PHARMACOLOGY/THERAPEUTICS II BLOCK III HANDOUTS – 2016-17

67. Hypothalamic/Pituitary Hormones – Clipstone

68. & 69 Estrogens and Progesterone I & II – Clipstone

70. Androgens – Clipstone

71. & 72 Diabetes Drugs I & II – Clipstone

73. Thyroid/Anti-Thyroid Drugs – Clipstone

74. Calcium Metabolism – Clipstone

75. Adrenocorticosteroids and Antagonists - Clipstone

The Pharmacology of Hypothalamic & Pituitary Hormones

Date: Thursday, March 16th, 2017 – 10:30am-12:00pm

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Describe the role of the Hypothalamic-Pituitary axis in regulating the production of the major anterior pituitary hormones and discuss the role of negative feedback mechanisms.

2. Describe the principal physiological effects of the major anterior pituitary hormones on their primary target organs.

3. List the drugs used in the treatment of growth hormone deficiency and describe their specific indications, contraindications, mechanism(s) of action and major adverse effects.

4. List the drugs used in the treatment of growth hormone excess and describe their specific indications, contraindications, mechanism(s) of action and major adverse effects.

5. List the drugs used to treat disorders of the Hypothalamic-Pituitary-Prolactin axis and describe their indications, contraindications, mechanism(s) of action and major adverse effects.

6. Describe the role of the Hypothalamus/Pituitary-gonadal axis and the gonadotrophin and ovarian hormones in the regulation of events during the ovarian cycle.

7. List members of the GnRH agonist and antagonist class of drugs and describe their indications, contraindications, mechanism of action and major adverse effects.

8. List the members of the gonadotropin agonist class of drugs and describe their indications, contraindications, mechanism of action and major adverse effects.

9. Describe the application of neuroendocrine approaches in assisted fertilization technologies and the treatment of infertility

10. Describe the physiological roles of the major posterior pituitary hormones oxytocin and antidiuretic hormone (ADH)/vasopressin.

11. Describe the indications, mechanism of action, and major adverse effects of oxytocin.

12. Describe the indications, mechanism of action and major adverse effects of desmopressin and the vasopressin receptor antagonists

Drugs to be covered in this lecture:

Drugs affecting the Hypothalamus/Pituitary-growth hormone axis

Somatropin (recombinant human Growth hormone)

Mecasermin (recombinant human IGF1)

Octreotide & Lanreotide (Somatastatin analogues)

Pegvisomant (Growth Hormone receptor antagonist)

Drugs affecting the Hypothalamus/Pituitary-prolactin axis

Bromocriptine & Cabergoline (Dopamine D2 receptor agonists)

Drugs affecting the Hypothalamus/Pituitary-gonadal axis

Leuprolide, goserlin, Buserelin, Triptorelin & naferelin (GnRH agonists)

Ganirelix, Cetrorelix & Degarelix (GnRH antagonists)

Gonadotropins: Menotropins (hMG)- purified human FSH + LH
Urofollitropin (uFSH)- purified human FSH
Recombinant FSH
Recombinant Human choriogonadotrpin (rHCG)

Drugs affecting hormones of the posterior pituitary

Oxtyocin

Desmporessin (long lived analog of ADH/vasopressin)

Vasopressin

Conivaptan (non-selective antagonist of Vasopressin V1 and V2 receptors)

Tolvaptan (selective antagonist of vasopressin V2 receptors)

	INDICATIONS	MOA	Adverse Effects	Misc.
Somatropin (rGH)	HRT for children w GH deficiency Other conditions of small stature Prader-willi syndrome Turner's syndrome Noonan's syndrome Chronic renal insufficiency Idiopathic short stature	Somatropin is a direct agonist of the growth hormone Receptor stimulating gene expression e.g. IGF1	***Children:*** • Idiopathic intracranial HTN • Increased intraocular pressure • Development of insulin resistance ***Adults:*** • Peripheral edema • Arthralgias • Carpal tunnel • Parathesis • Worsening glucose intolerance • Acute pancreatitis	<u>Contraindications:</u> Active malignancy Uncontrolled diabetes Proliferative retinopathy Children with closed epiphyses Prader-willi with severe obesity and/or respiratory obstruction
Somatastatin Analogues *Octreotide* *Lanreotide*	GH excess Gigantism Acromegaly	• Octreotide/Lanreotide are somatostatin receptors agonists • Stimulate pathways that inhibit production of GH	Nausea/Diarrhea (~50%) Gallstones (~25%)	<u>Other clinical uses</u> Esophageal varices Carcinoid syndrome Gastrinoma glucagonoma
Pegvisomant	GH excess Gigantism Acromegaly	Direct antagonist of the GHR		
Dopamine agonists *Bromocriptine* *Carbergoline*	Hyperprolactinemia	Direct agonists of D2 dopamine receptors	Nausea/headache Orthostatic HTN Psychiatric symptoms	Other clinical uses At high doses -treatment of Acromegaly/gigantism

	INDICATIONS	MOA	Adverse Effects	Misc.
GnRH agonists *Leuprolide* *Goserlin* *Buserlin* *Triptorelin* *Naferelin*	• Controlled ovarian stimulation • Palliative therapy of hormone-dependent tumors • Suppression of inappropriate growth of hormone-dependent tissues e.g. endometriosis & fibroids • Treatment of precocious puberty • Suppression of endogenous puberty in gender dysmorphic adolescents	Sustained activation of GnRH receptor inhibits release of gonadotropins	Side effects associated with Gonadal hormone deprivation e.g. hot flashes Decreased bone density Vaginal dryness/atrophy Erectile dysfunction	Contraindications: Pregnacy
GnRH Antagonists *Ganirelix* *Cetrorelix* *Degarelix**	***Ganirelix/Cetrorelix*** • Controlled ovarian stimulation ***Degarelix*** • Advanced prostate cancer	• Antagonize GnRH receptors • Reduce gonadotropin release	Side effects associated with Gonadal hormone deprivation e.g. hot flashes Decreased bone density Vaginal dryness/atrophy Erectile dysfunction	Contraindications: Pregnacy
Gonadotropins *hMG (FSH/LH)* *Urofollitropin (FSH)* *Follitropin α/β (rFSH)* *HCG*	• Infertility treatment in anovulatory women • Ovarian hyperstimulation • Male infertility in hypogonadotopic hypogonadism	***Female:*** • FSH & hMG used to stimulate follicular development • HCG used to trigger ovulation via the LH receptor ***Male:*** • HCG used to trigger endogenous testosterone synthesis via the LH receptor	***Female:*** • Multiple pregnancies • Ovarian Hyperstimulation Syndrome - Increased vascular permeability/ potentially life threatening ***Male:*** • Gynecomastia	

	INDICATIONS	MOA	Adverse Effects	Misc.
Oxytocin	• Induction of labor requiring expedited vaginal delivery e.g. uncontrolled diabetes worsening pre eclamsia Intrauterine infection Ruptured membrane protracted labor • To treat uterine atony (failure of uterus to contract following delivery)	Acts through cognate GPCR expressed on uterine SMC & breast	Toxicity is rare Excessive stimulation of uterine Contractions can cause fetal distress, placental abruption or uterine rupture At very high concentrations can activate vasopressin receptors Leading to excessive fluid retention	
Desmopressin (long lived analogue of ADH)	• Neurogenic Diabetes Insipidus • Nocturnal enuresis • Minor bleeding in mild hemophilia & von Willebrand's disease	• Selectively activates V2 vasopressin receptors in kidney to promote water reabsorption • Activates V2 receptors on endothelial cells to release vWF	Headache Hyponatremia Acute thrombotic events (Rare)	
Vasopressin	Second line agent used in Treatment of vasodilatory shock refractory to epinephrine	Direct full agonist of both V1 & V2 vasopressin receptors	Atrial fibrillation Low cardiac output Cardiac arrhthymia Hyponatremia	
Vasopressin receptor Antagonists *Conivaptan* *Tolvaptan*	Hypervolemic hyponatremia Due to SIADH (syndrome of Inappropriate ADH secretion)	Conivaptan: Antagonizes both V1 and V2 receptors Promotes increased water excretion and raises serum Na+ Tolvaptan: Selectively blocks V2 receptors	Tolvaptan associated with hepatotoxicity (treatment limited to < 30d) Osmotic demylination syndrome	

The Pharmacology of Estrogens & Progestins

Date: Friday, March 17th, 2017 – 8:30am-10:30am

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Describe the principal physiological actions of both estrogens and progestins.

2. Describe the role of the Hypothalamic-Pituitary gonadal axis in the regulation of gonadal hormone synthesis.

3. Describe the biosynthesis and pharmacokinetics of the major endogenous estrogens estradiol, estrone and estriol, especially the role of aromatase.

4. Compare and contrast the principal pharmacological and pharmacokinetic differences between ethinylestradiol, conjugated equine estrogens, esterified estrogens and estrogen esters

5. Describe the major indications, contraindications, clinical uses and major adverse effects of estrogen and progestin therapy.

6. Describe the pharmacokinetic effects of CYP450 inducers on the clinical efficacy of estrogens and progestins

7. Discuss the underlying rationale behind the use of HRT in the pharmacotherapy of menopause

8. Define the term Selective Estrogen Receptor Modulators (SERMs).

9. Describe the mechanism(s) of action, indications, contraindications, clinical uses and major adverse effects of the most commonly used SERM agents including tamoxifen, clomiphene and raloxifene.

10. Describe the mechanism(s) of action, indications, contraindications, clinical uses and major adverse effects of fulvestrant.

11. List the mechanism(s) of action, indications, contraindications, clinical uses and major adverse effects of the aromatase inhibitor class of drugs.

12. Describe the indications, contraindications, mechanism(s) of action, major adverse effects and potential for drug interactions of the three kinds of oral contraceptive pill.

13. Describe the indications, contraindications, clinical use, mechanism of action, and major adverse effects of mifepristone

Drugs to be covered in this lecture:

Estrogens
Estradiol
Estrone
Estriol
Ethinylestradiol
Conjugated equine estrogens
Esterified estrogens
Estrogen esters

Progestins
Norgestrel
Levongestrel
Norethindrone
Desogestrel
Gestodene
Norgestimate

SERMS
Tamoxifen
Raloxifene
Clomiphene

SERD
Fulvestrant

Aromatase inhibitors
Anastrozole
Letrozole
Exemestane

Progesterone receptor partial agonists and antagonists
Ulipristal
Mifepristone (RU-486)

	INDICATIONS	MOA	Adverse Effects	Misc.
Estrogens	• HRT for postmenopausal women • Component of oral contraceptive • Primary hypogonadism • Primary ovarian insufficiency *Note if uterus present also need a progestin to reduce risk of endometrial cancer*	Direct agonist of Estrogen receptor	Increased risk of: • Endometrial cancer • Thromboembolic disease • Gallbadder disease • Post menopausal bleeding • Dementia (older patients) • Breast tenderness • Severe migraine headaches	Contraindications: • High risk/Prior history Breast Cancer • History endometrial cancer • History thromboembolic disease • History of genital bleeding • Liver disease • Heavy smoking
Tamoxifen	• Primary prevention of high risk Breast cancer • Treatment of advanced breast cancer • Treatment male gynecomastia	Acts as a SERM • ER antagonist in breast • ER partial agonist –endometrium & bone	• Hot flashes • Increased risk of thromboembolic events • Increased risk of endometrial cancer	• Prior history thromboembolic events • Prior history endometrial cancer
Raloxifene	• Treatment of osteoporosis in post menopausal women • Alternative to tamoxifen in breast cancer primary prevention	Acts as a SERM • Partial agonist bone (induces ER-dependent bone promoting genes) • ER Antagonist in endometrium & breast	• Hot flashes • Increased risk of thromboembolic events • Leg cramps	• Prior history of thromboembolic events • Pregnancy (birth defects)
Clomiphene	• Female infertility due to anovulation e.g. PCOS	Acts as a SERM • ER antagonist hypothalamus/pituitary -inhibits ER negative feedback & maintains gonadotropin release • ER partial agonist in ovary	• Hot flashes • Multiple pregnancies	
Fulvestrant	Treatment of advanced ER+ metastatic breast cancer Typically following failure of tamoxifen therap	Binds the Estrogen receptor And promotes its degradation via the proteosome - inhibits ER signaling	• Hot flashes • Increased risk of thromboembolic events • Elevated liver enzymes	Pregnancy/lactation

	INDICATIONS	MOA	Adverse Effects	Misc.
Aromatase Inhibitors *Anastrozole* *Letrozole* *Exemestane*	Adjuvant therapy of ER+ Breast cancer in post menopausal women	Inhibit aromatase ➔Prevent the conversion of androgens into estrogens	• Symptoms of estrogen deficiency • Increased bone fractures • Unlike tamoxifen does not Increase endometrial cancer	Premonopausal women since there is little effect due to increased homeostatic expression of aromatase
Progestins *Norgestrel* *Levongestrel* *Norethindrone* *Desogestrel* *Gestodene* *Norgestimate*	Hormone replacement Hormonal contraception	Agonists of the PR (some also weakly activate AR) Results in: (A)➔Decrease in frequency of GnRH pulses ➔Decreased gonadotropins ➔Decreased ovulation (B) Thickens cervical mucus ➔ impairs sperm penetration (C) Reduces endometrial growth & impairs blastocyst implantation	• Menstrual irregularities • Brest tenderness • Ovarian cysts • Acne	
Combined Oral Contraceptive Estrogen + progestin	Contraception Other clinical uses • Treatment of menstrual cycle disorders • Hyperandrogenism (e.g. Acne) • Bleeding due to fibroids • Treatment of endometriosis • Decrease risk of endometrial & ovarian cancer	Estrogen + progestin ➔inhibit GnRH release ➔Inhibit LH + FSH ➔Inhibit follicular development & ovulation Progestin also: Promotes thickening of cervical mucus Reduces endometrial growth	• Bloating, nausea • breast tenderness • Breakthrough bleeding • Risk of venous thrombosis • Risk of MI • Increased risk hepatic adenoma	<u>Contraindications</u> • Age > 35 y & smoking • Coronary artery disease • History venous thrombosis • History of stroke • Systemic lupus • History breast cancer • History liver disease <u>Drug interactions</u> Estrogen metabolized by CYP3A4 Decreased clinical efficacy In presence of CYP3A4 inducers

	INDICATIONS	MOA	Adverse Effects	Misc.
Emergency Contraception I *High Dose levonorgestrel*	Prevention of pregnancy Following unprotected sex or failure of barrier contraception	Activates PR Inhibits or delays ovulation by inhibiting the LH surge	Nausea Delay of menses	Only effective if given 1-2d prior to LH surge Must be given within 72h of intercourse - Taken once daily for 5 d
Emergency Contraception II *Ulipristal*	Prevention of pregnancy Following unprotected sex or failure of barrier Contraception Also- treatment of uterine fibroids	Partial agonist of PR - acts a antagonist in presence of progesterone Inhibits or delays ovulation by antagonizing PR-dependent genes involved in follicular rupture Effective even if given at time of LH surge	Nausea Delay of menses	Effective when given up to 5 days after sex <u>Contraindications:</u> Pregnancy
Mifepristone + misprostol	Medical Abortifacient (<70 d gestation)	PR antagonist impairs development of endometrium & promotes menses Also GR & AR antagonist Misprostol (PGE1 analog) promotes uterine contraction and expulsion of blastocyst	Excessive vaginal bleeding Abdominal cramps	<u>Contraindications:</u> • Chronic adrenal insufficiency as can precipitate an adrenal crisis • Bleeding disorder or anticoagulants

The Pharmacology of Androgens

Date: Tuesday, March 21st, 2017 –10:30-11:30am

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Describe the principal physiological actions of testosterone.

2. Describe the role of the Hypothalamic-Pituitary gonadal axis in the regulation of gonadal hormone synthesis.

3. Describe the biosynthesis and peripheral metabolic fate of testosterone, especially the role of aromatase and 5α-reductase.

4. Describe the basic mechanism of androgen action

5. Describe the major indications, contraindications, clinical uses and major adverse effects of testosterone therapy.

6. Discuss how testosterone and drugs that influence testosterone levels have been used as performance enhancing drugs and the major adverse effects that can result from their use

7. Discuss the use of androgen deprivation therapy in the treatment of advanced prostate cancer including the most common therapeutic approaches and their major adverse effects.

8. Describe the indications, mechanism of action and major adverse effects of the androgen receptor antagonist class of drugs including flutamide, bicalutamide, nilutamide, enzalutamide and spironolactone.

9. Describe the indications, contraindications, mechanism of action and major adverse effects of abiraterone and the 5α-reducatse inhibitors.

