Chapter 16
Drugs and the Endocrine System

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Abstract The endocrine system regulates many aspects of important physiological processes in the body. Our body produces hormones from different glands and these hormones are kept in balance by various regulatory feedback mechanisms. Autoimmune problems, tumors, metabolic dysregulation and genetic predisposition may disrupt normal regulation of hormones causing excessive production, hormone deficiency or resistance of target organs to hormones. Three hormones, i.e., thyroid hormones, insulin and glucocorticoids are at issue more often compared to the rest of the hormones in the endocrine system. In hyperthyroidism, various antithyroid drugs are used, which target the different stages in thyroid hormone synthesis and release. In hypothyroidism, thyroxine is used in replacement therapy. Diabetes mellitus is an increasing problem worldwide where high blood glucose level is attributed to the deficiency of insulin (Type 1 diabetes) or insulin resistance (Type 2 diabetes.) Type 1 diabetes is managed with human insulin or insulin analogues. In Type 2 diabetes, where there is insulin resistance and relative insulin deficiency, insulin secretagogues and insulin sensitizers are used. Newer agents target the incretin hormones which play an important role in the regulation of insulin, glucose and satiety. The adrenal glands which produce the glucocorticoids and mineralocorticoids regulate many metabolic processes and are important in inflammatory and immune responses. Synthetic glucocorticoids are used clinically in a wide variety of clinical conditions not related to hormone deficiencies due to its potent anti-inflammatory and immunosuppressant effects. However, the use of glucocorticoids therapeutically is associated with many adverse effects, among them impaired response to infection and Cushing's syndrome.

Keywords Hormone replacement • Antithyroid drug • Thyroid hormone replacement • Insulin therapy • Oral antidiabetic agents • Corticosteroids

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Introduction

The endocrine system is important in regulating metabolic processes in the body. The hormones may act on an organ or a specific metabolic process. Most of the endocrine organs are controlled by feedback mechanisms either through stimulating hormones produced centrally by the hypothalamus or pituitary, or through the effects of the index hormone. Dysfunction in endocrine system results in either a deficiency or an over-production of the hormone, causing significant morbidity. When the hormone levels are elevated, pharmacological strategies are required to bring down the levels and to treat the effects of these elevated hormones. On the other hand, if the hormone levels are low, replacement therapy or therapy to stimulate hormone production is instituted. Sometimes, the target organ becomes resistant to the effect of the hormone, in which case drugs are used to improve the sensitivity of target organs to the hormone. Synthetic hormones such as glucocorticoids are also used therapeutically in clinical conditions not related to hormone deficiency.

Thyroid Hormones

The thyroid gland synthesizes two hormones, triiodothyronine (T_3) and thyroxine (T_4). In the process of synthesizing thyroid hormones, it utilizes iodine. The release of T_3 and T_4 are controlled by hypothalamic thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) from the pituitary, which are inhibited in the presence of T_3 and T_4. This is a negative feedback mechanism. More than 99 % of thyroid hormones are bound to proteins such as the thyroid-binding globulin (TBG). Free forms of T_4 and T_3 dissociate from TBGs and enter cells via diffusion or active transport. Within the cells, T_4 is converted to T_3, which is the active form. T_3 enters the nucleus, activating the transcription of genes, causing the synthesis of proteins and other substances. Thyroid hormones regulate carbohydrate, protein and lipid metabolism and are required for growth and development. The overall effect in cellular metabolism is to increase oxygen consumption and basal metabolic rate. In addition, thyroid hormones also have an effect on the sympathetic nervous system.

Drugs Used in Management of Hyperthyroidism

In hyperthyroidism, drugs are administered to stop the production of thyroid hormone, prevent its release from the thyroid gland and block the adrenergic effects of excessive hormonal levels.

Antithyroid Drugs (Thioureylenes)

Thioureylenes (also known as thioamides) include carbimazole and its active metabolite, methimazole, as well as propylthiouracil (PTU). These drugs block de novo synthesis of thyroid hormone by inhibiting the iodination process of tyrosine residues in thyroglobulin. Tyrosine residues are iodinated to form monoiodotyrosine (MIT) and in some, di-iodotyrosine (DIT). These molecules are coupled in pairs, MIT with DIT to form T_3, or two DIT molecules to form T_4. PTU has the extra advantage of inhibiting the peripheral conversion of T_4 to T_3. Stored T_3 and T_4 are unaffected. The clinical effects of carbimazole and PTU may be delayed until the thyroid hormone stores are depleted, which may take 2–4 weeks. The well-known but rare and potentially fatal adverse effect of thioureylenes is agranulocytosis, which renders the patients prone to infection. Agranulocytosis is reversible when the drug is stopped. PTU is associated with hepatotoxicity. Long-term or high-dose treatment with these agents may cause hypothyroidism. Thioureylenes cross the placenta and should be used with caution in pregnant patients.

