Revised & Approved

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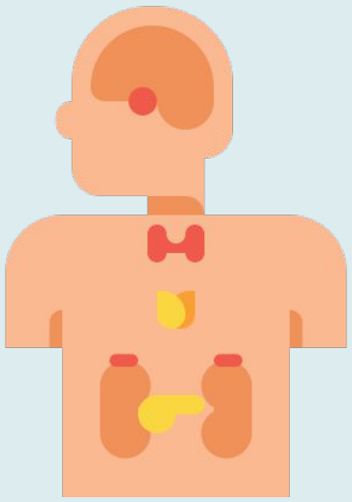
Pharmacology 439

MED439



Endocrine Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

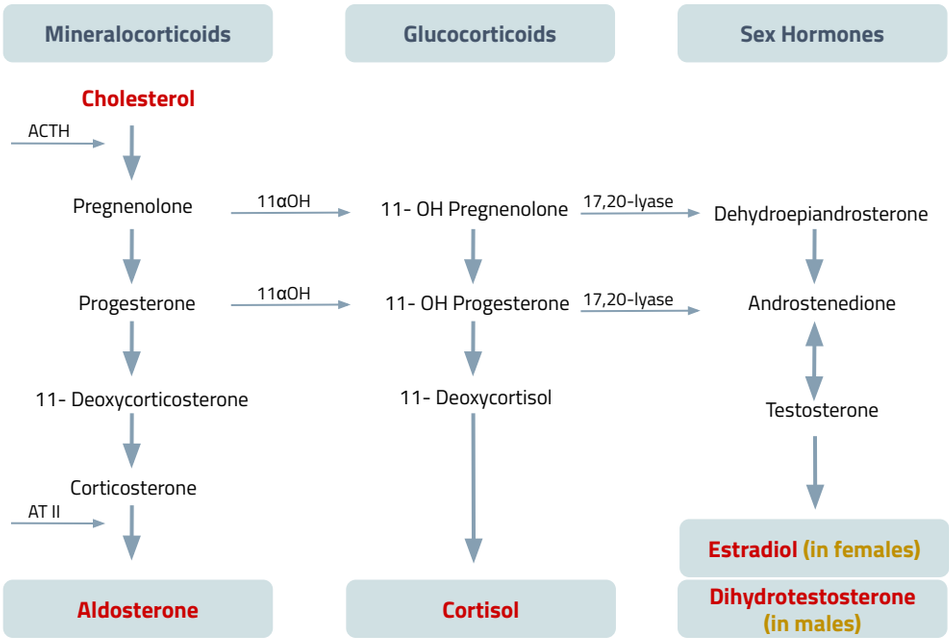
Pharmacology of Corticosteroids

Objectives:

1- Revise the synthesis of steroids
2- Mechanism of action
3- Pharmacokinetics of cortisol, pharmacodynamic actions and therapeutic uses
4- Adverse effects
5- Steroids agonists and antagonists and their therapeutic applications.

Editing file | Summary

Biosynthesis of Adrenal Hormones



Dr Alia: All i want you to remember is that the starting material for all of the three types is Cholesterol.

Corticosteroids

Corticosteroids are steroid hormones produced by the adrenal cortex. They consist of two groups:

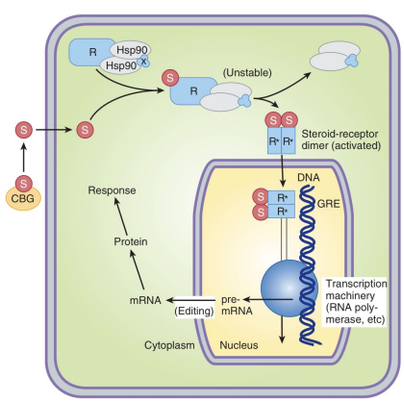
1. **Glucocorticoids:** Major: Cortisol (Hydrocortisone, the pharmaceutical form of cortisol)
   They have important effects on intermediary metabolism, catabolism, immune responses, growth & inflammation. (All reactions related to generation and storage of metabolic energy).