Drugs to be covered in this lecture:

Androgens
Testosterone
Testosterone cypionate
Testosterone ethanate
Methyltestosterone

Androgen receptor antagonists
Flutamide
Bicalutamide
Nilutamide
Enzalutamide
Abiraterone
Spironolactone

5α-reducatase inhibitors
Finasteride
Dutasteride

	INDICATIONS	MOA	Adverse Effects	Misc.
Testosterone	Male hypogonadism	Direct agonism of the AR To restore testosterone to the normal level	Acne Increased risk prostate cancer Increased risk BPH Worsening of sleep apnea Erythrocytosis Increased risk VTE Increased risk CVD Hepatic dysfunction Suppression of spermatogenesis	<u>Contraindications:</u> Prostate cancer High level of PSA Untreated sleep apnea
Androgen Receptor Antagonists *Flutamide* *Bicalutamide* *Nlutamide* *Enzalutamide*	Treatment of advanced Prostate cancer Used in combination with androgen deprivation therapy (e.g. GnRH agonist/antagonist) Flutamide also used For treatment of hyperandrogenism in women	Directly inhibits action of testosterone and Dihydrotestosterone at the AR	Men- typical effects Of androgen deprivation e.g. sexual dysfunction, gynecomastia , vasomotor responses <u>Rare side effects:</u> 1st Gen- Hepatotoxicity 2nd Gen-increased seizure risk	
Abiraterone	Hormone-resistant prostate cancer Not responding to androgen deprivation therapy	Inhibition of CYP17A1 Inhibits synthesis of testosterone (also effects corisol, but not aldosterone)	Adrenocorticol insufficiency Mineralocorticoid excess	
Spironolactone	Treatment of women with acne, hirsutism, or androgenic alopecia	Antagonist/ weak partial agonist of AR Also mineralocorticoid receptor antagonist- used as diuretic to treat HF	Menstrual irregularities Breast tenderness Orthostatic HTN	<u>Contraindication:</u> Should not be used in men with prostate cancer
5α-reductase Inhibitors *Finasteride* *Dutasteride*	BPH Male pattern baldness Female hirsutism	Inhibits peripheral conversion of testosterone to dihydrotestosterone	Male sexual dysfunction	<u>Contraindication:</u> Pregnancy

Drugs used to treat Diabetes I and II

Date: Diabetes I/II Wednesday March 22nd, 9:30-11:30am

Optional reading assignment: Katzung Chapter 41 p743

Key Concepts and Learning Objectives

1. Describe the fundamental differences between type 1 and type 2-diabetes.

2. List the current diagnostic criteria and therapeutic goals for the treatment of diabetes.

3. Explain the pharmacological differences between the various insulin formulations used in the treatment of diabetes, especially their duration of action and how this affects their influence on the control of postprandial glucose levels versus fasting glucose levels.

4. Explain the biological effects of insulin therapy on muscle, liver and adipose tissue

5. Discuss the relative benefits and disadvantages between a conventional and intensive insulin therapy regimen.

6. Identify the major adverse effects of insulin therapy and the therapeutic approaches to treat this condition

7. List the indications, contraindications and clinical uses for each of the major classes of hypoglycemic agents used in the treatment of type-2 diabetes.

8. Describe the mechanism of action and physiological effects of each of the major classes of hypoglycemic agents, especially their effects on fasting versus post-prandial glucose levels.

9. List the major adverse effects associated with each of the major classes of hypoglycemic agents

10. Discuss the use of combination hypoglycemic drug therapy including the use of insulin in the treatment of type-2 diabetes

11. Apply your knowledge of the pharmacology of the major classes of hypoglycemic drug agents to select the most appropriate medication for a specific patient based upon patient-specific criteria

Drugs to be covered in this lecture:

1. Insulin Formulations

Rapid acting insulin
- Insulin aspart (Novolog®)
- Insulin lispro (Humalog®)
- Insulin glulisine (Apidra®)

Regular Insulin
- Regular Insulin (Humulin R®, Novolin R®)

Intermediate-acting insulin
- NPH Insulin (Humulin N®, Novolin N®)

Long-lasting insulin
- Insulin detmir (Levemir®)
- Insulin glargine (Lantus®)

2. INSULIN SECRETAGOGUES

SULFONYLUREAS

1st Generation:
- Chlorpropamide (Diabinese®),
- Tolbutamide

2nd Generation:
- Glimepiride (Amaryl®)
- Glyburide (DiaBeta®, Micronase®)
- Glipizide (Glucotrol®)

MEGLITINIDES
- Repaglinide (Prandin®)
- Nateglinide (Starlix®)

3. INSULIN SENSITIZERS

BIGUANIDES
- Metformin (Glucophage®)

THIAZOLIDINEDIONES
- Pioglitazone (Actos®)
- Rosiglitazone (Avandia®)

4. Incretin mimetics/modulators
- Exenatide (Byetta®)
- Liraglutide (Victoza®)
- Sitagliptin (Januvia®)
- Saxagliptin (Onglyza®)

5. INHIBTORS OF CARBOHYDRATE DIGESTION

ALPHA-GLUCOSIDASE INHIBITORS
- Acarbose (Precose®)
- Miglitol (Glyset®)

6. SGLT2 inhibitors
- Canagliflozin (Invokana®)
- Dapagliflozin (Farxiga®)

7. Bromocriptine (Cycloset®)

8. Bile acid binding resin
- Colesevelam (Welchol®)

9. Amylin homolog
- Pramlintide (Symlin®)

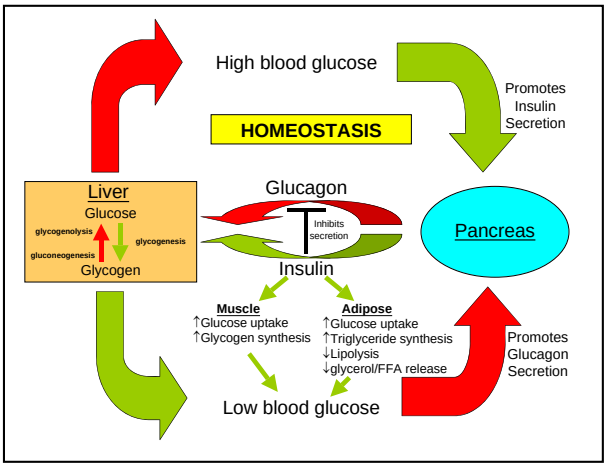
1. DIABETES MELLITUS

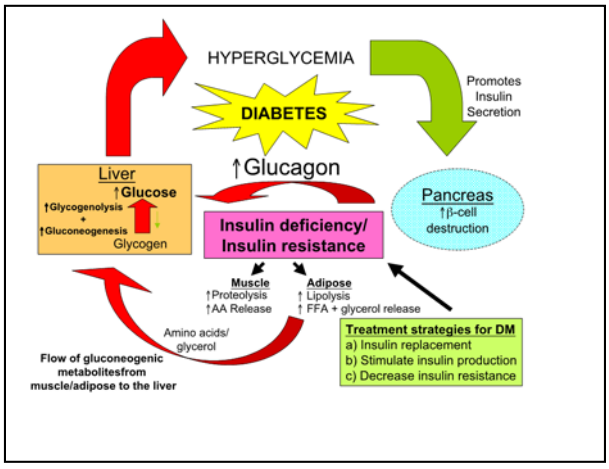
a) Diabetes Mellitus is a metabolic disorder that is characterized by hyperglycemia caused by either a defect in insulin production, insulin action, or a combination of the two.

b) Chronic hyperglycemia is associated with long-term damage, dysfunction and failure of various organs including the eyes, kidneys, nerves, heart and blood vessels.

	Type 1	**Type 2**
Defect	Autoimmune destruction of pancreatic beta cells	Insulin resistance with progressive loss of pancreatic beta cell function
Insulin levels	zero	Typically higher than normal
Insulin resistance	No	Yes
Age of onset	Typically < 30yrs	Typically > 40yrs
Nutritional status at time of onset	Undernourished	Typically obese
Frequency	10-20%	80-90%
Genetic predisposition	moderate	strong
Acute complications	Ketoacidosis/wasting	Hyperglycemia
Chronic complications	Neuropathy, Retinopathy Nephropathy, CVD, Peripheral vascular disease, Lower extremity amputations	Same as type 1
Treatment	Insulin replacement	Oral hypoglycemics/insulin

Regulation of glucose levels during homeostasis and Diabetes





2. DIAGNOSIS AND GOALS OF DIABETES THERAPY

Symptoms of diabetes: polyuria, polydipsia, unexplained weight loss + polyphagia, blurred vision, and a causal plasma glucose concentration > 200mg/dL or FPG of > 126mg/dL.

	Normal	Pre-diabetes IFG/IGT	Diabetes	Treatment Goal
Fasting plasma glucose	**<100 mg/dL**	100-125 mg/dL	**>126 mg/dL**	**90-130 mg/dL**
2hr Peak postprandial plasma glucose	**<140 mg/dL**	140-199 mg/dL	**>200 mg/dL**	**<180 mg/dL**
Glycated hemoglobin (HbA1c)	**<6.0%**		**>6.5%**	**<6.5%**

Treatment Goals: To achieve and maintain glycemic levels as close to the non-diabetic range as possible in order to prevent the development of complications of chronic diabetes.

3. DRUGS TO TREAT TYPE 1 DIABETES

Insulin

a) Insulin replacement therapy is the only treatment available for patients with type 1-diabetes.
b) Commercially available insulin preparations are available in a variety of formulations that differ based upon their time of onset, peak activity and duration of action.

	Formulation	Onset	Peak	Duration	Usage
Rapid-acting Insulin aspart Insulin lispro Insulin glulisine	Amino acid substituted insulin variants that are monomeric for faster absorption	5-15 mins	45-75mins	2-4 hrs	For meals or acute Hyperglycemia; Can be injected immediately before meals
Regular Insulin	Zinc ions added for stability; forms hexamers that dissociate into monomers prior to absorption	30-60 mins	2-4 hrs	6-8 hrs	For meals or acute Hyperglycemia; Needs to be injected 30-45 mins prior to meal
Intermediate acting NPH Insulin	Conjugated with protamine peptide which delays absorption until it is proteolytically cleaved by endogenous tissue proteases	1.5-2 hrs	6-10 hrs	16-24 hrs	Provides basal insulin And overnight coverage
Long acting Insulin glargine	Amino acid substituted insulin variant that forms large ppt at body pH and is slow to be absorbed	~2 hrs	No Peak	20->24 hrs	Provides basal insulin And overnight coverage
Insulin detmir	Insulin with fatty acid side chain that associates with tissue bound albumin that slows its absorption	~2 hrs	No Peak	6-24 hrs	

Mechanism of Action.

a) Insulin acts through its plasma membrane cell surface receptor
b) Insulin corrects hyperglycemia by:
(i) promoting glucose uptake in muscle, liver and adipose
(ii) inhibiting hepatic glucose production (gluconeogenesis/glycogenolysis)
(iii) inhibiting the flow of gluconeogenic precursors from muscle/adipose to the liver
(iv) inhibiting the secretion of the counter-regulatory hormone glucagon

Insulin Administration

a) Subcutaneous injection with syringe: upper arms, upper legs, abdomen (most effective), and buttocks-sites of injection should be rotated to avoid injection site lipodystrophy
   - Initial dose 0.2-0.6 units/kg/day in divided doses
   - Typically 50-75% of dose is given as intermediate/long-acting insulin and the remainder is administered as rapid-acting or short acting insulin at meal times
b) Continuous subcutaneous insulin pump (regular insulin or rapid-acting insulin)
c) Inhaled Insulin (Exubera®; powder formulation of rapid-acting insulin)
   - As effective as regular insulin in type 1 and type 2 diabetes
   - NOW DISCONTINUED due to poor patient adoption

Adverse reactions

Hypoglycemia, tachycardia, fatigue, mental confusion, Injection site lipodystrophy, diapheresis, and hypersensitivity (less common with human insulin).

Drug Interactions.

a) Drugs which DECREASE hypoglycemic effect of insulin: oral contraceptives, corticosteroids, dlitiazem, niacin, ephinephrine, thiazide diuretics, Ca2+ channel blocker, beta2-adrenergic agonists and HIV protease inhibitors.
b) Drugs that INCREASE hypoglycemic effect of insulin: alcohol, beta-blockers, salicylates, lithium, sulfonamides and tetracylines

<u>Hypoglycemia</u>

a) Blood glucose levels < 60 mg/dL
b) Potentially fatal if not promptly treated
c) Caused by lack of glucose availability to the brain and CNS

<u>Symptoms</u>

Mild Hypoglycemia: Tremor, palpitations, sweating and intense hunger

Moderate hypoglycemia: Headache, mood changes and irritability, decreased attention, drowsiness, Patients may require assistance to help themselves

Treatment- oral dose of a simple carbohydrate

Severe hypoglycemia: Unresponsiveness, Unconciousness, convulsions, prolonged severe hypoglycemia can result in death, patients require assistance.

Treatment. Either IV glucose or IV/IM GLUCAGON (stimulates release of glucose from liver.

Insulin Therapy Regimens

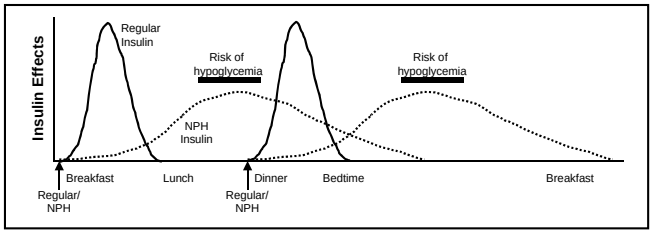
Goal - To achieve near normaoglycemia, which has been demonstrated in clinical trials to prevent and/or slow the onset of diabetic complications
- Achieving normoglycemia requires the administration of multiple doses of insulin every day

Glycemic Goals:	Fasting blood glucose	90-120 mg/dL
	2hr Postprandial BG	<180 mg/dL
	HA1c	<6.5% (higher value in those with significant hypoglycemia risk)

Typical Insulin dose: 0.5-0.8 units/kg/day in a divided dose split between a basla insulin (50-75% of total) and pre-prandial insulin

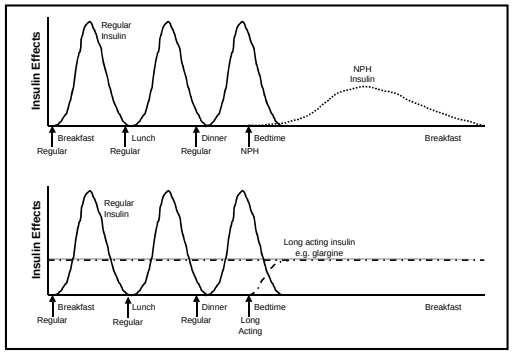
(A) Conventional Insulin Therapy

a) A simple non-physiological insulin regime consisting of either a single or two daily injections of insulin usually a mixture of regular or rapid acting insulin together with intermediate (i.e. NPH) insulin given in fixed amounts in the same syringe before breakfast and dinner
b) Convenient, but will not adequately control glycemia
c) NOT recommended unless patient cannot or will not comply with an intensive insulin regime



(B) Intensive Insulin Therapy/Standard insulin therapy

a) Aims to provide a more physiological profile of insulin by administration of a basal level of insulin to lower fasting glucose (provided by daily or twice daily injections of long-acting insulin preparations e.g. NPH or glargine) together with pre-meal boluses of a rapid or very rapid acting insulin to control postprandial glucose elevations
b) The dose of the pre-meal bolus is determined by the ambient blood glucose level before the meal, the size and composition of the meal and anticipated activity levels.
c) Essentially near normal glycemia can be achieved using an intensive insulin regime
d) Significantly reduces the risk of diabetic complications
e) Recommended for the majority of type-1 patients



Drawbacks to intensive insulin therapy

a) Greater effort required by patient
b) Incidence of hypoglycemia/coma is higher
c) Weight gain more likely
d) Cost (~3x conventional therapy)

4. DRUGS TO TREAT TYPE 2 DIABETES

4.1 ORAL ANTI-DIABETIC DRUGS- INSULIN SENSITIZERS

4.1.1 BIGUANIDES

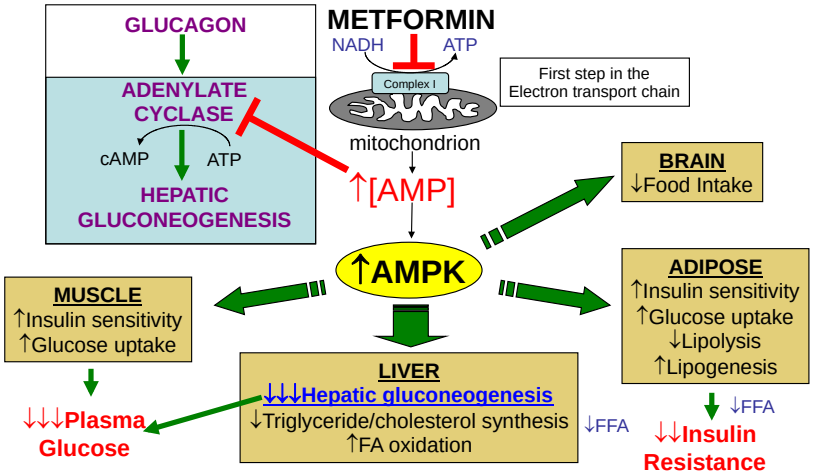
Metformin (Glucophage®)

4.1.1A DESCRIPTION

a) An oral anti-hyperglycemic medication that acts to lower plasma glucose levels primarily by reducing hepatic glucose production.
b) Does NOT act by promoting insulin production
c) **Recommended** by ADA and EASD as **first line treatment** for type 2 diabetes concurrent with lifestyle changes, diet and exercise

4.1.1B MECHANISM OF ACTION

a) Reduces hepatic glucose production by inhibiting both gluconeogenesis and glycogenolysis
b) Increases peripheral glucose uptake and utilization in muscle and fat tissues
c) Effective only in the presence of insulin
d) Acts by inhibiting complex I in the electron transfer chain of mitochondrion resulting in an increase in the cellular concentration of AMP that in turn:
   (i) Inhibits GLUCAGON-induced hepatogluconeogenesis by inhibiting the glucagons-induced activation of adenylate cyclase
   (ii) activates the AMP-dependent protein kinase (AMPK), an important metabolic enzyme involved in cellular and systemic energy homeostasis.
      - Activation of AMPK in muscle and adipose tissue promotes glucose uptake
      - Activation of AMPK in the liver inhibits hepatic glucose production, as well as inhibiting hepatic cholesterol and triglyceride biosynthesis (potentially explains favorable effects of metformin on lipid profiles and the development of CVD- see below).
      - AMPK activation promotes fatty acid oxidation, thereby reducing FFA stores that contribute towards the development of insulin resistance
      - AMPK activity inhibits the activity of inhibitors of the insulin signaling pathway thereby enhancing insulin signaling and preventing insulin resistance.



