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HORMONES AND RELATED DRUGS: A REVIEW ARTICLE

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ABSTRACT

The Endocrine System is made up of glands that produce and secrete chemical substances in the body that regulates the activity of cell or organ. These review information allows candidate to explore how hormones are used as drugs and other related drugs that modify hormonal signals in the body. Mainly hormonal drugs are used in the stage of hormonal regulation deficiency and during hyper hormone secretions by the glands. So hormonal drugs either shows enhancing or inhibitory effects on the target cells. This review presents an comprehensive outlook on the recently available FDA approved drugs on Endocrine system and also the detail study about hormone and related drugs their classification, mode of action, side effects associated with it and sites of hormonal action.

INTRODUCTION

Hormone (from Greek word 'hormaein-to stir up) is a substance of intense biologically active that is produce by specific cells in the body and is transported through circulation to act on its target cell. Hormones from Endocrine glands are released directly into the blood stream which carries them to all parts of the body where they regulate growth, metabolism, reproduction and behaviour. Some hormones affect many tissues eg: Growth hormone, Thyroid hormone and Insulin. Hormones regulate the body functions to bring about a programmed pattern of life events and maintain the homeostasis. The hormones trigger there effects by binding to the specific receptors on target cells where it acts as a switch which influencing chemical or metabolic reactions inside the cell. The receptor for peptide hormones is situated on the cell membrane and those for lipid based hormones are situated inside the cell membrane. Examples of the lipid (steroids) based hormones Are: glucocorticoids, mineralocorticoids, Thyroid hormone and peptide (protein) based hormones are: Adrenaline, Noradrenaline, Insulin, and Glucagon. Hormones are commonly referred as ductless glands because hormones diffuse directly into the blood stream. The level of hormone in blood are variable and self regulating within the normal range. A hormone is released in response to a specific stumules and usually its action reverse or negates the stimulus through a negative feedback mechanism. This may be controlled either indirectly through the release of hormones by the hypothalamus and anterior pituitary gland. Eg: steroid and thyroid hormone or directly by blood level of the stimulus. Eg: Insulin and Glucagon. The effect of positive feedback mechanism is amplification of the stimules and increasing release of the hormone until a particular process is completed and the stimulus ceases. Eg: release of Oxytocin during labour.

Regulation of body functions by major regulator hormones:

Body functions	Major regulator hormones
1. Availability of fuel	: Insulin, Glucagon, GH
2. Metabolic rate	: Triiodothyronine, Thyroxine
3. Somatic Growth	: GH, Insulin-like growth factor
4. Sex and reproduction	: Gonadotropines, Androgen, Estrogen,
5. Circulating volume	: Androgens, Antidiuretic hormones
6. Adaptation to streets	: Glucocorticoids, Adrenaline
7. Calcium Balance	: Parathormone, Calcitonin, Vitamin

Types of hormones secreted by endocrine or ductless glands:

On the basis of the chemical structure the hormones of the human body can be divided into two major groups:

- (1) Hormones derived from amino acids including amines, peptides and proteins.
- (2) Hormones derived from lipids including steroids.

Sr. no	Endocrine Glands	Associated Hormones	Chemical Class	Effects
1]	Pituitary gland (Anterior)	Growth Hormone (GH)	Protein	Promotes growth Of body tissue
2]	Pituitary gland (Anterior)	Prolactin (PRL)	Peptide	Promotes milk production
3]	Pituitary gland (Anterior)	Adrenocorticotrophic Hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
4]	Pituitary gland (Anterior)	Follicle stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production
5]	Pituitary gland (Anterior)	Luteinizing Hormone (LH)	Glycoprotein	Stimulates Androgen production by gonads
6]	Pituitary gland (Posterior)	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by kidneys
7]	Pituitary gland (Posterior)	Oxytocin	Peptide	Stimulates uterine contraction during child birth
8]	Thyroid gland	Thyroxine (T4) Triiodothyronine (T3)	Amine	Stimulates basal Metabolic rate
9]	Thyroid gland	Calcitonin	Peptide	Reduce blood ca ⁺ Levels
10]	Parathyroid gland	Parathyroid hormone (PTH)	Peptide	Increases blood ca ⁺ level
11]	Adrenal (Cortex) gland	Aldosterone	Steroid	Increase blood Na ⁺ level
12]	Adrenal (Cortex) gland	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose level
13]	Adrenal (medulla)	Epinephrine and Norepinephrine	Amine	Stimulates flight or fight response
14]	Pineal gland	Melatonin	Amine	Reduce blood glucose level
15]	Pancreas	Glucagon	Steroid	Stimulates development of male secondary sex characteristics and sperm production

Sites and Mechanisms of Hormone Action :

1) At cell membrane receptor:

A) Although alteration of Intracellular (CAMP) concentration.

