabolism to make cortisol. The common pathway of cholesterol metabolism also produces a range of other hormones, such as aldosterone, mineralocorticoids, and sex hormones for men and women. Some of the negative reactions and side effects linked to pharmacologic dosages of cortisol and its synthetic analogs can be explained by the hormones' shared route and structural resemblances.

Corticosteroids are used in "steroid therapy," which is the use of these drugs to treat various medical diseases. Because of its anti-inflammatory properties, it is helpful in treating asthma, autoimmune disorders, immune system suppression to prevent transplant rejection (liver, kidney, heart, lung, and hand transplants), and cancer symptoms.

Significant side effects that affect body form are related to dosage amount. Among these are increased body weight, the recognizable "moon face," edema, osteoporosis, and, if used during puberty, growth retardation. Iatrogenic Cushing's syndrome, which is related to the "buffalo hump" linked to HAART and is characterized by upper body obesity, a round face, increased neck fat, and slender arms and legs, can be brought on by prolonged steroid medication. Research on the elements that can encourage acceptance of a steroid-induced change appearance is scarce. Time since the transplant (as well as the start of the immunosuppressive treatment) may have an effect on adaptation. For instance, it has been shown that during the first year following a kidney transplant, adult patients experience significant body image problems as they get used to their new bodies. In the second year, when the sense of improved physical function and self-assurance about health increase, these can return to normal levels. However, as patients become more conscious of the costs associated with a long-term medication regimen and its adverse effects, body image issues may resurface in the third year.

Production of glucocorticoids, their secretion, and bioavailability

Glucocorticoids, also known as cortisol in humans and corticosterone in rodents, are steroid hormones that the adrenal glands produce on a diurnal basis in response to stress and physiological causes. The hypothalamic-pituitary-adrenal (HPA) axis controls the circadian profile of the adrenal glands' secretion of glucocorticoids. Corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) are released by the paraventricular nucleus (PVN) of the hypothalamus in response to inputs from the suprachiasmatic nucleus (SCN). By activating corticotroph cells in the anterior pituitary, these hormones release adrenocorticotrophin hormone (ACTH) into the bloodstream. The production and release of glucocorticoids are then stimulated by ACTH's action on the adrenal cortex. Glucocorticoids reach target tissues once they are released from the adrenal glands and enter the bloodstream, where they regulate an array of various physiological functions, including as immunological response, skeletal development, cardiovascular function, metabolism, reproduction, and cognitive activities. Glucocorticoids must be quickly generated (using a variety of enzymatic processes) upon ACTH stimulation since they are lipophilic and it is not able to be stored in the adrenal glands for pre-synthesis. The HPA system's feed-forward mechanism is counteracted by glucocorticoids, which act in the anterior pituitary inside the hypothalamus to stop further release of CRH and ACTH, respectively.[16,17]



The multienzyme process known as steroidogenesis produces glucocorticoid which is biologically active from cholesterol. Through the activation of Protein Kinase A (PKA), it is not able to be stored in the adrenal glands for pre-synthesis. The HPA system's feed-forward mechanism is counteracted by glucocorticoids, which act in the anterior pituitary inside the hypothalamus to stop further release of CRH and ACTH, respectively. ACTH enhances adrenal gland activity, which in turn leads to the non-genomic control of steroidogenic proteins. These include phosphorylating hormone-sensitive lipase (HSL), a protein that raises intracellular cholesterol levels, and phosphorylating steroidogenic acute regulatory protein (StAR), a protein that facilitates the cholesterol passage into the mitochondria, where it is cleaved by the enzyme CY P450 (P450scc) to produce pregnenolone. Following this process, a series of enzymatic processes occur in the mitochondria and endoplasmic reticulum, which ultimately result in the synthesis of glucocorticoids within the cells. These glucocorticoids are then released into the general blood circulation.[18,19]