2. **Mineralocorticoids:** Most important: Aldosterone
   They have salt-retaining activity which regulate **Na & K reabsorption** in the collecting tubules of the kidney (Maintain salts, body volume, and increase blood pressure).

Mechanism of Action

Glucocorticoids and Mineralocorticoids have the same MOA

- Corticosteroid (S) is present in the blood bound to the **corticosteroid binding globulin (CBG)** (CBG) and enters the cell as the free molecule.
- The **intracellular** receptor (R) is bound to the stabilizing proteins, including **heat shock protein 90 (Hsp90)** (Hsp90) and several others (X).
- When the complex binds a molecule of steroid, the Hsp90 and associated molecules are released
- The steroid receptor complex **enters the nucleus** as a dimer, binds to the **glucocorticoid response element (GRE) on the gene**, and regulates gene transcription by **RNA polymerase 2** and associated transcription factors.
- The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the **final hormone response**.



Glucocorticoids

Effects of Glucocorticoids

Occur when the patient is treated with 100 mg (high dose) of hydrocortisone for longer than 2 weeks.

Metabolic effects:

Stimulation of gluconeogenesis resulting in:

- ↑ Blood glucose
- Insulin secretion is stimulated → Lipolysis and lipogenesis are stimulated.
  How can lipolysis & lipogenesis occur in the same time? Because glucocorticoids share a characteristic with catecholamines; they stimulate breakdown of lipids (which will liberate fatty acids into the blood). Then, lipogenesis will happen due to the effect of insulin. This mechanism is the reason behind fat redistribution effect of corticosteroids showing as moonface or buffalo hump!
- Net increase of fat deposition in certain areas [e.g. the face (moon facies), shoulder and back (buffalo hump)]

Catabolic effects:

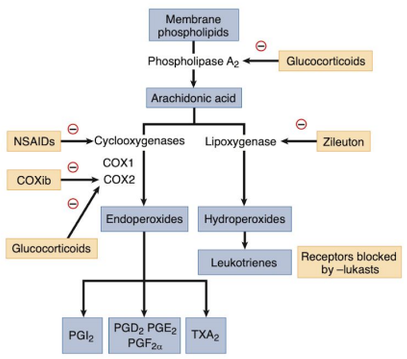
- Muscle protein catabolism (to help in gluconeogenesis): ↓**muscle mass** and muscle wasting
- Lymphoid and connective tissue fat and skin undergo wasting (you can see the blood vessels underneath the skin)
- Catabolic effects on bone lead to osteoporosis and decrease calcium absorption
- Growth is inhibited in children, that's why steroids are not recommended in children

Immunosuppressive effects: (2nd main use after the anti-inflammatory effect)

- Inhibiting cell mediated immunologic functions, especially dependent on lymphocytes & decrease interleukins secretion
- Glucocorticoids do not interfere with the development of normal acquired immunity (adaptive immunity ie. the immunity after being exposed to a certain pathogen) but delay rejection reactions in patients with organ transplants.

Anti inflammatory effects: (they are **MAINLY** used for this effect)

- Inhibitory effects on the distribution, function and migration of leukocytes.
- Suppressive effect on the inflammatory cytokines & chemokines
- Increase neutrophils and decrease lymphocytes, eosinophils, basophils and monocytes.
- Inhibit **phospholipase A2** and subsequently inhibit Prostaglandins synthesis.



