

McCance: Pathophysiology, 6th Edition

Chapter 21: Alterations of Hormonal Regulation

Key Points – Print

SUMMARY REVIEW

Mechanisms of Hormonal Alterations

1. Abnormalities in endocrine function may be caused by hypersecretion or hyposecretion of hormones, causing alterations in normal hormone levels.
2. Endocrine abnormalities also may be caused by alterations in receptor function through a variety of mechanisms: (a) a decrease in number of receptors, (b) receptor insensitivity to the hormone, (c) antibodies against specific receptors, and (d) defects in second messenger generation or postreceptor defects.
3. Abnormally high levels of circulating hormones sometimes are caused by hormone release from tissues outside the endocrine system (ectopic foci) that may not respond to normal feedback mechanisms, in which case they are said to function autonomously.

Alterations of the Hypothalamic-Pituitary System

1. Dysfunction in the release of hypothalamic hormones probably is related to interruption of the connection between the hypothalamus and pituitary—namely, the pituitary stalk.
2. Disorders of the posterior pituitary include SIADH secretion and DI. SIADH secretion is characterized by abnormally high ADH secretion; DI is characterized by abnormally low ADH secretion.
3. In SIADH, high ADH levels interfere with renal free water clearance, leading to hyponatremia and hypoosmolality. SIADH secretion is associated with certain forms of cancer, apparently because of ectopic secretion of ADH by tumor cells.
4. DI may be neurogenic, caused by insufficient amounts of ADH, or nephrogenic, caused by an inadequate response to ADH. Its principal clinical features are failure to concentrate urine with polyuria and polydipsia.
5. Hypopituitarism is dysfunction of the anterior pituitary that causes failure of hormonal functions. Symptoms may be mild to severe.
6. The most common cause of hypopituitarism is a tumor of the pituitary or subsequent treatment of the tumor (surgical or radiation therapy). Symptoms are variable depending on which hormones are deficient (i.e., TSH, ACTH, GH, etc.).
7. Hyperpituitarism is caused by pituitary adenomas. These are usually benign slow-growing tumors that arise from cells of the anterior pituitary.

8. Expansion of a pituitary adenoma causes neurologic and secretory effects. Pressure from the expanding tumor causes hyposecretion of cells, dysfunction of the optic chiasm (leading to visual disturbances), and dysfunction of the hypothalamus and some cranial nerves.
9. Hypersecretion of GH causes acromegaly, in which GH secretion becomes high and unpredictable. Pituitary adenoma is the most common cause of acromegaly.
10. Prolonged, abnormally high levels of GH lead to proliferation of body and connective tissues. Renal, thyroid, and reproductive dysfunction develop slowly, together with a change in bony proportions.
11. GH deficiency in children results in growth failure and fasting hypoglycemia. Adult GH deficiency results in fatigue, osteoporosis, and increased mortality.
12. Pituitary prolactinomas, renal failure, and medications can result in increased prolactin and affects reproductive organs and function in both men and women.

Alterations of Thyroid Function

1. Thyrotoxicosis is a general condition in which TH levels are elevated and produce an exaggerated physiologic response in tissues. The condition can be caused by a variety of specific diseases, each of which has its own pathophysiology and course of treatment.
2. In general, hyperthyroidism has a range of endocrine, reproductive, gastrointestinal, integumentary, and ocular manifestations. These are caused by increased circulating levels of TH and by stimulation of the sympathetic division of the autonomic nervous system.
3. Graves disease, the most common form of hyperthyroidism, is caused by an autoimmune mechanism that overrides normal mechanisms for control of TH secretion.
4. Manifestations of Graves disease can include symptoms of hyperthyroidism, diffuse thyroid enlargement, disorders of the skin, and enlargement of extraocular muscles.
5. The cutaneous manifestation of Graves disease is pretibial myxedema, a condition characterized by subcutaneous swelling of the legs and, occasionally, the hands.
6. Ocular manifestations of Graves disease are caused by hyperactivity of the sympathetic division of the autonomic nervous system and by immune-induced infiltration of extraocular muscles.
7. Toxic nodular goiter and toxic multinodular goiter occur when hyperplastic regions of the thyroid become autonomous.
8. Toxic nodular goiters are follicular-cell adenomas that produce symptoms similar to those of Graves disease.
9. Toxic multinodular goiters result from multiple functioning adenomas.
10. Thyrotoxic crisis is a severe form of hyperthyroidism that often is associated with physiologic stress. Without treatment, death occurs quickly.
11. Hypothyroidism is caused by deficient production of TH by the thyroid gland. The condition may be primary or secondary.