4.1.1C INDICATIONS AND CLINICAL USE

b) Approved for either monotherapy, or in combination with other oral hypoglycemic drugs, for the treatment/prevention of hyperglycemia in type 2-diabetes.
c) Metformin is rapidly absorbed from the small intestine, it is not metabolized and is secreted in the urine with a half life of 1.5-5 hrs. Peak plasma concentration is achieved in 2 hrs & the duration of its biological effect is ~ 6hrs
d) Primarily affects fasting blood glucose levels (i.e. inhibition of hepatic gluconeogenesis) rather than postprandial glucose increases.
e) Lowers fasting blood glucose by 20% and HbA1c by ~1.5% points
f) Does NOT cause WEIGHT GAIN and can even promote WEIGHT LOSS
g) Does NOT cause HYPOGLYCEMIA
h) Multiple clinical trials show that metformin treatment DECREASES the frequency of MI, diabetes-related death and all-cause mortality in type-2 obese patients compared to other oral hypoglycemic agents
i) Potential beneficial effect on CVD outcomes likely due to the effects of metformin on improving lipid profiles- decreased TG and FFA, small decrease in LDL, modest increase in HDL

4.1.1D ADVERSE EFFECTS

a) Generally well tolerated - only ~5% of patients discontinue due to adverse effects
b) Most common adverse effect is on the GI tract- metallic taste, nausea, diarrhea and abdominal pain, which are minimized by taking the drug with food.
c) Decreases absorption of Vitamin B12, although rarely causes megalobalstic anemia
d) Lactic Acidosis is a rare (<1:100,000), but potentially fatal complication
    - Most associated with use in high risk patients- esp RENAL INSUFFICIENCY
    - Symptoms- deep/rapid breathing, vomiting, abdominal pain, muscle weakness
    - Caused by a build up of lactate in the blood due to the fact that lactate is a substrate for hepatic gluconeogenesis, which is inhibited by metformin.
    - In normal circumstances lactate is cleared by the kidney, but in renal insufficiency the lactate levels increase causing acidification of the blood

N.B. phenformin an earlier biguanide was removed from the market because of increased frequency of lactic acidosis

4.1.1E CONTRAINDICATIONS

a) Women who are pregnant or that are lactating (insulin is the preferred treatment)
b) Impaired renal function, since both metformin and lactate are entirely cleared by the kidney and patients with decreased renal function are more susceptible to drug accumulation and lactic acidosis
c) Not to be given to the elderly >80 yrs due to renal insufficiency
d) Should be discontinued in patients injected with iodinated contrast agents for radiographic studies and not started until 48hrs later to avoid contrast-induced acute renal failure which can increase metformin levels- insulin used during this time period to control hyperglycemia
e) Conditions pre-disposing to lactic acidosis:
    - Congestive heart failure requiring drug therapy
    - Myocardial Infarction- immediate withdrawal
    - Impaired liver function/excessive alcohol consumption

- Impaired renal function
- Shock/septicemia
- Serious acute illness or hypoxic condition
- Hypoxic or ischemic states i.e. lung disease

4.1.2 THIAZOLIDINEDIONES

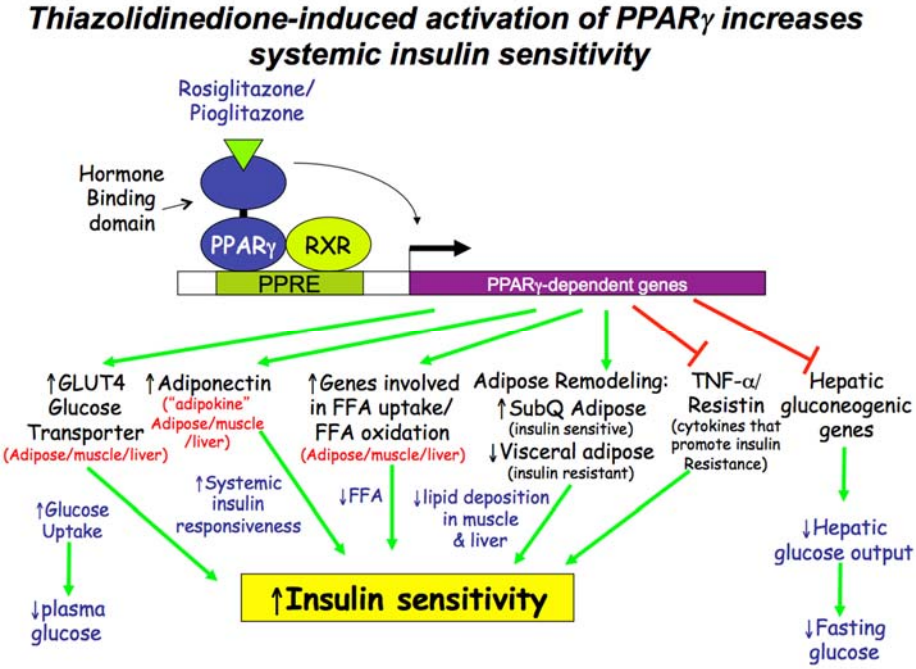
Pioglitazone (Actos®)
Rosiglitazone (Avandia®)

4.1.2A DESCRIPTION

"Insulin Sensitizers" that increase the sensitivity of adipose tissue, skeletal muscle and liver to endogenous insulin

4.1.2B MECHANISM OF ACTION

Thiazolidinediones act as agonists of the peroxisome proliferators-activated receptor gamma (PPARγ) transcription factor, which influences the expression of multiple genes involved in the regulation of insulin sensitivity.



Activation of PPARγ results in the:

(i) Increased expression of GLUT4- the insulin-sensitive glucose transporter
(ii) Increased expression of Adiponectin- an adipocytokine involved in promoting systemic insulin sensitivity
(iii) Increased expression of genes involved in FFA uptake and FFA oxidation, which acts to decrease serum FFA that has been implicated in promoting insulin resistance.
(iv) Decreased expression of the TNF-alpha cytokine involved in promoting insulin resistance

(v) Decreased expression of Resistin an adipocytokine involved in inhibiting systemic insulin sensitivity
(vi) Remodels adipose tissue: Reduces insulin-resistant visceral adipose tissue and increases the appearance of newly differentiated insulin-sensitive subcutaneous adipocytes.
(vii) Inhibits hepatic genes involved in gluconeogenesis
Overall these effects act to improve systemic insulin sensitivity and lower plasma glucose levels.

4.1.2C INDICATIONS AND CLINICAL USE

a) Approved for monotherapy or in combination with either metformin, sulfonylureas or insulin in the treatment of hyperglycemia in type 2-diabetes.
b) Typically decreases FPG with moderate effect on postprandial glucose
c) Decrease Hb1Ac by 0.5-1.4% points
d) Takes 6-14 weeks to achieve maximum effect

4.1.2D ADVERSE EFFECTS

a) Weight gain – mainly subcutaneous not visceral
b) Fluid retention resulting in peripheral edema
- Fluid retention is more common with concurrent insulin use
- Fluid retention caused by increased expression of gamma subunit of Na+ channel in the collecting tubule cells of the nephron leading to increased Na+ reabsorption
- Maybe related to increased risk of heart failure – BLACK BOX WARNING
c) Increased risk of bone fractures in women

4.1.2E CONTRAINDICATIONS

a) Should be used cautiously in patients with underlying liver disease- 1st Thiazolidinedione drug Troglitazone was removed from market due to increased fatalities due to liver failure
b) Heart Failure- should not be given to patients with Class III/Class IV cardiac disease
c) Not recommended for pregnancy (Insulin is preferred therapy)

4.2 ORAL ANTI-DIABETIC DRUGS: INSULIN SECRETAGOGUES

4.2.1 SULFONYLUREAS- INSULIN SECRETAGOGUES

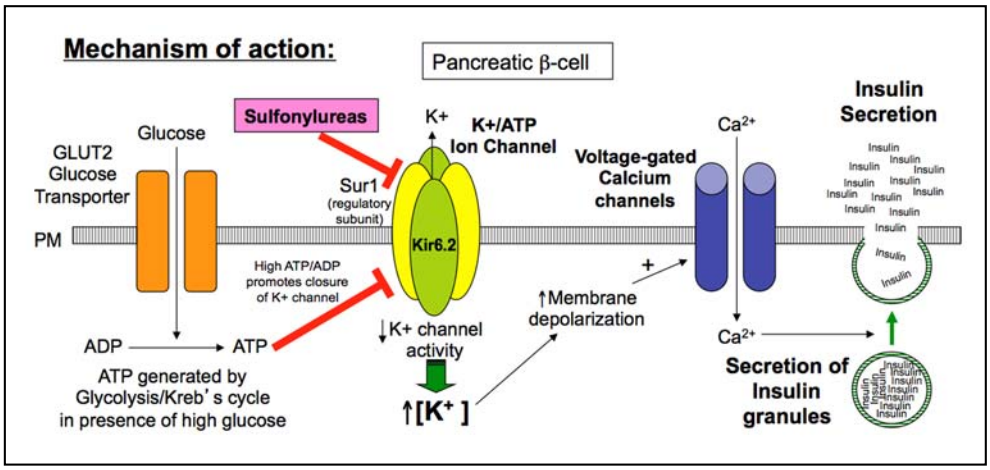
1st Generation:	2nd Generation:
Chlorpropamide (Diabinese®),	Glimepiride (Amaryl®)
Tolbutamide	Glipizide (Glucotrol®)
	Glyburide (DiaBeta®, Micronase®)

4.2.1A DESCRIPTION

Insulin secretagogues that rapidly lower blood glucose levels by promoting insulin secretion from the beta cells of the pancreas.

4.2.1B MECHANISM OF ACTION

Sulfonylureas act by interacting with the SUR1 subunit of ATP-sensitive K+ channels (Kir6.2) expressed on pancreatic beta cells, this inhibits channel activity resulting in cell depolarization that triggers voltage-gated Ca2+-channels leading to Ca2+ influx and the secretion of insulin.



4.2.1C INDICATIONS AND CLINICAL USE

a) For control of blood glucose levels in type 2 diabetes
b) Primarily reduce FPG, with little effect on postprandial glucose increases
c) Decreases blood glucose by ~20% and HbA1c by ~1.5% points
d) Approved for either monotherapy or in combination with other oral hypoglycemic drugs
e) Typically given once per day
f) Most effective in patients who have had diabetes for less than 10 years, whose weight is normal or slightly elevated and that can still secrete considerable amounts of insulin
g) During the chronic progression of diabetes, as the total number of beta cells decrease, the sulfonylureas become less effective.
h) 2nd generation drugs are more potent than 1st generation drugs, are associated with a lower frequency of inducing hypoglycemia and have fewer drug interactions.
i) 2nd generation drugs are similar to each other in efficacy, but differ in dosage and duration of action

	Duration of Biological Effect
First Generation	
Chlorpropamide	24-72 hrs
Tolbutamide	14-16 hrs
Second Generation	
Glipizide	14-16 hrs
Glyburide	20-24+hrs
Glimepiride	24+ hrs

4.2.1D ADVERSE EFFECTS

a) Modest weight gain (~2 kg) – primarily subcutaneous adipose tissue not visceral
b) Can cause hypoglycemia- especially in elderly patients with impaired RENAL and/or HEPATIC function- all drugs metabolized in liver and secreted in urine
c) Severe hypoglycemia is rare

4.2.1E CONTRAINDICATIONS

a) Elderly Patients – lack of awareness of hypoglycemia
b) Patients with sulfa allergies
c) Patients with type 1-diabetes
d) Pregnant or lactating patients (Insulin is the preferred medication)
e) Impaired RENAL/LIVER function – all sulfonylureas metabolized in the liver and metabolites are excreted in the urine.

Note: Glipizide is a short acting sulfonylurea that is metabolized in the liver and is excreted in the urine as inactive metabolites- it is therefore the drug of choice in the elderly or patients with chronic renal failure

4.2.1F DRUG INTERACTIONS

Sulfonylureas are highly protein bound and therefore interact with many drugs e.g. salicylates, beta-blockers, warfarin & phenylbutazone, which compete for binding and act to increase serum concentrations of sulfonylureas thereby resulting in increased potential for hypoglycemia

4.2.2 MEGLITINIDES: NON-SULFONYLUREA INSULIN SECRETAGOGUES

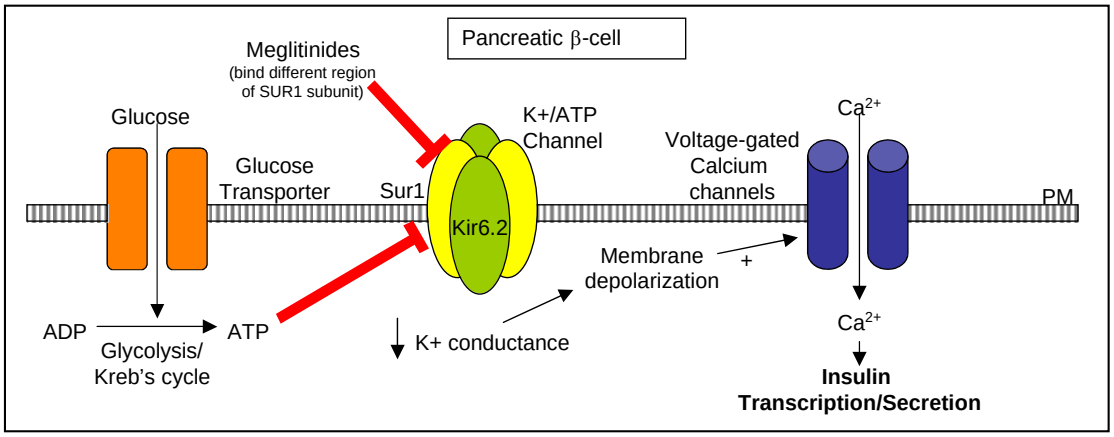
Repaglinide (Prandin®) and Nateglinide (Starlix®)

4.2.2A DESCRIPTION

Short acting glucose-lowering drugs that are structurally distinct from the sulfonylureas, but act similarly to lower blood glucose levels by promoting insulin secretion.

4.2.2B MECHANISM OF ACTION

Meglitinides trigger insulin secretion by a similar mechanism to the sulfonylureas, but interact with a different region of the SUR1 subunit of the beta cell ATP-sensitive K+ channel.



4.2.2C INDICATIONS AND CLINICAL USE

a) Meglitinides are short acting glucose-lowering drugs used for the treatment of hyperglycemia in type 2-diabetes.
b) Both drugs are rapidly absorbed and their peak action is at 1 hr and lasts for 4 hrs, they must therefore be given frequently, typically three times per day with meals. If meal is missed drug should be omitted
c) Primarily affect postprandial glucose elevations with less effect on FPG
d) Likely to be beneficial to patients with barely elevated FPG but prominent postprandial hyperglycemia
e) Monotherapy is indicated early in type-2 diabetes when FPG is not greatly elevated
f) They decrease Hb1Ac by ~1-1.5% points
g) Approved for either monotherapy, or together with metformin and/or a thiazolidinedione.
h) Nateglinide is less effective than repaglinide, which is as effective as sulfonylureas or metaformin at lowering Hb1Ac
i) Considerably more expensive than sulfonylureas (~5-8X)

j) Useful as a replacement for sulfonylureas in patients with sulfa allergies
k) Repaglinide is metabolized to inactive metabolites and is therefore safe to use in patients with renal insufficiency

4.2.2D ADVERSE EFFECTS

a) Weight gain – similar to sulfonylureas
b) Hypoglycemia – although less frequent than with sulfonylureas

4.2.2E CONTRAINDICATIONS

a) Liver disease- both drugs are metabolized primarily in the liver and excreted in the bile – increased risk of hypoglycemia
b) Not to be used during pregnancy

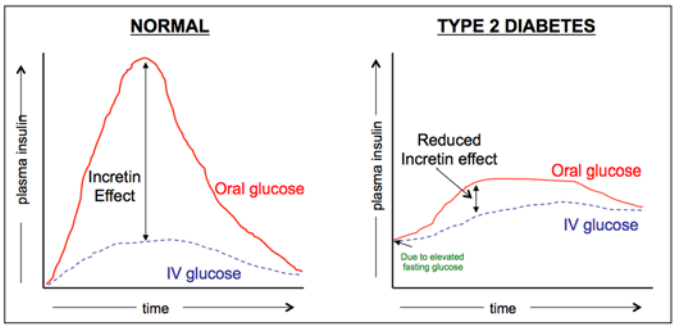
4.3 INCRETIN MIMETICS AND MODULATORS

4.3.1 GLP-1 ANALOGS

Exenatide (Byetta®); Liraglutide (Victoza®)

4.3.1A DESCRIPTION

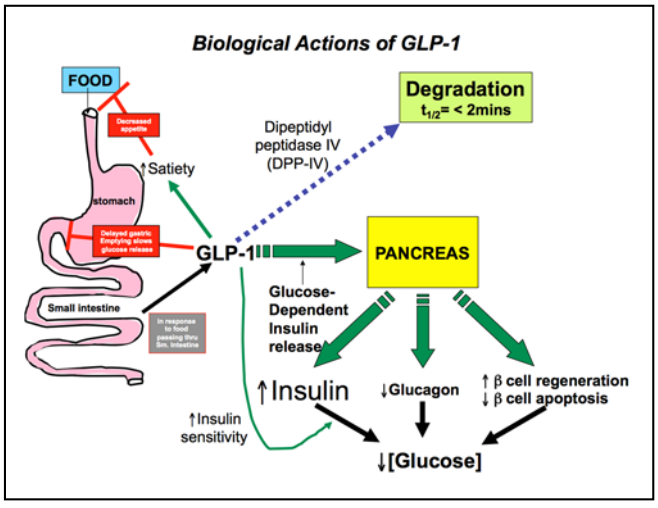
a) Exenatide is a stable analog of Glucagon-like peptide-1 (GLP-1) that binds to the GLP-1 receptor on the pancreatic beta cells and potentiates glucose-mediated insulin secretion
b) GLP-1 is produced by the L-cells of the small intestine and helps mediates the INCRETIN EFFECT on plasma insulin levels



c) Incretin Effect: Observation that plasma insulin levels are higher in response to oral glucose compared to intravenous glucose- indicating that factors produced in the GI tract (i.e. GLP-1) influence insulin secretion.