The availability of glucosecorticoids within cells is maintained by metabolic enzymes particular to each tissue, known as 11β-hydroxysteroid dehydrogenases (11β-HSDs). The interconversion of active glucocorticoids is catalyzed by 11β-HSDs. 11β-HSD2 is a powerful dehydrogenase that quickly inactivates glucocorticoids (turns cortisol into cortisone), enabling aldosterone to selectively bind to mineralocorticoid receptors in the kidney and pancreas that would otherwise be non-selective. Unlike natural glucocorticoids, the majority of synthetic glucocorticoids are not metabolized by 11β-HSD2 and do not bind CBG. But in all glucocorticoid target tissues, including the liver, adipose tissue, brain, and lung, 11β-HSD1 functions as the predominant 11β-reductase. It makes it easier to convert inactive precursor cortisone to bioactive cortisol, which helps tissues regenerate active glucocorticoids by taking advantage of the high levels of inert cortisone that are circulating11. Consequently, the differing roles that the isoenzymes.[20,21]

The glucocorticoid receptor (GR, NR3C1), a member of the nuclear receptor superfamily of ligand-dependent transcription factors mediates the physiological and pharmacological effects of glucocorticoids. Target genes, which make up 10–20% of the human genome, are transcriptionally induced or repressed by GR after glucocorticoid binding As required for life after birth, GR is expressed in almost all body cells and is consistent with the pleiotropic effects of glucocorticoids The way that cells react to glucocorticoids is extremely varied, with wide variations in both sensitivity and specificity. For instance, glucocorticoids increase the survival of hepatocytes and cardiomyocytes while inducing the death of thymocytes and osteoblasts.

Uses

AS ANTIINFLAMMATORY AGENTS

Since elevated expression of inflammatory genes is linked to chronic inflammatory disorders such as

1. Autoimmune diseases
2. Rheumatoid arthritis
3. Asthma
4. Inflammatory bowel disease

Glucocorticoids are frequently used to control inflammation in these conditions. The most common clinical use of glucocorticoids is for the treatment of asthma; the molecular processes behind this anti-inflammatory activity are addressed. Increased transcription results from glucocorticoids binding in the cytoplasm to the giucocorticoid receptor, which dimerize and go to the nucleus where they bind to glucocorticoid response elements (GRE) on glucocorticoid-responsive

genes. Though it is unlikely to explain all of the widely observed anti-inflammatory effects, glucocorticoids may stimulate the transcription of genes coding for anti-inflammatory proteins, such as lipocortin-1, interleukin-10, interleukin-1 receptor antagonist, and neutral endopeptidase. CREB-binding protein (CBP), a co-activator of transcription that binds multiple different transcription factors that compete for binding sites on this molecule, is another molecule with which glucocorticoid receptors interact. The uncoiling of DNA coiled around histones, which is linked to increased transcription, is a result of CBP's enzymatic acetylation of the histone residues. Glucocorticoids may cause deacetylation of histones, which tightens DNA coiling and restricts transcription factors' ability to bind to their binding sites, inhibiting the expression of some genes. Although the endocrine function of steroids is intact, patients with chronic inflammatory illnesses seldom do not respond to glucocorticoids. This could be because of increased activator protein-1 accessible to inhibit genes that cause inflammation. . Because of the endocrine and metabolic effects of steroids, fresh insights into glucocorticoid mechanisms may result in the creation of novel steroids with a lower risk of adverse effects. They have recently created "dissociated" steroids, which are more active in transrepression (interaction with transcription factors) than transactivation (binding to GRE). Novel anti-inflammatory medicines target some of the transcription factors, such nuclear factor-kappa B, that are suppressed by glucocorticoids. production at the region of inflammation, which eats up active glucocorticoid receptors to prevent them from.[22,23]

ANTIINFLAMMATORY ACTION

GLUCOCORTICOIDS are commonly utilized in the treatment of asthma because they are strong inhibitors of inflammatory processes. The glucocorticoid/glucocorticoid receptor complex either directly binds to glucocorticoid responsive elements in the promoter region of genes to produce the anti-inflammatory effects, or this complex interacts with other transcription factors, such as nuclear factor-kappaB or activating protein-1. Numerous molecules linked to inflammation, including adhesion molecules, chemokines, cytokines, and metabolites of arachidonic acid, are inhibited by glucocorticoids. On the other hand, glucocorticoids frequently cause an upregulation of anti-inflammatory mediators. According to in vivo research, administering inhaled glucocorticoids to asthmatic patients reduces bronchial inflammation while also enhancing lung function. This study summarizes what we now know about glucocorticoids' mechanisms of action and their ability to reduce inflammation in asthma.[24]