- Alteration of protein kinase A.
- Regulation of cell function Ca^{+} acting as third messenger in some situations.
- Hormones that shows there mechanism of action by acting on the cell membrane receptors are: Adrenaline, Glucagon, TSH,FSH, LH, PTH, Calcitonin, ACTH, some Hypothalamic Releasing Hormones, Vasopressin (V2).

(B)Through IP3 /DAG generation release of Intracellular Ca^{+} and protein kinase C activation

- Hormones : Vasopressin (V2),Oxytocin

(C)Direct transmembrane activation of tyrosine protein Kinase

- Phosphorylation cascade
- Regulation of various enzymes.
- Hormones :Insulin, Growth hormone, prolactin

2) At Cytoplasmic Receptors:

1. By penetrating cell membrane, hormone combines with a cytoplasmic receptors
2. Exposes it's DNA binding domain
3. Migrates to nucleus and binds to specific genes
4. DNA mediated (mRNA) synthesis
5. Synthesis of functional proteins
6. Hormones those shows there mechanism of action by acting on cytoplasmic receptors are: Steroid hormones: Glucocorticoids, Mineralocorticoids Androgens, Estrogen, Progesterone, Calcitriol.

3) At Nuclear receptor:

1. The hormones penetrate the nucleus
2. Combine with its receptors
3. Alters DNA-RNA mediated protein synthesis
4. Hormones those shows there mechanism of action by acting on nuclear receptors are: Thyroid hormone, Thyroxine, Triiodothyronine.

Hormones and related drugs classification:

A) Anterior Pituitary Hormone and related drugs:

1] Anterior pituitary hormones: Growth hormone [GH] , Prolactin [PRL] , Thyroid Stimulating Hormone [TSH Throtropin] ,Adrenocorticotropin [ACTH Corticotropin], Gonadotropins [Gns]: Follicle Stimulating Hormone [FSH], Luteinizing Hormone [LH]

2]Drugs altering Anterior Pituitary Hormone secretion:

1. Drugs inhibiting Growth hormone release :Somatostatin Octreotide, Somavert
2. Drugs inhibiting Prolactin release :Bromocriptine, Cabergoline, Apomorphine
3. Drugs Enhancing Prolactin release :chlorpromazine and other Neuroleptics, Metclopamide, Reserpine
4. Super active long acting GnRHagonist:Nafarelin, triptorelin, Buserelin, Goserelin, Leuprolide.

B] Thyroid Hormone and Related Drugs:

1] ThyroidHormone: Thyroxine (T4) ,Triiodothyronine (T3)

2] Thyroid Hormone Inhibitors/ AntithyroidDrugs :

1. Inhibiting Hormone Synthesis :Propylthiouracil, Methimazole, Carbimazole.
2. Inhibiting Iodine Trapping (Ionic Inhibitors) :Thiocyanates (-SCN), Perchlorates (-C104), Nitrates (-NO3).
3. Inhibiting Hormone Release: Iodine, Iodides of Na and K.
4. Destroy Thyroid Tissues : Radioactive Iodine

C] Antidiabetic Drugs :

1] Oral HypoglycaemicDrugs :

i. Enhance Insulin Secretion :

1. Sulfonylureas :Tolbutamide, Glibenclamide, Glipizide
2. MeglitinideAnaloges: Repaglinide, Nateglinide.
3. Glucagon like Peptide – 1(GLP-1) receptor agonist (injectable drugs) :Exenatide, Liraglutide.
4. DipeptidylPeptidase – 4 (DDP-4) Inhibitors :Sitagliptin, Vildagliptin.

ii. Overcome Insulin Resistance:

1. Biguanide :metformin.
2. Thiazolidinediones (PPAR alpha activator) : Pioglitazone

iii. Miscellaneous Antidiabetic Drugs :

1. Alpha –GlucosidaseInhibitors:Acarbose, Miglitol, Voglibose
2. Sodium-Glucose Cotransport-2 (SGLT-2) Inhibitors :Dapagliflozin.

