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Федеральное государственное автономное образовательное учреждение высшего образования Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет)

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CLINICAL PATHOPHYSIOLOGY

CONCISE LECTURES, TESTS, CASES

STUDENT MANUAL

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4. DISORDERS OF REGIONAL CIRCULATION AND MICROCIRCULATION

Typical forms of disorders of regional circulation include disorders of circulation in the medium size vessels and in microvessels. Typical disorders or regional circulation are presented in fig. 4.

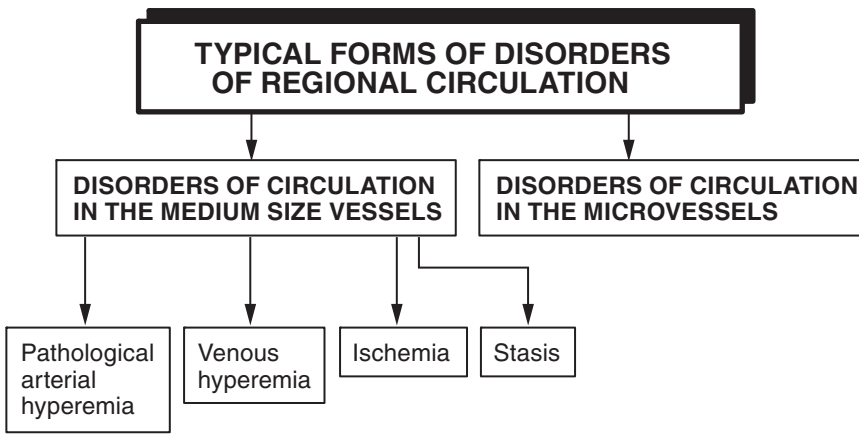

Fig. 4. Typical forms of disorders of regional circulation

Arterial hyperemia is characterized by a local deposition of the blood and an increased blood flow rate through the organ or tissue resulting from a dilation of arterial vessels. Pathological arterial hyperemia, compared physiological one, does not correspond to metabolic demands of the organ or tissue.

Mechanisms of arterial hyperemia:

- neurogenous mechanism — a decrease in the sympathetic drive tone;
- humoral mechanism — local accumulation of vasodilator substances: kinins, histamine, prostaglandins, leukotrienes, nitric oxide, adenosine, hydrogen and potassium ions, carbon dioxide;

- neuromyoparalytic — atrophy of sympathetic fibers and vessel smooth muscles following a prolonged compression of organs or tissues.

Manifestations and their mechanisms:

- redness — reduction of deoxygenated hemoglobin in the capillaries and venules;
- an increased temperature — an increased inflow of the warm blood from the body core;
- vessel pulsation;
- slight swelling — mild accumulation of fluid in the interstitial space resulted from an increase in filtration rate;
- an increased number of functioning capillaries — opening of precapillary sphincters;
- an increased lymphatic outflow — mild elevation of interstitial hydrostatic pressure.

The most common form of arterial hyperemia seen clinically is reactive hyperemia.

Reactive hyperemia is due to humoral and myoparalytic mechanisms. When the blood supply to tissue is blocked and then is unblocked, the flow through the tissue can increase to about five times normal. The duration of reactive hyperemia corresponds to the duration of the ischemic period. Reactive hyperemia may exert harmful effects that result from increased production of free oxygen radicals with the following membrane damage and an impairment of intracellular calcium exchange. Moreover accumulation of the blood during arterial hyperemia increases intracranial pressure that may cause a reduction of the cerebral blood flow and brain mass displacement.

Venous hyperemia is characterized by a local deposition of the blood and a decrease in the blood flow rate through the organ or tissue resulting from a reduction or cessation of the blood outflow via the venous vessels.

Mechanisms of venous hyperemia:

- compression — tumor, swelling tissue, scar or tourniquet;
- obstruction thrombus or embolus;
- heart failure;
- a decrease in venous wall elasticity combined with vein extension and constriction;
- venous valves failure.

Manifestations and their mechanisms:

- cyanosis: accumulation of deoxygenated hemoglobin in the capillary bed;

- edema: elevation of hydrostatic pressure in veins and capillaries;
- decreased local temperature — a decrease in the rate of metabolic process and a reduced inflow of the warm arterial blood from the body core;
- distension of venous vessels;
- a decreased lymphatic outflow — high interstitial hydrostatic pressure that impairs the mechanisms of the lymph outflow.

Consequences of venous hyperemia: hypoxia, hypotrophy, hypoplasia, sclerosis and necrosis. Venous hyperemia is one of the major factor that predisposes to thrombosis.

Ischemia is an imbalance between the supply and demand of the organ or tissue for blood. Therefore ischemia may be classified as ischemia of supply, demand or both. Ischemia implies insufficient oxygen and nutrients delivery and inadequate removal of metabolites.

Mechanisms of ischemia:

- obstruction or compression of arterial vessels by tumor, scar, tourniquet, atherosclerotic plaque, thrombus and embolus;
- an increase in blood viscosity resulting from polycytemia;
- spasm of arterial vessels: increased sympathetic drive, excessive production of adrenaline, angiotensin II, thromboxane, some leukotrienes and endothelin;
- an increase in metabolic demand outpacing the blood supply;
- rapid lowering of the systemic blood pressure as in shock or collapse;
- the combination of the listed above.