USED AS A TO TREAT RHUMETOID ARTHRITIS

When the disease is active, insufficient cortisol secretion is reinforced by a circadian rise in nighttime inflammation, which is connected to the morning symptoms of rheumatoid arthritis (RA). EULAR and ACR therefore advise exogenous glucocorticoid dosing in RA from the outset of the illness, as it may function in part as "replacement therapy." Additionally, it has been demonstrated that using a night-time-release formulation for exogenous glucocorticoid administration improves the efficacy of both preventing and treating the immune/inflammatory response being overexpressed at night.

For RA patients who are not on glucocorticoids and who are eligible for therapy with biologic disease-modifying antiarthritic drugs (DMARDs), chronotherapy with night-time-release prednisone has been recognized as a cost-effective option, despite being significantly more expensive than conventional prednisone (immediate release). Remarkably, given that distinct cell types implicated in the inflammatory process are notably stimulated Other RA treatment strategies, such (NSAIDs) and conventional DMARDs, should adhere to the similar principles of GC chronotherapy when it comes to nighttime immune responses (monocytes, macrophages). As a result, it was discovered that bedtime methotrexate chronotherapy was more effective in managing RA symptoms. Additionally, a number of NSAIDs that are currently on the market, including aceclofenac, indomethacin, ketoprofen, flurbiprofen, and lornoxicam, have recently had their formulations changed to produce more concentrated night activity.[25]

ADVERSE EFFECT OF CHRONIC THERAPY OF GIUCOCORTICOSTEROIDS

Glucocorticoids (GCs) are drugs with anti-inflammatory and immunosuppressive qualities that are prescribed to treat a wide range of disorders. For the treatment of common diseases, general practitioners at primary care centers may prescribe them; specialists may do the same for the outpatient management of more complex diseases, hospitalized patients, or critically sick patients in intensive care units. Since the earliest reports of GCs' efficacy in treating rheumatoid arthritis in the 1950s, GCs have been utilized frequently and extensively in medicine.[26] Edward Kendall, Tadeusz Reichstein, and Philip Hench were awarded the Nobel Prize in Medicine and Physiology for their discovery of this class of medication because it enabled for the isolation of cortisone.

Despite their well-established advantages, using them can have major negative consequences on a variety of organs; in patients using them for longer than 60 days, this risk can rise to 90%. Even at modest dosages of GCs, adverse effects can still happen and are dependent on the length of the treatment and the mode of administration.

Weight gain, hyperglycemia, diabetes mellitus (DM), adrenal suppression, osteoporosis, dermatological changes, cardiovascular complications, cataracts, glaucoma, peptic ulcer, myopathy, increased

susceptibility to infections, and neuropsychiatric disorders are the main side effects of long-term systemic corticosteroid therapy for patients. These side effects have been documented in the literature. For these drugs to have the least negative effect on the patient's health, the doctor should be informed of their side effects from the beginning of treatment used for medicinal purposes.[27,28,29]

HYPERGLYCEMIA AND DM

GCs have a significant impact on the metabolism of carbohydrates. They directly impact pancreatic β-cells, lowering their viability and preventing the release of insulin.[30] GCs promote gluconeogenesis in the liver and induce insulin resistance in peripheral tissues. As a result, they encourage weight gain, contribute to a significant hyperglycemic condition, and either cause or exacerbate DM.

