PHARMACOLOGY

Corticosteroids

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DISCLOSURE

None

OBJECTIVES

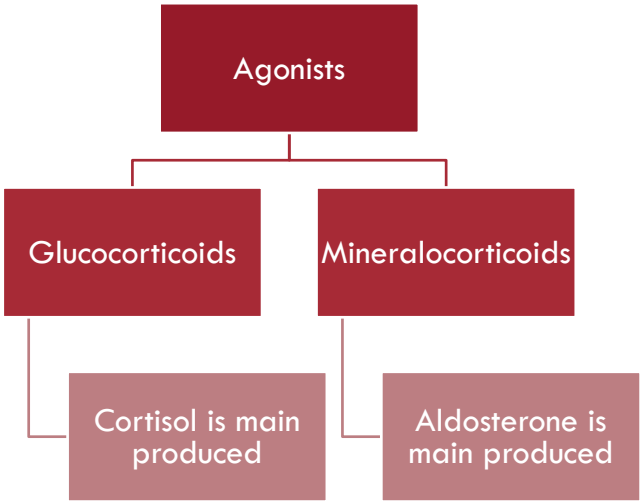
1. Identify disease states that utilize corticosteroids in their management.
2. Compare and contrast glucocorticoids and mineralocorticoids.
3. Explain the mechanism of action of corticosteroids (including corticosteroid-binding globulin, heat shock protein 90, and the glucocorticoid response element) and how this relates to the underlying pathophysiology of disease states that utilize corticosteroids in their management.
4. State adverse effects and contraindications to corticosteroids.
5. Describe the clinically important drug interactions of corticosteroids.

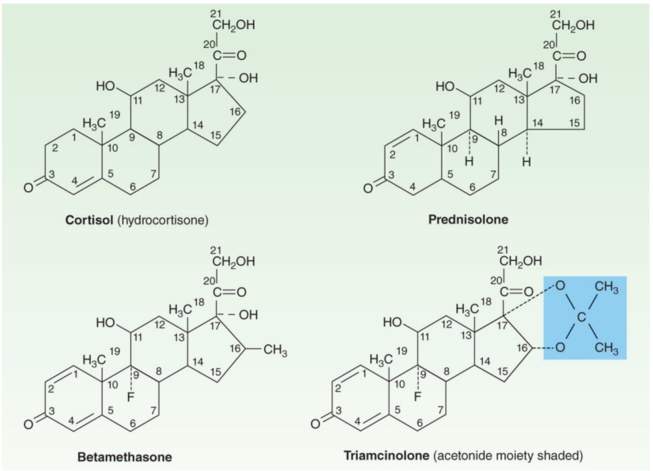
CORTICOSTEROIDS

Term steroid relates to the main structural frame of the compounds in the drug class

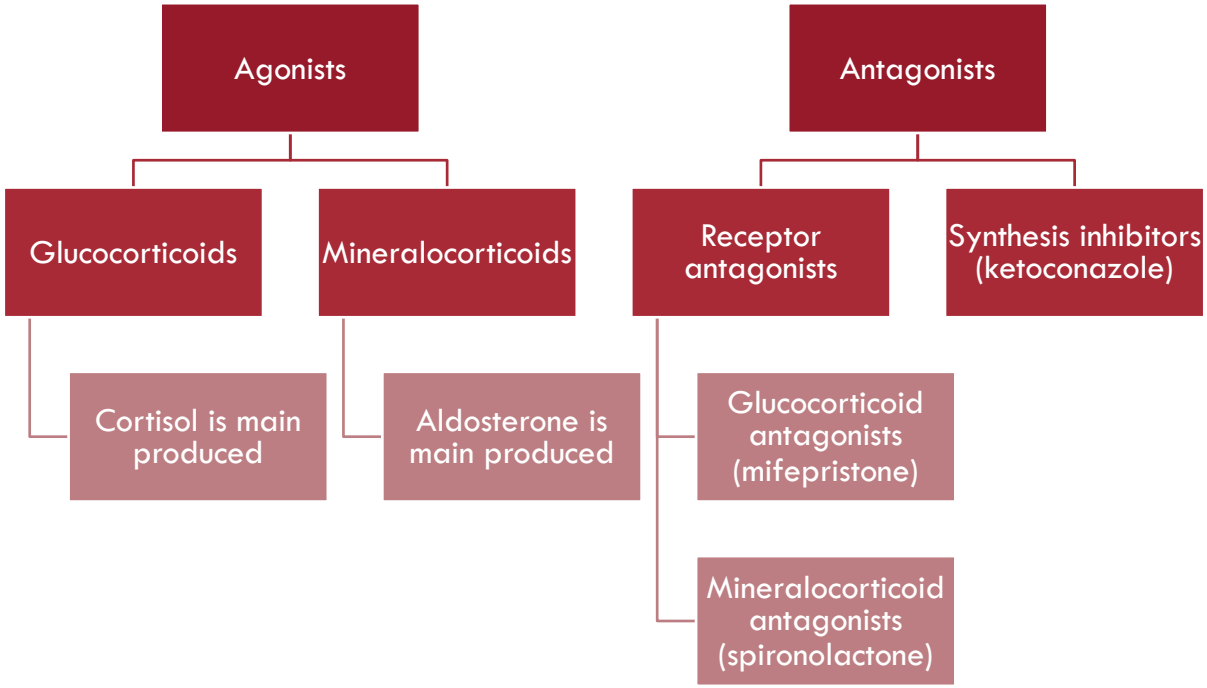
Almost every cell in the body responds to corticosteroids

CORTICOSTEROID AGONISTS





CORTICOSTEROID AGONISTS & ANTAGONISTS



ADRENAL GLAND ANATOMY & PHYSIOLOGY

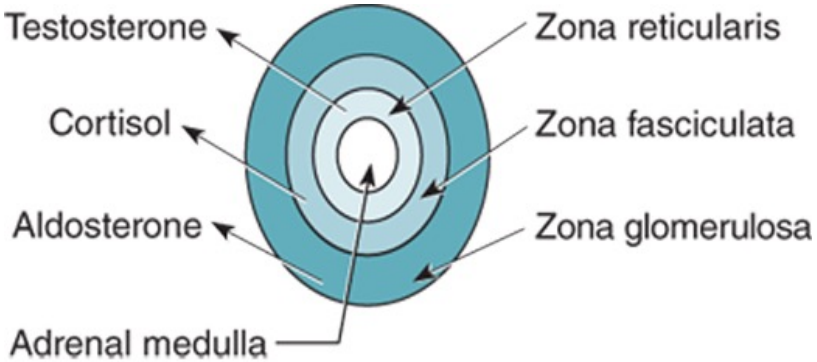
Adrenal medulla produces epinephrine and norepinephrine

Adrenal cortex

- Zona glomerulosa (outer layer) produces the compounds that control electrolyte balance, such as aldosterone
- Zona fasciculata (middle layer) produces the compounds that regulate metabolism, such as cortisol
- Zona reticularis (inner layer) produces the sex hormones (DHEA)

The pituitary hormone adrenocorticotropic hormone (ACTH or corticotropin) controls the secretion of, primarily, the inner two layers

Production of mineralocorticoids is mainly controlled by the renin-angiotensin system.