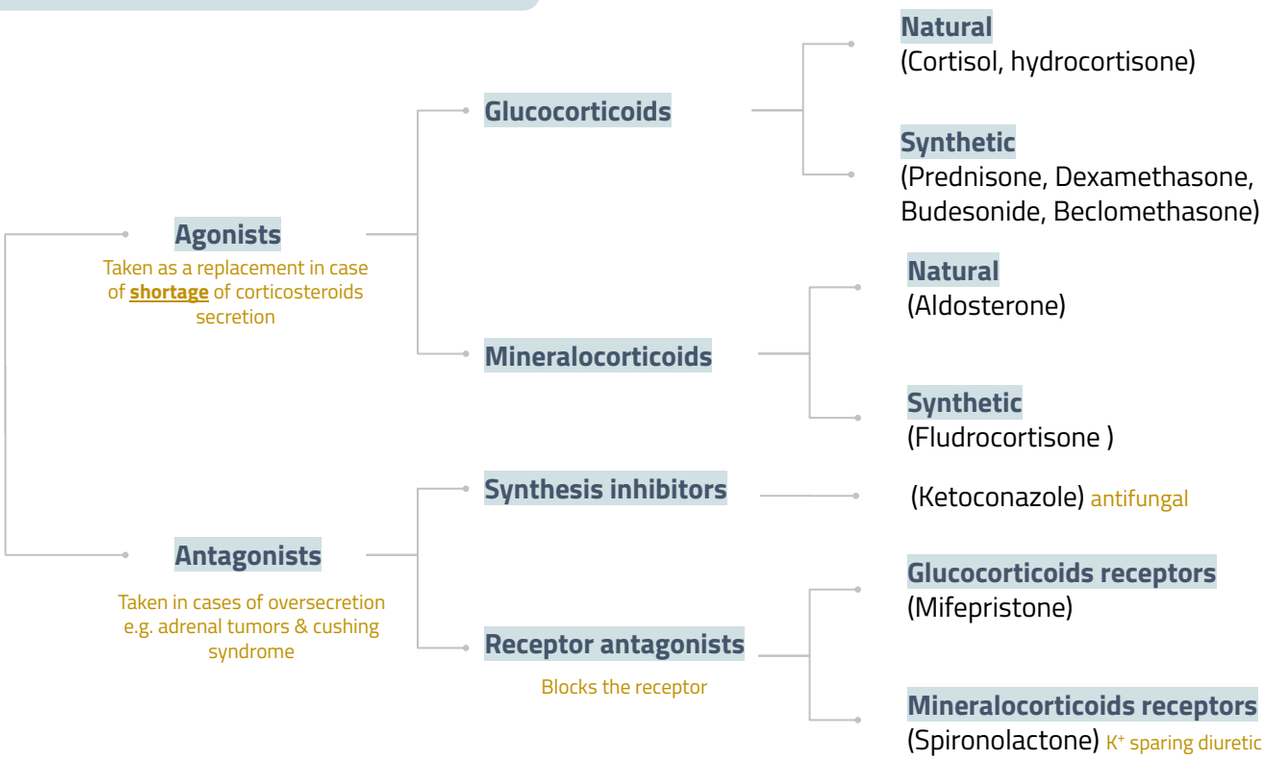
Phospholipase A2 initiates the activation of the arachidonic acid pathway, leading to biosynthesis of Prostaglandins in the end.

Other effects:

- **Renal:**
  Glucocorticoids such as cortisol are required for normal renal excretion of water loads.
- **CNS**:
  When given in large doses these drugs may cause profound behavioral changes (first insomnia & euphoria then depression).
- **GIT:**
  Large doses also stimulate gastric acid secretion and decrease resistance to ulcer formation. (it increases the ulceration if given chronically due to the inhibition of the protective effects of prostaglandins)

