Pharmacodynamic Evaluation: Endocrinology

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Abstract

In this chapter, pharmacodynamic evaluations for the most common clinical endocrine disorders are discussed.

Special attention is given to new classes of oral antidiabetics and new sophisticated insulin analogues.

Clinical pharmacology in endocrine disorders is reviewed along the classical hypothalamus-pituitary- adrenal-gonadal axis, while thyroid disorders are viewed separately.

There is a focus on the hormone receptor interaction similarities and the drug-ligand-receptor binding.

The concept of hormone agonists and antagonists has a prominent place.

Neuroendocrinology pharmacodynamic evaluation is not included in this chapter.

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Introduction

Endocrinology is the communication science in internal medicine.

Communication takes place by "classical" hormones and paracrine and intracrine mechanisms and by neuroendocrine signals. Hormones are classified traditionally as amines, peptides, proteins, and steroids.

Endocrinology focuses primarily on the endocrine organs that secrete hormones as the pituitary, thyroid, adrenals, ovaries, testes, and pancreas.

Endocrine diseases are disorders of deficiency, excess, or end-organ resistance to one or more hormones. Most endocrine diseases are chronic diseases that need lifelong treatment. Diabetes mellitus is one of the most common as is hypothyroidism and metabolic syndrome, including obesities and dyslipidemia.

Hormones exert their effect in the body by binding to a hormone-receptor complex. These are a wide family of proteins made up of receptors located on the cell surface as insulin and steroid hormone receptors or in the cytoplasma, so-called intracellular or nuclear receptors, used, for example, by testosterone.

After hormone binding to the receptor complex, several pathways can be signaled and activate the target cells. This process frequently shows similarities with the process of ligand (drug), receptor, and ligand-receptor interaction in pharmacodynamics (Salahudeen and Nishtala 2017).

In this chapter, the latest pharmacodynamic developments for the most common endocrine disorders will be discussed.

Diabetes Mellitus

Pharmacodynamics in DM can be studied at a population level, a mechanism-based mode, a metric model, or a drug-targeted-mediated pharmacodynamic model (Salahudeen and Nishtala 2017). In this section, the clinical pharmacodynamics of the most used oral antidiabetics, insulins, and its analogues will be viewed shortly.

Metformin-Biguanides

Metformin improves glucose tolerance in patients with type 2 DM lowering both basal and postprandial plasma glucose by decreasing hepatic glucose production, intestinal absorption of glucose, and insulin sensitivity by increasing peripheral glucose uptake and utilization (Thonos and Gregg 2017).

Metformin does not produce hypoglycemia under normal circumstances. Absolute bioavailability is around 50–60%. Increasing doses results in decreased absorption. Food delays the absorption of metformin. Peak plasma levels are achieved at a median 7 h. Metformin has a negligible protein bound and is excreted unchanged by tubular secretion in the urine. No hepatic metabolites have been found. The elimination half-life is approximately 17 h. Plasma half-life is 6 h. Metformin uses the erythrocyte mass as a compartment of distribution.

In elderly the total plasma clearance of metformin is delayed due to an age-related decline in renal function. No pharmacokinetic studies of metformin have been done in patients with hepatic insufficiency.

Metformin is contraindicated in severe renal impairment (eGFR below 30 ml/min.), known hypersensitivity to metformin, and acute or chronic metabolic acidosis, including diabetic ketoacidosis. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency are susceptible to the hypoglycemic effects. Beta-adrenergic blockers can mask this effect.

Lactic acidosis can be an infrequent complication in metformin users. Metformin decreases

liver uptake of lactate. Risk factors are renal impairment; use of carbonic anhydrase inhibitors, topiramate, and radiologic contrast agents; hypoxia; and alcohol intoxication.

In a minority of patients, metformin can lead to vitamin B12 depletion, mostly without clinical symptoms. In these cases, metformin interferes with vitamin B12 absorption from the B12-intrinsic factor complex.

Sulfonylureas

Sulfonylureas are insulin secretagogues which means they work by causing the body to secrete insulin (Riddle 2017). Sulfonylureas bind to a channel of proteins in the pancreas. This is an ATP-potassium channel. Glucose-generated ATP is the ligand in the pancreatic beta cell to produce insulin.

Members of this drug class are glimepiride (Amaryl), glibenclamide (Daonil), gliclazide (Diamicron), glipizide (Glibenese), and tolbutamide (Rastinon). Another class of diabetes drugs which work in this way is the prandial glucose regulators, the meglitinides.

All sulfonylureas are absorbed by the intestine, each one with its specific absorption and bioavailability. After absorption, sulfonylureas bind almost completely to plasma proteins on an average of 95%. The volume of distribution is about 0.2 l/kg.

The biological effect of sulfonylureas lasts much longer than their plasma half-life because of receptor interaction and formation of active metabolites persisting 24 h or more. Moreover their half-life is prolonged in renal failure.

Genetic differences can also change the response to sulfonylureas. Some of these gene polymorphisms were identified in the genes encoding the potassium-ATP channel (KNCJ11 andABCC8). These mutations cause a change in insulin secretion and insulin response to treatment.

Most sulfonylureas are characterized by renal excretion. Gliclazide and above all cliquidone show a predominant biliary clearance. Sulfonylureas lower blood glucose by 20% and HbA1C by 1–2%.