4.3.1B MECHANISM OF ACTION

a) Exenatide potentiates glucose-induced insulin secretion when glucose levels are high.
b) As glucose levels fall, the enhancing effects of exenatide on insulin secretion diminishes.
c) Suppresses pancreatic production of glucagon
d) Suppresses glucose release from liver
e) Slows stomach emptying
f) Increases satiety
g) Acts to maintain beta cell mass



4.3.1C INDICATIONS AND CLINICAL USE

a) Exenatide and Liraglutide are approved as an alternative to starting insulin therapy in type 2 diabetic patients who have not achieved adequate glycemic control with either metformin, a sulfonylurea, or both.
b) Need to be injected once or twice daily
c) Mainly acts by reducing postparandial glucose concentrations
d) Decreases Hb1Ac by ~0.5-1% point
e) Little risk of hypoglycemia as the enhancing effects of exenatide on insulin secretion diminish as glucose levels fall
f) Do NOT cause WEIGHT GAIN and may cause WEIGHT LOSS

4.3.1D ADVERSE EFFECTS

a) Frequent (30-45%) Nausea vomiting, diarrhea
b) Increased risk of mild to moderate hypoglycemia when used with a sulfonylurea

4.3.1E DRUG INTERACTIONS

Due to the slowing of gastric emptying it can affect the absorption of other orally administered drugs (e.g. contraceptives & antibiotics), which should be taken 1 hr before or 2 hrs after.

4.3.2 DIPEPTIDYL PEPTIDASE-IV (DPP-IV) INHIBITORS

Sitagliptin (Januvia®); Saxagliptin (Onglyza®)

DESCRIPTION

a) Sitagliptin is an inhibitor of DPP-IV, the peptidase that cleaves and inactivates GLP-1
b) Sitagliptin therefore promotes the action of endogenous GLP-1 by increasing its half-life
c) Sitagliptin is an oral medication that is taken once daily.
d) It is rapidly absorbed, reaches a peak 1-4 hrs after ingestion and is effective over 24hrs.
e) Sitagliptin can decrease both FPG and postprandial glucose elevations, although is less effective than either pramlintide or exenatide in limiting postprandial hyperglycemia
f) Stagliptin is approved for adjunct therapy of type-2 diabetes in combination with either metformin or a thiazolidinedione
g) It reduce Hb1Ac almost as effectively as exenatide i.e. 0.6-0.8%
h) There is no effect on weight loss
i) It is not associated with hypoglycemia

4.4 ORAL ANTI-DIABETIC DRUGS: INHIBTORS OF CARBOHYDRATE DIGESTION

4.4.1 ALPHA-GLUCOSIDASE INHIBITORS

Acarbose (Precose®) and Miglitol (Glyset®)

4.4.1A DESCRIPTION

Drugs that reduce postprandial blood glucose levels by inhibiting the rate of digestion of polysaccharides in the small intestine

4.4.1B MECHANISM OF ACTION

Acarbose and Miglitol inhibit the alpha-glucosidase enzyme that lines the brush border of the small intestine and is responsible for the hydrolysis of carbohydrates thereby delaying the absorption of glucose and other monosaccharides.

4.4.1C INDICATIONS AND CLINICAL USE

a) The control of postprandial hyperglycemia- should be taken with each meal
b) Acarbose and Miglitol do NOT cause HYPOGLYCEMIA
c) Acarbose and Miglitol are less potent than sulfonylureas or metformin – they decrease Hb1Ac by 0.5-0.8% points
d) Because different mechanism of action Acarbose and Miglitol have an additive effect on reducing glycemia together with either a sulfonylurea, metformin or insulin
e) Acarbose and Miglitol are not considered to be first line anti-diabetic drugs because of their reduced efficacy and poor tolerance due to side effects (see below)

4.4.1D ADVERSE EFFECTS

a) Unabsorbed carbohydrate causes abdominal pain, diarrheas and flatulence due to osmotic effect and bacterial fermentation
b) Many patients (25-45%) stop taking the drugs due to side effects
c) Do not cause hypoglycemia by themselves, but can increase the risk when given with a sulfonylurea or insulin
d) In event of hypoglycemia patients should be treated with oral administration of glucose not sucrose due to inhibitory effects of drug on the breakdown of sucrose

4.4.1E CONTRAINDICATIONS

a) Chronic intestinal disease
b) Inflammatory bowel disease
c) Colonic ulceration or any degree of intestinal obstruction

4.5 ORAL ANTI-DIABETIC DRUGS: SODIUM GLUCOSE LINKED TRANSPORTER 2 PROTEIN INHIBITORS

4.5.1 SGLT2 INHIBITORS

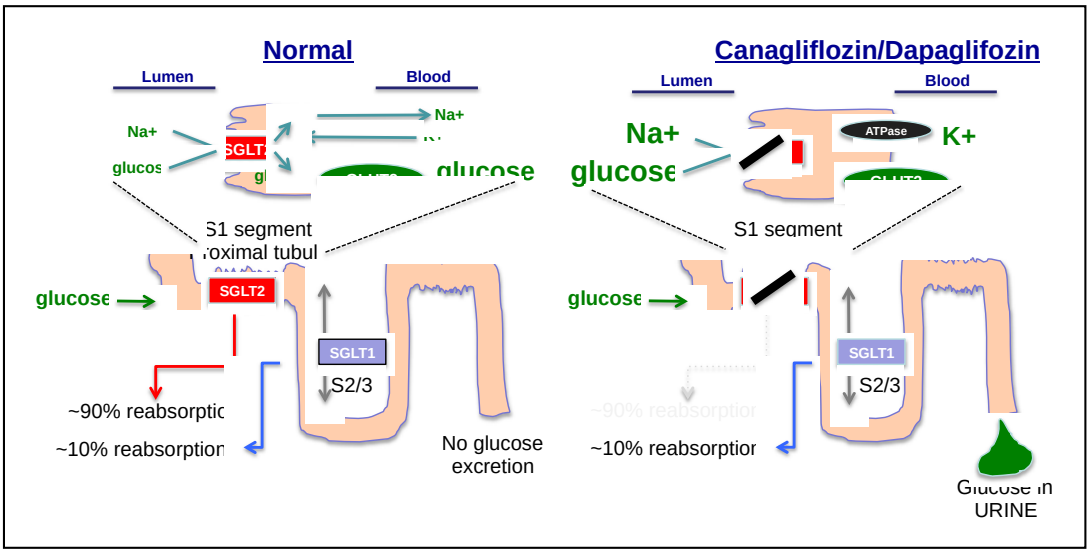
Canagliflozin (Invokana®) & Dapagliflozin (Farxiga®)

4.5.1A DESCRIPTION

Drugs that reduce hyperglycemia by promoting glucose excretion in the urine

4.5.1B MECHANISM OF ACTION

a) Inhibition of Sodium-Glucose Linked Transporter 2 protein (SGLT2) activity in the S1 segment of the proximal renal tubule prevents the normal process of glucose reabsorption leading to excretion of glucose in the urine



4.5.1C

INDICATIONS AND CLINICAL USE

a) Improving glycemic control in Type 2 Diabetes- monotherapy or in combination
b) Decreases HbA1c by **0.5-0.9%**- low risk hypoglycemia when used as monotherapy
c) ↓Body weight- ~ 80g of glucose (200-300 kCal) eliminated each day
d) ↓BP- H_20 eliminated by increased Osomotic diuresis

4.5.1D ADVERSE EFFECTS

a) Urinary Tract Infections- genital mycotic infections
b) Thirst/Dehydration
c) Hypotension
d) ↑LDL-Cholesterol
e) Hypoglycemia **when given with other** anti-hyperglycemia medications
f) Hyperkalemia- especially patients taking Meds that interfere with K+ excretion (e.g. K+ sparing diuretics)

4.5.1E CONTRAINDICATIONS

a) Renal impairment

4.6 ORAL ANTI-DIABETIC DRUGS: BROMOCRIPTINE

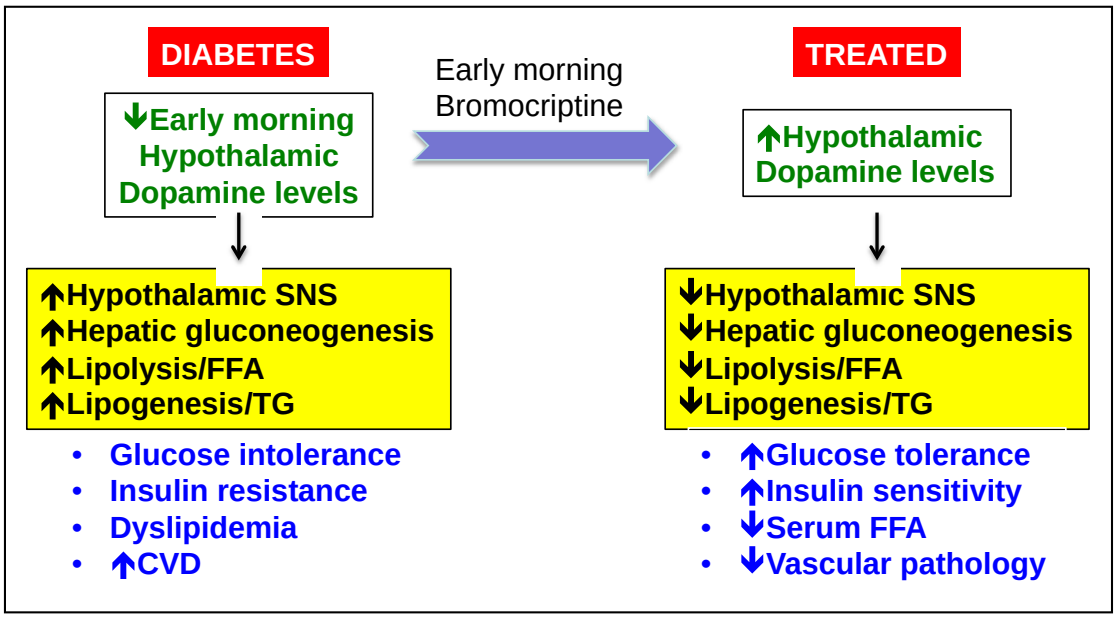
4.6.1 Bromocriptine (Cycloset)

4.6.1A DESCRIPTION

a) Sympatholytic Dopamine D2 receptor agonist
b) Quick Release formulation- taken within 2 hrs of waking
c) decreases HbA1c by ~ 0.5%
d) Dosage much lower than that used in Parkinson's

4.6.1B MECHANISM OF ACTION

a) Exact MOA in diabetes is unknown
b) thought to act on the CNS to normalize the decreased AM dopamine levels present in Type 2 patients
c) Increased morning dopamine signaling antagonizes hypothalamic sympathetic nervous system leading to a decrease in hepatic gluconeogenesis, reduced lipolysis and lipogenesis, which in turn results in an increase in insulin sensitivity and glucose tolerance.



4.7

ORAL ANTI-DIABETIC DRUGS: COVELESELAM (Bile Acid-Binding resin)

4.7.1 Coveleselam

4.7.1A DESCRIPTION:

a) A lipid-lowering drug used in the treatment of hypercholesterolemia
b) Serendipitously found to have beneficial effects in diabetes
c) Used as an **Adjunct "Add On"** anti-diabetic therapy to reduce blood glucose levels by indirectly increasing expression of **GLP-1**

4.7.1B MECHANISM OF ACTION

a) Colesevelam binds bile acids in the small intestine forming insoluble complexes that are excreted in the feces
b) Prevents reabsorption of bile acids
c) Allows bile acids to enter the colon
d) Bile acids bind to the TGR5 GPCR expressed on intestinal cells in the colon to stimulate GLP-1 secretion

4.7.1C INDICATIONS AND CLINICAL USE

a) Add on therapy to metformin, sulfonylureas or insulin
b) Decreases HbA1c by ~ 0.5%
c) NOT considered FIRST LINE anti-diabetic drugs
d) Useful in patients that also exhibit elevated LDL-cholesterol levels

4.8 INSULIN THERAPY THE TREATMENT OF TYPE 2 DIABETES

a) As type 2 diabetes progresses beta cell function gradually declines and insulin therapy is often required to achieve satisfactory glycemic control. Insulin is the most effective medication at lowering glycemia.

b) Insulin can be considered a first-line therapy for all patients with type-2 diabetes and should be the initial therapy for patients HbA1c>10%, fasting plasma glucose >250 mg/dL and random glucose consistently >300 mg/dL, Insulin is also the preferred 2nd line agent in patients with HbA1c > 8.5%.

c) Insulin is indicated in patients presenting with a sudden onset of diabetes, significant recent weight loss, and polyuria accompanied by polydipsia- some of these patients may have late onset type 1 diabetes.

d) Initial therapy is aimed at providing basal insulin with either intermediate (NPH) or long-term insulin (glargine) given once/twice daily before breakfast/dinner. The primary goal of basal insulin is to lower fasting glucose by inhibiting hepatic gluconeogenesis. Note that because of increased obesity and insulin resistance in type 2 diabetics considerably more insulin is required to treat these patients compared to those with type 1 diabetes.

e) If necessary, insulin therapy can be intensified by the addition of regular- or rapid-acting insulin before selected meals in order to reduce postprandial glucose elevations. In this case, any insulin secretagogue medications should be eliminated.

f) Disadvantages of insulin therapy: hypoglycemia, weight gain, and injection site lipodystrophy.

4.9 AMYLIN HOMOLOGS

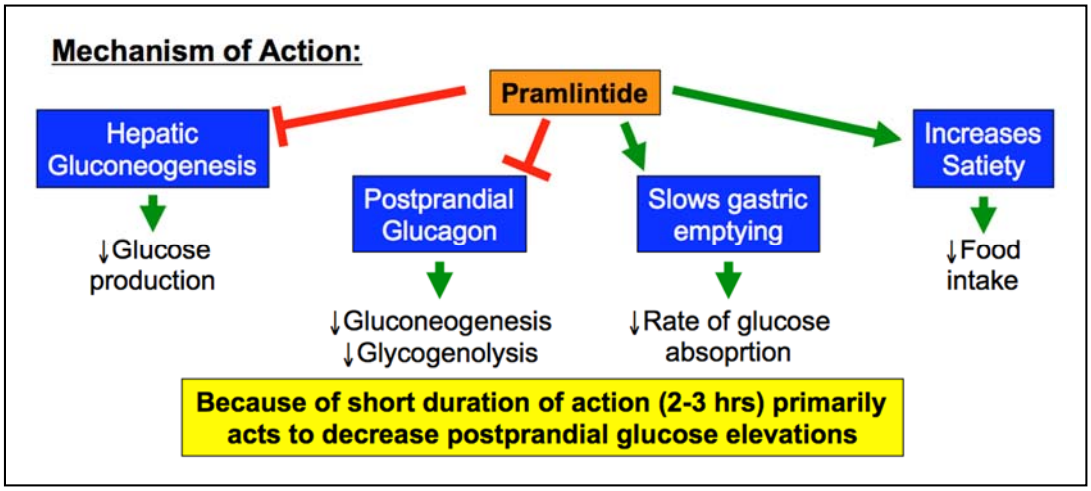
Pramlintide (Symlin®)

4.9A DESCRIPTION

a) Pramlinitide is a synthetic analog of human Amylin, an endogenous neuroendocrine hormone that is synthesized by pancreatic beta cells and co-secreted with insulin, which contributes to glucose control in the postparandial period
b) Amylin production is absent in patients with diabetes

4.9B MECHANISM OF ACTION

a) Decreases hepatic gluconeogenesis
b) Decreases postprandial glucagon levels – i.e. resulting in a decrease in gluconeogenesis, glycogenolysis and lipolysis
c) Slow gastric emptying - this slows the rate of delivery of glucose to the circulation thereby helping prevent excessive increases in the postprandial glucose concentration N.B. gastric emptying is often increased in type1 and type 2 diabetic patients and contributes to rapid rises in postprandial glucose seen in these patients
d) Increases Satiety – i.e. reduces food intake



4.9C INDICATIONS AND CLINICAL USE

a) Pramlinitide is indicated as an ADJUNCT therapy in patients with either TYPE 1 or TYPE 2 diabetes who are using mealtime insulin therapy and who have not achieved adequate glycemic control.
b) The effects of pramlinitide are additive to insulin
c) Provides postprandial control of glucose levels and limits glucose fluctuations
d) Pramlinitide needs to be injected subcutaneously before each meal
e) Pramlinitide therapy decreases Hb1Ac by 0.5-0.7% points
f) Decreases amount of short acting insulin required
g) Can promote WEIGHT LOSS ~1-1.5kg over 6 months (may be due to GI side effects)
h) Most appropriate for highly motivated patients who can tolerate nausea and are willing to add 2-4 more injections per day and more frequent glucose monitoring
i) Most likely to have greatest benefit in type 1 patients who are obese

4.9D ADVERSE EFFECTS

a) Nausea, vomiting, anorexia, headache
b) Together with insulin it increases the risk of severe hypoglycemia- the dose of insulin should be reduced ~50%.