Glucocorticoids

Classification of Glucocorticoids



	Natural cortisol (Synthetic prep. hydrocortisone)	Synthetic Glucocorticoids
Drug	• Cortisol is the major natural glucocorticoid • The physiologic secretion of cortisol is regulated by adrenocorticotropic (**ACTH**) & secretion rate varies during the day (Follows circadian rhythm: internal body clock). • Peaks in the morning (because we need energy and one of its effects is gluconeogenesis), and declines in midnight.	**Prednisone, prednisolone** (its active metabolite) **Dexamethasone** (mainly in neurological disorders) **Beclomethasone** (mainly in respiratory problems) **Budesonide** (mainly in respiratory problems)
P.K	• Given orally, well absorbed from GIT • Cortisol in the plasma is 95% bound to **CBG** (corticosteroid binding globulin). • Metabolized by the liver & has short duration of action compared with the synthetic congeners(analog). • Diffuses poorly across normal skin & mucous membranes. (Natural form can't be used topically) • Cortisol molecule also has a small but significant mineralocorticoid effect, This is an important cause of **hypertension** in patients with cortisol secreting adrenal tumor or a pituitary ACTH secreting tumor (Cushing's syndrome). Meaning that when cortisol exceeds the physiological dose, it can give a little effect of mineralocorticoids (resulting water retention → hypertension).	Their properties in **compared to cortisol**: • Longer half life • Longer duration of action • Reduce salt retaining effect (no hypertension) • Better penetration of lipid barriers for topical activity

Glucocorticoids

Drug	Natural cortisol (hydrocortisone)	Synthetic Glucocorticoids

Uses

Adrenal Disorders

- **Addison's disease** (chronic adrenocortical insufficiency) opposite of Cushing.
- **Acute adrenal insufficiency** associated with life threatening shock, infections or trauma
- **Congenital adrenal hyperplasia** (in which synthesis of abnormal forms of corticosteroids (can't give the expected response) are stimulated by ACTH).

Non-adrenal Disorders

- **Allergic reactions:** due to their immunosuppressive effect
  (e.g. bronchial asthma, angioneurotic edema(tissue swelling),drug reactions, urticaria, allergic rhinitis):
  - **Beclomethasone & Budesonide** have been developed for use in **asthma** and other condition in which **good surface activity on mucous membrane or skin is needed** and systemic effects are to be avoided.
  - Rapidly penetrate the airway mucosa but have very short half lives after they enter the blood, so that systemic effects and toxicity are greatly reduced. (advantage)
- **Collagen vascular disorders:**, a group of disorders of connective tissues. (e.g rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, polymyositis, mixed connective tissue syndrome)
- **Organ transplants** (prevention & treatment of **rejection** – immunosuppression)
- **GI disorders** (e.g inflammatory bowel disease)
- **Hematologic disorders** (leukemia, multiple myeloma, acquired hemolytic anemia, acute allergic purpura)
- **Infections** (acute respiratory distress syndrome (associated with high immune response), sepsis)
- **Neurologic disorders** (to minimize cerebral edema after brain surgery, multiple sclerosis).
  Dr: write it please: **(Dexamethasone** is mostly used in neurological disorders due to its long duration of action and low salt-retaining activity**)**
- **Pulmonary diseases** (e.g. aspiration pneumonia, bronchial asthma, sarcoidosis)
- **Thyroid diseases** (autoimmune diseases: malignant exophthalmos, subacute thyroiditis)
- **Renal disorders** (nephrotic syndrome)
- **Miscellaneous** (hypercalcemia it helps increase urinary calcium excretion, mountain/motion sickness)

ADRs

Toxicity:

- ★ **Cushing's syndrome** like effect (iatrogenic, by higher doses > than 100 mg hydrocortisone daily for > than 2 weeks characterized by moon shape face & buffalo hump).
- Increased growth of fine hair on face, thighs & trunk
- Myopathy, muscle wasting, thinning of skin (due to poor healing , connective tissue wasting)
- Diabetes Mellitus
- Osteoporosis due to the catabolic effect & aseptic necrosis of the hip because it reduces blood circulation to hip
- Wound healing is impaired (because it slows cell migration)
- Peptic ulcer (↑GI acidity)
- Acute psychosis, depression
- Subcapsular cataract (loss of lense transparency)
- Growth suppression (because it accelerates bone maturation in early ages)
- Hypertension (due to sodium/water retention)
- Adrenal suppression, Body gets used to cortisol being supplied externally, so the adrenal gland is slowed down / suppressed.