2] Rapid Acting:

1. Insulin lispro
2. Insulin Aspart
3. Insulin glulisine

3] Short Acting:

1. Regularly soluble insulin
2. Prompt Insulin zinc suspension (amorphous or semilente).

4] Intermediate Acting :

1. Insulin zinc suspension or Lents (Ultra:semi:7:3)
2. Neural protamineHagedorn(NPH) or Isophane Insulin.

5] LongActing :

1. Extended insulin zinc supplement (crystalline) or ultralente.
2. Protamine zinc insulin (PZI)
3. Insulin glargime.

D] Corticosteroids:

1] Glucocorticoids:

1. Short Acting: Hydrocortisone (cortisol), Cortisone.
2. Long Acting: Prednisolone, Methyl-prednisolone, Triamcinolone.
3. Long Acting: Dexamethasone, Beta methadone, Deflazacort.

2] Mineralocorticoids :Desoxycorticosterone acetate, Fludrocortisone,Aldosteron

3] Topical Steroids:

1. Very Potent: Clobetasolpropionate 0.05%
2. Potent: BeclometasoneDipropionate 0.05%,Betamethasone Dipropionate 0.05%,
Betamethasone Valerate0.1%, Fluocinolone Acetonide 0.025%,Mometasone
Furoate 0.1%
3. Moderate :Alclometasone Dipropionate 0.05%, Clobetasone Butyrate
0.05%,Fluocortolone 0.25%.
4. Mild: Hydrocortisone 0.1%-2.5%, Fluocinolone Acetonide
0.0025%,Hydrocortisone Butyrate – 0.001%.

E] Androgens and Related Drugs :

- 1] Natural Androgens : Testosterone, Dihydrotestosterone.
- 2] Synthetic Androgens :Methyl Testosterone, Fluoxymesterone, Mesterolone
- 3]Anabolic Steroids : Methandienone (2-5 mg OD-BP , Children 0.04 mg/Kg/day, Nandrolone Phenyl Propionate : 10.50 mg, Children 10 mg. Once or twice weekly.
- 4] Impeded Androgen: Danazol 200-800 mg/day
- 5] Antiandrogens: Cyproterone acetate, Danazol, Cyproterone acetate, Flutamide, Finasteride, Bicalutamide.
- 6] 5-alpha reductaseInhibitors :Finasteride, Dutasteride
- 7] Drugs on Erectile Dysfunction : Androgens, phosphodiesterase – 5 (PDE-5) Inhibitors: Sildenafil, Tadalafil, Vardenafil. Papaverine/Phentolamine (Intracavernosalinj), ProstaglandinE1 (PGE), Alprostadil (Intracavernosalinj).

F] Estrogen and Drugs :

- 1) Natural Estrogens: Estradiol, Estrone, Estriol, Equilin.
- 2) Synthetic Estrogens:
 - i. Steroids: Ethinylestradiol, Mestranol, Tibolone.
 - ii. Nonsteroidal: Diethyl Stilbesterol, Hexesterol, Dienesterol.
- 3] Antiestrogens: Clomiphene Citrate, Fluvestrant.
- 4] Selective Estrogen receptor Modulators (SERMs) :Tamoxifen Citrate (10-20 mg) Toremifene (60 mg OD), Raloxifene (6 mg/day)
- 5] AromataseInhibitors :Letrozole (2. 5 mg/day), Anastrozole (1mg/day),Exemestane (25 mg/day)

G] Progestins:

- 1]Progesterone Derivatives :Medroxyprogesterone, Acetate, Megesterol acetate, Dydrogesterone, Hydroxyprogesterone, Caproate, Nomegestrolacetate,
- 2] 19-Nortestosterones:
 1. Estrans:Norethindrone, Norethindrone acetate, Lystrenol, Norethynodrel,
 2. Gonanes: Norgestrel, Levonorgestrel, Norgestimate, Desogestrel, Gestodene.
- 3] Spironolactone: Drospirenone

H] Oral Contraceptives:

- 1] Combined Pills:
 1. Norgestrel (0.3 mg) + Ethinylestradiol 50mcg

2. Norgestrel (0.5 mg) + Ethinylestradiol 50mcg
3. Levonorgestrel (0.25 mg) +Ethinylestradiol 50mcg
4. Desogestrel (0.15 mg) + Ethinylestradiol 30mcg

2] Postcoital Pills :

1. Levonorgestrel (0.25 mg) +Ethinylestradiol 150mcg
2. Levonorgestrel (0.75 mg)
3. Mifepristone (600 mg)

3] Mini Pills :

1. Norethindrone 0.35 mg
2. Norgestrel 75mcg

4] Antiimplantation (SERM) :

Centchroman (Ormeloxifene) 30 mg twice weekly for 12 weeks and then 30 mg weekly.