The most common side effect is hypoglycemia, sometimes lasting for hours and requiring hospital admission. Undesired weight gain due to increasing insulin secretion is around 2 kg. Sulfonylureas act directly on beta cells leading to progressive worsening of DM at the end. This phenomenon is called "secondary failure." Since ATP-potassium-dependent channels are present in cardiac cells and coronary vessels, sulfonylureas if present at the time of a myocardial infarction may impair adequate vasodilatation, resulting in a greater area of myocardial damage (Riddle 2017).

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors (AGIs) sometimes referred as starch blockers are antidiabetic medicines that help to reduce post-meal blood glucose levels (Laar van de 2008).They do not have a direct effect on insulin secretion or sensitivity. They work by slowing down the digestion of carbohydrates found in starchy foods. Examples of AGIs include acarbose (Glucobay) and miglitol (Glyset). AGIs are normally used as a single treatment but can be taken in combination with sulfonylureas. AGIs slow down digestion by blocking enzymes in the small intestine that break down carbohydrates.

Pharmacokinetic evaluation of acarbose is difficult because only 2% is absorbed. Acarbose reversely binds to pancreatic-alpha-glucoside hydrolases. Those enzymes inhibit hydrolysis of complex starches to oligosaccharides. Acarbose raises the glucagon-like peptide (GLP-1) response due to inhibiting gastric emptying. The use of AGIs is limited by gastrointestinal side effects as meteorism, flatulence, and diarrhea. Unexplained severe liver function test disturbances have been reported.

Thiazolidinediones

The thiazolidinediones are also called TZDs or glitazones. TZDs work by targeting the PPAR-gamma receptor which activates a number of genes in the body and plays an important role how the body metabolizes glucose and fat (Marathur et al. 2016). TZDS can therefore help boost insulin sensitivity. Pioglitazone (Actos) is

the most known member of this group. Peroxisome proliferate-activated receptors (PPARs) are structural similar to steroid or thyroid hormone receptors and are subcellular organelles found in most plant and animal cells.

TZDs are high-affinity ligands for PPAR-gamma, a nuclear receptor. PPAR-gamma has been known to regulate adipocyte differentiation, fatty acid storage, and glucose metabolism and is a target of antidiabetic drugs. PPAR-gamma agonists improve insulin resistance by opposing the effect of tumor necrosis factor-alpha (TNF-alpha) in adipocytes.

Pioglitazone can be used in type 2 DM alone or in combination with metformin, a sulfonylurea or in combination with insulin. Pioglitazone has been linked to a significant risk of bladder cancer in long-time users (Marathur et al. 2016).

DPP-4 Inhibitors

DPP-4 inhibitors are also called gliptins. Gliptins work by blocking the action of dipeptidyl peptidase-4 (DPP-4), an enzyme which destroys a group of gastrointestinal hormones called the incretins (Hippisley-Cox and Compland 2016; Karagiannis et al. 2012). Incretins stimulate the production of insulin after eating and reduce the production of glucose by the liver during digestion by its effect on glucagon.

Oral glucose stimulates the release of the endogenous incretins glucagon-like peptide (GLP-1) and glucose-dependent insulin-releasing peptide (GIP).The incretin effect is diminished in type 2 DM. Drugs in this class include sitagliptin (Januvia), vildagliptin (Galvas), and saxagliptin (Onglyza). DPP-4 inhibitors have been linked with an increased risk of pancreatitis.

GLP-1 Agonists

The GLP-1 agonists are also known as the incretin mimetics. These drugs work by mimicking the functions of the natural incretin hormones that help lower post-meal blood sugars (Lovshin 2017).

GLP-1 agonists stimulate the release of insulin and inhibit the release of glucagon and slow glucose absorption by slowing gastric emptying. The GLP-1 receptor is a cell surface receptor which internalizes after stimulation and exerts its effect by the second messenger adenylyl cyclase. The GLP-1 receptor is expressed in pancreatic beta cells and also in the brain where it is involved in the control of appetite. The GLP-1 receptor binds glucagon-like peptide (GLP-1) and glucagon as its natural agonist.

Members of this drug class are exenatide (Byetta), lixisenatide (Lyxumia), dulaglutide (Trulicity), and liraglutide (Victoza).

SGLT-2 Inhibitors

SGLT-2 inhibitors are a new class of type 2 DM medications They are also called the glifozins. They block the reabsorption of glucose in the kidney, increase glucose excretion, and lower blood glucose levels (Zou et al. 2017).

SGLT-2 is a low-affinity, high-capacity glucose transporter located in the proximal tubule in the kidneys. The pharmacodynamic response to SGLT-2 inhibitors as assessed by urinary glucose excretion declines with increasing severity of renal impairment. SGLT-2 inhibitors have a rapid oral absorption, a long elimination half-life, and an extensive hepatic metabolism mainly via glucuronidation to inactive metabolites and a low renal excretion as a parent drug.

Drugs in this class are dapagliflozin (Forxiga) and empagliflozin (Jardiance). Adverse effects are yeast infections, urinary tract infections, and diabetic ketoacidosis.

Prandial Glucose Regulators

Prandial glucose regulators or “glinides” are insulin secretagogues working similar like sulfonylureas by the ATP-potassium channel but at a different site. Unlike sulfonylureas, they have a rapid onset but relatively short effect. Drugs in this class are repaglinide (Prandin) and nateglinide (Starlix) (Mondoza et al. 2013).