4.9E DRUG INTERACTIONS

Due to the slowing of gastric emptying it can affect the absorption of other orally administered drugs (e.g. contraceptives & antibiotics), which should be taken 1 hr before or 2 hrs after

5. CURRENT RECOMMENDATIONS OF THE ADA/EASD FOR THE MANAGEMENT OF TYPE 2 DIABETES

a) Patients should initially undergo life style changes including diet and exercise to improve glycemia, blood pressure and lipid profile.
b) However, continuous treatment with oral anti-diabetic mediations will typically be required to maintain normal or near normal glycemia.
c) Metformin therapy should be the first drug of choice in most patients. The Metformin dose should be titrated over a two-month period to the maximally effective dose (typically 850 mg twice a day). Advantages: Efficacy, Safety, Weight Loss, no risk of hypoglycemia and beneficial effects on CVD mortality.

d) In cases where metformin is specifically contraindicated (e.g. elderly patients, renal hepatic, or cardiac disease, excess alcohol) another oral agent should be used (i.e. a sulfonylurea or thiazolidinedione).
e) If after 2-3 months adequate glycemic control is NOT achieved (i.e. HbA1c remains >7%), another medication should be added e.g. a sulfonylurea (least expensive), thiazolidinedione (no hypoglycemia), exenatide (maybe useful in overweight patients), or insulin (most effective; especially if HbA1c is > 8.5%).
f) Further adjustments to therapy should be made no less frequently than every three months.
g) In those patients that fail to achieve adequate control of glycemia on a combination of two drugs a third drug or insulin can be added, or the insulin therapy regimen can be intensified.

SUMMARY: INSULIN PREPARATIONS

Properties of commercially-available Insulin Preparations

	Formulation	Onset	Peak	Duration	Usage
Rapid-acting Insulin aspart Insulin lispro Insulin glulisine	Amino acid substituted insulin variants that are monomeric for faster absorption	5-15 mins	45-75mins	2-4 hrs	For meals or acute Hyperglycemia; Can be injected immediately before meals
Regular Insulin	Zinc ions added for stability; forms hexamers that dissociate into monomers prior to absorption	30-60 mins	2-4 hrs	6-8 hrs	For meals or acute Hyperglycemia; Needs to be injected 30-45 mins prior to meal
Intermediate acting NPH Insulin (Isophane)	Conjugated with protamine peptide which delays absorption until it is proteolytically cleaved by endogenous tissue proteases	1.5-2 hrs	6-10 hrs	16-24 hrs	Provides basal insulin and overnight coverage
Long acting Insulin glargine	Amino acid substituted insulin variant that forms large ppt at body pH and is slow to be absorbed	~2 hrs	No Peak	20->24 hrs	Provides basal insulin and overnight coverage
Insulin detmir	Insulin with fatty acid side chain that associates with tissue bound albumin that slows its absorption	~2 hrs	No Peak	6-24 hrs	

SUMMARY DRUGS TO TREAT TYPE 2 DIABETES

	HbA1c Decrease	Duration of Effect	Mechanism	Advantage	Adverse Effects	Contraindications
Metformin	~1.5%	6 hrs	Inhibits mito complex I ⇒↑AMP ↓Adenylate cyclase/↑AMPK Opposes GLUCAGON **↓Hepatic gluconeogenesis** ↑Glucose utilization ↑Insulin sensitivity	**Lowers fasting glucose** Weight loss, Improved lipid profile, No hypoglycemia ↓ Frequency MI/Death	**Lactic Acidosis**, GI side effects, ↓absorption B12	Elderly >80 yrs pregnancy **Renal failure, MI** **Congestive heart failure,** Liver disease/alcohol abuse, Hypoxia/Shock/septicemia, Iodinated contrast agent
Sulfonylureas Chlorpropamide/Tolbutamide Glimepiride/Glipizide/ Glyburide	~1.5%	Tol/Glip 14-16 hrs Chlor/Gly/Glim 24+ hrs	Inhibits β-cell K+ channel (Kir6.2/Sur1) resulting in **↑Insulin secretion**	**Slow onset** **Long duration** **Lowers fasting glucose**	**↑ Hypoglycemia risk** Weight gain	Pregnancy **Renal/Liver disease** Sulfa allergies Type-1 diabetes Elderly
Meglitinides Repaglinide/nateglinide	1-1.5%	2-4 hrs	Inhibits β-cell K+ channel (Kir6.2/Sur1) resulting in ↑glucose-dependent Insulin secretion	**Fast acting** **Short duration** ↓Postprandial glucose	Hypoglycemia Weight gain	Pregnancy Liver disease
Thiazolidinediones Pioglitazone/Rosiglitazone	0.5-1.4%	weeks	Agonist of PPARγ Transcription Factor **↑Insulin sensitivity** **↑Glucose utilization** **↓Insulin resistance**	Lowers fasting glucose ↓triglycerides	**Weight gain (subQ)** **Fluid retention** **↑HF risk** **↑Bone fractures in women** Increased risk bladder cancer	**Liver disease** **Stage III/stage IV** **Congestive Heart Failure** **CVD** Pregnancy
Alpha-glucosidase Inhibitor Acarbose/Miglitol	0.5-0.8%	3-4 hrs	Inhibits carbohydrate Digestion in GI tract **↓Glucose absorption**	↓Postprandial glucose No risk hypoglycemia	Significant GI side effects	Chronic intestinal Disease Inflammatory bowl disease Colonic ulceration
Incretin Mimetics Exenatide/Liraglutide	0.5-1.0%	Ex ~6-8 hrs L ~11-15 hrs	GLP-1 analog **Potentiates glucose-induced Insulin release** **↓Pancreatic glucagon** **↓Hepatic gluconeogenesis** Slows gastric emptying ↑Satiety	**↓Fasting glucose** **↓ Postprandial glucose** Little risk hypoglycemia Weight loss	Requires Injections Nausea	
DPP-IV inhibitors Sitagliptin/Saxagliptin	0.48-0.61%	~24 hrs	Inactivates DPP-IV the GLP-1 peptidase (potentiates GLP-1 action)	**↓ Fasting glucose** **↓Postprandial glucose** Little risk hypoglycemia		

	HbA1c Decrease	Duration of Effect	Mechanism	Advantage	Adverse Effects	Contraindications
Pramlintide (Used as adjunct therapy with insulin in both Type 1 and Type 2 -reduce insulin by 50%)	0.5-0.7%	2-3 hrs	Amylin mimetic Adjunct to insulin therapy ↓Postprandial glucagon ↓Hepatic gluconeogenesis Slows gastric emptying ↑Satiety	↓Postprandial glucose Weight loss	Requires injections Nausea Hypoglycemia (especially with insulin -need to reduce insulin by 50%)	
SGLT2 inhibitors Canagliflozin dapagliflozin	0.5-0.9%	>24 hrs	Inhibits glucose renal reabsorption by inhibiting SGLT2 promotes increased glucose excretion in urine	↓Blood pressure Weight loss	Urinary tract infections Thirst/Dehydration Hypotension ↑LDL Cholesterol Risk of hyperkalemia	Renal impairment Type 1 diabetes
Bromocriptine (Cycloset)	~0.5%		Dopamine D2 agonist acts on the CNS to normalize hypothalamic dopamine levels thereby decreasing Sympathetic tone resulting in: ↓Hepatic glucogenogenesis ↓Lipolysis/FFA ↓Lipogenesis/TG ↑Glucose tolerance ↑Insulin sensitivity			
Bile acid-binding resin Covelesalam	~0.5%		Prevent Bile acid reabsorption Allow bile acids to enter the colon Bile acids bind TGR5 GPCR expressed on intestinal cells and induce GLP-1 secretion			

Thyroid and Anti-Thyroid Drugs

Date: Friday March 24th, 2017, 10:30am -11:30am

Reading assignments: Basic and Clinical Pharmacology. B.G. Katzung, 12th Edition. Chapter 38, p681

Key Concepts and Learning Objectives

1. Describe the role of the Hypothalamus-Pituitary-Thyroid axis in the regulation of thyroid hormone production and the feedback mechanisms involved in the regulation of this pathway.

2. Describe the steps in the biosynthesis of the thyroid hormones: Tetraiodothyronine (T4) and triiodothyronine (T3), and identify the steps that are targeted by anti-thyroid drugs

3. Compare and contrast the pharmacological properties of tetraiodothyronine (T4) and triiodothyronine (T3) and discuss how these properties influence their use in the treatment of thyroid disease.

4. Describe the indications, contrainindications, mechanism of action, and major adverse effects of the major drug classes used in the treatment of hyperthyroidism

5. Discuss the role of surgery in the treatment of thyroid disorders and the role of thyroid and antithyroid drugs used in pre/postoperative care

6. Discuss the use of drugs in the medical management of thyroid storm

7. Describe the role of thyroid hormone and antithyroid drugs used in the postoperative therapy of a patient with thyroid carcinoma

	Indications	MOA	Major Adverse Effects	Misc.
Levothyroxine/ Tetraiodothyronine (T4)	Hypothyroidism	Pro-hormone converted in vivo to the active T3 form, which acts as an agonists of the TR transcription factor	Hyperthyroidism with overdose ↑ risk atrial fibrillation ↑Bone loss in premenopausal women	Slow onset 3-5 days Peak effect 4-6 weeks Half life ~7 days Smooth dosing
Liothyronine/ Triiodothyronine (T3)	Hypothyroidism when rapid onset of action is required e.g. myxedema coma Preparation of thyroid cancer Patient for radioiodine therapy To avoid extended period of thyroid hormone withdrawal	Active hormone acts as an agonists of the TR transcription factor	Risk of thyrotoxicosis with over dose	Fast onset 2-4 hrs Half life ~19 hrs Extreme troughs and peaks
Beta blockers e.g. propanolol or esmolol	To ameliorate adrenergic symptoms associated with hyperthyroidism	Antagonists at beta-adrenergic receptors Propanolol also inhibits peripheral conversion of T4 to T3 (small effect)	Exacerbation of HF ↑Airway resistance Exacerbation of peripheral artery disease	Contraindicated in Asthma, COPD or HF Alternative drug choices: Diltiazem (Ca2+ blocker) Metropolol/atenolol (cardiac-selective beta blocker)

	Indications	MOA	Major Adverse Effects	Misc.
Thionamides/ Thiourylenes Propylthiouracil (PTU) Methimazole (MMI)	Hyperthyroidism e.g. Grave's Disease	Inhibit Thyroid Peroxidase Organification Coupling Do not inhibit release of Preformed thyroid hormone PTU (not MMI) partially inhibits Peripheral deiodination of T4 to T3	Common: Skin rash/joint pain Rare but serious: Hepatotoxicity PTU>>>>MMI ANCA-positive vasculitis PTU>>>>MMI Agranulocytosis PTU=MMI Teratogenicity MMI>>>>PTU	MMI is preferred agent in Non-pregnant patients PTU preferred for 1st trimester in pregnant patients
Iodide Saturated potassium Iodide Potassium Iodide-Iodine (Lugol's solution)	a) Severe Hyperthyroidism e.g. Thyroid storm b) Preoperative prep of patients for thyroidectomy c) After major nuclear accidents To prevent radioiodine uptake	Acutely inhibits hormone secretion Inhibits hormone synthesis via Wolff-Chaikoff effect (Transient) Decreases thyroid organ vascularity		Wolff-Chaikoff effect is Transient lasts ~ 10 days
Radioactive Iodine	Hyperthyroidism e.g. Grave's Disease Toxic nodular goiter	Emission of beta particles cause Necrosis of follicular cells	Radiation Thyroiditis Exacerbation of Grave's Ophthalmopathy	Contraindications: Pregnancy, breast feeding, Severe ophthalmopathy Takes 2-3 months for effect
Bile acid sequestrant e.g. cholestyramine	Thyroid Storm	Prevents reabsorption of Thyroid hormone		

Agents used to treat Mineral Ion Homeostasis and Bone Disorders

Date: Monday March 27th, 2017, 9:30am -10:30am

Reading assignments: Basic and Clinical Pharmacology. B.G. Katzung, 12th Edition. Chapter 42, p747

Key Concepts and Learning Objectives

1. Describe the hormonal pathways regulating daily calcium and phosphate homeostasis

2. Describe the mechanisms regulating bone remodeling

3. Describe the principal functions of parathyroid hormone and the negative feedback mechanisms that regulate its synthesis

4. Describe the synthesis of active Vitamin D3 and its principal effects on mineral ion and bone homeostasis

5. Discuss the regulation and function of calcitonin

6. Describe the indications, mechanisms of action, major adverse effects and contraindications of the principal drug classes used in the treatment of mineral ion and bone disorders

7. Compare and contrast the recommended treatment options for the treatment of the major mineral ion and bone disorders

Drugs covered in this lecture:

Vitamin D and its analogues
Sevelamer
Bisphosphonates
Denosumab
Teriparitide
Raloxifene
Calcitonin
Cincalcet

Drug Class	Indications	Mechanism of Action	Adverse Effects	Miscellaneous
Vitamin D Calcitriol Doxercalciferol Ergocholecalciferol Cholecalciferol	Nutritional Supplements Rickets & Osteomalacia Prevention of Osteoporosis Hypoparathyroidism Secondary Hyperparathyroidism	Agonists of VitD receptor ↑Ca2+/PO4 intestinal absorption ↑Ca2+/PO4 renal absorption ↓PTH expression	Hypercalcemia	Not to be administered in presence of hyperphosphatemia due to risk of **metastatic calcification**
Bisphosphonates Alendronate Pamidronate Risendronate Zoledronate	**Diseases associated with excessive bone resorption** • Osteoporosis • Hypercalcemia • Paget's Disease of the bone • Metastatic bone disease • Osteogenesis imperfecta	Inhibit Farensyl Pyrophosphate Synthase ↓ Protein farnesylation ↓ Osteoclast activity ↓ Bone resorption	Esophageal Irritation Occular side effects Osteonecrosis of the Jaw Renal impairment	<u>Contraindications:</u> Esophageal disease Chronic kidney disease
Denosumab	Osteoporosis (High fracture risk) Hypercalcemia of malignancy refractory to bisphosphonates Giant Cell tumor of the bone Metastatic bone disease	Anti-RANKL mAb RANKL antagonist ↓ Osteoclast bone resorption	Hypocalcemia Osteonecrosis of the Jaw	<u>Contraindications:</u> Hypocalcemia
Teriparatide	Osteoporosis (High fracture Risk) - Failed other therapies - Intolerance to bisphosphonates	PTH receptor agonist Intermittent activity -Stimulates osteoblasts -Promotes bone growth	Transient Hypercalcemia Hyperuricemia ↑ Risk of osteosarcoma	<u>Contraindications:</u> History of gout Hypercalcemia Risk of osteosarcoma: -Active malignancy of the bone -Radiation therapy of the bone -Paget's Disease of the bone -Children/adolescents

Drug Class	Indications	Mechanism of Action	Adverse Effects	Miscellaneous
Raloxifene	Osteoporosis (post menopausal women)	SERM ER agonist in bone Anti-estrogen in breast & uterus ↓ Genes involved in osteoclast activation ↓ Osteoclast activity	• ↑ Risk venous thromboembolism • Worsening vasomotor symptoms	
Calcitonin	• Severe hypercalcemia • Osteoporosis (not 1st line) • Paget's Disease of the bone In those intolerant to bisphosphonate • Bone pain associated with osteoporotic fracture	• Calcitonin Receptor agonist • Inhibits osteoclast activity • Inhibits Ca2+ reabsorption In the kidney	• Hypocalcemia • Concern regarding ↑rates of cancer	Rapidly reduces serum Ca2+ in 4-6 hrs
Cinacalcet	• Primary hyperparathyroidism • Secondary hyperparathyroidism due to CKD (on dialysis) • Hypercalcemia associated with parathyroid carcinoma	• Calcimimetic • Allosterically enhances affinity of CaSR for Ca2+ • Inhibits PTH expression	Hypocalcemia ↑ Seizure risk	<u>Contraindicated:</u> If serum Ca2+ is < 8.4 mg/dL
Sevelamer	Hyperphosphatemia in CKD	• Cationic polymer • Binds phosphate in GI tract & blocks absorption • Lowers serum phosphate without affecting Ca2+		Used to protect from metastatic calcification in treatment with calcitrol

Adrenocorticosteroid Hormones and Adrenocorticoid synthesis inhibitors

Date: Tuesday, March 28th, 2017, 8:30am -10:00am

Reading assignments: Basic and Clinical Pharmacology. B.G. Katzung, 12th Edition. Chapter 39, p697

Key Concepts and Learning Objectives

1. Describe the principal physiological responses to both glucocorticoids and mineralocorticoids.

2. Describe the role of the Hypothalamus-Pituitary-Adrenal (HPA) axis in the regulation of aldosterone, cortisol and androgen synthesis and the mechanisms by which cortisol and exogenous glucocorticoids act to negatively regulate the HPA axis.

3. Describe the differences between the differential temporal synthesis of endogenous cortisol and aldosterone that occurs throughout the day.

4. Describe the mechanism of action of glucocorticoids and mineralocorticoids, including the mechanisms by which glucocorticoids act to inhibit the immune system

5. Discuss the structure/function relationships of endogenous and synthetic glucocorticoids, and the role of 11-beta hydroxysteroid dehydrogenase enzymes in the regulation of cortisol activity.

6. Discuss the role of corticosteroid structure and the 11-beta hydroxysteroid dehydrogenase enzymes in influencing the clinical effectiveness of synthetic glucocorticoids administered via different routes.

7. Describe the indications and clinical use of synthetic adrenocorticosteroids in the treatment of adrenal deficiency diseases: Adrenal insufficiency and Congenital Adrenal Hyperplasia

8. Describe the indications and clinical uses of synthetic glucocorticoid drugs in the treatment of non-endocrine diseases such as rheumatoid arthritis, asthma, inflammation, respiratory distress syndrome, cancer and cerebral edema.