Source: Janet L. Stringer: Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, Fifth Edition, www.accesspharmacy.com

ADRENAL STEROID BIOSYNTHETIC PATHWAYS

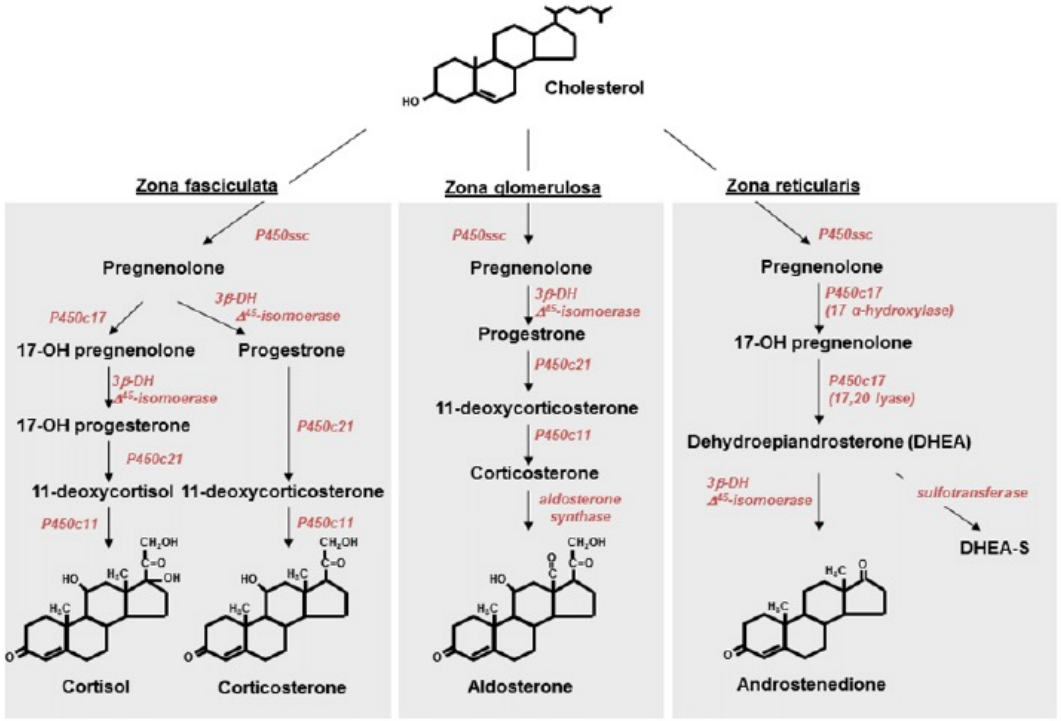
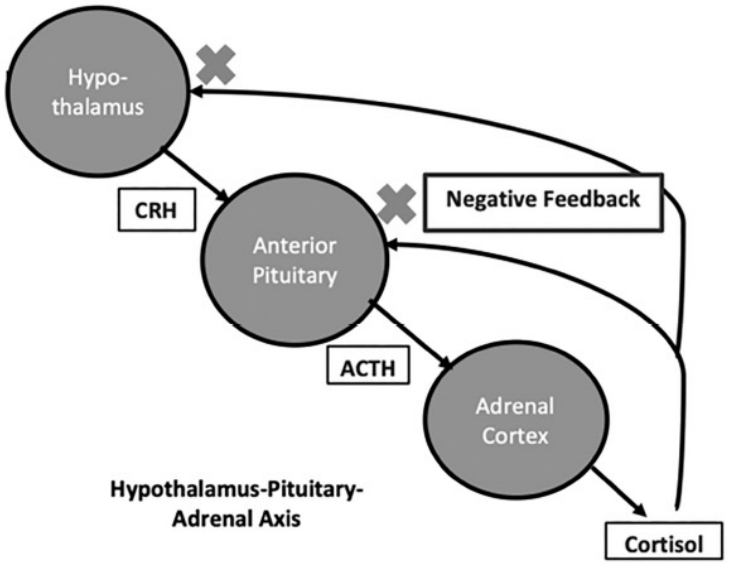


Image credit: https://www.researchgate.net/profile/Henrik-Ortsaeter/publication/231614936/figure/fig1/AS:300502542766081@1448656797244/Synthesis-of-steroid-hormones-in-the-adrenal-cortex-Synthesis-of-the-adrenal-steroid.png



Hypothalamus-Pituitary-Adrenal Axis

https://www.reliasmedia.com/articles/144073-evaluation-and-treatment-of-adrenal-insufficiency-in-the-emergency-department

ACTIVE LEARNING

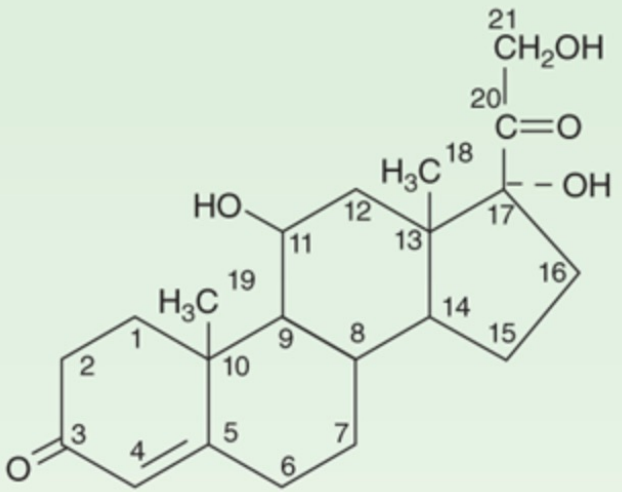
What is the main glucocorticoid produced? Where in the adrenal cortex is it produced?