Amylin Analogues

Amylin analogues or agonists are injectable drugs that work similar to the hormone amylin and can be used in both type 1 and type 2 DM (Marathur et al. 2016). Amylin is released by the pancreas at the same time as insulin but in much smaller quantities, about 1% compared to insulin.

It inhibits the release of glucagon, slows food emptying from the stomach, and curbs appetite. Pramlintide acetate (Symlin) is the best known member of this drug class. Symlin is unbound in plasma. The half-life is around 50 min.

Insulin Types and Forms

Until the 1980s, animal insulin was the only treatment for insulin-dependent DM. Nowadays, largely human insulins and human insulin analogues are used. These are rapid, short-acting, intermediate, and long-acting insulins (Lispkak et al. 2017).

Examples of rapid-acting insulins are insulin lispro (Humalog) and insulin aspart (Novorapid). Action starts at 15–20 min after s.c. injection and lasts 2–5 h.

Short-acting insulins are Actrapid, Humulin S, and Velosulin. Action starts at 20 min and lasts 6–8 h.

Intermediate insulins are represented by the premixed insulin Humulin I, a human insulin made up of 30% short-acting (neutral) insulin and 70% intermediate-acting (isophane) insulin. It has a peak activity between 1 and 8 h with a duration of action lasting to 22 h.

Long-acting insulins have no peak activity which allows for a basal delivery through the day. Examples of long-acting insulins are insulin glargine (Lantus), insulin detemir (Levemir) or insulin degludec (Tresiba). Lantus has a consistent activity of 24 h. The duration of Levemir is slightly shorter than Lantus and therefore is often injected twice daily. Tresiba has an action duration of more than 42 h.

In addition, there are also premixed human insulin analogues which combine a rapid and a long-acting insulin. Examples are Humalog Mix 25, Humalog Mix 50, and Novomix 30.

All insulins use the insulin receptor, a transmembrane tyrosine kinase receptor, acting by the phosphorylation pathway. Ligands for this receptor are insulin; IGF-1 (insulin growth factor); IGF-2; the relaxin peptides 1, 2, and 3; and the insulin-like peptides 3–6.

There are important pharmacokinetic and pharmacodynamic differences between the long-acting and rapid-acting insulin analogues (Mondoza et al. 2013). These depend on the site of injection, concentration of the insulin formula, volume of the injected dose, depth of injection, thickness of the subcutaneous fat layer, exercise, local massage, heat exposure, and finally intrinsic properties of the insulins (Lispkak et al. 2017).

Insulin is usually cleared by receptor-mediated uptake and intracellular degradation. The main site of plasma extraction is the liver with smaller contributions by adipose tissue and muscle.

Glucagon

Glucagon is produced by the alpha cells and raises the blood glucose. Glucagon and insulin are part of a feedback system that keeps blood glucose levels stable.

Glucagon belongs to the secretin families of hormones. Blood glucose is elevated by promoting gluconeogenesis and glycogenolysis. Glucagon also regulates the role of glucose production through lipolysis. Glucagon induces lipolysis under conditions of insulin suppression such as type 1 DM.

The glucagon receptor is a membrane G-protein-coupled receptor using the adenylate cyclase system as a second messenger. Secretion of glucagon is merely stimulated by hypoglycemia and epinephrine and inhibited by insulin and somatostatin.

Glucagon (GlucaGen) is used as an emergency medicine to treat severe hypoglycemia in diabetic patients treated with insulin, who have passed out or cannot take some form of sugar by the mouth. Alternatively, an epinephrine emergency kit (Epipen) can be used in these circumstances (Posner and Camarga 2017).

Abnormally elevated levels of glucagon may be caused by pancreatic tumors, such as glucagonoma, which include necrolytic erythema migrans. It may occur alone or in the context of the genetic multiple endocrine neoplasia (MEN) type 1 syndrome.

Pituitary-Hypothalamus

The pituitary gland produces various hormones. In the anterior pituitary gland, ACTH, TSH, LH, FSH, PRL, GH, and MSH are produced, which act on different target glands or cells. The posterior pituitary produces ADH and oxytocin. The hypothalamus releases ADH, CRH, GnRH, GHRH, GHIH (somatostatin), oxytocin, PRH or PIH (dopamine), and TRH.

ACTH

ACTH (Synachten) is used as a diagnostic aid in the assessment of suspected adrenocortical hypofunction, Addison's disease. The binding sites of ACTH are located in the adrenal cortex where it becomes bound to a specific receptor. By activating the adenylate cyclase pathway, the pregnenolone is synthesized from cholesterol. From pregnenolone various corticosteroids are formed.

Pharmacodynamics are measured as the cortisol response at 0, 30, and 60 min after intravenous administration of 250 microgram synachten.

Growth Hormone

Human growth hormone (GH) is secreted by somatotrope cells in the anterior pituitary in a pulsatile fashion. The secretion is regulated by two hypothalamic peptides, growth hormone-releasing hormone (GHRH) which stimulates GH secretion and somatostatin which inhibits GH secretion by backregulation.

The growth hormone receptor belongs to the family of transmembrane proteins that includes the prolactin receptor. Signal transduction is by tyrosine phosphorylation.