12. Primary hypothyroidism transiently occurs in either subacute or painless thyroiditis and spontaneous resolution of hypothyroidism is nearly universal. Chronic lymphocytic thyroiditis, an autoimmune disease, is associated with permanent hypothyroidism.
13. Subacute thyroiditis, a form of hypothyroidism, is a self-limited nonbacterial inflammation of the thyroid gland. The inflammatory process damages follicular cells, causing leakage of triiodothyronine (T₃) and thyroxine (T₄). Hyperthyroidism then is followed by transient hypothyroidism, which is corrected by cellular repair and a return to normal levels in the thyroid.
14. Autoimmune thyroiditis is associated with infiltration or fibrosis of the thyroid, circulating thyroid antibodies, and gradual loss of thyroid function. Autoimmune thyroiditis occurs in those individuals with a genetic susceptibility to an autoimmune mechanism that causes thyroid damage and eventual hypothyroidism.
15. Hypothyroidism also can be caused by hypothalamic-pituitary dysfunction in which TRH and TSH are not produced in sufficient amounts.
16. Thyroid carcinoma is a relatively rare cancer. The most consistent causal risk factor associated with thyroid carcinoma is exposure to ionizing radiation, especially in childhood.
17. Hypothyroidism affects all body systems. Symptoms depend on the degree of TH deficiency. Common manifestations include decreased energy metabolism and heat production.
18. Myxedema is the characteristic sign of hypothyroidism. Myxedema is caused by alterations in connective tissue with water-binding proteins. The excess water leads to edema and thickened mucous membranes.
19. Myxedema coma is a severe form of hypothyroidism, which may be life threatening without emergency medical treatment.
20. Congenital hypothyroidism occurs with thyroid agenesis and results in hypothyroidism, growth failure, and mental retardation from absence of thyroxine.
21. Thyroid carcinoma is probably caused by exposure to ionizing radiation, particularly during childhood, with the development of nodules and normal thyroxine levels.

Alterations of Parathyroid Function

1. Hyperparathyroidism may be primary or secondary and is characterized by greater than normal secretion of PTH.
2. Primary hyperparathyroidism is caused by an interruption of the normal mechanisms that regulate calcium and PTH levels, usually a parathyroid adenoma. Manifestations include chronic hypercalcemia, increased bone resorption, and hypercalciuria.
3. Secondary hyperparathyroidism is a compensatory response to hypocalcemia and often occurs with chronic renal failure.
4. Pseudohypoparathyroidism and familial hypocalciuric hypercalcemia are inherited conditions. In pseudohypoparathyroidism there is resistance to PTH action and familial hypocalciuric

hypercalcemia mimics hyperparathyroidism with failure of calcium sensing by the parathyroid gland.

5. Hypoparathyroidism, defined by abnormally low PTH levels, is caused by thyroid surgery, autoimmunity, or genetic mechanisms.
6. The lack of circulating PTH in hypoparathyroidism causes depressed serum calcium levels, increased serum phosphate levels, decreased bone resorption, and eventual hypocalciuria.