Hyperglycemia brought on by GC may manifest as early at the 2nd week. enhanced glucose level in serum, particularly postprandial blood glucose, which is one of the primary markers of GC-induced DM, are its defining characteristic. Obesity, aging, genetic susceptibility, and chronic inflammation are the key risk factors linked to GC-induced hyperglycemia/DM. Risk factors include high blood pressure, smoking, and elevated glycated hemoglobin levels.[31]

ADRENAL INSUFFIENCY

GCs serve as the hypothalamic-pituitary-adrenal axis' last mediators. When they are overproduced, they have a negative feedback effect on the anterior pituitary gland and the paraventricular nucleus of the hypothalamus, which lowers the production of adrenocorticotropic hormone and corticotropin-releasing hormone. Consequently, the adrenal gland's zona reticularis and zona fasciculata atrophy, together with a decreased release of cortisol and androgens, occur. While the adrenal response to GC use may differ between persons, the danger of adrenal suppression should be taken into account in patients receiving equal daily doses of prednisone (> 20 mg for ≥ 3 weeks. Additional risk factors for adrenal insufficiency appear to be fractionated daily doses and corticoid treatment used at night.

Acute withdrawal or fast GC tapering may result in adrenal problem l insufficiency (GC withdrawal syndrome), which manifests as fatigue, arthralgia, myalgia, fever, nausea, vomiting, diarrhea, and asthenia. In more extreme circumstances, coma (adrenal crisis), hypotension, lethargy, reduced consciousness, seizures, and hypoglycemia may happens.[32,33]

OSTEOPOROSIS

Direct and indirect interference with bone tissue health is caused by GCs. When they are overindulged, they promote osteocyte and osteoblast death and suppress osteoblastogenesis. Additionally, through promoting osteoclast activity, they heighten bone resorption. The IGF1 hormone, which stimulates bone production, is inhibited indirectly through increased renal excretion of calcium and decreased intestine absorption. This imbalance causes secondary hyperparathyroidism and increases bone reabsorption.[34]

As a result, long-term GC use significantly lowers bone mass in trabecular bones, particularly vertebral bodies, which increases the risk of osteoporosis and bone fractures. It is now thought to be the primary iatrogenic cause of osteoporosis; after receiving continuous corticosteroid therapy, the risk of fracture can rise by up to 75%.[35]

CHANGES IN DERMATOLOGY

Another vital organ impacted by long-term GC use is the skin. Skin thinning is caused by suppression of keratinocyte proliferation and dermal fibroblasts' synthesis of hyaluronic acid and collagen. Complications such as telangiectasias, ecchymosis/hematomas, lacerations, and broad purple striae are anticipated. A breakdown in the skin's protective layer known as dermatoporosis causes atrophy, fragility, and impaired wound healing. Even at low dosages (less than 5 mg/day of prednisone), being widespread to 5% in patients who use GCs for long term. Excessive dosages may also cause hirsutism, hair loss, and acne.As such, the administration of corticosteroid medication is thought to have a direct bearing on management.

MUSCLE CHANGES

Because of their higher molecular resistance to the hormone, GCs in skeletal muscle are in charge of reducing the action of insulin. Additionally, they cause a condition of tissue atrophy by stimulating muscle catabolism and interfering with protein synthesis.

GCs are the main cause of medication-induced myopathy, which is characterized by painless muscle weakening and progressive atrophy, initially in the lower limbs' proximal musculature.

Although treatment duration and dose have not been thoroughly examined in the literature, they do raise the risk of GC-induced myopathy. Due to their increased risk of this consequence, fluorinated GCs (betamethasone and dexamethasone) should be avoided or substituted.[36]

TB

In patients who have already been exposed, long-term GC use may encourage TB reactivation. Prednisone dosages ≥15 mg/day for more than a month have already been linked to this disease's risk; however, the precise dose and duration of this relationship are yet unknown. Additionally, there is no explicit suggestion in the literature for TB test prior to beginning GC medication.[37]

In general, it is advised to use tuberculin testing for TB screening in groups that are deemed at risk in order to

ensure that patients receive proper treatment and do not reactivate the bacillus during GC treatment. Patients who have had prior close contact with TB patients, those who have spent extended periods of time in jails or medical facilities, those who abuse drugs, and those who live in endemic areas are all regarded as at-risk population.

