Lecture 5

Pharmacology of corticosteroids

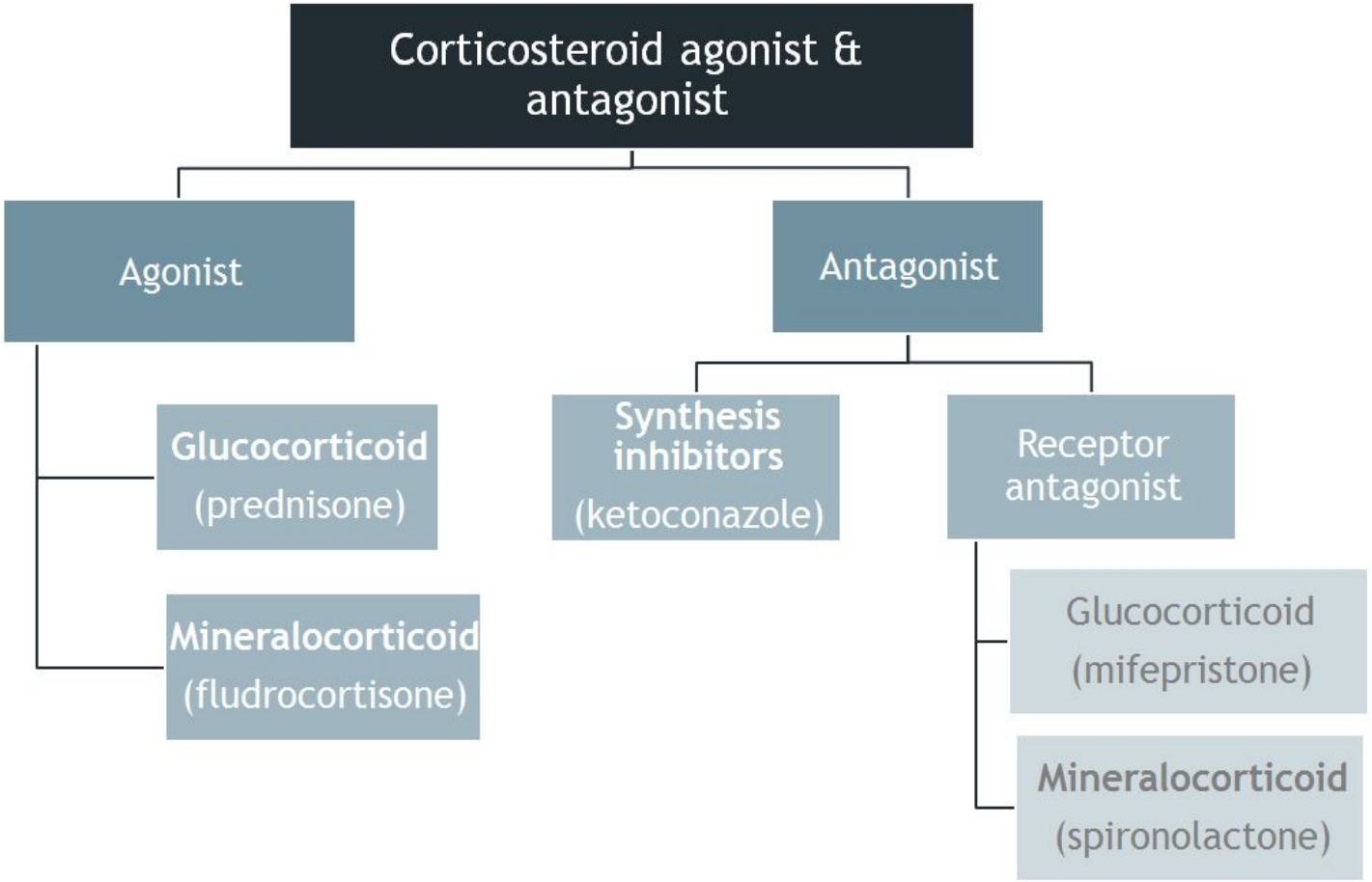
Objectives:

★ not given

- Additional Notes
- Important
- Explanation –Extra-

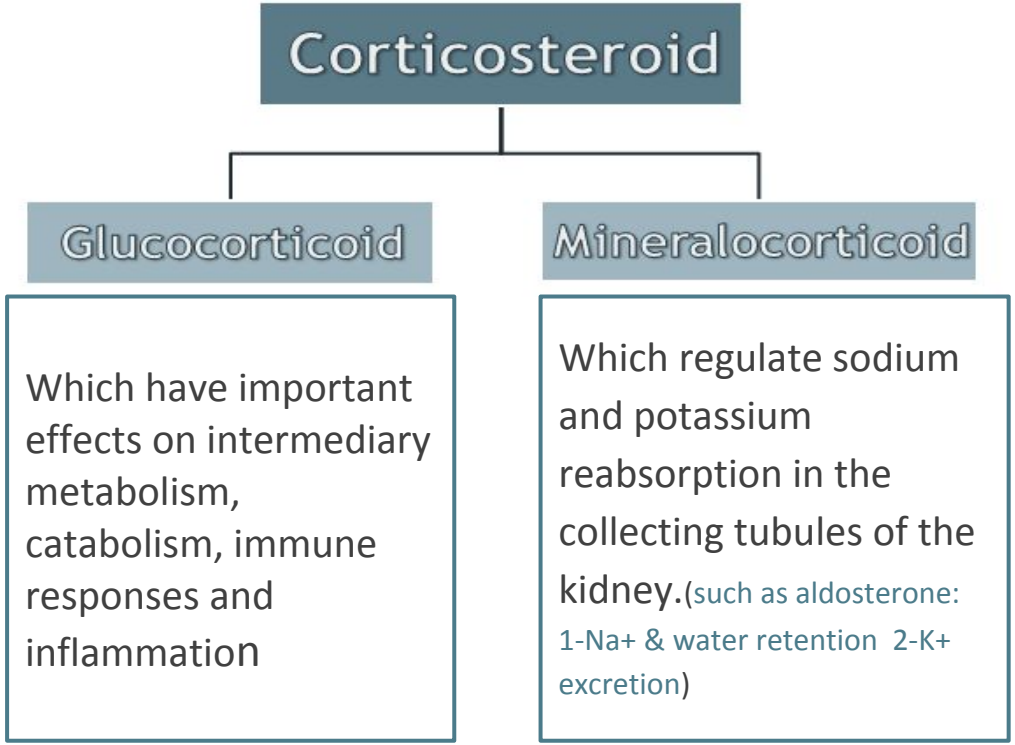
before starting, please check our Endocrine block correction

For any correction, suggestion or any useful information
do not hesitate to contact us: Pharmacology434@gmail.com


Corticosteroid agonist & antagonist
Agonist
Antagonist
Glucocorticoid (prednisone)
Mineralocorticoid (fludrocortisone)
Synthesis inhibitors (ketoconazole)
Receptor antagonist
Glucocorticoid (mifepristone)
Mineralocorticoid (spironolactone)

Introduction

- The Corticosteroids are steroid hormones produced by the adrenal cortex.
- They consist of two major physiologic and pharmacologic groups.



Classification of corticosteroid -they are classified on the basis of their duration of action

Agent	Activity[1]			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	4	Oral, injectable
Meprednisone[2]	5		0	4	Oral, injectable
Intermediate-acting glucocorticoids					
Triamcinolone	5	5[3]	0	4	Oral, injectable, topical
Paramethasone[2]	10		0	2	Oral, injectable
Fluprednisolone[2]	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[2]	0	0	20		Injectable, pellets

6h-12h

12h-36h

>36h

The ideal corticosteroid who has **more** anti-inflammatory activity, **less** salt retention & **more** power to penetrate through the normal skin & mucous membrane