What is the main mineralocorticoid produced? Where in the adrenal cortex is it produced?

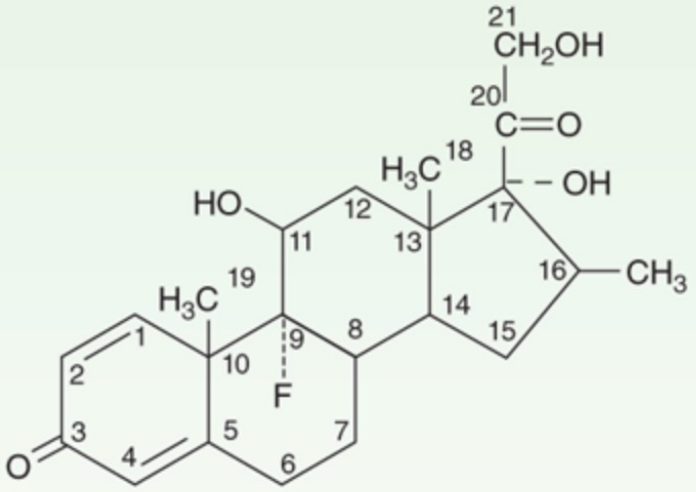
GENERAL MECHANISM FOR CORTICOSTEROID EFFECTS

Corticosteroids bind to specific receptor proteins in target tissues

- Regulates expression of corticosteroid-responsive genes
  - Changes levels/array of proteins synthesized by the various target tissues
- Many effects are not immediate but become apparent after several hours
  - Immediate effects exerted by nongenomic mechanisms (glucocorticoid receptors and mineralocorticoid receptors)
  - Prolonged effects exerted by increasing gene transcription



Cortisol (hydrocortisone)



INTRACELLULAR MOA OF THE GLUCOCORTICOID RECEPTOR (GR)

Cortisol (labeled S) enters cells and interacts with the GR to change GR conformation

Induces GR nuclear translocation

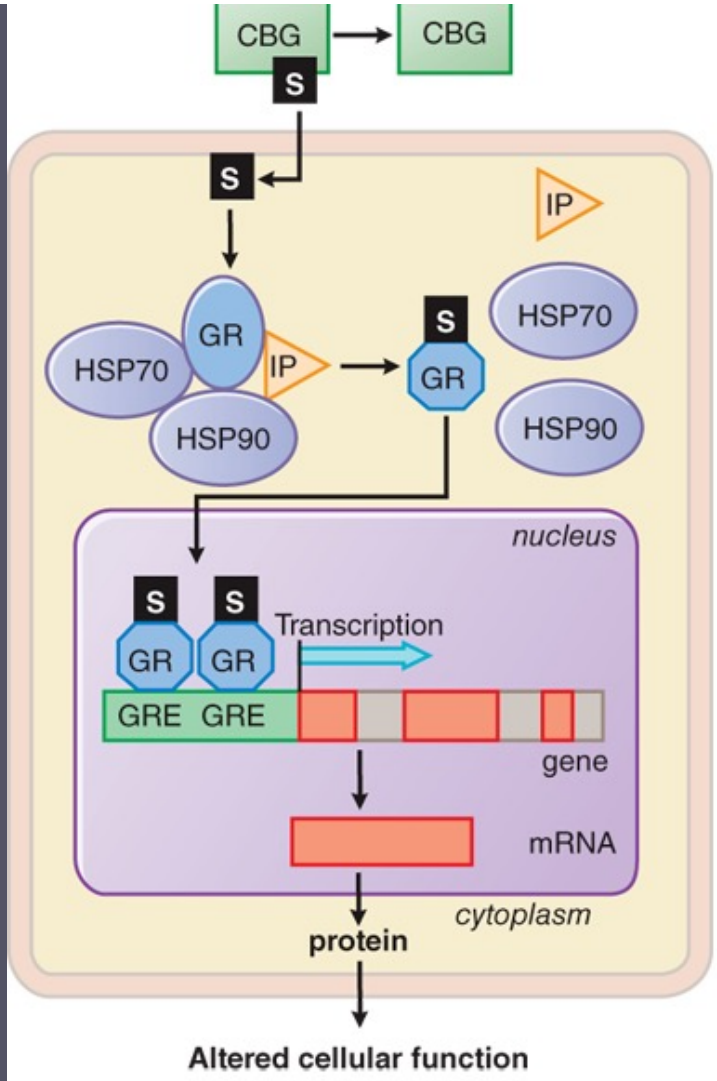
- GR-S complex binds to glucocorticoid-response element (GRE)
  - GREs are specific nucleotide (DNA) sequences
  - Provides specificity of induction of gene transcription by S

Activates transcription of target genes

- S inhibits expression of certain genes (POMC)

Transcription and mRNA processing → splicing/removal of introns (gray) and assembly of exons (red) into mRNA

Altered cell function



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

PHYSIOLOGIC FUNCTIONS & EFFECTS OF CORTICOSTEROIDS

Alter carbohydrate, protein, lipid metabolism

Maintain fluid and electrolyte balance

Preserve normal function of cardiovascular system, immune system, kidney, skeletal muscle, endocrine system, and nervous system