Skipped by Male doctor: بس للإطلاع مارح اسألكم عنه
Dr Alia: you have to memorize which is short and which is intermediate etc. & properties (But no need to memorize numbers/doses)

Glucocorticoids

Some commonly used natural and synthetic corticosteroids for general use:

Agent	Activity			Equivalent Oral Dose (mg)	Forms Available
	Anti-Inflammatory	Topical	Salt-Retaining		
Short to medium acting glucocorticoids					
Hydrocortisone (cortisol)	1	1	1	20	Oral, injectable, topical
Cortisone	0.8	0	0.8	25	Oral
Prednisone	4	0	0.3	5	Oral
Prednisolone	5	4	0.3	5	Oral, injectable
Methylprednisolone	5	5	0.25	4	Oral, injectable
Meprednisone	5	-	0	4	Oral, injectable
Intermediate acting glucocorticoids					
Triamcinolone	5	5^3	0	4	Oral, injectable, topical
Paramethasone	10	-	0	2	Oral, injectable
Fluprednisolone	15	7	0	1.5	Oral
Long acting glucocorticoids					
Betamethasone	25-40	10	0	0.6	Oral, injectable, topical
Dexamethasone	30	10	0	0.75	Oral, injectable, topical
Mineralocorticoids					
Fludrocortisone	10	0	250	2	Oral
Desoxycorticosterone acetate	0	0	20	-	Injectable, pellets

Explanation of the table #Team438:

- First, you need to understand that all the numbers compare the drugs to the physiological glucocorticoid cortisol.
- All synthetic drugs have better anti-inflammatory action than cortisol.
- Most synthetic drugs (except the ones that are indicated with 0 activity) have better topical action than cortisol (which means they penetrate lipid barriers better).
- All synthetic drugs have less salt retaining action (advantage) EXCEPT Mineralocorticoids.

Methods for minimizing corticosteroid toxicity

- Local application (e.g; aerosol for asthma)
- Alternate day therapy (to reduce pituitary suppression)
- Tapering the dose soon after achieving a therapeutic response. (start with high dose, then when we reach the therapeutic effect decrease the dose gradually)
- To avoid adrenal insufficiency in patient who have had long term therapy, additional stress doses may need to be given during serious illness or before major surgery. If a patient is already on hydrocortisone and he will undergo surgery, we will have to give him additional higher stress doses because the body needs time to adjust cortisol levels.

Mineralocorticoids

Drug	**Aldosterone** (natural)	**Fludrocortisone** (synthetic)
MOA	Same as that of glucocorticoids (Page2). (but binds to **mineralocorticoids response element** on the gene instead of Glucocorticoids response element)	
P.K	• The major natural mineralocorticoid in human • Aldosterone has short half life & little glucocorticoid activity.	
P.D	• Aldosterone is the **main salt-retaining hormone**, promotes Na Reabsorption, K excretion, in the distal convoluted tubule & thus it is very important in the regulation of blood volume & blood pressure. • Its secretion is regulated by ACTH & by the renin-angiotensin system.	
Uses	• **Fludrocortisone** is favored for replacement therapy **after adrenalectomy** (removal of adrenal cortex) & in other conditions in which mineralocorticoid therapy is needed.	

Corticoids Antagonists

1) Receptor Antagonists

Drug	**Spironolactone**	**Mifepristone**
MOA	• **Mineralocorticoid antagonist** & **K-sparing diuretic** • Antagonists of aldosterone at its receptor. Leads to Na excretion and K reabsorption	**Competitive** inhibitor of glucocorticoid receptors
Uses	Treatment of primary aldosteronism (Conn's syndrome). Excessive production of aldosterone	Treatment of Cushing's syndrome

2) Synthetic Inhibitors

Drug	**Ketoconazole (Anti Fungal)**
MOA	• In low doses it acts as an **antifungal** • In high doses it blocks the synthesis of mineralocorticoids. • Inhibits cytochrome p450 enzymes necessary for synthesis of all steroids
Uses	Number of conditions in which reduced steroid level are desirable such as: • Adrenal cancer, when surgical therapy is impractical or unsuccessful because of metastasis. • Hirsutism • Breast cancer* • Prostate cancer* * these types of cancer depend on androgens for proliferation and growth, the inhibition of steroid hormones cause improvement or synergistic effect with chemotherapy