NEUROPSHYCIATRIC DISORDER

However, other experts urge that the screening be performed before beginning corticosteroid therapy.In immunosuppressed patients, a tuberculin skin test (Mantoux reaction) of > 5 mm should be deemed positive. However, consuming GC dosages of ≥15 mg/day for two to four weeks may result in a false negative test. Another screening method is the The hormone interferon Gamma Release Assay (IGRA), which seems to be less impacted by the use of GC.[38]

To ascertain whether an infection is active or latent, every patient who has a positive screening result should have a chest X-ray and have their sputum examined. They should also be sent to an infectious disease specialist. Before starting corticosteroid therapy, not all patients are screened for tuberculosis in the authors' clinical practice. Therefore, professional judgment is required to decide whether to screen, particularly in populations that are at risk.[39]

GASROINTESTINAL TRACT

The chronic use of Glucocorticoids is considered as risk factor for (GIT) adverse effects, such as gastritis, peptic ulcer, and gastrointestinal bleeding, but there are conflicting evidence in the literature proving their risk when used as monoth.

However, when used with nonsteroidal anti-inflammatory medicines (NSAIDs), the risk of stomach ulcers and bleeding significantly increases. It has been suggested that GCs may enhance the risk of pancreatitis, although the literature is the The equivocal.

Prophylaxis for gastrointestinal problems is indicated for all patients receiving combination GC treatment with NSAIDs, with p-p inhibitors being the preferred 1st choice.

Prophylaxis should be utilized with GC monotherapy if the patient has risk factors (prior peptic ulcer, smoking, drunkenness, bisphosphonate use). Patients who exhibit indicators of gastrointestinal bleeding should always be referred to a gastroenterologist and should always be informed about symptoms for clinical suspicion of an adverse event.[40]

CONCLUSION

Glucocorticosteroids (GCS) remain a cornerstone in the management of various inflammatory and autoimmune diseases, including rheumatoid arthritis, asthma, and inflammatory bowel disease (IBD), due to their potent anti-inflammatory and immunosuppressive effects. Their ability to modulate immune responses and reduce inflammation makes them invaluable in acute and chronic conditions. However, long-term or chronic consumption of GCS is arised with significant adverse effects, like osteoporosis, hypertension, hyperglycemia, adrenal suppression, and increased risk of infections.

Despite these risks, careful management of dosing regimens and treatment duration, along with adjunctive therapies such as calcium supplementation or bone-sparing agents, can help mitigate some of these side effects. Clinicians must weigh the benefits of GCS therapy against the potential for harm, using the lowest effective dose for the shortest duration to achieve therapeutic goals. Future research and development of alternative therapies may reduce the reliance on GCS, especially in chronic conditions, where minimizing adverse effects is a primary concern.

REFERANCES

1. Stewart PM, Krone NP. The adrenal cortex. In: Melmed S, Polonsky K, Larsen PR, Kronenberg H, editors. *Williams Textbook of Endocrinology. 12th ed*. Philadelphia, PA: Saunders, 2011. In. eds.
2. Porcu P., Barron A.M., Frye C.A., Walf A.A., Yang S.Y., He X.Y., Morrow A.L., Panzica G.C., Melcangi R.C. Neurosteroidogenesis today: novel targets for neuroactive steroid synthesis and action and their relevance for translational research. *J. Neuroendocrinol.*, 2016; 28.
3. Schiffer L, Barnard L, Baranowski ES, Gilligan LC, Taylor AE, Arlt W, Shackleton CHL, Storbeck KH. Human steroid biosynthesis, metabolism and excretion are differentially reflected by serum and urine steroid metabolomes: A comprehensive review. J Steroid Biochem Mol Biol., 2019 Nov; 194: 105439. Doi: 10.1016/j.jsbmb.2019.105439. Epub 2019 Jul 27. PMID: 31362062; PMCID: P5. Gwynne J.T., Strauss J.F. The role of lipoproteins in steroidogenesis and cholesterol metabolism in steroidogenic glands. *Endocr. Rev.*, 1982; 3: 299–329.
4. Gwynne J.T., Strauss J.F. The role of lipoproteins in steroidogenesis and cholesterol metabolism in steroidogenic glands. *Endocr. Rev.*, 1982; 3: 299–329.
5. Azhar S., Leers-Sucheta S., Reaven E. Cholesterol uptake in adrenal and gonadal tissues: the SR-BI and “selective” pathway connection. *Front. Biosci.*, 2003; 8: 998–1029.
6. Lin D., Black S.M., Nagahama Y., Miller W.L. Steroid 17 alpha-hydroxylase and 17, 20-lyase activities of P450c17: contributions of serine106 and P450 reductase. *Endocrinology*, 1993; 132: 2498–2506.
7. Yamada M., Ohta Y., Bachmanova G.I., Nishimoto Y., Archakov A.I., Kawato S. Dynamic interactions of rabbit liver cytochromes P450IA2 and P450IIB4 with cytochrome b5 and NADPH-cytochrome P450