5] Injectable Contraceptives:

1. Depot medroxyprogesterone acetate. (DMPA) 150 mg.
2. Norethindrone (Norethisterone) Enanthate (NEE) :200 mg.

I] Uterine Stimulates:

- 1] Posterior Pituitary Hormone : Oxytocin, Des-amino Oxytocin
- 2] Ergotalkaloids: Ergometrine(Ergonovine), Methylergometrine.
- 3] Prostaglandin : PGE₂, PGF_{2a}, 15-methyl PGF_{2a}.
- 4] Miscellaneous :Ethacridine, Quinine.

J] Uterine Relaxants:

- 1] Beta-Adrenergic agonist: Salbutamol, Terbuterol, Ritodrine, Isoxsuprine
- 2] Calcium Channel blockers: Verapamil, Diltiazem, Nifedipine, Amlodipine, Felodipie.
- 3] Magnesium Sulfate
- 4] Progesterone
- 5] Oxytocinantagonists :Atosiban
- 6] Miscellaneous Drugs : Nitrates, Diazoxide, Atropine Ethyl alcohol, PG synthesis inhibitors.

Physiological and pharmacological functioning of hormones and related drugs

A] Anterior Pituitary Hormone :

Anterior pituitary (adenohypophysis). A master endocrine gland. Which regulates number of important hormones. All of these are peptide in nature. They act on extracellular receptors located on their target cells. It releases hormones which affect the working of other glands such as Thyroid gland, Gonads and Adrenal gland.

• Hormones of Anterior Lobe are:

1] Growth Hormone (GH) / Somatotropin:

It is 191 amino acid, single chain peptide of MW 22000.

- **Physiological Functioning :** Growth hormone promotes growth of all organs by inducing hyperplasia. It promotes retention of nitrogen and other tissue constituents more protoplasm is formed. The positive nitrogen balance results from increased uptake of amino acids by tissues and their synthesis into proteins. (GH) promotes utilization of fat and spares carbohydrates uptake of glucose by muscles is reduce while its output from liver is enhanced. Fat is broken down. (GH) acts on cell surface (JAK-STAT) protein kinase receptors (present on particular cells) binding of one (GH) molecule to the extracellular domain of two (GH) receptor molecules induce their dimerization and activates the Intracellular domain to associate with cytoplasmic (JAK-STAT) tyrosine protein Kinase resulting in metabolic effects as well as regulation of gene expression. The growth promoting nitrogen retaining and certain Metabolic actions of GH are exerted indirectly through the elaboration of peptides called Somatomedins or Insulin like growth factors. (mainly IGF-1 and also IGF-2). (IGF-1) promotes lipogenesis and glucose uptake by muscles.

Liver is major source of Circulation (IGF-1).

2] Growth Hormone inhibitors:

The hypothalamus produces (GH) releasing (GHRH) as well as inhibitory (Somatostatin) hormone. And both are peptides.

Somatostatin: Somatostatin is produced by D-cells of islets of langerhans in the Pancreas and by few other tissues. Receptors for (GHRH) and Somatostatin are G-protein-coupled receptors which enhance or inhibits GH secretion by increasing or decreasing

CAMP formation respectively in pituitary Somatotropins. Somatostatin inhibits Ca⁺ channels and open K⁺ channels. (GH) secretion is inhibited by increase in plasma free fatty acid levels and by high dose of glucocorticoids.

3] Prolactin :

It is a 199 amino acid single chain peptide of MW 23000. It is described as the hormone which promotes secretion of milk from crop glands of pigeon and has been shown to be of considerable importance in human beings as well.

Physiological Function: Prolactin is primary stimulus which in conjunction with Estrogens, Progesterone, and several other hormones causes growth and development of breast during pregnancy. It promotes proliferation of ductal as well as acinar cells in the breast and induce synthesis of milk proteins and lactose. After Parturition, it induce milk secretion by inhibiting influence of high Estrogen and progesterone level is withdrawn. Prolactin suppresses Hypothalamic-pituitary-gonadal axis by inhibiting GnRH release. A specific receptor is expressed on the surface of target cells which is structurally and functionally analogous of GH receptors. Action is exerted by transmembrane activation of cytoplasmic tyrosine protein kinase. Placental lactogen and GH also bind to prolactin receptor and exert similar effects. Dopaminergic agonists (DA, bromocriptine, Cabergoline) decrease plasma prolactin levels. While Dopaminergic antagonists (Chlorpromazine, haloperidol, metoclopramide) causes hyper-prolactinemia.

4] Prolactin Inhibitors :

Action: decreases prolactin release from pituitary by activating dopaminergic receptors and lactotroph cells a strong antilactogenic

Increases GH release in normal individuals but decrease the same for pituitary tumors that causes acromegaly.