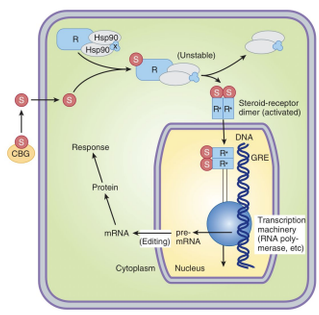
Summary

<table>
<tr><th>Class</th><th>Drug</th><th>M.O.A</th><th>Uses</th><th>ADRs</th></tr>
<tr><td rowspan="2">Natural Glucocorticoids</td><td>Cortisol (hydrocortisone)</td><td rowspan="4">1- Steroid in the blood that is bound to corticosteroid binding globulin (CBG)

2- Enters the cells & activates the intracellular receptor that is bound to the stabilizing proteins (Hsp90) and several others (X). Then, Hsp90 and (X) are released.

3- The Steroid–receptor complex enters the nucleus, binds to the (Glucocorticoid or Mineralocorticoids) response-element on the gene, and regulates gene transcription by RNA polymerase 2.

4- The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings the final hormone response.

 
</td><td>Adrenal Disorder:

1. Addison’s disease
2. Acute adrenal insufficiency
3. Congenital adrenal hyperplasia

Non-adrenal Disorder:

1. Allergic reactions.
2. Collagen vascular disorder
3. Organ transplants
4. GI disorders
5. Hematologic disorders
6. Infections
7. Neurologic disorders (Dexamethasone)
8. Pulmonary diseases
9. Thyroid diseases
10. Renal disorders
11. Miscellaneous (hypercalcemia)</td><td rowspan="2">Only natural:

- Hypertension

Toxicity:

- Cushing’s syndrome
- Diabetes Mellitus
- Osteoporosis
- Cataract
- Peptic ulcer
- Impaired wound healing</td></tr>
<tr><td>Synthetic Glucocorticoids</td><td>Prednisone
Dexamethasone</td></tr>
<tr><td></td><td>Budesonide
Beclomethasone</td><td>Asthma</td></tr>
<tr><td rowspan="2">Mineralo-corticoids</td><td>Aldosterone</td><td>Salt-retaining hormone (important in regulation of blood volume & blood pressure)</td><td>-</td></tr>
<tr><td>Fludrocortisone</td><td>Replacement therapy after adrenalectomy</td><td>-</td></tr>
<tr><td rowspan="2">Receptor Antagonists</td><td>Spironolactone</td><td>Mineralocorticoid antagonist & K-sparing diuretic</td><td>Primary aldosteronism
(Conn’s syndrome)</td><td>-</td></tr>
<tr><td>Mifepristone</td><td>Competitive inhibitor of glucocorticoid receptors</td><td>Cushing’s syndrome</td><td>-</td></tr>
<tr><td>Synthetic Inhibitors</td><td>Ketoconazole</td><td>Antifungal in low doses

Blocks the synthesis of mineralocorticoids in high doses

Inhibits cytochrome p450</td><td>Adrenal cancer
Hirsutism
Breast cancer
Prostate cancer</td><td>-</td></tr>
</table>