Owing to the fact that GH has a short half-life, several approaches have been taken to create long-term agonists. These include the pegylation-sustained release formulations and ligand-receptor fusion proteins. Pegylation of a GH analogue (pegvisomant, Somavert) forms the basis of a successful treatment of acromegaly (Freda et al. 2015).

GH receptor expression can be modified by insulin, thyroid hormones, and sex hormones. Pharmacodynamic response to GH analogue injection in GH-deficient children is measured by plasma GH levels, IGF-1 (insulin-like growth factor), glucose, and free fatty acid (FFA) levels.

Synthetic human growth hormone is used in children with HGH deficiency or insufficiency, children born small for gestational age, and girls with Turner syndrome, Prader-Willi syndrome, and chronic kidney disease. In adults, the use of HGH includes HGH deficiency to rare pituitary tumors or their treatment, short bowel syndrome, or muscle wasting associated with HIV/AIDS.

However, the most common use is doping in combination with other performance drugs as anabolic steroids in an attempt to build muscle and improve athletic performance. Yet HGH's effect on athletic performance is unknown.

Members of the somatotropin drug class are Norditropin, Nutropin, Humatrope, Genotropin, and Saizen.

Prolactin

Prolactin (PRL) is a hormone that promotes lactation in mammals. Prolactin is produced in the front portion of the pituitary. Production of PRL is controlled by two hormones, dopamine and estrogen. Dopamine inhibits and estrogen increases PRL production.

Hyperprolactinemia leads to menstrual disturbances, estrogen and testosterone deficiency reproduction, and disease. Naturally occurring GnRH has a half-life of 2–4 min. GnRH agonists have substitutions for glycine which significantly increases the plasma half-life (Niamh 2013).

GnRH agonists can be used in pulsatile or continuous regimen to treat estrogen-dependent

conditions as endometriosis, uterine leiomyomas, precocious puberty, and menorrhagia. GnRH analogues are used extensively during in vitro fertilization cycles to prevent an LH surge and allow for retrieval of the mature oocytes (Singh et al. 2014).

The GnRH receptor belongs to the G-protein-coupled transmembrane intracellular receptor family. They are also present in the gonads.

In men GnRH agonists are used in the treatment of prostate carcinoma by reducing the levels of testosterone (Shipley et al. 2017).

Members of this drug class are goserelin (Zoladex) and leuprorelin (Lupron). Pharmacodynamic response is measured by suppressed testosterone and PSA (prostate-specific antigen) levels.

In women GnRH antagonists are used in infertility treatment. Members of this drug class are ganirelix acetate (Ganirelix) and cetrorelix (Cetrotide) (37).

Pharmacodynamic response is measured by LH, FSH, and E2 concentrations.

Somatostatin

Somatostatin is also known as growth hormone-inhibiting hormone (GHIH). Somatostatin inhibits insulin and glucagon secretion. Somatostatin is produced by the hypothalamus and uses the membrane G-protein-coupled receptor and the adenylate cyclase system as a second messenger.

Somatostatin is also produced by the delta cells in the pyloric antrum, the duodenum, and the pancreatic islets. Somatostatin inhibits the release of growth hormone by opposing growth hormone-releasing hormone (GHRH), inhibits TSH, and inhibits the release of prolactin (PRL). It further inhibits the release of gastrin, cholecystokinin, motilin, vasoactive intestinal polypeptide (VIP), gastric inhibitory polypeptide (GIP), and enteroglucagon. It also suppresses the exocrine action of the pancreas.

Octreotide (Sandostatin) is a synthetic somatostatin analogue used in the treatment of acromegaly, carcinoid syndrome, insulinomas, glucagonomas, and the VIPomas (Freda et al. 2015; Der-Nigoghossian et al. 2017).

Melanocyte-Stimulating Hormones

The melanocyte-stimulating hormones, alpha, beta, and gamma MSH, are collectively known as the melanotropins. MSH is produced in the hypothalamus. Acting in the hypothalamus, alpha MSH suppresses appetite and contributes to sexual arousal. Keratinocytes in the skin use the melanocortin receptor to produce melanin.

An increase in MSH will cause darker skin. MSH increases in humans during pregnancy. This causes increased pigmentation in pregnancy. MSH and ACTH share the same precursor molecule proopiomelanocortin (POMC).

For these reasons, patients with Cushing's disease, due to excess ACTH, can have hyperpigmentation as acanthosis nigricans. Patients with primary Addison's disease can have hyperpigmentation too.

Different levels of MSH are not the major cause of racial variation in skin color. However, in many red-headed people and other people who do not tan well, there are variations in their hormone receptors, causing them not to respond to MSH in the blood.

Alpha-MSH analogues as Melanolux are primarily used for their tan-stimulating effect and in erythropoietic porphyria. Melatonin is an alpha-MSH antagonist and is produced in the hypofyse from tryptophan precursors. Synthetic melatonin (Bio-Melatonin) is used in insomnia and jet lag (De Leo et al. 2016).

Oxytocin

Oxytocin is a hormone that causes contractions during labor and helps shrink the uterus after delivery. Oxytocin orders the body to let down milk when the baby suckles. It is also known as the "cuddle hormone" because it is released when people snuggle up or bond socially (Zanos et al. 2017).

The oxytocin receptor is a member of the G-protein-coupled receptor family. Oxytocin receptors are expressed by the myoepithelial cells of the mammary and in both the myometrium and endometrium at the end of pregnancy. Oxytocin receptors are also present in the central nervous system.