Dysfunction of the Endocrine Pancreas: Diabetes Mellitus

1. Diabetes mellitus is a complex syndrome associated with glucose intolerance and hyperglycemia in genetically susceptible individuals that causes a number of metabolic and vascular changes. The two most common types of diabetes mellitus are type 1 and type 2.
2. Type 1 diabetes mellitus includes an autoimmune (most common) and a nonimmune type. The immune type is associated with autoantibody, T cell, and macrophage destruction of pancreatic beta cells with loss of insulin production and a relative excess of glucagon. Antibodies also can be formed against glutamic acid decarboxylase and insulin.
3. In type 1 diabetes mellitus, lack of insulin and excess glucagon cause hyperglycemia and subsequent loss of glucose in the urine. Polyuria and polydipsia result from osmotic diuresis. Weight loss is a classic symptom of type 1 diabetes.
4. Ketoacidosis is caused by abnormally low levels of insulin and increased levels of glucagon resulting in increased lipolysis, increased gluconeogenesis, and production of ketone bodies leading to ketoacidosis.
5. A diagnosis of diabetes mellitus is based on elevated plasma glucose concentrations and classic signs and symptoms.
6. Type 2 diabetes mellitus is caused by genetic susceptibility that is triggered by environmental factors. The most compelling environmental risk factor is obesity. Insulin production continues but the weight and number of beta cells decrease.
7. Several mechanisms of insulin resistance (hyperinsulinemia) cause reduced glucose uptake and metabolism in type 2 diabetes. These mechanisms include alteration in production of adipokines by adipose tissue (i.e., leptin resistance), elevated serum free fatty acids and intracellular lipid deposits, release of inflammatory cytokines from adipose tissue, and obesity-associated insulin resistance.
8. In type 2 diabetes myelin deficiency results in increased glucagons secretion and hyperglycemia. Deposition of amyloid in the pancreas contributes to beta cell loss.
9. Decreased gherlin levels have been associated with insulin resistance in type 2 diabetes.
10. Other specific types of diabetes mellitus include MODY associated with autosomal dominant gene mutations, and gestational diabetes with onset of glucose intolerance during pregnancy.
11. Acute complications of diabetes mellitus include hypoglycemia, DKA, HHNKS, the Somogyi effect, and the dawn phenomenon.

12. Hypoglycemia is a lowered blood glucose level that may be related to exogenous (i.e., insulin shock or insulin reaction), endogenous, or functional causes.
13. Symptoms of hypoglycemia are divided into adrenergic, caused by activation of the sympathetic nervous system; and neuroglycopenic, reflecting defective central nervous system metabolism resulting from impaired energy generation.
14. DKA develops when there is an absolute or relative deficiency of insulin and an increase in the insulin counterregulatory hormones of catecholamines, cortisol, glucagon, GH, and FFAs with accelerated gluconeogenesis and ketogenesis.
15. HHNKS is pathophysiologically similar to DKA, although levels of FFAs are lower in HHNKS and lack of ketosis indicates that some level of insulin is present. The hyperosmolar state can cause osmotic diuresis and profound dehydration.
16. The Somogyi effect is a combination of hypoglycemia with rebound hyperglycemia caused by effects of counterregulatory hormones. It is most common in persons with type 1 diabetes mellitus and in children.
17. The dawn phenomenon is an early morning rise in glucose levels caused by nocturnal elevations of GH.
18. Chronic complications of diabetes mellitus include diabetic neuropathies, microvascular disease (e.g., retinopathy, nephropathy and neuropathy), macrovascular disease (e.g., CAD, stroke, peripheral vascular disease), and infection. Metabolic changes contributing to complications include shunting of glucose to the polyol pathway, activation of protein kinase C, induction of ROS (oxidative stress), formation of AGEs, and accumulation of hexosamines.
19. Microvascular complications are associated with vascular alterations in endothelium, the basement membrane, and thrombosis.
20. Diabetic retinopathy is caused by several mechanisms including microvascular changes and thrombosis that lead to microvascular occlusion, increased vascular permeability, retinal ischemia and hemorrhages.
21. Diabetic nephropathy is related to hyperglycemia, hyperperfusion, oxidative stress, and inflammation with glomerular enlargement and glomerular basement membrane thickening, diffuse intercapillary glomerulosclerosis, expansion of the mesangial matrix, and progressive renal failure.
22. Diabetic neuropathies may be caused by vascular and metabolic mechanisms, or a combination of both, with axonal and Schwann cell degeneration and abnormalities in sensory and motor nerve conduction velocity, including involvement of the autonomic nervous system.
23. Macrovascular disease associated with diabetes mellitus is associated with hyperglycemia, hyperlipidemia, inflammation, and altered endothelial function.
24. Incidence of coronary heart disease, peripheral vascular disease, and stroke is greater in persons with diabetes than in nondiabetic individuals.
25. CAD and stroke in diabetes are a consequence of accelerated atherosclerosis, hypertension, and increased risk for thrombus formation.