Resist stressful or noxious stimuli and environmental changes

Actions also related to other hormones

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GLUCOCORTICOIDS

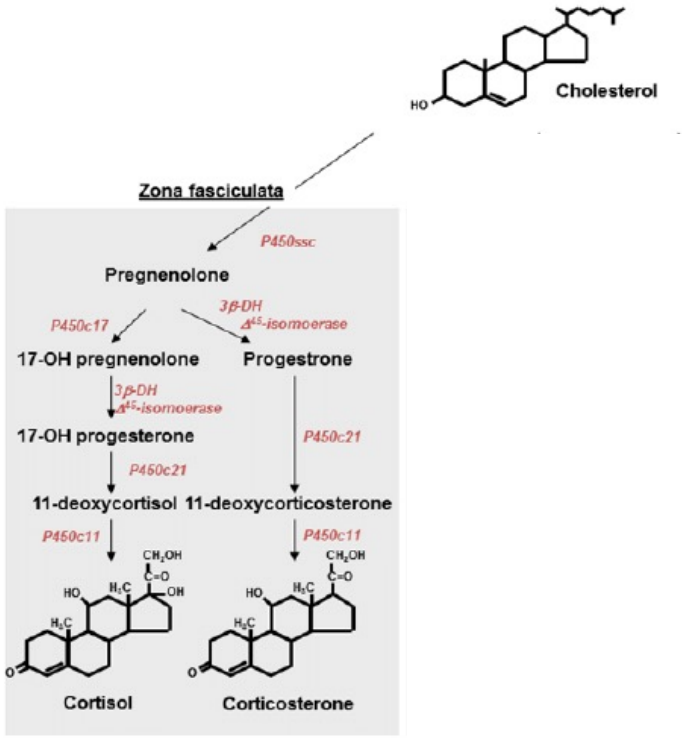
Corticosteroids Agonists

ENDOGENOUS GLUCOCORTICOID PRODUCTION

Cortisol and corticosterone are endogenously produced glucocorticoids

- Humans primarily produce cortisol

Cortisol production is regulated by ACTH



GLUCOCORTICOID BACKGROUND

Glucocorticoid receptors (GRs) are found in most cells in the body → complications appear in all organ systems

- Primarily reside in cytoplasm in inactive form complexed with other proteins

GRs belong to the nuclear receptor structural family and the steroid receptor functional family

Glucocorticoids promote catabolism of protein and gluconeogenesis

- Stimulate formation of glucose (hence, "gluco-")
- Cause breakdown of proteins into amino acids
- Net effect increases liven glycogen levels, fasting blood glucose levels, and urinary nitrogen output

EXOGENOUS GLUCOCORTICOID BACKGROUND

Among one of the most prescribed drug classes

Steroids are considered in terms of their relative strength with respect to hydrocortisone and with respect to their ability to interact with the mineralocorticoid receptor

Glucocorticoids inhibit inflammatory and immunological responses. This is the basis of their therapeutic use and adverse effects.

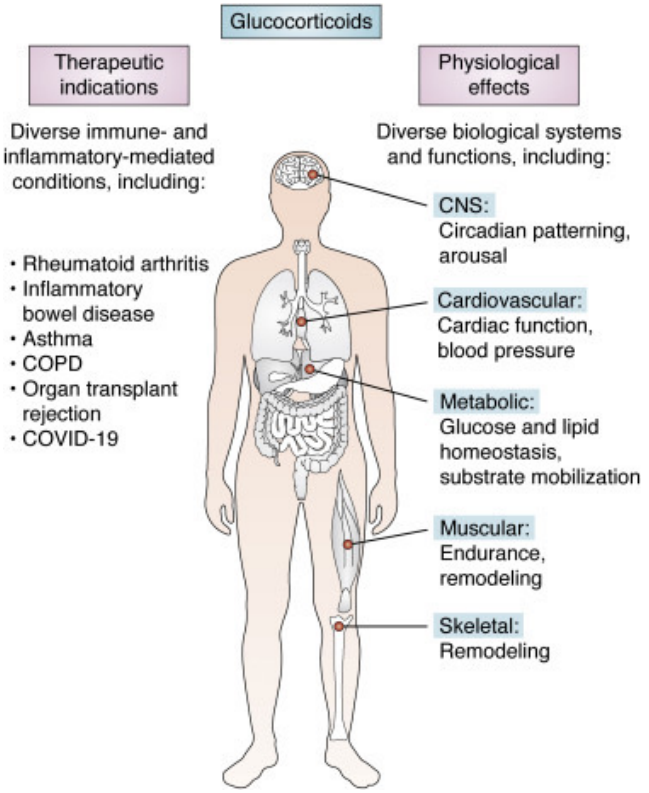
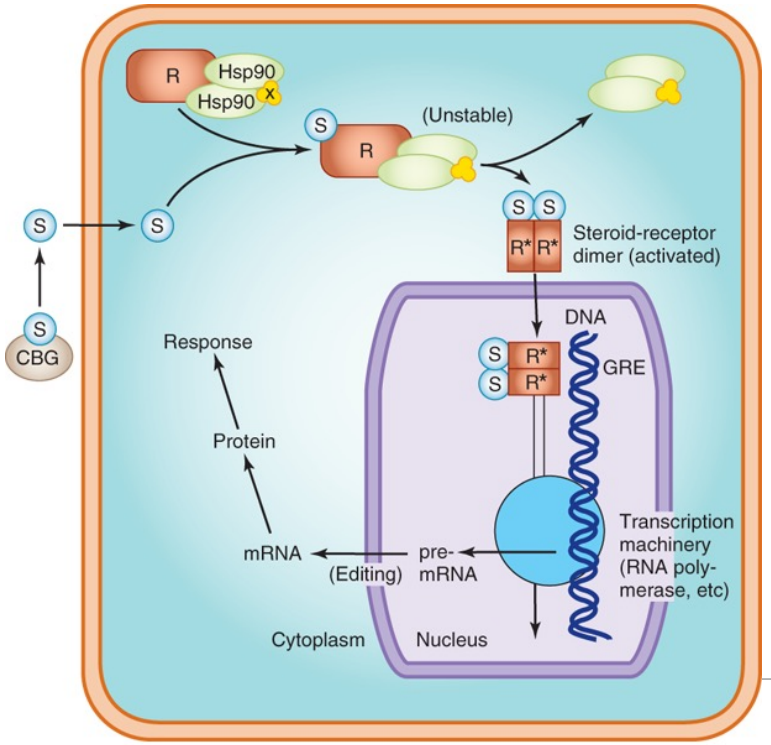


Image credit: https://www.jbc.org/article/S0021-9258%2821%2900476-2/fulltext

GLUCOCORTICOID MOLECULAR MECHANISM OF ACTION



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

GRs reside primarily in the cytoplasm

Glucocorticoid (S) binds to corticosteroid-binding globulin (CBG) and enters cell as free molecule

- Intracellular receptor (R) is bound to stabilizing protein heat shock protein 90 (Hsp90) and others (X)