Oxytocin is used in inducing labor in problematic pregnancies or in helping to abort the fetus in cases of incomplete abortion or miscarriage.

Oxytocin (Pitocin) is usually used as an intravenous infusion. Pitocin is also used as a nasal spray in the treatment of autism.

Pharmacodynamics of oxytocin are measured by clinical outcomes. After prolonged exposure, desensitization of oxytocin receptors can occur.

Antidiuretic Hormone

Antidiuretic hormone (ADH) or vasopressin acts on the kidney and blood vessels. Vasopressin helps prevent loss of water from the body by reducing urine output and helping the kidneys reabsorb water. Vasopressin is used to treat diabetes insipidus which is caused by a lack of naturally occurring pituitary hormone (Christ-Crain and Fenske 2016).

Vasopressin receptors belong to the G-protein-coupled receptor family. They are located in the basolateral membrane of the kidney collecting ducts, pituitary gland, and vascular smooth muscle.

Vasopressin is used as an intravenous infusion (Pitressin) or as a nasal spray (desmopressin).

Vasopressin antagonists (VRAs) are drugs that block vasopressin receptors. Most commonly VRAs are used to treat hyponatremia caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), congestive heart failure (CHF), and cirrhosis (Alagiakrishnan 2016).

Members of this drug class are the "vaptans" as conivaptan (Vaprisol) and tolvaptan (Jinarc). Pharmacodynamic response can be measured by serum electrolytes and serum and urine osmolarities (Streeten et al. 2017).

The Thyroid Gland: Hyper- and Hypothyroidism

The thyroid gland controls metabolism, the way your body uses energy. The thyroid uses iodine in your food to make two hormones, triiodothyronine (T3) and thyroxine (T4). The hypothalamus and the pituitary communicate to maintain T3 and T4 balance. The hypothalamus produces TSH-releasing hormone (TRH) to tell the pituitary to release thyroid-stimulating hormone (TSH).

When T3 and T4 levels are low in the blood as in hypothyroidism, the pituitary releases more TSH to order the thyroid gland to produce more T3 and T4. If T3 and T4 levels are high as in hyperthyroidism, the pituitary gland releases less TSH to the thyroid gland to slow the production of these hormones (Campbell et al. 2015).

The thyroid hormone receptor is a nuclear retinoid X receptor.

Symptoms of hyperthyroidism are anxiety, irritability, moodiness, palpitations, sweating, eye symptoms as exophthalmus, hand trembling, hair loss, weight loss, and missed or light menstrual periods.

Symptoms of hypothyroidism are trouble in sleeping, tiredness and fatigue, difficulty in concentrating, dry coarse skin, weight gain, depression, sensitivity to cold temperature, frequent heavy periods, and joint and muscle pain.

Hyperthyroidism can be treated with antithyroid medication, thyreostatics, primarily methimazole (Strumazol) and propylthiouracil (PTU). Another option is radioactive iodine or surgery.

Methimazole

Thiamazole inhibits the enzyme thyroperoxidase which normally acts in thyroid hormone synthesis by oxidizing the anion iodide (I-) to iodine I2, hypoiodous acid (HOI), and enzyme-linked hypoiodite (EOI) facilitating iodine's addition to tyrosine residues on the hormone precursor thyroglobulin (TBG) to synthesize T3 and T4. It does not inhibit the sodium-dependent iodide transporter in the thyroid follicular cells. Inhibition of this step requires competitive inhibitors as perchlorate or thiocyanate.

Potassium perchlorate is used in the treatment of amiodarone (Cordarone), an iodide-containing cardiac arrhythmic-induced thyrotoxicosis.

Pharmacodynamic response of the thyreostatics are measured by T4 and TSH levels.

Propylthiouracil

Propylthiouracil (PTU) is mainly used in patients with hypersensitivity or allergic reactions to methimazole. PTU inhibits the conversion of T4 to T3 in peripheral tissues and may therefore be an effective treatment for thyroid storm.

Hypothyroidism is treated with levothyroxine (Thyrax) or triiodothyronine (Cytomel). Cytomel is used in patients allergic to L-thyroxine.

Pharmacodynamic responses are measured by serum T4, T3, and TSH levels.

The Parathyroids

Parathyroid hormone (PTH) is secreted by the chief cells of the parathyroid glands and acts to increase the concentration of ionic calcium. In the blood calcitonin, a hormone produced by the C cells of the thyroid decreases ionic calcium concentration. The PTH receptor is located in the bone and the kidney.

PTH reduces the reabsorption of phosphate in the proximal tubulus of the kidney and stimulates 1,25 dihydroxyvitamin D, the active vitamin D metabolite, from 25-hydroxyvitamin D by its effect on renal 1 alpha-hydroxylase. PTH increases calcium absorption in the intestine in conjunction with vitamin D3.

PTH is important in bone remodeling and has a direct stimulating effect on the osteoblast and an indirect inhibiting effect on the osteoclast.

PTH uses the G-protein-coupled protein receptor with the adenylyl cyclase system as the second messenger.

Hyperparathyroidism, the presence of excess PTH in the blood, occurs in two distinct clinical circumstances. Primary hyperparathyroidism is due to abnormal levels of PTH from the parathyroid glands by either hyperplasia or an adenoma. Secondary hyperparathyroidism is due to an inappropriate high PTH level seen as a physiological response to hypocalcemia, as seen in renal insufficiency and vitamin D deficiency.