9. List the major adverse effects associated with the clinical use of chronic glucocorticoid therapy

10. Describe the consequences of abrupt withdrawal of chronic glucocorticoid therapy and the underlying mechanisms involved.

11. Describe the use of dexamethasone in the diagnosis of Cushing's Disease

12. List the drugs used in the medical treatment of Cushing's disease and describe the mechanisms involved.

Drugs to be covered in this lecture:

Principal synthetic corticosteroids
Hydrocortisone (Cortisol)
Cortisone
Fludrocortisone
Prednisone
Prednisolone
Dexamethasone

Inhaled forms of gluccocorticoids used in asthma:
Triamcinolone acetonide, beclometasone & fluticasone

Drugs used to treat Cushing's Disease

Adrenocorticoid synthesis inhibitors
Ketoconazole
Metyrapone
Etomidate

Adrenocorticolytic Drugs
Mitotane

Glucocorticoid Receptor Antagonists
Mifepristone

ADRENOCORTICOID HORMONES

1. Hormones of the Adrenal Cortex: An overview

(A) The adrenal cortex synthesizes two major classes of steroid hormones:

Corticosteroids

(i) Glucocorticoids
- the principal glucocorticoid is CORTISOL
- regulation of intermediary metabolism
- regulation of the immune system

(ii) Mineralocorticoids – the principal mineralocorticoid is ALDOSTERONE
- regulation of electrolyte and fluid balance

Corticosteroids are essential for life and play a critical role in the physiological response to stress and changes in the environment

Androgens
- female sexual development (major source of testosterone)
- Conditions leading to increased androgen levels in females can lead to increased virilization of the genitalia
- Little significance in males

The focus of this lecture is on the physiology and pharmacology of the corticosteroids

(B) Regulation of corticosteroid synthesis

(i) Adrenal steroid hormones are synthesized from cholesterol in distinct regions of the Adrenal Cortex

Zona glomerulosa- outermost zone of the cortex
- Synthesizes ALDOSTERONE
- Regulated by the Renin-angiotensin system and by the serum concentrations of potassium ions. ACTH is permissive for aldosterone synthesis

Zona fasiculata- middle zone of the cortex
- Produces glucocorticoids, principally CORTISOL
- Regulated by pituitary production of ACTH

Zona reticularis- inner zone of the cortex next to the adrenal medulla
- Responsible for androgen production
- Regulated by ACTH

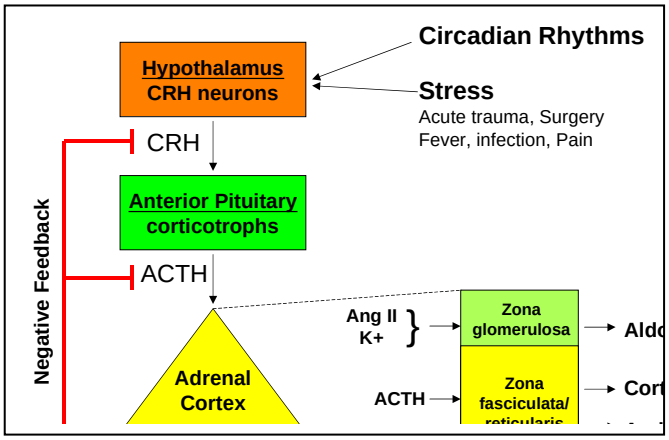
(ii) The synthesis of adrenal steroid hormones by the adrenal cortex is regulated by the Hypothalamic -Pituitary-Adrenal (HPA) axis.

(iii) Corticotropin-releasing hormone (CRH) is released by the hypothalamus in response to circadian rhythms and a number of stress inducers such as acute trauma, surgery, fever, infection and pain.

(iv) CRH acts via its GPCR expressed on the cells of the corticotropes of the Anterior Pituitary to induce the synthesis and release of adrenocorticotrophic hormone (ACTH).

(v) ACTH binds to its adenylcyclase-coupled receptor on the adrenal cortex and induces the expression of genes involved in the synthesis of all adrenal steroid hormones.

(vi) Importantly, Cortisol produced by the adrenal cortex acts in a negative feedback loop to inhibit HPA axis by inhibiting the production of both CRH and ACTH.



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2. Physiological effects of glucocorticoids

2.1. Carbohydrate and Protein metabolism:

Liver - ↑gluconeogenesis and ↑ glycogen storage

Periphery - ↑Protein catabolism (muscle) = ↑substrate for gluconeogenesis
- ↓ Peripheral glucose utilization
- ↑ Blood glucose

2.2. Lipid Metabolism:

- ↑ Lipolysis by facilitating action of GH/β-adrenergic agents
- ↑ glycerol = ↑substrate for liver gluconeogenesis
- ↑ FFA contributes to ↑ Insulin resistance
- Redistribution of Fat:
  - ↑ Truncal obesity
  - ↑ Back of neck (Buffalo hump)/Upper Chest
  - ↑ Facial plethora/Moon Facies
  - ↓ Extremities

2.3. Response to Stress

- Cortisol levels increase in times of stress
- the corresponding increase in blood glucose acts to protect glucose-dependent tissues (e.g. brain/kidney/heart) from starvation

2.4. Cardiovascular system

- modulate vascular reactivity to vasoactive agents e.g. norepinephrine and vasopressin
- Adrenal insufficiency results in HYPOTENSION
- Excess glucocorticoids (i.e. Cushing's Disease) results in HYPERTENSION

2.5. Inhibition of the immune system:

- ↓ numbers of circulating T cells, B cells, macrophages, eosinophils & basophils- redistribution to lymphoid tissues
- inhibition of cytokine synthesis

- inhibition of PLA2 activity- by upregulation of Annexins
- inhibition of COX-2 synthesis- ↓prostaglandin production
- serves to limit the extent of the immune and inflammatory responses

2.6. Skeletal muscle

- permissive concentrations of glucocorticoids required for muscle function
- muscle weakness is a sign of adrenocortical deficiency (Addison's Disease)

2.7. Other Systems

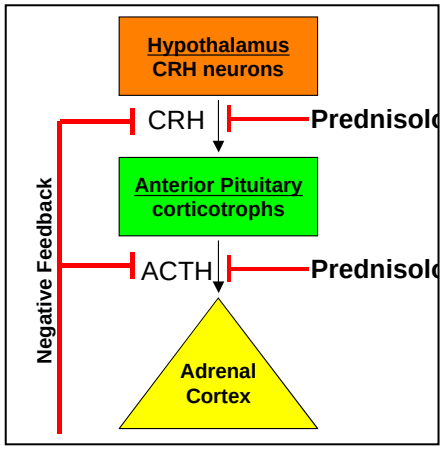
GI tract- gluococorticoids promote synthesis of gastric acid & pepsin
- ↓GI absorption of Ca^{2+}

Bone - glucocorticoids promote bone loss: ↓osteoblasts & ↑osteoclasts

CNS - affect mood behavior and brain excitability
glucocorticoid excess (e.g. Cushing's Disease)- mood elevation
glucocorticoid deficiency (Addison's Disease)- apathy/depression

2.8. ***Feedback inhibition of the Hypothalamic-Pituitary-Adrenal Axis***

- Homeostatic mechanism to prevent excessive glucocorticoid synthesis
- Cortisol/glucocorticoids act to inhibit synthesis of both CRH & ACTH
- Inhibition of ACTH production blocks Adrenal synthesis of cortisol
- In cases of chronic **exogenous glucocorticoid drug** treatment the production of **ACTH** is directly suppressed.
- As ACTH is a **trophic** factor for the **Zona fasiculata/Zona reticularis,** this results in the atrophy of these regions, thereby resulting in the loss of endogenous **Cortisol** production (Aldosterone production is left largely intact).
- This loss of endogenous cortisol production results in adrenal insufficiency (**a life-threatening condition**).
- **Recovery of normal adrenal function can take many months (up to 12 months)**



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3. Physiological effects of Mineralocorticoids

a) Aldosterone is the primary mineralocorticoid

b) Controls body fluid volume and electrolyte balance

c) Aldosterone acts on the kidney tubules and collecting ducts to promote:
↑ expression of the Na+/K+ ATPase
↑ reabsorption of Na+ and H2O

↑ excretion of K+ and H+

Aldosterone excess
- ↑ Na+ reabsorbtion
- ↑ extracellular fluid volume
- ↑ Alkalosis
- **Hypertension**

Aldosterone deficiency
- ↑ Na+ wasting (results in salt craving)
- ↓extracellular fuid volume
- ↑ acidosis
- **Hypotension**

4. Corticosteroids: Synthesis and Metabolism

a) Both cortisol and aldosterone are synthesized from cholesterol

b) Normal adults secrete: 10-20 mg of cortisol daily
0.125 mg of aldosterone daily

c) The rate of secretion of cortisol is controlled by a circadian rhythm that peaks at ~8AM
Cortisol plasma concentration: ~16 mcg/dL at 8AM
~4 mcg/dL at 4PM

Aldosterone plasma concentrations are constant at ~0.01 mcg/dL

d) Cortisol levels are also significantly increased (4-6 fold) in response to stress.
- this is caused by stress inducing the hypothalamus to increase production of CRH, which in turn leads to increased production of ACTH that acts directly on the adrenal cortex to induce cortisol production.

e) ~95% of cortisol is bound to plasma proteins
CBG
- Corticosteroid Binding Globulin (high affinity/low capacity)
- only unbound cortisol is bioavailable
- binding is saturated when cortisol concn > 20-30 mcg/dL
- most synthetic corticosteroids do not bind CBG

Aldosterone does not bind to plasma proteins

f) Cortisol, aldosterone and all synthetic corticosteroids are metabolized by the **LIVER**, where they are reduced and conjugated to glucuronic acid making them more water soluble and thereby greatly enabling **RENAL** excretion in the urine.

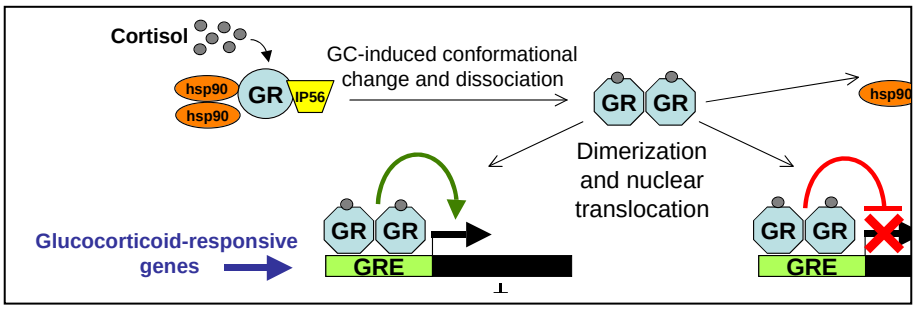
Serum half lives:
- Cortisol 60-90 mins
- Aldosterone 15-20 mins

g) The half-life of corticosteroids can be elevated in patients with HEPATIC dysfunction.

5. Corticosteroids: Mechanism of Action

a) Cortisol and other glucocorticoids are steroids that readily cross the plasma

membrane and mediate their effects through specific glucocorticoid receptors (GR) that act as transcription factors



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b) In unexposed cells GR exist in the cytoplasm in a complex with a number of proteins including Heat shock-90 and immunophilin-56 proteins

c) The binding of cortisol to GR promotes (i) a conformational change, (ii)) dissociation from Hsp90 and IP56, (iii) dimerization and (iv) translocation into the nucleus

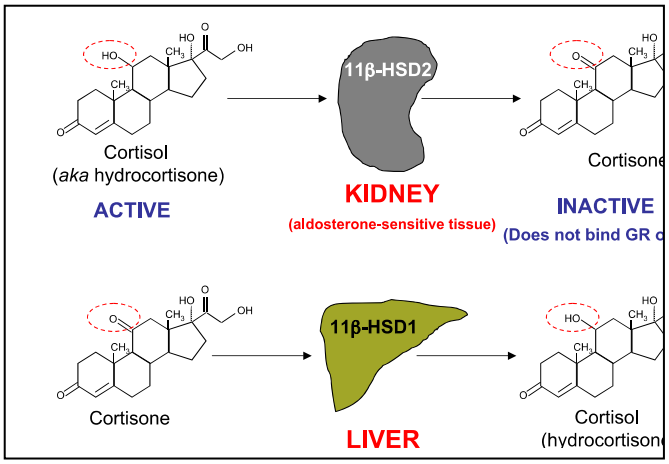
d) Once in the nucleus, GR binds to specific promoters via its cognate target sequence the glucocorticoid-response element (GRE), where it recruits additional transcriptional cofactors and acts to either promote or inhibit gene expression.

e) **Aldosterone works in a similar fashion via the mineralocorticoid receptor (MR)**

6. The role of 11β-hydroxysteroid dehydrogenase in corticosteroid specificity

a) Cortisol is not a "pure" glucocorticoid- it also exhibits somemineralocorticoid activity.
- In fact, cortisol binds with equal affinity to both the GR and the MR

b) Furthermore, cortisol is found at much higher concentrations in plasma than aldosterone (4-16 mcg/dL versus 0.01 mcg/dL aldosterone)



c) The specificity of corticosteroid action is maintained by the enzyme hydroxysteroid dehydrogenase (**11β-HSD**)

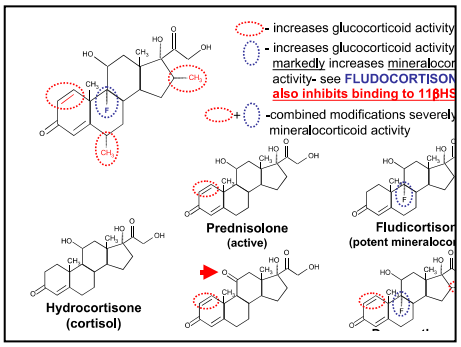
d) The **11β-HSD2** enzyme isoform is expressed in key aldosterone-sensitive tissues (kidney, salivary gland & colon) and converts **cortisol** to the inactive metabolite **cortisone** (which doesn't bind to either GR or MR).
- this prevents higher serum levels of cortisol from inappropriately

activating the MR in the kidney & colon to induce an aldosterone-like response.

e) The liver expresses the **11β-HSD1** enzyme isoform that converts cortisone back into active cortisol

7. Structure function of synthetic Corticosteroids

A large number of synthetic corticosteroids have been synthesized and are used in clinical practice. These synthetic drugs differ based upon their respective levels of glucococrticoid and mineralocorticoid activity, as well as their topical potency and duration of biological activity.



Relative potencies of some synthetic corticosteroids

	Glucocorticoid potency	Topical potency	Mineralocorticoid potency
Short Acting (8-12hrs)			
Hydrocortisone/cortisol	1	1	1
Cortisone	0.8	0	0.8
Intermediate acting (12-36 hrs)			
Fludrocortisone	10	0	250
Prednisone	4	0	0.3
Prednisolone	5	4	0.3
Triamcinolone	5	4	0
Long acting (36-72hrs)			
Dexamethasone	30	10	0
Betamethasone	30	10	0

Effects of Structure Function on Routes of Administration

a). Oral administration

- can use both active and inactive agents
- inactive agents will be converted to active agents in liver (11b-HSD1)

b). Topical application to skin to treat inflammation/insect bites

- 11beta-HSD1 not expressed in the skin
  i.e. cortisone/prednisone will be inactive
- must use active ingredient i.e. hydrocortisone/prednisolone

c). Direct injections into the joint for treatment of RA

- 11beta-HSD1 not expressed in the joint
- must use active agent e.g. prednisolone **NOT** prednisone

d). *In utero* treatment of fetus

- placenta expresses 11 beta-HSD2 (inactivates maternal hormone)
- fetal liver not active, so unable to activate inactive agents
- therefore use dexamethasone-treatment of mother which can cross the placenta without inactivation (not a substrate for 11bHSD2) and acts directly on target tissues in the fetus

8. Corticosteroids: Clinical Uses

Hormone replacement therapy **- PHYSIOLOGICAL DOSES**

- hydrocortisone/fludrocortisone
- Acute adrenal insufficiency
- Chronic adrenal insufficiency
- Congenital adrenal hyperplasia

Non-endocrine therapy

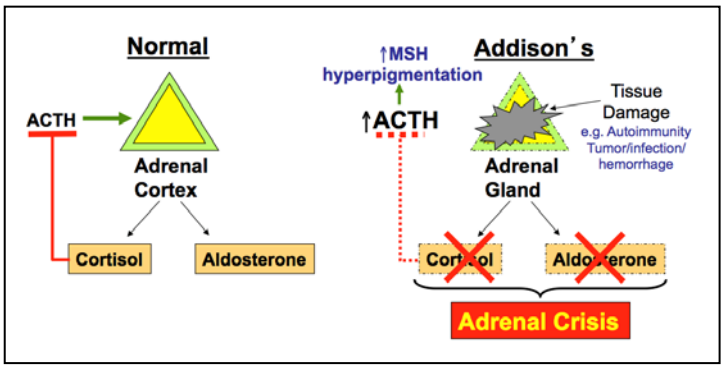
- PHARMACOLOGICAL DOSES
- prednisone/dexamethasone etc
- Rheumatoid Arthritis
- anti-inflammation
- asthma
- cancer
- respiratory distress syndrome
- cerebral edema

9. Adrenal Insufficiency

i) Inability of the Adrenal cortex to produce adequate amounts of hormones
ii) Potentially life threatening disorder, although some patients do not exhibit symptoms unless severely stressed