MCQs

Q1: An 8-year-old boy with persistent asthma was in the chest clinic. He had been only moderately controlled on inhaled albuterol. Physical examination showed expiratory wheezes, and pulmonary function test revealed a peak expiratory flow rate 60% of predicted. The Dr decided to add Glucocorticoid to the therapy, One of the following would be the drug of choice			
A- Beclomethasone	B- Aldosterone	C- Fludrocortisone	D- Hydrocortisone
Q2: A 57-year-old woman complaining of muscle weakness, recurrent epigastric distress, aching back pain. She was diagnosed with severe ulcerative colitis, had been taking therapy for 5 months. Laboratory values showed a decreased lymphocytes and increased neutrophils. Which of the following drugs most likely caused the patient's symptoms?			
A- Prednisolone	B- Budesonide	C- Beclomethasone	D- Aldosterone
Q3: Which of the following statements about spironolactone is TRUE?			
A- Spironolactone reverses the manifestations of aldosterone	B- Spironolactone is used in the treatment of (Conn's syndrome)	C- Spironolactone is useful as a diuretic	D- All of the above
Q4: A 43-year-old man presented to the hospital complaining of weight gain, mild but continuing facial acne, and decreased muscle strength. A computed tomography scan disclosed an adrenal adenoma in the left adrenal gland, and the patient was scheduled for surgery. Which of the following drugs would be appropriate as a replacement therapy after adrenalectomy			
A- Fludrocortisone	B- Aldosterone	C- Mifepristone	D- Spironolactone
Q5: A 57-year-old man suffering from severe dermatomyositis had been receiving high-dose prednisone for 6 months. Which of the following laboratory results would be most likely to occur in this patient?			
A- Hyponatremia	B- Hypocalcemia	C- Hyperkalemia	D- Hypoglycemia
Q6: A 42-year-old woman, recently diagnosed with SLE, started a therapy with high-dose dexamethasone. Which of the following explains why synthetic glucocorticoids are preferred over cortisol in the therapy of nonendocrine disorders?			
A- Lack of ulcerogenic activity	B- Reduce salt retaining effect	C- Shorter duration of action	D- Shorter half life
Q7: A 45-year-old man complained to his physician of severe shoulder pain. Further exams led to the diagnosis of acute bursitis, and intra-articular injections of dexamethasone were prescribed. Which of the following actions most likely contributed to the therapeutic efficacy of the drug in the patient's disease?			
A- Inhibition of (ACTH) release	B- Increased catabolism of prostaglandins	C- inhibition of phosphodiesterase	D- inhibition of phospholipase A2
Q8: A 46-year-old male patient has Cushing's syndrome due to an adrenal tumor. Which of the following drugs would be expected to reduce the signs and symptoms of this man's disease?			
A- Dexamethasone	B- Budesonide	C- Ketoconazol	D- Hydrocortisone
Q9: Which of the following synthetic steroids shows predominantly mineralocorticoid action?			
A- Hydrocortisone	B- Spironolactone	C- Dexamethasone	D- Fludrocortisone

1	2	3	4	5	6	7	8	9
A	A	D	A	B	B	D	C	D

SAQ

Case1: A 52-year-old man with Addison disease presented to the hospital complaining of e sodic weakness, paresthesias, and constipation for the past week. Physical examination revealed increased pigmentation, especially on skinfolds and extensor surfaces. Bluish black discoloration of the areolae and mucous membranes was also noted

Q1) Mention 3 drugs that can be used to treat Addison's disease

1)
2)
3)

Q2): Mention the MOAs of the drugs mentioned in Q1

Ans:

Q3) Mention the possible ADRs in the case of toxicity for the drugs mentioned in Q1

1)
2)
3)
4)
5)
6)

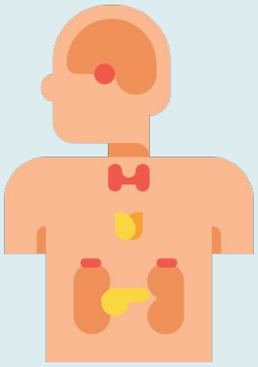
Answers

A1) Prednisone, Dexamethasone, Hydrocortisone

A2) By binding to the intracellular receptor -> The steroid receptor complex enters the nucleus as a dimer, binds to the glucocorticoid response element (GRE) on the gene, and regulates gene transcription by RNA polymerase 2 and associated transcription factors .-> The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response

A3) Cushing's syndrome, Diabetes Mellitus, Osteoporosis, Cataract, Peptic ulcer, Impaired wound healing

Feedback Form



Endocrine Block

Pharmacology Team 439

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