Hypoparathyroidism is a decreased function of the parathyroids with low PTH levels leading to hypocalcemia, causing cramping and twitching of muscles or even tetany. The condition can be inherited, but it is also encountered after thyroid or parathyroid surgery. Teriparatide injection can be used as a treatment. Calcium replacement and vitamin D can ameliorate the symptoms but can increase the risk of kidney stones and chronic kidney disease (Black and Rosen 2016).

There are a number of rare but well-described genetic conditions affecting PTH metabolism, including pseudohypoparathyroidism, familial hypocalciuric hypercalcemia (FHH), and autosomal dominant hypocalciuric hypocalcemia.

In osteoporotic women, administration of the exogenous 1-34 PTH analogue teriparatide (Forsteo) by daily s.c. injection in conjunction with estrogens produced increases in bone mass and reduced vertebral and non-vertebral fractures. The intact1-84 PTH analogue Natpara is also used in the treatment of osteoporosis. These analogues can be used in sequential courses with anti-resorptive bone agents as the bisphosphonates (Loriaux 2017; Rossi et al. 2017). The bisphosphonate drug class includes APD (Pamidronate), alendronate (Fosamax), risedronate (Actonel), and ibandronate (Boniva).

Bisphosphonates inhibit the digestion of bone by stimulating the osteoclast to undergo apoptosis or cell death. While bone formation and bone resorption are normally coupled and are in balance, the net effect will be increased bone formation.

Calcitonin (Miacalcin Nasal) has a modest place in the treatment of osteoporosis, because more effective drugs as bisphosphonates are available in the prevention of bone loss.

The Adrenals

The adrenal cortex produces glucocorticoids, mineralocorticoids, androgens, estrogens, and progestins.

Glucocorticoids have a broad physiological role in the regulation of glucose metabolic pathways, stress, and modulation of the immune system. Mineralocorticoids are key regulators of mineral and water balance.

Cholesterol is the precursor to all steroid biosynthesis and is converted to a variety of steroid molecules in a series of reactions catalyzed by several cytochrome P450 enzymes. The vast majority of cholesterol is taken up from the LDL cholesterol pool.

Cortisol levels are highest in the morning and are increased by stress or severe infection. Too much cortisol from any cause lead to Cushing's syndrome, the symptoms and signs of which include fat redistribution to the face, upper back, and abdomen, weight gain, stretch marks, bruising, extra hair growth, irregular periods in women, loss of muscle, and trouble in sleeping (Posner and Camarga 2017).

Too little cortisol is part of the syndrome called Addison's disease marked by low energy, joint and abdominal pain, weight loss, diarrhea, fever, and electrolyte disturbances. If the adrenals make too little cortisol, ACTH levels rise. If the pituitary is not working, both ACTH and cortisol levels are low.

The glucocorticoid receptor is a G-protein-coupled nuclear receptor. The receptor is expressed in almost every cell of the body.

Glucocorticosteroids are used as classical glucosteroids or as glucocorticosteroid (GR) agonists that can be divided in selective and nonselective agonists. Classical glucocorticoids are hydrocortison, prednisone, prednisolone, and methylprednisolone.

Beclomethasone is a potent nonselective glucocorticoid agonist. Fluticasone is a highly selective GR agonist.

Mifepristone and ketoconazole, an antimycoticum, are GR antagonists used in the treatment of Cushing's syndrome. Mifepristone has a fourfold higher affinity for the glucocorticoid receptor than dexamethasone being in essential an antiprogestin. For this reason, it is used to abort early pregnancies (Singh et al. 2014).

The primary mineralocorticoid is aldosterone. Aldosterone is involved in the retention by sodium by active reabsorption in the collecting tubule of the kidney, while potassium is actively secreted by the collecting tubule, and water is passively reabsorbed. Aldosterone production is under the influence of ACTH. The mineralocorticoid receptor is located in the cytosol in the cell. Aldosterone and cortisol have similar affinity to the mineralocorticoid receptor.

Primary hyperaldosteronism, Conn's syndrome, is caused by either adrenal hyperplasia or by an adrenal adenoma. This results in hypertension and edema due to excessive sodium and water retention and accelerated excretion of potassium ions (Steinman et al. 2017).

Secondary hyperaldosteronism is caused by extra adrenal stimuli, such as renal hypoperfusion, which stimulates the renin-angiotensin-aldosterone system (RAAS) with resultant hypersecretion of aldosterone and edematous disorders as congestive heart failure cirrhosis with ascites and nephrotic syndrome. Causes of reduced renal blood flow include obstructive renal artery disease (atheroma, fibromuscular dysplasia of the renal artery).

Important antimineralocorticoids are spironolactone (Aldactone) and amiloride (Midamor).

Mitotane (Lysodren) is a steroidogenesis inhibitor used in the treatment of Cushing's syndrome and adrenocortical carcinoma. It inhibits the enzymes 11-beta-hydroxylase, 18-beta-hydroxylase, and 3-beta-hydroxysteroidgenase.

Epinephrine

Epinephrine also known as adrenalin is a hormone, a neurotransmitter, and a drug.

It plays a role in the fight-or-flight response by increasing blood flow to muscles, output of the heart, pupil dilation, and blood sugar. It does by binding to adrenergic alpha- and beta-receptors.