5] Prolactin Stimulators:

Action: They block dopamine receptor in gut to increase gut motility.

Block dopamine receptor in the pituitary increase prolactin secretion to affect or promote milk production.

6] Thyroid Stimulating Hormone :

It is 210 amino acid, two chain glycoprotein (22% sugar), MW 30000.

Physiological Function : (TSH) stimulates thyroid to synthesis and secrete Thyroxine (T4) and Triiodothyronine (T3).

Action: promotes trapping of Iodine by thyroid.

Promotes organification of trapped Iodine and its incorporation into T3 and T4 by increasing peroxidase activity.(TSH) receptors are present on thyroid cells is a coupled G-protein receptors.

Pathological involvement : Only few cases of hypo or hyper thyroidism are due to inappropriate (TSH) secretion. In majority of cases of Myxoedema. Thyroid Stimulating Hormone level are markedly elevated. Because of deficient feedback inhibition. Hypothyroidism is due to (TSH) deficiency.

7] Adrenocorticotrophic Hormone (ACTH) :

It is 39 amino acid single chain peptide. MW 4500.

Physiological Function : (ACTH) promotes steroidogenesis in Adrenal cortex by stimulating (CAMP) formation in cortical cells through specific cell surface G-protein-coupled receptors which increase (ACTH) synthesis.

Corticosteroids exerts inhibitory feedback influence on (ACTH)production by acting directly on pituitary as well as indirectly through hypothalamus. Lack of ACTH results in adrenal atrophy . Excessive production of ACTH from basophil pituitary tumors is responsible for some cases of Cushing's syndrome.

B] Thyroid Hormone :

The thyroid gland secrete three hormones thyroxine (T4), triiodothyronine (T3), and calcitocine.

Action : the action of t3 and t4 are quantitatively similar and are nicely depicted in the figures of hypo and hyper thyroidism they are affect the function of practically all body cells.

Mecanism of action: both T3 and T4 penetrate cells by active transport and produce majority of their action by combining with a nuclear thyroid hormone receptor which belongs to steroid and retinoid super family of intracellular receptor. Many of the effects example: tachycardia, arrhythmias, raise BP, tremor, hyperglycemia.

C] Diabetes Mellitus (DM):

Two major types of diabetes mellitus are:

Type 1: insuline dependent diabetes mellitus (IDDM) : there are Beta cells destruction in pancreatic islet cell majority of cases or autoimmune (Type 1A) antibodies that destroy Beta cells are detectable in blood cells, but some are idiopathic (Type 1B) beta cells antibodies is found. In all type 1 cases circulating insulin level are low or very low, patients are prone to ketosis this type is less common and have a low degree of genetic predisposition.

Type 2: non insulin dependent diabetes mellitus (NIDDM)/maturity on set diabetes mellitus: there is no loss or moderate reduction in beta cells mass insulin in circulation is low normal or even high no antibeta cells antibody is demonstrable has a high degree of genetic predisposition generally has a late on cell. Over 90 cases are type 2 diabetes mellitus.

Drugs:

1] Jatenzo 158mg :

Generic name: testosterone

Imprint: 158

Strength: 158mg

Color: Red

Shape : capsule shape

Availability : prescription only

Drug class : androgens and anabolic steroids

General information :Jatenzo (testosterone undecanoate) is an endogenous androgen. Jatenzo is specifically indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

Side effects : adverse effect associated with the use of jatenzo may include, but are not limited to the following.

Polycythemia

Diarrhea

Dyspepsia

Eructation

Peripheral edema

Nausea

Increased hematocrit

Headache

Prostatomegaly

Hypertension

Mechanism of action :Jatnzo (testosterone undecanoate) is an endogenous androgen.Endogenous Androgens including testosterrone and dihydrotestosterone (DHT) , are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicle penis and scrotum the development of male hair distribution such as facial pubic chest and axillary hair, laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution.

2] Myxredlin:

1. Generic name : insulin humanin sodium chloride
2. Dosage form : injection
3. Company :baxter international inc.
4. Treatmen for : diabetes Type1 and 2
5. Adverse effect :
6. Hypoglycemia
7. Hypersensitivity
8. Hypokalemia
9. Mechanism of action : The primary activity of insulin, including myxredlin is the regulation of glucose metabolism. Insulins lower blood glucose by stimulation peripheral glucose by stuimulating peripheral glucose uptake, especially by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

CONCLUSION:

This review present an complete viewpoint on the newly available FDA approved drugs on Endocrine system and furthermore the detail study regarding hormone and related drugs their classification, mode of action, side effects associated with it and sites of hormonal action.

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