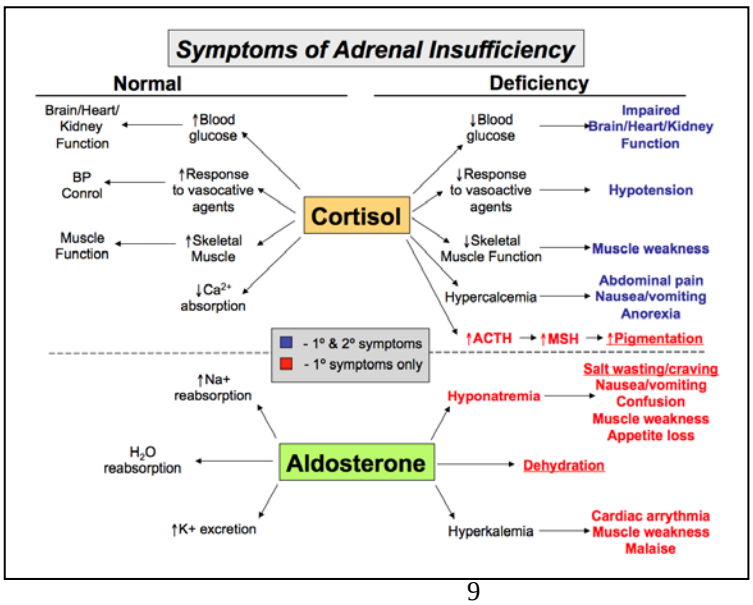
A. Primary Adrenal Insufficiency (Addison's Disease):

- Autoimmune destruction of the adrenal cortex (70%)
- Tuberculosis (20%)
- Other e.g. fungal infection/hemorrhage/cancer (10%)
- **Affects both cortisol and aldosterone production**



B. Secondary Adrenal Insufficiency:

- Defects in either ACTH or CRH production (10%)
- Iatrogenic suppression of HPA axis with exogenous glucocorticoids (90%)
- **Primarily affects only cortisol production (zona glomerlusoa intact)**



Treatment Goal: To replace the physiological activity of the "missing hormones"

Cortisol Replacement Therapy:
- **Hydrocortisone** (20-30 mg/day) given 2-3 times/day in divided doses

- alternatively, longer acting glucocorticoids such as either **Prednisone** (5 mg/day) or **Dexamethasone** (0.5 mg/day) can be given once daily, typically before bedtime (smoother effect)

- although hydrocortisone has some mineralocorticoid activity this is not sufficient to replace aldosterone, while both prednisone and dexamethasone completely lack any salt-retaining activity

Aldosterone Replacement Therapy:
- aldosterone itself is not used for replacement therapy due to high cost and rapid hepatic metabolism to inactive metabolites

- drug of choice is **Fludrocortisone** (0.1 mg/day) a potent synthetic mineralocorticoid

- although Fludrocortisone also has some glucocorticoid activity it does not exhibit anti-inflammatory activity at the doses given

C. Treatment Regimens

Primary Adrenal Insufficiency
- Hydrocortisone (or Dexamethasone)- CORTISOL REPLACEMENT
- Fludrocortisone - ALDOSTERONE REPLACEMENT

Secondary Adrenal Insufficiency
- Hydrocortisone (or equivalent dose of Dexamethasone)
- Mineralocortocoid therapy is **not usually necessary** as the zona glomerulas remains intact

Acute Adrenal Insufficiency/Acute Adrenal Crisis
- may occur: a) in an undiagnosed patient after serious illness
  b) in a patient that does not increase dose of glucocorticoid during acute infection
  c) after abrupt withdrawal of chronic glucocorticoid therapy

- typically presents as hypovolemic circulatory shock plus nausea, vomiting, weakness, fatigue, fever, hyponatremia and hyperkalemia

- initial treatment is **ELECTROLYTE REPLACEMENT** 0.9% saline followed by **IV hydrocortisone (or Dexamethasone)**

- mineralcorticoid therapy is not useful initially as it takes days for effect

- once patient is stable, IV hydrocortisone is tapered over 1-3 days to an oral

maintenace dose of **hydrocortisone plus fludrocortisone**

10. Assesment of treatment efficacy and dosage adjustments

a) Lowest dose that relieves the symptoms of glucocorticoid deficiency and decreases hyperpigmentation (only present in primary disease due to increased MSH as a result of ACTH overproduction)

b) Evidence of ↑weight gain, facial plethora and other "Cushingoid symptoms" is indicative of excessive dosing

c) In normal individuals Cortisol levels are naturally increased in response to stress. Therefore dosage adjustments are made under the following conditions:

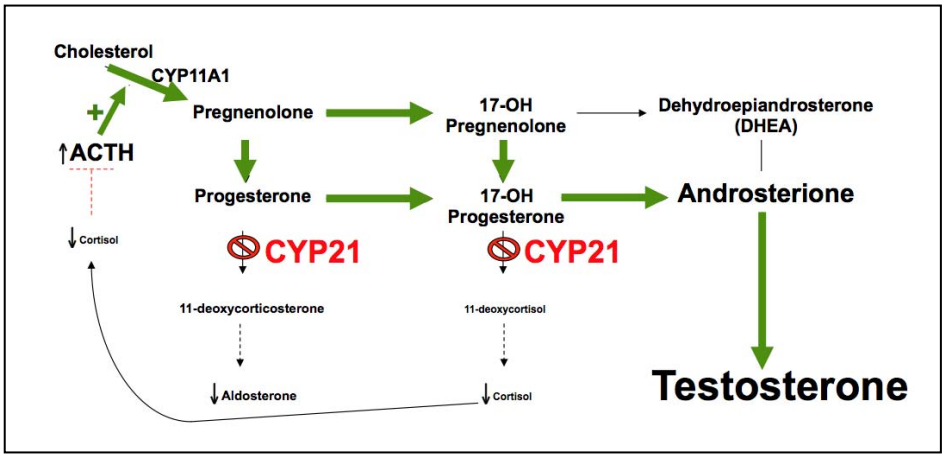
(i) Minor illness
(ii) Surgery
(iii) Pregnancy

11. Congenital Adrenal Hyperplasia

a) A group of genetic disorders that cause a deficiency in the activity of certain enzymes(i.e. steroid 21-hydroxylase) involved in the synthesis of Glucocorticoids

b) Impaired production of cortisol results in a lack of negative feedback and increased expression of ACTH, resulting in excess production of other hormonally active steroid hormones e.g. **ANDROGENS**

c)



Affected female newborns are born with ambiguous genitalia

d) Affected males are normal at birth, but may develop precocious secondary sexual characteristics

e) In a subset of patients mutations in CYP21 can severely inhibit enzyme activity resulting in a deficiency in aldosterone synthesis- as a result these patients are unable to retain Na+ and are referred to as "Salt Wasters". If untreated these newborns will typically develop an acute adrenal crisis within 2-3 weeks of birth

f) Treatment: **Hydrocortisone** AND (if necessary) **Fludrocortisone**

g) Treatment Goal: Restore hormones to the normal range to avoid adrenal crisis and to suppress **ACTH** production thereby abrogating **ANDROGEN** overproduction
- Sudden growth spurts indicate inadequate treatment
- Growth failure suggests excessive glucocorticoid treatment

h) Prenatal screening of amniotic fluid for 17-hydroxypregnenolone identifies affected individuals. These patients can be treated *in utero* by administration of dexamethasone to the mother. Prior to the 9th week of gestation this effectively suppresses the excess production of androgens and prevents female virilization and related problems. If subsequent karyotype analysis from chorionic villus sampling at approximately 16 weeks reveals a male child, treatment can be delayed until birth.

12. Non-Endocrine Uses of Glucocorticoids

12.1. Rheumatoid Disorders: e.g. RA, SLE, vasculitis

a) Prednisone is typically the drug of choice- **Acts by inhibiting the ongoing active autoimmune response**

b) used for short periods (usually < 3-4 weeks) to provide **symptomatic pain relief** and to control disease "flare ups"
N.B. treatment does not **cure** the underlying disease etiology

c) used as a therapeutic bridge while waiting for effects of long acting DMARDs

d) more effective than NSAIDs when used for < 1 month
- ↓ Joint tenderness, ↓ pain & ↑ grip strength

f) short-term low-dose (<15 mg/day) is seldom associated with adverse effects

g) drugs can be administered directly into joint (max. once every 3 months)
- active form of drug e.g. Prednisolone must be used

h) In more severe cases low dose chronic treatment has also been shown to reduce bone erosions- however decreased efficacy after 6 months and increased potential for adverse effects especially **OSTEOPOROSIS**
- patients should take daily Ca^{2+} and Vitamin D supplementation

i) Once there is clinical improvement, the dose of glucocorticoid should be slowly tapered to avoid serious adverse effects

12.2. Treatment of Allergies

a) e.g. bronchial asthma, allergic rhinitis, drug/serum/transfusion-related allergic diseases, contact dermatitis, urticaria, bee stings and insect bites

b) Treatment is **not curative** - only treats symptoms

c) Acts to inhibit the inflammatory response and cytokine production

d) for respiratory-system allergies drugs can be administered in inhaled form
e.g. triamcinolone and/or beclomethasone
- Allows delivery of high concentrations of drug directly to the lung

- Due to significant 1st pass effect only < 1% of any swallowed glucocorticoid is bioavailable, limiting risk of adverse effects and reducing the risk of HPA suppression

- If asthmatic patient is treated chronically with systemic oral glucocorticoids and is then **switched** to inhaled glucocorticoids
  - (i.e. a **much lower systemic dose**)- care must be taken to not abruptly stop the administration of the systemic drug, as this can precipitate an **ACUTE ADRENAL CRISIS**

e) for serious acute cases of asthma short term oral glucocorticoids or IV administration can be used e.g. prednisolone

12.3. Organ transplants

- prevents graft rejection by inhibiting host immune system

12.4. Kidney

- glucocorticoids are used in treating the nephrotic syndrome caused by minimal change disease, which results from an inflammatory infiltrate into the kidney

12.5. Treatment of a number inflammatory conditions

- Skin: treatment of inflammatory dermatoses e.g. psoriasis
- Inflammatory eye diseases: e.g. allergic conjunctivitis
- GI tract e.g.inflammatory bowel disease and ulcerative colitis

12.6. Cancer

- treatment of acute lymphocytic leukemias and lymphomas
- reduces the numbers of lymphocytes/leukocytes in the blood

12.7. Respiratory distress syndrome

- respiratory distress is common in premature infants
- mothers treated with **dexamethasone** prior to birth
- **dexamethasone** is **not metabolized by 11βHSD2** and freely crosses the placental barrier where it can **promote lung maturation**
- **prednisone** is **NOT USED** as prednisolone formed in the maternal liver is converted to prednisone by placental 11bHSD2, and since the fetal liver **does not** operate during fetal life it **cannot** be converted to the **active prednisolone** in the fetus

12.8 Treatment of cerebral Edema

Dexamethasone is used to decrease intracranial pressure due to vasogenic cerebral edema in the following conditions:

Primary and metastatic brain tumors
Bacterial meningitis (prevents hearing loss)
Brain radiation exposure
High altitude cerebral edema

Not to be used for traumatic brain injury, stroke or intracerebral hemorrhage

Mechanism of action though to involve: ↓inflammation and ↓cytokine production
↑Stabilization of blood brain barrier

↓Endothelial permaeability
↓CSF production ↑reabsorption
↑CSF-mediated fluid clearance

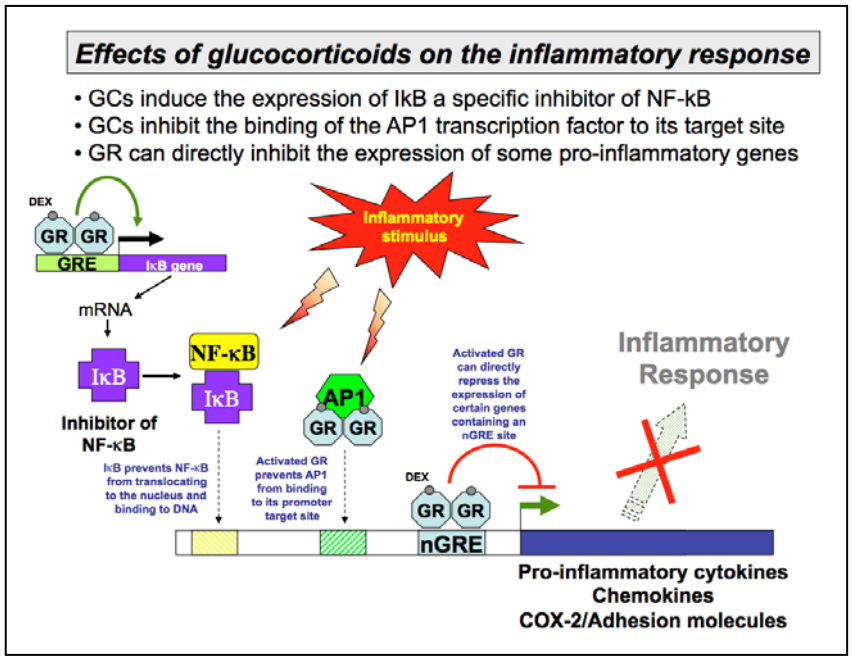
13. Effects of glucocorticoids on the immune system.

Glucocorticoids can inhibit the immune response by several mechanisms:

a) The NF-kB transcription factor is involved in the regulation of many genes involved in the regulation of the immune response including cytokines, cytokine receptors, chemokines, and COX-2. One of the target genes of glucocorticoids is IκB, a specific inhibitor of NF-κB that binds to NF-kB causing it to dissociate from DNA and recycle back into the cytoplasm.

b) Glucocorticoids can also directly inhibit the activity of other transcription factors known to play a critical role in the regulation of the immune response e.g. AP-1

c) Glucocorticoids can also specifically directly repress the expression of other genes known to be critical for the regulation of the immune response



14. Glucocorticoid: Adverse effects

Glucocorticoids can cause adverse effects by two major mechanisms:

I. Abrupt withdrawal of glucocorticoid drugs

a) HPA suppression and acute adrenal insufficiency (serious)

- chronic glucocorticoid treatment (>20 mg prednisone for >3 weeks) can result in significant HPA suppression i.e. inhibition of ACTH/CRH

- the inhibition of ACTH production (a trophic factor for the zona fasciculata/reticularis) results in **atrophy** of the adrenal cortex and a subsequent **deficiency** in **endogenous cortisol** production

- **ABRUPT** withdrawal of chronic glucocorticoid therapy will uncover this cortisol production deficiency and can precipitate an **ACUTE ADRENAL CRISIS**

To **avoid adrenal crisis**, chronic glucocorticoid therapy should be **slowly tapered** (~10-20% decrease in dose every 1-2 weeks)

b) "Flare up" of underlying disease (common) e.g. Rheumatoid Arthritis

- withdrawal of glucocorticoids allows the underlying overactive immune system to re-establish the disease process
- this can be significantly exacerbated if there is any significant suppression of the HPA axis i.e. reduced endogenous cortisol

II. Exaggerated supraphysiological responses caused by pharmacological doses of glucocorticoids

↑Appetite- increased production of neuropetide Y promotes feeding behavior
↑Weight gain- *especially truncal obesity/upper chest/neck*
Facial plethora/Moon Facies - *puffy face*
Diabetes - *hyperglycemia/insulin resistance*
Edema-*electrolyte & water imbalance caused by excess mineralocorticoid activity*
Hypertension- due to enhancement of vasoactive agent response
↑Cardiovascular disease- *MI and stroke*
Muscle myopathy - *specifically upper/lower extremities (common)*
↑Osteoporosis- *↓GI Ca^{2+} uptake; ↑osteoclasts; ↓osteoblasts*
↑Osteonecrosis
↑Peptic Ulcers - *increased production gastric acid/pepsin*
↑Risk of infection - *inhibition of immune system - e.g. pneumonia*
Impaired wound healing- decreased expression of growth factors/matrix proteins
Emotional disturbances - *euphoria/psychosis*
Glaucoma/Cataracts - *common, especially with eye drop use*
Growth retardation in children
Cushing's syndrome- caused by chronic excess of glucococorticoids in the blood and includes many of the above symptoms

15. Disease of glucocorticoid excess: Cushing's Disease/Cushing's Syndrome

Causes: An excess of glucocorticoid activity (either endogenous or exogenous)

Symptoms: truncal obesity, buffalo hump, moon facies, muscle weakness, hypertension, hyperglycemia/insulin resistance, thinning of the skin, easy bruising and female hirsuitism

Exogenous:

- most commonly caused by prolonged exogenous administration of glucocorticoids

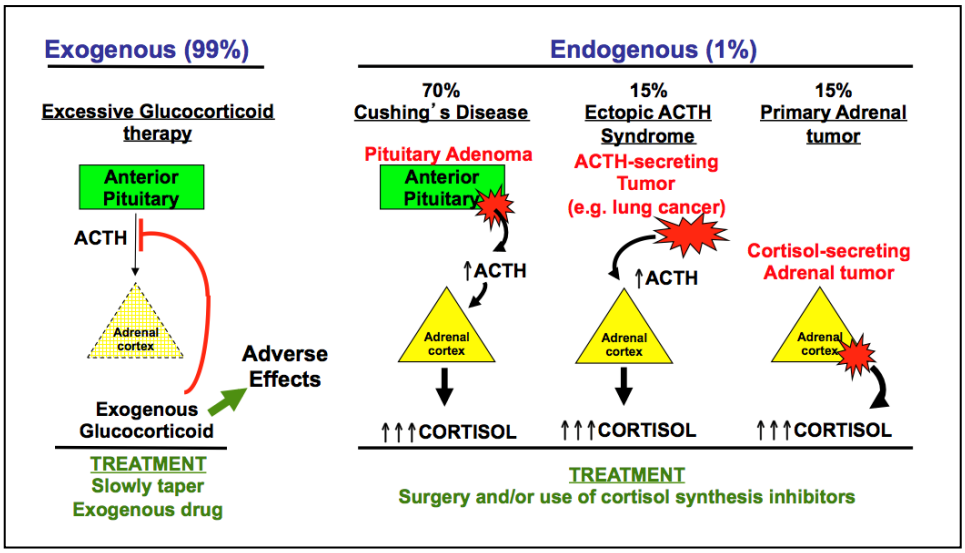
Treatment: Slow tapering of exogenous glucocorticoids