As a medication, it is used in anaphylaxis, cardiac arrest, and superficial bleeding by i.m. or i.v. administration. Inhaled epinephrine may be used in croup and asthma. Epinephrine is widely used as a nasal decongestant. In anaphylaxis, it is used as an Epipen Autoclick. Side effects include anxiety, shakiness, sweating, and sometimes broad complex ventricular tachycardia (Kuiper et al. 2016).

Norepinephrine is a sympathomimetic drug. When given by i.v. injection, it increases heart rate and force and constricts blood vessels making

it very useful in the treatment of shock. Sympathomimetic and sympatholytic drugs mimic or block the effects of norepinephrine. These are called beta- and alpha-blockers.

Beta-blockers are used in the treatment of hypertension, atrial fibrillation, angina pectoris, congestive heart failure, and performance anxiety (Bangalore 2017). Members of this drug class are atenolol (Tenormin), acebutolol (Sectral), metoprolol (Lopressor), pindolol (Viskeen), and propranolol (Inderal).

Alpha-blockers are used in the treatment of hypertension and benign prostate hyperplasia through their relaxing effect on the muscles of the neck of the bladder and help in the expulsion of bladder stones. They are also used in the treatment of anxiety disorders, panic disorders, and posttraumatic stress disorders (PTSD).

Alpha-blockers include doxazosin mesylate (Cardura), prazosin hydrochlorie (Minipress), and dutasteride (Avodart).

Alpha-1-adrenoceptor agonists act as systemic vasoconstrictors. Members of this class are nose and eye drops (Neo-Synephrine, Mydrin). Alpha-2-adrenoceptor agonists are antihypertensive drugs such as clonidine (Catapresan) and alpha-methyldopa (Aldomet).

Pheochromocytomas are rare adrenal medulla tumors oversecreting the catecholamines epinephrine and norepinephrine. Sometimes they are part of a genetic syndrome of multiple endocrine neoplasia (MEN) type 2 syndrome.

The Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is a hormone system that is involved in the regulation of the plasma sodium concentration and arterial blood pressure. When the plasma sodium concentration is lower than normal or the renal blood flow is reduced, the juxtaglomerular cells in the kidney convert prorenin, an intracellular protein, into renin. Plasma renin then cuts a short ten-amino acid-long peptide off a plasma protein known as angiotensinogen. This short peptide is then converted to angiotensin-2 by cleaving off two amino acids by the angiotensin-converting enzyme (ACE) found in the capillaries in the body, the lungs, and the epithelial cells of the kidney.

Angiotensin-2 is a potent vasoconstrictor that causes arterioles to constrict resulting in increased arterial blood pressure. Angiotensin-2 also stimulates the secretion of aldosterone from the adrenal cortex.Angiotensin-2 stimulates the release of antidiuretic hormone (ADH), also called vasopressin, a vasoconstrictor too, mainly stimulating water reabsorption in the kidney and the sense of thirst.

ACE inhibitors, angiotensin receptor blockers (ARBs), and direct renin blockers are used in the treatment of hypertension and congestive heart failure, preventing stroke, preventing nephropathy including diabetic nephropathy, or preventing recurrent atrial fibrillation (Boggish et al. 2017).

Members of the class of ACE inhibitors are captopril (Capoten), enalapril (Renitec), quinapril (Accupril), and ramipril (Altace).

Members of the class of ARBs are valsartan (Diovan), losartan (Cozaar), and candesartan (Atacand).

Aliskiren (Tekturna) is an example of a direct renin inhibitor.

The Gonadal Sex Steroids

Testosterone and its more potent metabolites dihydrotestosterone, progesterone, and estradiol are classified as sex steroids. Cholesterol is the precursor for these hormones like it is for cortisol and aldosterone. The nonsteroidal hormones, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and gonadotropin-releasing hormones, are usually not regarded as sex hormones, although they play major sex-related roles.

Natural sex steroids are made by the gonads, ovaries, and testes, by adrenal glands, or by conversion from other sex steroid in other tissues as the liver or fat. Sex steroids include the androgens consisting of androstenedione and dehydroepiandrosterone (DHEA). Estrogens include estradiol, estriol, and estrone. Progesterone belongs to the progestogens. Synthetic sex steroids as synthetic androgens are often referred to as anabolic steroids.

Testosterone induces male secondary sex characteristics. It has an effect on spermatogenesis and has an androgenic anabolic effect in the maintenance of muscle mass.

Androgen agonist steroids (AASs) are synthetic modifications of testosterone that are more or less anabolic or more or less androgenic, having different affinity for the testosterone receptor. The testosterone receptor is an intracellular cytosol receptor. These receptors are located in tissues as the scalp, prostate, and skin.

Androgenic effects are likely mediated under the influence of dihydrotestosterone (DHT), which is produced by the conversion of testosterone by the enzyme 5-alpha reductase. DHT has an affinity for the testosterone receptor three to four times higher than testosterone.

Other mechanisms of direct and indirect anabolic effects include anti-glucocorticoid effects by displacement of glucocorticoids from their receptor and increases in circulating insulin-like growth factor (IGF-1) as well as upregulation of IGF-1 receptors.