Iodides

Potassium iodide (Lugol's iodine) is given orally and is converted to iodide in vivo. It inhibits the synthesis and release of thyroid hormone and reduces the vascularity of the thyroid gland. Iodides also block peripheral conversion of T_4 to T_3. Lugol's iodine is used in thyroid crisis and before thyroidectomy in vascular goiters.

Radioiodine ^{131}I

^{131}I emits beta and gamma radiation. The beta rays are absorbed by thyroid tissues and are cytotoxic. The cytotoxic effect is quite delayed with maximal effect observed around 4 months post-treatment. Hypothyroidism is commonly seen after treatment, especially in patients with Grave's disease. Sialadenitis which manifest as xerostomia, altered taste or pain is another adverse effect. Radioiodine should be avoided in children, pregnant and nursing women due to the radiation.

Beta Adrenoceptor Blockers

Beta blockers used in the management of hyperthyroidism include propranolol and esmolol. They block the peripheral adrenergic manifestations of hyperthyroidism such as palpitations, tremors and anxiety. Propranolol has additional function in hyperthyroidism as it can block peripheral conversion of T_4 to T_3.

Hyperthyroid Emergencies

Thyrotoxic crisis or thyroid storm is an extreme form of thyrotoxicosis with severe symptoms including tachycardia, vomiting, diarrhea, dehydration and delirium. Urgent treatment is required as mortality is high. Reduction of thyroid hormone is achieved by giving thioureylenes (PTU or carbimazole). Potassium iodide is given 1 h after thioureylenes (to prevent the iodine from being used as a substrate for new thyroid hormone synthesis) to produce a complete block of thyroid hormone production. Beta blockers are given to treat autonomic symptoms and hydrocortisone administered to treat hypoaldosteronism which is associated with Grave's disease.

Drugs Used in the Management of Hypothroidism

Hypothyroidism can be due to a defect in the hypothalamus, the pituitary gland or the thyroid gland. The standard thyroid replacement therapy is levothyroxine (T_4), which is available both in oral and intravenous form ($t_{1/2}$ 7 days) and liothyronine (T_3) which is available in the oral form ($t_{1/2}$ 2 days) and is four times more potent than levothyroxine. Liothyronine has a faster onset of action than levothyroxine.

Hypothyroid Emergencies

In myxedema coma, a hypothyroid emergency which is life threatening, clinical features of profound decrease in metabolic activity are seen, such as hypothermia, hypotension, bradycardia and depressed level of consciousness. Replacement thyroid hormone is given intravenously until the patient is able to take orally. Supportive therapy includes gradual rewarming and appropriate oxygen therapy as necessary to manage hypercapnia and hypoxia. Intravenous dextrose is given for hypoglycemia and hydrocortisone if adrenal insufficiency is present. Hypotension and hyponatremia may be corrected with saline infusion and associated infections must be treated.

Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is characterized by insulin deficiency while type 2 diabetes mellitus (T2DM) is commonly due to resistance of the principal cells to the effects of insulin. It can progress to insulin deficiency.

Insulin

Insulin is secreted by the beta cells of the pancreas. It is an anabolic hormone involved in the metabolism of carbohydrate, protein and lipid in the body and acts on three principal cells, i.e. muscles liver and adipose tissues. The main functions are to increase the storage of glucose (glycogenesis), reduce glucose production (gluconeogenesis) and decrease release of glucose (glycogenolysis) by the liver as well as to increase glucose uptake and utilization in adipose tissues. In addition, insulin increases lipid synthesis in the liver and adipose tissues whilst reducing lipolysis. Insulin is also important in protein breakdown in the liver and protein uptake and synthesis in the muscles.

Insulin Therapy for Diabetes Mellitus (T1DM and Some T2DM)

The application of genetic engineering enabled human insulin to be produced using recombinant DNA technology. In the 1990s, insulin analogues were developed and these analogues are now gradually replacing human insulin.

Insulin, being a protein, is destroyed in the gastrointestinal tract and so is administered parenterally, usually via subcutaneous injections. Once absorbed, insulin has a short half-life of 10 min. Insulin is given as replacement therapy in patients with T1DM and some patients with T2DM. Intravenous insulin is used as a short-term measure for situations like surgical procedures and insulin is also given to pregnant patients with diabetes mellitus.

Hypoglycemia is the most common adverse effect of insulin therapy. It is exacerbated by an inappropriately high dose of insulin, low carbohydrate intake and/or excess physical activity. Some patients may acquire ‘hypoglycemic unawareness’ in which autonomic signs of hypoglycemia are reduced or absent. Other adverse effects include weight gain, lipodystrophy at injections sites and insulin allergy (hypersensitivity). Insulin edema is a rare adverse reaction due to sodium and water retention seen at the start of treatment in patients with poor glucose control.