S binds to intracytosolic R and Hsp90 and X are released

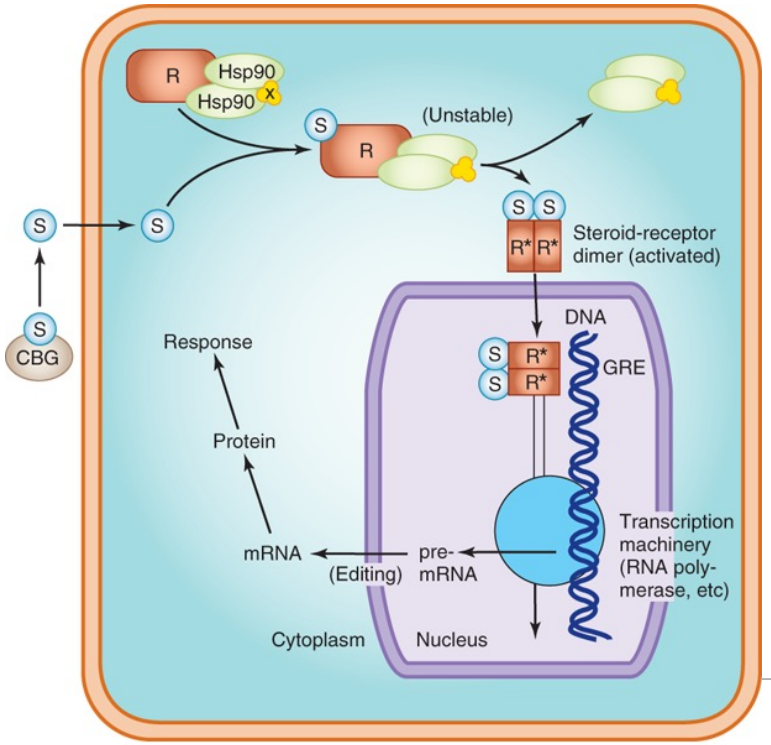
S-R complex enters nucleus as a dimer and binds to GREs on the gene

- Regulates gene transcription
- Resulting mRNA is edited and exported to cytoplasm
- Brings about various cell functions and metabolic effects in the body

ACTIVE LEARNING

Explain the mechanism of action of glucocorticoids to your neighbor.

GLUCOCORTICOID MOLECULAR MECHANISM OF ACTION



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COMPLICATIONS OF GLUCOCORTICOIDS

Appear in all organ systems

Short-term use is typically safe; adverse reactions still present

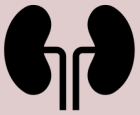
Longer term therapy associated with issues

ACTIVE LEARNING

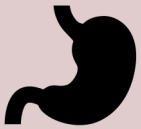
Sketch the arachidonic acid pathway. Please make note of where glucocorticoids and COX inhibitors exert their actions.

Now recall adverse effects of COX inhibitors. How might adverse effects of corticosteroids compare to the adverse effects of COX inhibitors?

GLUCOCORTICOID ADVERSE EFFECTS BY SYSTEM

Organ System	Adverse Effect
Dermatologic & Appearance 	Skin thinning, ecchymoses Cushingoid features Weight gain Muscle protein catabolism Bone catabolism → osteoporosis
Ophthalmologic 	Cataracts Increased intraocular pressure Exophthalmos
Cardiovascular/ renal  	Fluid retention Hypertension Premature atherosclerotic disease Arrhythmias Thromboembolic events Dyslipidemia

GLUCOCORTICOID ADVERSE EFFECTS BY SYSTEM

Organ System	Adverse Effect
Gastrointestinal 	Ulcers Bleeding
Bone 	Osteoporosis Osteonecrosis
Neuro-psychiatric 	Mood disorders Psychosis Memory impairment
Metabolic & Endocrine 	Stimulate gluconeogenesis (↑ plasma glucose, hyperglycemia) Insulin secretion stimulated Lipolysis and lipogenesis stimulated HPA axis suppression

GLUCOCORTICOID ADVERSE EFFECTS BY SYSTEM

Organ System	Adverse Effect
Immune (Anti-inflammatory) 	Inhibition of cell-mediated immunologic function (esp lymphocyte-dependent) Immunosuppression Reduced healing
Hematologic 	Leukocytosis

ACTIVE LEARNING

If corticosteroids inhibit cell-mediated immunologic function, why do patients experience leukocytosis within 5 to 24 hours of starting a corticosteroid?

CORTICOSTEROIDS AND WHITE BLOOD CELLS (WBCs)

WBC routine laboratory test

- Reflects number of leukocytes distributed in blood
  - 60-70% neutrophils
  - 28% lymphocytes
  - 5% monocytes
  - 2-4% eosinophils
  - 0.5 – 1% basophils

Neutrophils (PMNs) found in several compartments in body

- Marginal compartment – attached to endothelium of blood vessels
- Circulating – circulating in the blood vessels along with other cells

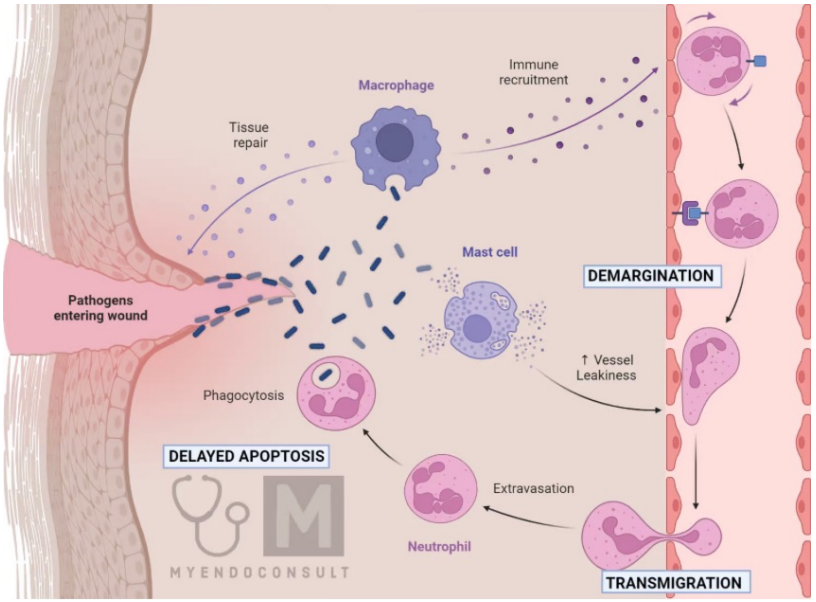
CORTICOSTEROIDS AND WHITE BLOOD CELLS (WBCs)