reductase in proteoliposomes. *Biochemistry.*, 1995; 34: 10113–10119.
8. Zöllner A., Kagawa N., Waterman M.R., Nonaka Y., Takio K., Shiro Y., Hannemann F., Bernhardt R. Purification and functional characterization of human 11β hydroxylase expressed in Escherichia coli. *FEBS J.*, 2008; 275: 799–810.
9. Luu-The V., Takahashi M., de Launoit Y., Dumont M., Lachance Y., Labrie F. Evidence for distinct dehydrogenase and isomerase sites within a single 3β-hydroxysteroid dehydrogenase/5-ene-4-ene isomerase protein. *Biochemistry*, 1991; 30: 8861–8865.
10. Thomas J.L., Frieden C., Nash W.E., Strickler R.C. An NADH-induced conformational change that mediates the sequential 3β-hydroxysteroid dehydrogenase/isomerase activities Is supported by affinity labeling and the time-dependent activation of isomerase. *J. Biol. Chem.*, 1995; 270: 21003–21008.
11. Thomas J.L., Berko E.A., Faustino A., Myers R.P., Strickler R.C. Human placental 3β-hydroxy-5-ene-steroid dehydrogenase and steroid 5→4-ene-isomerase: purification from microsomes, substrate kinetics and inhibition by product steroids. *J. Steroid Biochem.*, 1988; 31: 785–793.
12. Cutler G.B., Glenn M., Bush M., Hodgen G.D., Graham C.E., Loriaux D.L. Adrenarche: a survey of rodents, domestic animals, and primates. *Endocrinology.*, 1978; 103: 2112–2118.
13. Xing Y., Edwards M.A., Ahlem C.N., Kennedy M., Cohen A., Gomez-sanchez C.E., Rainey W.E. The effects of ACTH on steroid metabolomic profiles in human adrenal cells. *J. Endocrinol.*, 2011; 209: 327–335.
14. Simpson E.R., Waterman M.R. Regulation of the synthesis of steroidogenic enzymes in adrenal cortical cells by ACTH. *Annu. Rev. Physiol.*, 1988; 50: 427–440.
15. Handa R.J., Weiser M.J. Gonadal steroid hormones and the hypothalamo – pituitary – adrenal axis. *Front. Neuroendocrinol.*, 2014; 35: 197–220.
16. Lanciotti L., Cofini M., Leonardi A., Penta L., Esposito S. Up-to-date review about minipuberty and overview on hypothalamic-pituitary-gonadal axis activation in fetal and neonatal life. *Front. Endocrinol. (Lausanne)*, 2018; *9*: 410.
17. John CD, Buckingham JC. Cytokines: regulation of the hypothalamo-pituitary-adrenocortical axis. *Current opinion in pharmacology*, 2003; 3: 78–84.
18. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. *Annual review of immunology.*, 2002; 20: 125–163. *Endocrine reviews*, 2011; 32: 81–151.
19. Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocrine reviews*, 2011; 32: 81–151.
20. Seckl JR. 11beta-hydroxysteroid dehydrogenases: changing glucocorticoid action. *Curr Opin Pharmacol.*, 2004; 4: 597–602.
21. Cooper MS, Stewart PM. 11Beta-hydroxysteroid dehydrogenase type 1 and its role in the hypothalamus-pituitary-adrenal axis, metabolic syndrome, and inflammation. *The Journal of clinical endocrinology and metabolism.*, 2009; 94: 4645–4654.
22. Evans RM. The steroid and thyroid hormone receptor superfamily. *Science.*, 1988; 240(4854): 889–95.
23. Lu NZ, Cidlowski JA. Translational regulatory mechanisms generate N-terminal glucocorticoid receptor isoforms with unique transcriptional target genes. *Mol Cell.*, 2005; 18(3): 331–42.
24. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci (Lond), 1998 Jun; 94(6): 557-72. Doi: 10.1042/cs0940557. PMID: 9854452.
25. Paolino S, Cutolo M, Pizzorni C. Glucocorticoid management in rheumatoid arthritis: morning or night low dose? Reumatologia, 2017; 55(4): 189-197. Doi: 10.5114/reum.2017.69779. Epub 2017 Aug 31. PMID: 29056774; PMCID: PMC5647534.
26. M. Oray, K. AbuSamra, N. Ebrahimiadib, H. Meese, C.S. FosterLong-term side effects of glucocorticoids Expert Opin Drug Saf., 2016; 15: 457-465.
27. R. Alten, M. Mischkewitz New concepts to reduce glucocorticoid toxicityJoint Bone Spine., 2019; 86: 715-723.
28. A. Caplan, N. Fett, M. Rosenbach, V.P. Werth, R.G. MichelettiPrevention and management of glucocorticoid-induced side effects: a comprehensive review: a review of glucocorticoid pharmacology and bone healthJ Am Acad Dermatol., 2017; 76: 1-9.
29. C. Strehl, J.W. Bijlsma, M. de Wit, M. Boers, N. Caeyers, M. Cutolo, *et al.* Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task forceAnn Rheum Dis., 2016; 75: 952-957.
30. C. Beaupere, A. Liboz, B. Fève, B. Blondeau, G. Gu illemainMolecular mechanisms of glucocorticoid-induced insulin resistanceInt J Mol Sci., 2021; 22: 623.
31. S. Paredes, M. AlvesAbordagem e tratamento da hiperglicemia induzida por glicocorticóides [Management and treatment of glucocorticoid-induced Hyperglycemia]Acta Med Port., 2016; 29: 556-563.
32. A. Caplan, N. Fett, M. Rosenbach, V.P. Werth, R.G. MichelettiPrevention and management of glucocorticoid-induced side effects: a comprehensive review: gastrointestinal and endocrinologic side effects J Am Acad Dermatol., 2017; 76: 11-16.