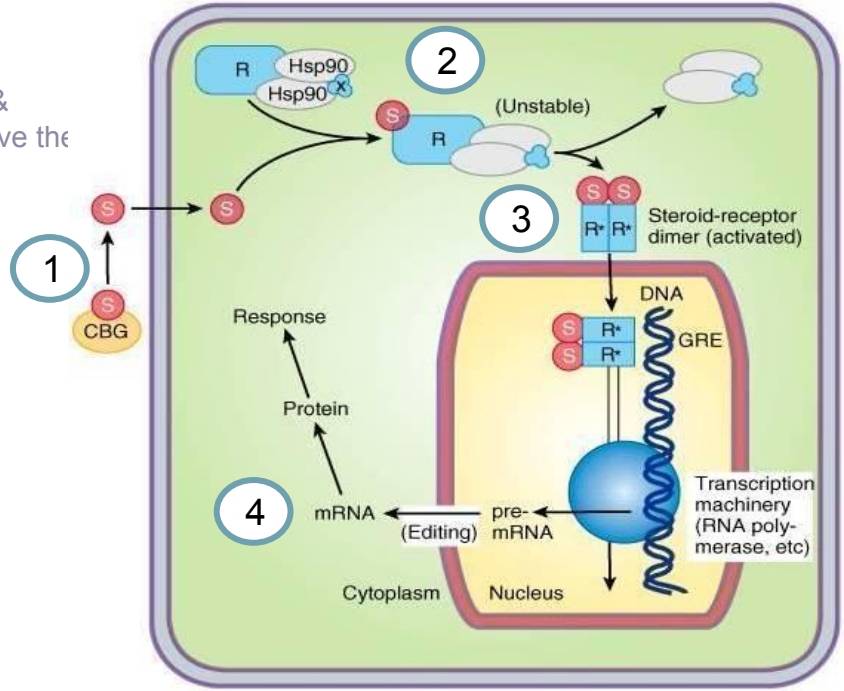
Pharmacodynamics:

A. Mechanism of Action:

glucocorticoid & mineralocorticoid have the same MOA

1-Corticosteroid is present in the blood bound to the corticosteroid binding globulin(CBG) and enters the cell as the free molecule.

2-The intracellular receptor is bound to the stabilizing proteins, including heat shock protein 90(Hsp90) and several others(X). When the complex binds a molecule of steroid, the Hsp90 and associated molecules are released.(When the drug is bound with the receptor the stable protein is detached from the receptor)



3-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 polymerase2 and associated transcription factors.

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

B. Organs and tissue effects (of glucocorticoid)

1-Metabolic effects	2-Catabolic effects
• Glucocorticoids stimulate gluconeogenesis, as a result • Blood glucose rises • Insulin secretion is stimulated • Lipolysis and lipogenesis are stimulated • With a net increase of fat deposition in certain areas e.g,the face (moon facies) and shoulder and back(buffalo hump)	• Glucocorticoids cause muscle protein catabolism (muscle weakness) • Lymphoid and connective tissue fat and skin undergo wasting. (skin becomes thin) • Catabolic effects on bone lead to osteoporosis • In children growth is inhibited

cont. B. Organs and tissue effects

3-Immunosuppressive effects	4-Anti – inflammatory effects (Inhibit the release of leukotrienes, prostaglandin & histamine)	5-Other effects
• Glucocorticoids inhibit cell mediated immunologic functions, especially dependent on lymphocytes. • Glucocorticoids do not interfere with the development of normal acquired immunity but delay rejection reactions in patients with organ transplants.	• Glucocorticoids have important effects on the distribution and function of leukocytes • These drugs increase neutrophils and decrease lymphocytes, eosinophils, basophils and monocytes. • The migration of leukocytes is also inhibited	• 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. • GIT: Large doses also stimulate gastric acid secretion and decrease resistance to ulcer formation

Cortisol Important Glucocorticoids

characteristic	• The major **natural** glucocorticoid is cortisol(hydrocortisone). • The physiologic secretion of cortisol is regulated by adrenocorticotropin(ACTH) and varies during the day(circadian rhythm). • The peak occurs in the morning and the trough occurs about midnight (The drugs will be more beneficial if we use in the morning)
Pharmacokinetics & dynamic	• Given orally ,cortisol is well absorbed from GIT • Cortisol in the plasma is 95% bound to CBG • It is metabolized by the liver and has short duration of action compared with the synthetic congeners. • It diffuses poorly across normal skin and mucous membranes
	• The cortisol molecule also has a small but significant salt – retaining (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).