Glucocorticoids increase WBC

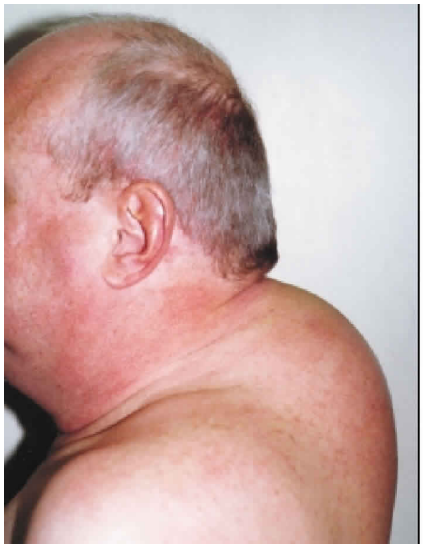
- PMNs main contributor to ↑

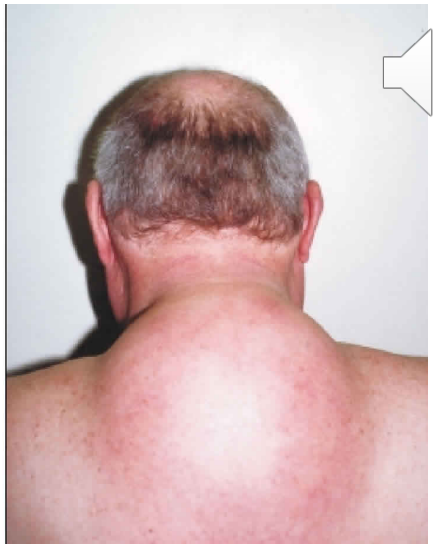
Several mechanisms

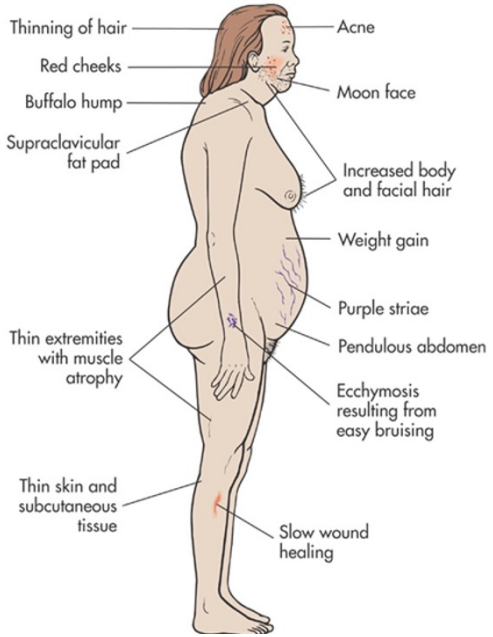
- MAIN is demargination of PMNs from endovascular lining
- PMNs attached to the endothelial lining of the blood vessels become detached → free in circulation
- When lab is drawn via venipuncture, there is > # of circulating PMNs
  - Total # of PMNs has not changed, just the % of PMNs residing in each compartment



SELECTED GLUCOCORTICOID ADVERSE EFFECTS







CUSHINGOID MAP MNEMONIC DEVICE

Cataracts

Ulcers

Striae

Hypertension

Infection risk

Necrosis of bone

Growth restriction

Osteoporosis

Increased intracranial pressure

Diabetes mellitus

Myopathy

Adipose tissue hypertrophy

Pancreatitis

NATURAL & SYNTHETIC GLUCOCORTICOIDS

Cortisol

- Major natural glucocorticoid
- Hydrocortisone

Synthetic glucocorticoids (longer $t_{1/2}$ and duration than cortisol)

- Prednisone and prednisolone
- Dexamethasone
- Triamcinolone
- Inhaled/nasal: beclomethasone, budesonide, fluticasone
- Others

EXOGENOUS GLUCOCORTICOIDS (-ONE, -SONE)

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Cortisone Hydrocortisone (cortisol) Methylprednisolone Prednisolone Prednisone Triamcinolone Dexamethasone	Peptic ulcer, heart disease or hypertension with heart failure, certain infectious illnesses such as varicella and tuberculosis, psychoses, diabetes, osteoporosis, or glaucoma. Monitor for the development of hyperglycemia, glycosuria, sodium retention with edema or hypertension, hypokalemia, peptic ulcer, osteoporosis, and hidden infections.	**Many** Withdrawal CV/renal CNS Endocrine GI Immunological Metabolic Musculoskeletal Ophthalmological	Anticoagulants (such as warfarin) Antihypertensives Antiepileptics Antidiabetics Antifungals Bronchodilators Diuretics Inducers → ↑ metabolism of steroids Inhibitors → ↓ metabolism of steroids

CLINICAL USE & ADME

Multiple clinic uses

- Adrenal disorders
- Non-adrenal disorders
  - Asthma, organ transplant rejection, collagen diseases, rheumatic disorders, cancers, neurologic disorders, chemotherapy-induced vomiting, hypercalcemia, mountain sickness, hastening maturation of fetal lungs

ADME varies based on drug and route of administration

Metabolized in liver

- Water-soluble conjugates are excreted in urine

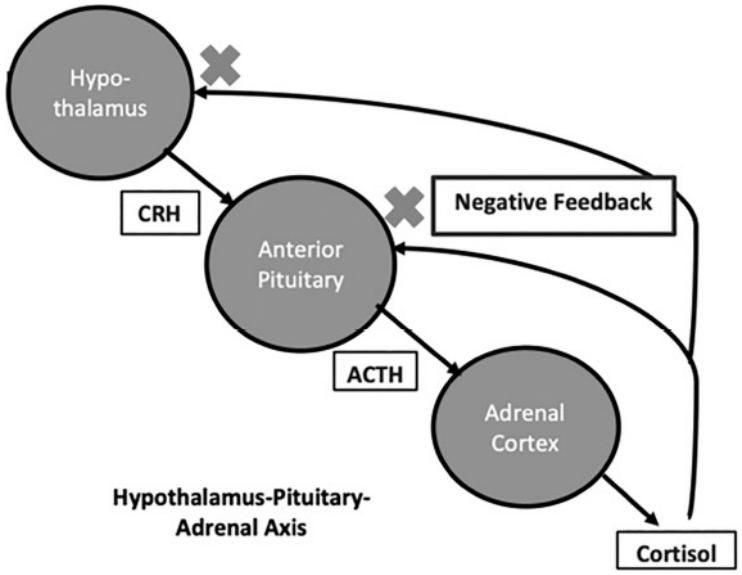
WITHDRAWAL & TAPERING

Withdrawal

- Flare-up of underlying disease for which prescribed
- Adrenal insufficiency due to too rapid withdrawal where HPA axis has been suppressed

Taper

- < 1 week: no taper
- 1-3 weeks: may consider taper
- > 3 week: consider quick taper to physiologic doses, then slow weaning
- Long-term, high-dose, suppressive therapy → HPA axis suppression up to 9 -12 months following withdrawal



Hypothalamus-Pituitary-Adrenal Axis

https://www.reliasmedia.com/articles/144073-evaluation-and-treatment-of-adrenal-insufficiency-in-the-emergency-department

ACTIVE LEARNING

What structural family do glucocorticoid receptors belong to?