Insulin Preparations

There are four types of insulin preparations: rapid or ultrashort-acting, short-acting, intermediate-acting and long-acting as presented in Table 16.1. Short-acting insulin is given before meals to increase the level of circulating insulin and thus target postprandial hyperglycemia. Intermediate-acting insulin is produced by combining insulin with neutral protamine, also known as Neutral Protamine Hagedorn insulin

Table 16.1 Pharmacological properties of the different insulin preparations

Type of insulin	Examples	Onset	Peak activity	Duration
Rapid/Ultrashort-acting insulin	Insulin lispro, Insulin aspart	15–30 min	30–90 min	3–4 h
Short-acting insulin	Regular insulin	30–60 min	2–4 h	6–10 h
Intermediate-acting insulin	Neutral protamine Hagedorn (NPH insulin)	1–4 h	4–12 h	12–24 h
Long-acting insulin	Insulin glargine Insulin detemir Insulin glulisine	1–2 h	3–20 h	24–30 h

Permission from Hermansen, K. Insulin and new insulin analogues, insulin pumps and inhaled insulin in type 1 diabetes, in Pharmacotherapy of Diabetes: New development (eds: Mogensen, C) Springer 2007 New York

or NPH insulin. Intermediate-acting insulin is also available as combined or premixed preparation with fast-acting insulin. Long-acting insulin is used at bedtime or in the morning to provide basal insulin replacement.

Antidiabetic Agents for Type 2 Diabetes Mellitus

In patients with T2DM, the available drugs are used to stimulate insulin secretion using insulin secretagogues or to improve target organ sensitivity to insulin using insulin sensitizers. New drugs acting on incretins such as glucagon-like peptide-1 (GLP-1) have been developed. Incretins are gastrointestinal hormones that have glucose-lowering actions. GLP-1 stimulates glucose dependant insulin secretion and mediates the satiety response. Antidiabetic agents currently available are summarized in Table 16.2. Metformin is the first-line antidiabetic agent according to many guidelines due to its weight loss effects and evidence linking it to decrease in cardiovascular complications in diabetes.

Hyperglycemic Emergencies

In diabetic ketoacidosis, patients present with depressed mental status, dehydration, rapid deep breathing, and fluid, electrolyte and acid-base derangement. Management is based on the following four principles: (1) fluid and electrolyte therapy (2) intravenous insulin therapy (3) treatment of co-morbidities such as infections and (4) close monitoring. Electrolyte therapy includes management of potassium, in certain cases, bicarbonate and phosphate levels. IV Insulin should be adjusted regularly according to glucose levels.

Table 16.2 Antidiabetic agents for type 2 diabetes mellitus

Drug class	Drug name	Main mechanisms of action	Adverse effects/ precaution
Biguanides	Metformin	Insulin sensitizer Increase glucose uptake by tissues Decrease hepatic gluconeogenesis Decrease glucose absorption from GIT	GI disturbance Lactic acidosis (Caution in those with moderate-severe renal impairment)
Sulfonylureas	Glibenclamide Gliclazide Glimepiride Glipizide	Insulin secretagogues Binds to sulfonylureas receptors associated beta cells K_{ATP} inward rectifier channels to stimulate production of insulin	Hypoglycemia Weight gain Many drug interactions Alcohol-flushing
Meglitinides	Repaglinide Nateglinide	Insulin secretagogues Binds to sulfonylureas receptors. MOA similar to sulfonylureas.	Hypoglycemia Drug interactions: Cytochrome P450
Thiazolidinedione	Pioglitazone	Insulin sensitizer Ligands of the peroxisome proliferator-activated receptor-gamma (PPAR-γ) receptors Increase glucose and lipid uptake and utilization by tissues	Fluid retention Weight gain Risk of osteoporosis Slight increased risk of bladder cancer
Incretin modulators	Exenatide*	Glucagon-like peptide-1 receptor agonists Action includes stimulating insulin release, suppress glucagon and decrease appetite	Reports of pancreatitis Hypoglycemia
	Sitagliptin	Dipeptidyl-peptidase-4-(DPP-4) inhibitor The DPP-4 enzyme is involved in inactivating GLP-1. Action is similar to GLP-1 agonist	Upper respiratory tract infections Drug interactions
α-glucosidase inhibitor	Acarbose	Reduces the absorption of carbohydrates in the intestine	GI disturbance

[a]Exenatide is administered via subcutaneous injections

Hypoglycemic Emergencies

Blood sugar level below 3.9 mmol/l (70 mg/dl) is defined as hypoglycemia. Clinical features include sweating and palpitations, and central nervous dysfunction such as blurred vision, headache and weakness which can progress to convulsions and coma. Patients with hypoglycemia can be given glucose orally or intravenously. In hypoglycemic emergencies outside hospital, when patients are unable to take orally, glucagon injections (packed in a kit) can be given, which will return blood glucose levels to normal in 10–15 min.