26. Peripheral vascular disease is a consequence of occlusion of large and small arteries with an increased risk of ischemia, necrosis, and amputation.
27. Individuals with diabetes are at risk for a variety of infections related to sensory impairment, vascular complications, impaired white blood cells and suppressed immunity, rapid proliferation of pathogens, and delayed wound healing.

Alterations of Adrenal Function

1. Disorders of the adrenal cortex are related to hyperfunction or hypofunction. No known disorders are associated with hypofunction of the adrenal medulla, but medullary hyperfunction causes clinically defined syndromes.
2. Hypercortisolism is divided into ACTH-dependent (Cushing disease or ectopic ACTH syndrome) and ACTH-independent (adrenal adenoma or adenocarcinoma) mechanisms.
3. Cushing disease is excessive anterior pituitary ACTH production most commonly by an ACTH-secreting pituitary microadenoma.
4. Cushing syndrome occurs whenever there is an excessive level of cortisol regardless [AU1]of cause. Exogenous forms result from exogenous administration of glucocorticoids. Endogenous forms are either corticotropin dependent (most common and caused by an ACTH-secreting pituitary tumor) or corticotropin independent, usually caused by an adrenal cortical tumor.
5. Individuals with Cushing disease lose diurnal and circadian patterns of ACTH and cortisol secretion, and they lack the ability to increase secretion of these hormones in response to a stressor. Individuals experience weight gain, glucose intolerance, protein wasting, bone disease, hyperpigmentation, and immunosuppression.
6. Primary hyperaldosteronism is a disorder of the adrenal cortex usually caused by an adrenal adenoma or bilateral nodular hyperplasia. The condition is characterized by hypertension, hypokalemia, renal potassium wasting, and neuromuscular manifestations.
7. Secondary hyperaldosterone secretion is related to a variety of conditions associated with elevated renin release and activation of angiotensin II. These include decreased circulating blood volume, decreased renal blood supply, elevated estrogen levels, Bartter syndrome, and renin-secreting tumors.
8. Hyperaldosteronism promotes increased sodium reabsorption, corresponding hypervolemia, increased extracellular volume (which is variable), hypertension, and hypokalemia.
9. Adrenal tumors, either adenomas or carcinomas, can autonomously secrete androgens or estrogens.
10. Hypofunction of the adrenal cortex can affect glucocorticoid or mineralocorticoid secretion or both. Hypofunction can be caused by a deficiency of ACTH or by a primary deficiency in the gland itself.
11. Hypocortisolism (low levels of cortisol) is caused by inadequate adrenal stimulation by ACTH or by primary cortisol hyposecretion. Primary adrenal insufficiency is termed Addison disease.

12. Addison disease is characterized by elevated ACTH levels with inadequate corticosteroid synthesis and output. Causes include idiopathic autoimmune disease, tuberculosis of the adrenal gland, familial adrenal insufficiency, amyloidosis, metastatic destruction of the adrenal glands, and adrenal hemorrhage.
13. Secondary hypercortisolism is characterized by low to absent ACTH levels, leading to inadequate adrenal stimulation, adrenal atrophy, and decreased corticosteroidogenesis. The most common cause is withdrawal of exogenous administration of glucocorticoids.
14. Manifestations of Addison disease are related to hypocortisolism and hypoaldosteronism. Symptoms include weakness, fatigability, hypoglycemia and related metabolic problems, lowered response to stressors, vitiligo, hyperpigmentation, and manifestations of hypovolemia and hyperkalemia.
15. Hyperfunction of the adrenal medulla is caused by a pheochromocytoma, which is a catecholamine-producing tumor. Symptoms of catecholamine excess are related to their sympathetic nervous system effects and include hypertension, palpitations, tachycardia, glucose intolerance, excessive sweating, and constipation.