Synthetic Glucocorticoids

prednisone and its active metabolite:(prednisolone, dexamethasone, triamcinolone).	Beclomethasone and budsonide
• longer half life • Longer duration of action • reduce salt retaining effect • better penetration of lipid barriers for topical activity Compared to cortisol	• 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 • These drugs rapidly penetrate the airway mucosa. • very short half lives after they enter the blood, so that systemic effects and toxicity are greatly reduced.

Toxicity (adverse effects)

Logically the AE are exaggerated action of cortisol ☺

Cushing's syndrome

(iatrogenic, by higher doses more than 100mg hydrocortisone daily for more than 2 weeks characterized by moon shape face and buffalo hump)

Increased growth of fine hair on face ,thighs and trunk.
Myopathy, muscle wasting, thinning of skin, Diabetes Mellitus

Osteoporosis

and aseptic necrosis of the hip.
wound healing is impaired
In general patients treated with corticosteroids should be on high protein and potassium-enriched diets

Peptic ulcer

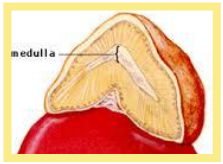
Acute psychosis, depression
Subcapsular cataracts
Growth suppression ,Hypertension

To avoid adrenal insufficiency in patients who have had long term therapy, additional stress doses may need to be given during serious illness, or before major surgery

Adrenal suppression
Methods for minimizing these toxicities include
Local application(e.g ,aerosol for asthma)
Alternate day therapy(to reduce pituitary suppression)
Tapering the dose soon after achieving a therapeutic response

Synthetic Glucocorticoids (clinical uses)

Adrenal disorders



- Addison's disease(chronic adrenal cortical insufficiency)
- Acute adrenal insufficiency associated with life threatening shock, infections or trauma
- Congenital adrenalhyperplasia (in which synthesis of abnormal forms of corticosteroids are stimulated by ACTH.

Collagen vascular disorders

- Rheumatoid arthritis
- systemic lupus erythematosus
- giant cell arteritis
- poly myositis,
- mixed connective tissue syndrome

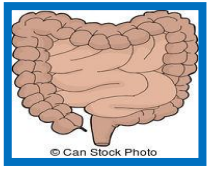
Allergic reaction

- Bronchial Asthma
- angioneurotic edema
- drug reactions
- Urticaria
- allergic rhinitis

Hematologic disorders

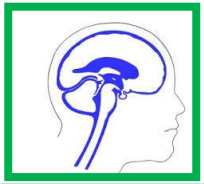
- Leukemia
- Multiplemyeloma
- Acquired hemolytic anemia
- acute allergic purpura

GIT



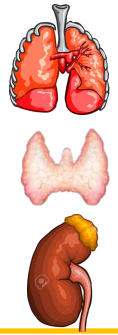
- inflammatory bowel disease
- non tropical sprue

Neurologic disorders



- cerebral edema
- after brain surgery to minimize cerebral edema
- multiple sclerosis

Others:



- Pulmonary diseases(e.g.; aspiration pneumonia, bronchial asthma, sarcoidosis
- Thyroid diseases(malignant exophthalmos, subacute thyroiditis)
- Renal disorders(nephrotic syndrome)
- Miscellaneous (hypercalcaemia, mountain sickness)
- Infections(acute respiratory distress syndrome, sepsis)
- Organ transplants (prevention and treatment of rejection – immunosuppression)