Endogenous:

a) **Cushing's Disease (70%)** - Pituitary adenoma hypersecreting ACTH resulting in increased cortisol production from the adrenal gland (incidence ~1-2 /100,000)

b) Ectopic ACTH syndrome (15%) e.g. ectopic production of ACTH by lung tumor

c) Primary adrenal cortisol-secreting tumor (15%)



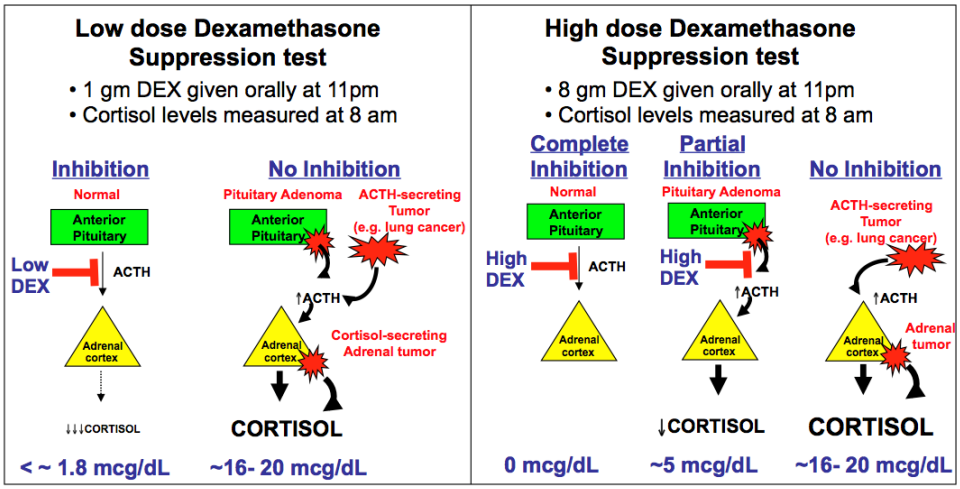
16.Diagnosis of Cushing's Syndrome

a) **Late Night Cortisol levels:** In normal individuals cortisol levels fluctuate based upon a circadian rhythm. Maximal levels occur around 8 AM (range 10-20 mcg/dL) and decline throughout the day reaching their minimum levels around midnight (~1.8-4 mcg/dL). Individuals with Cushing's syndrome exhibit elevated cortisol levels at midnight. Hence, one way of identifying putative Cushing's patients is by determining late night cortisol levels.

b) **Low dose dexamethasone suppression test:** In normal individuals cortisol levels are subject to negative feedback regulation. If a normal patient is administered 1 gm of dexamethasone at 11 pm it will act to inhibit the expression of ACTH resulting in a suppression of serum cortisol levels at 8 am (should be < 1.8 mcg/dL). Conversely, since someone with Cushing's disease is producing excess levels of ACTH due to the presence of a Pituitary tumor, the low level of dexamethasone used in this assay will likely not be sufficient to significantly reduce the level of 8 am serum cortisol.

c) **High dose dexamethasone suppression test:** This test distinguishes between Cushing's syndrome caused by an ACTH-producing pituitary tumor versus disease caused by a tumor ectopically secreting ACTH. In this test, individuals are monitored for 2 days to determine their basal levels of cortisol and are then administered 8 mg dexamethasone at 11pm. In normal individuals, their 8 am serum cortisol levels are typically close to 0 mcg/dL. In individuals with Cushing's disease due to production of ACTH from a pituitary tumor, this high level of dexamethasone will be sufficient to partially suppress the tumor production of

ACTH, resulting in an 8 AM cortisol level of ~5 mcg/dL. Conversely, if the ACTH is ectopically produced by a non-pituitary tumor, that tumor will not be subject to the negative influence of the dexamethasone and as a result 8AM cortisol levels will not be reduced.



17. Adrenocorticoid Synthesis Inhibitors used in the treatment of Cushing's SYndrome

The first line treatment for Cushing's Disease or Cushing's syndrome is removal of the tumur and or irradiation of the tumor. However, in cases where tumor surgery is either not possible or is refused, the disease can be treated medically with drugs that inhibit cortisol synthesis

Goal: To reduce elevated cortisol levels back to the normal range by inhibiting enzymes involved in cortisol biosynthesis

A. Ketoconazole:

a) An anti-fungal agent typically used to inhibit fungal P450 enzymes

b) When used at higher concentrations it inhibits:
CYP11B1- the final enzyme in cortisol biosythesis
CYP11A1- the enzyme involved in the conversion of cholesterol to pregnenolone- the first and rate-limiting step in the biosynthesis of **ALL** adrenal steroids

c) Also inhibits ACTH secretion by an unknown mechanism

d) Should not be used in pregnancy

B. Etomidate:

a) An IV anesthetic that inhibits both CYP11A1 and CYP11B1

C. Metyrapone:

a) Inhibits 11β-hydroxylase (CYP11B1)- the enzyme involved in the final step of cortisol biosynthesis. It also inhibits aldosterone synthase (CYP11B2), the last step in aldosterone production.

Note: The effects on electrolyte balance caused by decreased aldosterone production are mitigated by an increase in 11 deoxycorticosterone, which possess some mineralocorticoid activity

b) Can cause female hirsutism due to the build up of andgrogen precursors

c) Only adrenocortical inhibitor that is safe for use during pregnancy

Note: Individually these drugs diminish the high level of endogenous cortisol production caused by the tumor, but typically are unable to completely reduce cortisol to normal levels.

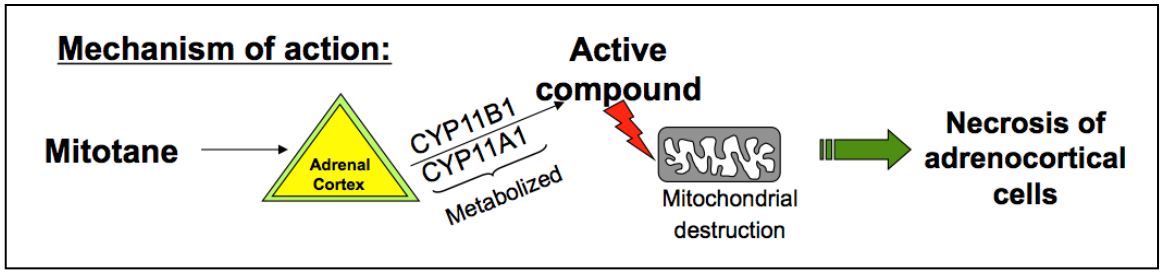
Combination therapy: Drugs act synergistically to inhibit cortisol biosynthesis, consequenty a combination of drugs gives greater therapeutic benefit than monotherapy and reduces the risk of side effects.

Risks
All of these drugs inhibit endogenous corticosteroid production and therefore can potentially precipitate adrenal insufficiency. Drugs must therefore be used at the appropriate dose and the activity of the HPA axis must be closely monitored.

D. Mitotane (Active ingredient of the DTT insecticide)

a) Adrenocorticolytic drug used to achieve medical adrenalectomy in cases of severe Cushing's Disease where patients are not cured by surgery or refuse surgery

b) Metabolized in the adrenal gland by CYP11B1 and CYP11A1 to a compound that induces mitochondrial destruction and necrosis of adrenocortical cells, thereby acting to prevent cortisol production



c) Goal of therapy is to completely ablate endogenous cortisol production

d) As serum cortisol levels fall patients will require glucocorticoid supplementation with either hydroxycortisone, prednisone or dexamethasone

e) Mitotane typically spares the zona glomerulosa, so mineralocorticoids are not usually required

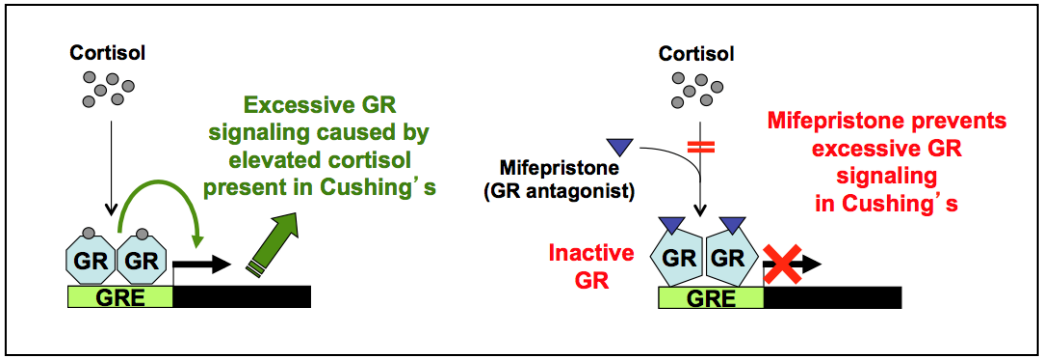
f) Contraindicated in Pregnancy- due to permanent fatal adrenal damage

g) Side Effects: nausea, vomiting, anorexia, rash, diarrhea, ataxia, hypercholesterolemia and hepatotoxicity - not well tolerated ~80% of

patients require dose reduction

E. Mifepristone

- Progesterone Receptor antagonist
- antagonizes Glucocorticoid receptors at high doses
- prevents excessive activation of GR in Cushing's Disease
- approved for treatment of refractory Cushings



Adverse Effects

Can cause Adrenal Insufficiency (needs to be monitored)
Contrainidicated in pregnant women (Abortifacient)

KEY LEARNING POINTS: STUDY GUIDE

1. Physiological effects of glucocorticoids

a) Carbohydrate and protein metabolism:
↑hepatic gluconeogenesis, ↓peripheral glucose uptake ⇒ net ↑blood glucose
protects glucose-dependent tissues in times of stress
b) Redistribution of Fat:
↓Extremities, ↑truncal obesity
c) Cardiovascular system:
↑glucocorticoids ⇒ hypertenstion; ↓glucocorticoids ⇒ hypotension
d) Inhibition of Immune and Inflammatory responses
e) GI tract: ↑gastric acid/pepsin synthesis
f) Skeleton: ↑bone loss
g) CNS: ↑mood elevation
h) Feedback inhibition of the HPA axis:
GC ⇒ ↓CRH + ↓ACTH production ⇒ ↓cortisol production (Adrenal Atrophy)

2. Physiological effects of mineralocorticoids

↑Aldosterone ⇒↑Na+ reabsorption + ↑extracellular fluid +↑alkalosis⇒ HYPERTENSION
↓Aldosterone⇒ ↑Na+ wasting + ↓extracellular fluid + ↑acidosis ⇒ HYPOTENSION

3. Mechanism of action

a) Both glucocorticoids and mineralococrticoids mediate their biological responses by binding to specific receptors that are latent transcription factors.

b) When bound by ligand these receptors translocate from the cytoplasm to the nucleus where they either activate or inhibit specific target genes.

4. Cortisol synthesis and metabolism

a) Normal adults secrete 10-20 mg cortisol and 0.125 mg aldosterone per day

b) Cortisol secretion is controlled by a circadian rhythm
max @ 8am~16 mcg/dL
min @ 11pm- midnight

c) 11β hydroxysteroid dehydrogenase enzymes regulate the activity of cortisol in various tissues.

- 11β HSD2 inactivates cortisol by converting it to cortisone in aldosterone-sensitive tissues such as kidney, salivary gland and colon- thereby preventing the more abundant cortisol from inappropriately activating mineralocorticoid receptors in these tissues

- 11β HSD1 expressed in the liver converts cortisone back to the active cortisol

5. Indications for glucocorticoids

(A) HORMONE REPLACEMENT THERAPY

(i) Adrenal Insufficiency: Primary (Addison's Disease)
Secondary (suppression of HPA by exogenous GC)

Treatment

a) Hydroxycortisone or prednisone/dexamethasone used for cortisol replacement
Levels must be increased in setting of stress:
e.g. illness, surgery & pregnancy

b) Fludrocortisone used for aldosterone replacement (not usually necessary in secondary disease)

(ii) Congential Adrenal Hyperplasia

- Enzyme defect in corticosteroid synthesis (e.g. CYP21)
- ↓Cortisol ⇒ loss of HPA regulation ⇒ ↑ACTH ⇒ ↑adrenal hyperplasia ⇒ ↑Androgens (due to build up of intermediate compounds that are shuttled into the androgen synthesis pathway)
- Hypervirilization of female sex organs and adrenal crisis due to lack of cortisol/aldosterone production

Treatment

Prenatal - *In utero* dexamethasone treatment initiated < 9 wks gestation (Female only; for males treatment can be delayed until birth)
- Inhibits ACTH and CRH production ⇒ ↓Androgen synthesis ⇒ suppresses female hypervirilization

Postnatal- lifelong hydroxycortisone + fludrocortisone to prevent adrenal crsis

(B) NON-ENDOCRINE INDICATIONS FOR GLUCOCORTICOIDS

(i) Rheumatoid arthritis and related diseases
(ii) Allergies
(iii) Organ transplantation
(iv) Nephrotic syndrome
(v) Inflammatory conditions e.g. psoriasis, allergic conjunctivitis, IBD
(vi) Treatment of leukemia & lymphoma
(vii) Respiratory distress syndrome- *in utero* DEX treatment of at risk pregnancies
(viii) Cerebral edema- brain tumors, bacterial meningitis, HACE

6, Adverse Effects

A. ABRUPT WITHDRAWAL

a) Disease flare up due to immune system rebound
b) Acute adrenal insufficiency due to HPA suppression and Adrenal atrophy

B. SUPRAPHYSIOLOGICAL EFFECTS OF CHRONIC GLUCOCORTICOIDS

a) Weight gain
b) Facial plethora
c) Diabetes
d) Risk of infection
e) Edema
f) Hypertension
g) Cardiovascular disease
h) Myopathy
i) Osteporosis
j) Peptic Ulcer
k) Impaired wound healing
l) Emotional disturbance/Euphoria
m) Glaucoma/Cataracts
n) Growth retardation in children

7. Cushing's Disease/Cushing's Syndrome

Caused by chronic exposure to glucocorticoid activity (exogenous or endogenous)

Symptoms: truncal obesity, buffalo hump, facial plethora, easy bruising, thinning of the skin, purple striae on stomach, hypertension, hyperglycemia, muscle weakness, mental changes

8. Treatment of Cushing's Disease

a) Surgical tumor resection if possible

b) Cortisol synthesis inhibitors as adjunct to surgery, or if surgery is not possible
Ketoconazole (inhibits CYP11A1 & CYP11B1)
Etomidate (inhibits CYP11A1 & CYP11B1)
Metyrapone (inhibits CYP11B1 & aldosterone synthase)- safe in pregnancy

GOAL: To reduce elevated cortisol levels back towards the normal range by inhibiting enzymes involved in cortisol biosynthesis
Note: All patients will require careful monitoring of cortisol production to avoid adrenal crisis.

c) Mitotane
- adrenolytic drug specifically destroys cortisol-producing adrenocortical cells
- not safe in pregnancy
- patients will ultimately require supplementation with hydrocortisone to prevent adrenal crisis (note: zona glomerulosa is spared)

d) Mifepristone
- Progesterone receptor antagonist
- antagonizes Glucocorticoid receptors at high doses
- prevents excessive activation of GR in Cushing's
- approved for treatment of refractory Cushings

Adverse Effects
Can cause Adrenal Insufficiency (needs to be monitored)
Contrainidicated in pregnant women (Abortifacient)

Glucocorticoids and Adrenal corticosteroid synthesis inhibitors

DRUGS	INDICATIONS	MOA	ADVERSE EFFECTS
Short acting Hydrocortisone Cortisone Intermediate acting Fludrocortisone Prednisone Prednisolone Triamcinolone Long acting Dexamethasone Beclamethasone	**Hormone replacement** Adrenal insufficiency Adrenal crisis Addison's Disease Congential Adrenal Hyperplasia **Non-endocrine uses** Rheumatoid Arthritis/Gout/SLE Allergies/Asthma/insect bites Inflammatory conditions Kidney nephrotic syndrome Organ transplantation Cancer therapy (leuk/lymph) Respiratory distress syndrome - *use Dexamethasone* Cerebral edema	Ligands for Glucocorticoid Receptor Except Fludrocortisone Mineralocorticoid Receptor ligand	**Abrupt withdrawal** - Disease flare up - HPA suppression - Risk of Adrenal crisis **Chronic treatment** - Cushingoid symptoms - Weight gain - Facial plethora - Hyperglycemia/Diabetes - Risk of infection - Edema - Hypertension/CVD - Euphoria/Mania - Bone loss - Peptic ulcers - Impaired wound healing

	INDICATIONS	MOA		ADVERSE EFFECTS	
Ketaconazole	Medical Treatment of Cushing's Disease	↓Cortisol Synthesis	Inhibits CYP11A1/CYP11B1	Hepatotoxicity Impotency Gynecomastia	↑Risk Adrenal Insufficiency
Etomidate (i.v)			Inhibits CYP11A1/CYP11B1		
Metyrapone (safe in pregnancy)			Inhibits CYP11B1/CYP11B2		
Mitotane			Ablation of adrenocortical cells	GI/Rash/Ataxia	
Mifepristone		↓Cortisol response	Glucocorticoid R antagonist (@ high dose)	Abortifacient	