Clinically, AASs have been used to treat a host of conditions including many forms of anemia, acute and chronic wounds, protein malnutrition, severe burns, short stature, osteoporosis, primary or secondary hypogonadism, catabolic states due to long-term use of corticosteroids, and HIV wasting syndrome. Testosterone and AASs have been used and abused by individuals to augment their anabolic and androgenic potential. By doing so, these persons aim to boost their physical performance in athletic endeavors or improve their physique (Taylor et al. 2017; Kshirsagar and Wankhede 2017).

Common testosterone esters include testosterone propionate, testosterone enanthate, testosterone cypionate, and methyltestosterone. Methyltestosterone can be aromatized to the potent estrogen 17-alpha-methylestradiol.

Adverse effects are numerous. Cardiovascular side effects include increased heart rate, increased blood pressure, lowering HDL cholesterol and increasing LDL cholesterol, lower left ventricular mass, and ventricular arrhythmias. Nearly all oral AAAs are hepatotoxic in a dose-dependent manner. AAAs use also results in suppression of clotting factors 2, 5, 7, and 10 as well as prolonging prothrombin time.

Gynecomastia can occur as a result of the aromatization of testosterone and AASs. Acne and male baldness are greatly exacerbated by most AASs in susceptible individuals. Worsening benign prostate hyperplasia (BPH) occurs frequently.

AASs as nandrolone decanoate are used in hemodialysis in combination with recombinant erythropoietin (EPO) to treat the anemia of chronic renal disease.

Antiandrogens

Antiandrogens are also known as androgen antagonists or testosterone blockers. They act by blocking the androgen receptor and/or inhibiting or suppressing androgen production.

In men antiandrogens are used in the treatment of prostate cancer, BHP, androgenic alopecia, hypersexuality, paraphilias, and precocious puberty.

In women antiandrogens are used to treat acne, seborrhea, hidradenitis suppurativa, hirsutism, and hyperandrogenism as seen in polycystic ovary syndrome (PCOS). Antiandrogens are also used in the hormone replacement therapy for transgender women.

In males the major side effects are demasculinization and feminization. The side effects of antiandrogens in woman are minimal.

A number of antiandrogens have been associated with hepatotoxicity. Cyproterone acetate, flutamide, and aminoglutethimide are known for this.

Androgen synthesis inhibitors include aminoglutethimide which inhibits the cholesterol side-cleaving enzyme CYP11A1 which is responsible for the conversion of cholesterol into pregnenolone. Ketoconazol and abiraterone are inhibitors of the enzyme CYP17A1 which converts pregnenolone into androgens, mineralocorticoids, and glucocorticoids. To prevent adrenal insufficiency, Addison's disease, all these inhibitors require concomitant treatment with a glucocorticoid.

5-alpha-reductase inhibitors such as finasteride and dutasteride are inhibitors of 5-alpha reductase, the enzyme that converts testosterone to dihydrotestosterone (Woljee et al. 2017).

Antigonadotrofins are drugs which suppress the GnRH-mediated secretion of LH and FSH (Crew et al. 2017).

GnRH agonists and GnRH antagonists are powerful antigonadotrofins that are able to suppress androgen levels by 95% in men. As mentioned before leuprorelin (Lupron) and goserelin (Zoladex) are examples of GnRH agonists. An example of a GnRH antagonist is cetolix (cetrorelix).

Estrogens and Progestogens

Estrogens are the primary female sex hormones and are important in the estrous cycle in females. Natural estrogens are steroid hormones, while some synthetics are nonsteroidal. Enzymatic actions produce estradiol from testosterone while estrone is made from androstenedione.

Phytoestrogens have analogous effects of human estrogens in serving to reduce menopausal symptoms as well the risk of osteoporosis and heart disease.

Progesterone is a steroid hormone involved in the luteal phase of the menstrual cycle. Progesterone is produced in the ovaries and adrenals and in pregnancy and is synthesized from pregnenolone. Progesterone is also called the "pregnancy hormone." It converts the endometrium in the luteal phase to prepare the uterus for implantation. If pregnancy does not occur, progesterone levels drop leading to menstruation.

During implantation and gestation, progesterone appears to decrease the immune response to allow pregnancy. Progesterone decreases contractility of the uterine smooth muscle. Progesterone inhibits lactation during pregnancy. A drop in progesterone levels is possibly one step that facilitates the onset of labor.

The combined oral contraceptive pill contains estrogens and progestogens. Morning-after pills and abortion pills contain only progestogens as Mifepristone and Misoprostol. Mifepristone is an antiprogestin. Antiprogestins bind strongly to both progesterone and glucocorticoid receptors.

Although antiprogestins delay ovulation, this effect is inconsistent unless high doses are given. Under these circumstances, the antiprogestin effect is associated with unopposed estrogen action.

Antiestrogens are mainly used as a means of estrogen deprivation therapy in the treatment of ER-positive breast cancer. They are also used to treat infertility, male hypogonadism, and gynecomastia in men and in the hormone replacement for transgender men.

Antiestrogens include selective receptor modulators (SERMs) like tamoxifen, clomifene, and raloxifene and selective estrogen receptor degraders (SERDs) such as fulvestrant and aromatase inhibitors (Ais) like anastrozole and progestogens and GnRH analogues.

Conclusion

This endocrinology pharmacodynamic evaluation clearly shows the enormous impact of endocrinology in nearly all areas of medicine. If you could take a look in the medicine cabinet of an older Western patient, you would recognize all classes of medicines that came along in this review.

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