What is the common drug stem for glucocorticoids?

List three cardiovascular adverse effects associated with glucocorticoid use.

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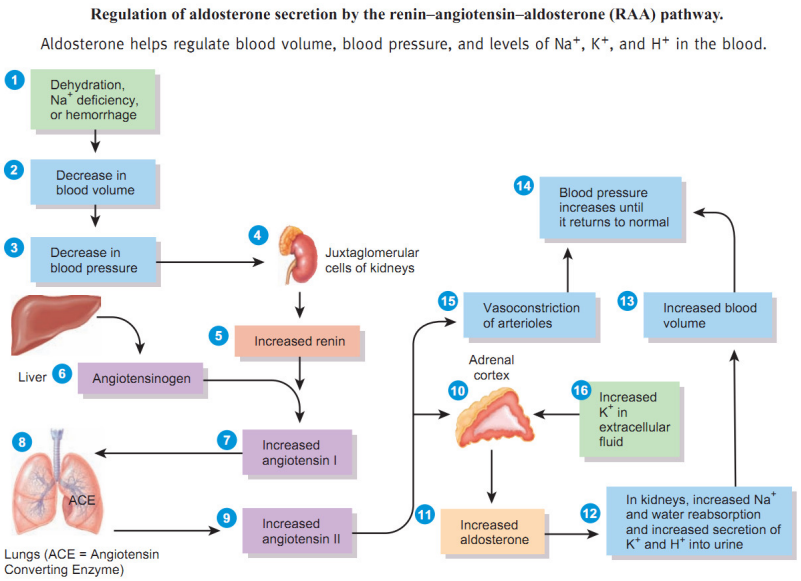
MINERALOCORTICOIDS

Corticosteroids

ENDOGENOUS MINERALOCORTICOID PRODUCTION

Aldosterone is an endogenously produced mineralocorticoid

Aldosterone production is regulated by the renin angiotensin aldosterone system (RAAS)



MINERALOCORTICOID BACKGROUND

Mineralocorticoid receptors (MRs) are found in kidneys, heart, fibroblasts, and inflammatory cells

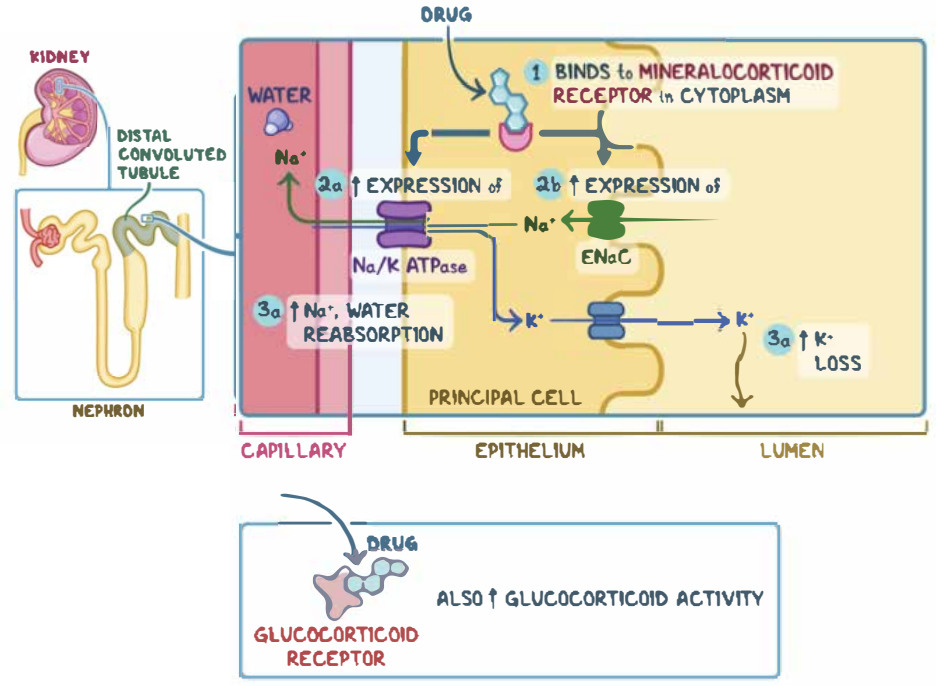
- Aldosterone and cortisol bind to MRs

Mineralocorticoid receptors belong to the nuclear receptor structural family and the steroid receptor functional family.

Principal role of mineralocorticoids in the kidneys is to control sodium reabsorption and potassium secretion

- Control minerals (hence, "mineralo-")
- Regulate blood volume, blood pressure, and levels of Na, K, and H^+ in the blood

MINERALOCORTICOID MECHANISM OF ACTION



1. Aldosterone (A) binds to MR forming A-MR complex
2. Translocated to nucleus and enhances epithelial sodium channel (eNaC) and Na/K ion pump expression
3. ↑ eNaC → Na exiting filtered urine via principal cells; ↑ Na/K ion pumps → Na driven from the cell into blood
4. Water follow Na and moves into blood → ↑ blood volume and blood pressure

EXOGENOUS MINERALOCORTICOIDS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Fludrocortisone (synthetic mineralocorticoid) *floo droe KOR ti sone*	Systemic fungal infections Adrenal suppression Immunosuppression	Hypokalemia Hypomagnesemia Edema Hypertension Heart failure Immunosuppression Cushing's syndrome **Hyperpigmentation of skin and nails**	Anti-hypertensives Immunosuppressants Medications that cause fluid retention

CLINICAL USE & ADME

Used for mineralocorticoid replacement

- Adrenal insufficiency, congenital adrenal hyperplasia, Addison's disease, idiopathic orthostatic hypotension, septic shock unresponsive to volume resuscitation/vasopressors

Fludrocortisone has long duration of action

Mineralocorticoids maintain sodium and potassium balance and blood pressure control. This is the basis of their therapeutic use and adverse effects.