Adrenal Hormones

The adrenal glands produce glucocorticoids, mineralocorticoids and sex hormones. Glucocorticoids are important in the maintenance of the hypothalamic-pituitary-adrenal (HPA) axis. Glucocorticoids also play important roles in stress response and metabolic regulations. They possess potent anti-inflammatory and immunosuppressive

properties. In acute inflammation, glucocorticoids decrease the activity of leucocytes while in chronic inflammation glucocorticoids reduce the clonal expansion and activity of lymphocytes. They also reduce angiogenesis and fibrosis associated with inflammation. In addition, glucocorticoids play an important role in regulating inflammatory mediators such as cytokines, prostaglandins, histamines and complement components.

The important mineralocorticoid synthesized by the adrenal glands is aldosterone. Aldosterone plays a vital role in salt and water balance in the body by regulating the renin-angiotensin-aldosterone system.

Synthetic Corticosteroids

Many synthetic corticosteroids have been developed with different potencies (Table 16.3). Corticosteroids possess potent anti-inflammatory and immunosuppressive properties and have become valuable treatment options for a wide range of clinical conditions. However, multiple adverse effects of corticosteroids have also been reported (Table 16.4). Most of the adverse effects of corticosteroids are related to the dosage given. In order to reduce adverse effects, the lowest possible dose and for the shortest duration of treatment that will produce the desired therapeutic response should be used. Steroid dose is tapered down gradually before being stopped. Sudden withdrawal of corticosteroids after prolonged or high dose may

Table 16.3 Potencies of different corticosteroids

Corticosteroids	Relative potency to hydrocortisone	Main route of administration	Duration of action
Hydrocortisone	1	IV	8–12 h
Prednisolone	4	Oral	12–36 h
Dexamethasone	30	IM, oral	36–54 h
Betamethasone	30	Topical	36–54 h

Table 16.4 Adverse effects of corticosteroids

Cushing's syndrome	Moon face, plethora, buffalo hump, purple striae, central obesity, poor wound healing, skin thinning, muscle wasting and weakness, avascular necrosis, increased appetite, insomnia, euphoria or dysphoria
Immunosuppression	Susceptibility to infections, poor wound healing, peptic ulcerations
Suppression of adrenal functions	Addisonian crisis
Metabolic	Hyperglycemia, hyperlipidemia, hypertension
Musculoskeletal	Osteoporosis, muscle wasting, proximal muscle weakness, disturbance of growth in children
Eye	Cataract, glaucoma
Central nervous system	Insomnia, euphoria, depression, steroid psychosis
Others	Hirsutism, dry mouth

precipitate acute adrenal insufficiency. Corticosteroids may be administered by many routes: oral, intravenous, intra-articular, inhalation, eye or nasal drops and topical skin application. They are transported in the plasma bound to corticosteroid-binding globulin (CBG) and to albumin. Some synthetic glucocorticoids are not bound to protein. They are metabolized by the microsomal enzymes in the liver.

Synthetic Mineralocorticoids

Fludrocortisone is a synthetic mineralocorticoid which is used as replacement therapy for adrenal insufficiency. It has a long duration of action (24–36 h) and is metabolized by the hepatic microsomal enzymes.

Adrenal Emergencies

In adrenal emergencies such as Addisonian's crisis, the adrenal insufficiency can cause headache, weakness, nausea and vomiting, diarrhea and confusion or coma. Patients present with hypotension, which when left untreated can progress to shock that does not respond to volume replacement and vasopressors, leading to death. Management involves immediate treatment with hydrocortisone 100–300 mg and aggressive volume replacement. Serum electrolytes and blood glucose should be monitored and corrected as necessary.

Key Concepts

- Excessive or deficiencies in hormones may present as acute and chronic medical problems.
- Replacement therapy is instituted for deficiencies of hormones.
- Other strategies in endocrine problems include targeting hormone synthesis and glands as well as targeting sensitivities of organs to hormones.
- Adverse effects of replacement therapy usually relates to its actions in the body.

Summary

Hormones control many physiological processes in our body and is kept in balance by various regulatory mechanisms. Conditions in which the hormone is deficient or target organ is resistant to hormone actions, as exemplified by hypothyroidism, diabetes mellitus and Addison's disease, require pharmacological replacement of

the deficient hormone or pharmacological strategies to improve sensitivities to hormone. Conditions in which hormones became excessive and unregulated, as exemplified by thyroid storm, require pharmacological strategies to bring down the hormone levels by targeting various stages of hormone synthesis, release and actions. Hormones such as corticosteroids are also used for other clinical conditions for their potent anti-inflammatory and immunosuppressant effects as well as for diagnostic purposes.

Further Reading

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