Mineralocorticoids

Aldosterone	Fludrocortisone
• The Major natural mineralocorticoid in human. • Regulation: by ACTH and by the renin-angiotensin system and is very important in the regulation of blood volume and blood pressure.	• Is a mineralocorticoid favored for replacement therapy after adrenalectomy and in other conditions in which mineralocorticoid therapy is needed
• Aldosterone has short half life. • little glucocorticoid activity.	• long duration of action • significant glucocorticoid activity

MOA:is same as that of glucocorticoids

Corticosteroid Antagonists

group	Receptor Antagonists		Synthenthtic inhibitors		
drugs	• Spironolactone • eplerenone	• Mifepristone	Aminogluthimide	ketoconazole	Metyrapone
MOA	Antagonize aldosterone at its receptor	competitive inhibitor of: • glucocorticoid receptors • progesterone receptors	It blocks the conversion of cholesterol to pregnelone Inhibits the synthesis of all hormonally active steroids	It inhibits the cytochrome p450 enzymes necessary for the synthesis of all steroids	
Uses	- REMEMBER: Spironolactone is a potassium-sparing diuretic. So we use it In conditions when we want less Aldosterone e.g.: hypertension , edema functioning adrenal adenoma involving zona glomerulosa	useful in the treatment of Cushing's syndrome	• Adrenal cancer, when surgical therapy is impractical or unsuccessful because of metastasis.		
			Adrenocortical cancer (steroid producing tumor) in conjuction with other drugs.	It is used in a no. of conditions in which reduced steroid level are desirable 1.Adrenal carcinoma 2. Hirsutism 3.Breast cancer 4. Prostate cancer	

MCQ's

1-Which one of the following is an effect of the glucocorticoid

A-increase the metabolism of the carbohydrates
B-it has a significant effect as anti-inflammatory agent
C-it is useful for delaying the rejection of the organ transplant
D-all of the above

2-Mineralocorticoid regulates the Na & k reabsorption by

A-water & Na retention
B- K excretion
C-water & Na excretion
D- K retention
E- A&B

3-The steroid–receptor complex enters the nucleus as

A-monomer
B-dimer
C-trimer
D-tetramer

4-Hydrocortisone is regulated by ACTH, however it reaches its peak

A-in the morning
B-at night
C-it is the same level the whole day
D-in the beginning of the month

5-Which of the following is NOT true about cortisol

A- 95% bound to CBG in the plasma
B-short duration of action
C-metabolized in the liver
D- diffuse strongly across normal skin & mucous membranes

6-drug-receptor complex is formed within

A-cytosol
B-nucleus
C-cell membrane
D-nucleolus

1-D
2-E
3-B
4-A
5-D
6-A

7- which of the following is true regarding prednisone?

A- it has shorter half life compared to cortisol.

B- has a significant mineralocorticoid activity.

C- used to topical activity.

D- Non

A 55 year old female who is recently transplanted -8 a kidney comes to the primary care unit because of sever backache she said maybe because of the weight I gained after sugary . What is the most :(probably cause of her symptoms: (pathology

A- steroid toxixity

B- Addison's disease

C- vitD deficiency

D- functioning adrenal adenoma

which one of the following is not related to -9 :mifepristone

.A- is an irreversible glucocorticoid blocker

B- useful for the treatment of AD

C-is an competitive inhibitor of Estrogen

D- is an glucocorticoid receptor antagonist

A 53 year old male has undergo adrenalectomy -10 after a serious bilateral injury. Which of the following is :best in this case

A- Spironolactone

B- ketoconazole

C- Fludrocortisone

D- budsonide

A 33 year old female who wae prescribed a -11 dexamethasone for her IBD. She has mood disturbances and latly she gained 19kg in weigt she also had an incrased hair growth. Which of the :following is the best drug for her

A- Beclomethasone

B- Metyrapone

C-Fludrocortisone

D-Mifepristone

7-C
8-A&D
9-D
10-C
11-B

Good luck!

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