ACTIVE LEARNING

What structural family do mineralocorticoid receptors belong to?

List three adverse effects associated with mineralocorticoid use.

CORTICOSTEROID ADMINISTRATION & RELATIVE POTENCY

Drug	Route	Anti-inflammatory	Mineralo-corticoid	Topical	Biologic half-life
Primarily glucocorticoid					
Hydrocortisone	PO, injectable, topical	1	1	+	Short - int (8-12 h)
Prednisone	PO	4	1	(+)	Short - int (12-36 h)
Triamcinolone	PO, injectable, topical	5	0	+++	Inter (15-24 h)
Dexamethasone	PO, injectable, topical	30	0	+++++	Long (> 36 h)
Primarily mineralocorticoid					
Aldosterone	N/A	0.3	3000	0	Short (1-2 h)
Fludrocortisone	PO	10	125-250	0	Short (8-12 h)

PRACTICE QUESTION

Which of the following best describes a glucocorticoid response element?

A A protein regulator that controls the interaction between an activated steroid receptor and DNA

B A short DNA sequence that binds tightly to RNA polymerase

C A small protein that binds to an unoccupied steroid receptor protein and prevents it from becoming denatured

D A specific nucleotide sequence that is recognized by a steroid hormone receptor-hormone complex

E The portion of the steroid receptor that binds to DNA

Which of the following best describes a glucocorticoid response element?

0

A protein regulator that controls the interaction between an activated steroid receptor and DNA

0%

A short DNA sequence that binds tightly to RNA polymerase

0%

A small protein that binds to an unoccupied steroid receptor protein and prevents it from becoming denatured

0%

A specific nucleotide sequence that is recognized by a steroid hormone receptor–hormone complex

0%

The portion of the steroid receptor that binds to DNA

0%

PRACTICE QUESTION

A 50-year-old woman, a known asthmatic for the past 30 years, presented to the emergency department with a 2-d history of worsening breathlessness and cough. Chest auscultation revealed bilateral polyphonic inspiratory and expiratory wheeze. Supplemental oxygen, nebulized albuterol (salbutamol) (5 mg) and ipratropium (250 mcg), as well as intravenous methyl prednisolone (40 mg) were administered. Which of the following is a pharmacologic effect of exogenous glucocorticoids?

A Increased muscle mass

B Hypoglycemia

C Inhibition of leukotriene synthesis

D Improved wound healing

E Increased excretion of salt and water

Which of the following is a pharmacologic effect of exogenous glucocorticoids?

0

Increased muscle mass 0%

Hypoglycemia 0%

Inhibition of leukotriene synthesis 0%

Improved wound healing 0%

Increased excretion of salt and water 0%

PRACTICE QUESTION

A 34-year-old woman with ulcerative colitis has required long-term treatment with pharmacologic doses of a glucocorticoid agonist. Which of the following is a toxic effect associated with long-term glucocorticoid treatment?

A A lupus-like syndrome

B Adrenal gland neoplasm

C Hepatotoxicity

D Osteoporosis

E Precocious puberty in children

A 34-year-old woman with ulcerative colitis has required long-term treatment with pharmacologic doses of a glucocorticoid agonist. Which of the following is a toxic effect associated with long-term glucocorticoid treatment?

0

PRACTICE QUESTION

A 56-year-old woman with systemic lupus erythematosus had been maintained on a moderate daily dose of prednisone for 9 months. Her disease has finally gone into remission and she now wishes to gradually taper and then discontinue the prednisone. Gradual tapering over 12 weeks of a glucocorticoid is required for recovery of which of the following?

A Depressed release of insulin from pancreatic B cells

B Hematopoiesis in the bone marrow

C Normal osteoblast function

D The control by vasopressin of water excretion

E The hypothalamic-pituitary-adrenal system

Gradual tapering over 12 weeks of a glucocorticoid is required for recovery of which of the following?

0

Depressed release of insulin from pancreatic B cells — 0%

Hematopoiesis in the bone marrow — 0%

Normal osteoblast function — 0%

The control by vasopressin of water excretion — 0%

The hypothalamic–pituitary–adrenal system — 0%

PRACTICE QUESTION

A patient presents with pain and stiffness in his wrists and knees. The stiffness is worse early in the morning. A blood test confirms rheumatoid arthritis. You advise a short course of steroids. Which one of the following is the most potent anti-inflammatory steroid?

A Cortisol

B Dexamethasone

C Fludrocortisone

D Prednisone

E Triamcinolone

Which one of the following is the most potent anti-inflammatory steroid?

0

Cortisol 0%

Dexamethasone 0%

Fludrocortisone 0%

Prednisone 0%

Triamcinolone 0%

BONUS PRACTICE QUESTION

Which of the following is a drug that, in high doses, blocks the glucocorticoid receptor?

A Aminoglutethimide

B Beclomethasone

C Ketoconazole

D Mifepristone

E Spironolactone

Which of the following is a drug that, in high doses, blocks the glucocorticoid receptor?

0

Aminoglutethimide 0%

Beclomethasone 0%

Ketoconazole 0%

Mifepristone 0%

Spironolactone 0%

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REFERENCE LIST

Bauersachs J, Jaisser F, Toto R. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. Hypertension. 2015 Feb;65(2):257-63. doi: 10.1161/HYPERTENSIONAHA.114.04488. Epub 2014 Nov 3. PMID: 25368026.

Chrousos GP. Adrenocorticosteroids & Adrenocortical Antagonists. In: Katzung BG, Vanderah TW. eds. Basic & Clinical Pharmacology, 15e. McGraw Hill; 2021. Accessed September 22, 2022. https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250600694

Hodgens A, Sharman T. Corticosteroids. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554612/

Schimmer BP, Funder W. Adrenocorticotropic Hormone, Adrenal Steroids, and the Adrenal Cortex. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e. McGraw Hill; 2017. Accessed September 22, 2022. https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=172482605

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ANY QUESTIONS?

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