33. A. Prete, I. Bancos Glucocorticoid induced adrenal insufficiency BMJ., 2021; 374: 1380.
34. P. Chotiyarnwong, E.V. McCloskey Pathogenesis of glucocorticoid-induced osteoporosis and options for treatmentNat Rev Endocrinol., 2020; 16: 437-447.
35. I. Chiodini, A. Falchetti, D. Merlotti, C. Eller Vainicher, L. Gennari Updates in epidemiology, pathophysiology and management strategies of glucocorticoid-induced osteoporosis Expert Rev Endocrinol Metab., 2020; 15: 283-298.
36. A. Caplan, N. Fett, M. Rosenbach, V.P. Werth, R.G. MicheletiPrevention and management of glucocorticoid-induced side effects: a comprehensive review: ocular, cardiovascular, muscular, and psychiatric side effects and issues unique to pediatric patientsJ Am Acad Dermatol., 2017; 76: 201-207.
37. J. Youssef, S.A. Novosad, K.L. Winthrop Infection risk and safety of corticosteroid use Rheum Dis Clin North Am., 2016; 42: 157-176.
38. A. Caplan, N. Fett, M. Rosenbach, V.P. Werth, R.G. Micheletti Prevention and management of glucocorticoid-induced side effects: a comprehensive review: Infectious complications and vaccination recommendationsJ Am Acad Dermatol., 2017; 76: 191-198.
39. B.V. Broberg, I.E. Sommer, M.E. Benros, B.Y. Glen thøj, C. Gasse, O. Köhler-Forsberg Glucocorticoids and the risk of schizophrenia spectrum disorder in childhood and adolescence - a Danish nationwide studySchizophr Res., 2018; 199: 116-122.
40. K.T. Amber, S.A. GrandoGastrointestinal prophylaxis in patients with autoimmune blistering disease treated with corticosteroids: an expert surveyInt J Dermatol., 2018; 57: e125-e126.