Manifestations of ischemia and their mechanisms:

- a decrease in diameter and number of visible vessels;
- pallor: a reduction of hemoglobin in the capillary bed;
- a decrease or disappearance of arterial pulsation;
- a reduction of lymph output resulting from a decrease in interstitial pressure caused by a reduction of water filtration from capillaries into the interstitial space;
- a decrease in local temperature due to a reduced blood inflow and a decreased rate of oxygen-dependent metabolism;
- a reduction in functioning the capillary bed.

The consequences of ischemia: necrosis, hypotrophy, atrophy and sclerosis. In moderate and prolonged ischemia apoptosis may also occur.

Stasis is a cessation of the blood flow in the microcirculatory bed.

Types of stasis: true stasis, ischemic stasis and venous-congestive stasis. True stasis begins with cell aggregation and cell adhesion to the vessel wall and is followed by hemodynamic changes.

Microcirculatory disorders

All disturbances of the microcirculation can be divided into intravascular, transmural and extravascular.

Intravascular disturbances of microcirculation

Causes of intravascular disturbances.

- Hemodynamic disturbances: ischemia, arterial and venous hyperemia, systemic hypotension.
- Alterations of blood fluidity: polycythemia, severe leukocytosis in leukemia, hyperproteinemia.
- Formation of microthrombi, aggregates of cells, sludging of blood.
- A decreased deformability of blood cells.

Forms of intravascular disorders of microcirculation:

- slowing of the blood flow;
- inadequate acceleration of the blood flow;
- non-laminar blood flow;
- excessive shunting of blood over arteriolar-venular anastomoses.

Transmural disturbances of microcirculation

They may be caused by increased or decreased permeability of blood vessels and take the form of:

1. An increased permeability of blood vessels.
2. A decreased permeability of blood vessels.

Mechanisms of an increased vascular permeability include: the formation of endothelial gaps, cytoskeletal reorganization, an increased transcytosis, the detachment of endothelial cells from the basement membrane and the distention of the capillary wall.

A decreased vascular permeability is caused by edema or accumulation of hyaline or amyloid.

Extravascular disturbances

Extravascular disturbances appear due to a decreased flow of the interstitial fluid. The rate of the interstitial fluid exchange depends on the rate of fluid filtration and lymphatic outflow. The rate of filtration depends on hydrostatic capillary pressure, the permeability of the capillary wall, and the density of the capillary bed. The lowering of lymph flow may result from an abnormal low or high interstitial hydrostatic pressure, and impairment contraction of endothelial cells forming lymphatic capillaries.

Sludge-phenomenon is defined as aggregation, adhesion and agglutination of blood cells, mainly erythrocytes, with further separation of blood into small and large cell aggregates and plasma. Mechanisms of the sludge-phenomenon are presented in fig. 5.

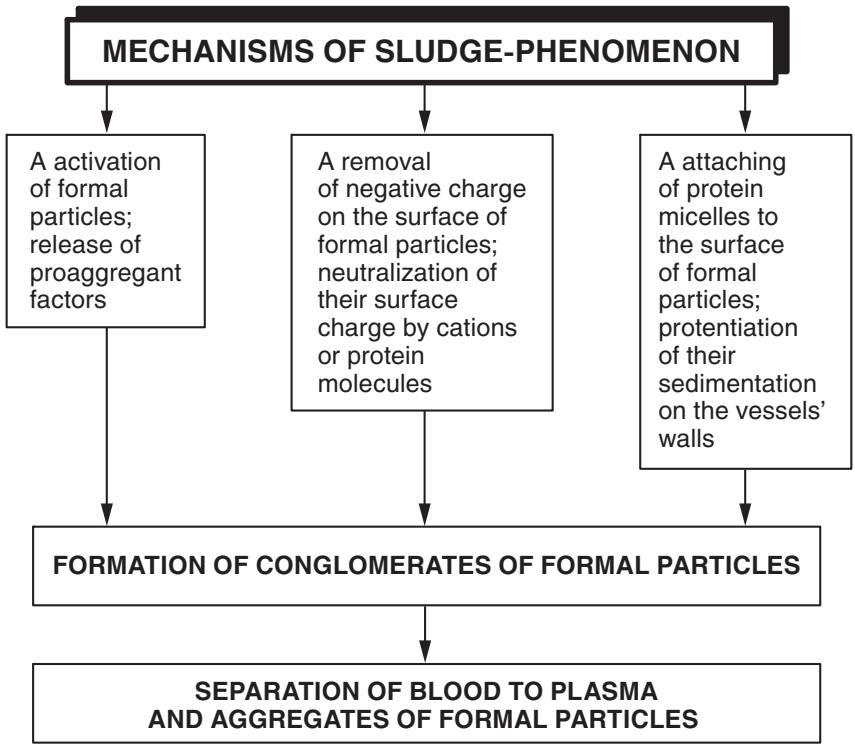

Fig. 5. Mechanisms of sludge-phenomenon

5. PATHOPHYSIOLOGY OF INFLAMMATION

Inflammation is a typical pathological process characterized by alteration, exudation and proliferation. It developed during evolution in organisms having vascular system to destroy, dilute, or wall off the injurious agents as well as to induce healing and reconstituting the damaged tissue.

Acute inflammation is characterized by a short duration (from minutes to few weeks), exudation of fluid and plasma proteins and emigration of leukocytes, predominantly neutrophils.

Chronic inflammation is manifested by a prolonged duration, persistent necrosis, accumulation of cells, predominantly macrophages and their derivates, lymphocytes, fibroblasts and sclerosis.

Most common causes of inflammation are: microbial infections, hypersensitivie reactions and autoimmunity, physical agents, irritant and corrosive chemicals, tissue necrosis.

Alteration may be divided into primary and secondary. Primary alteration is caused by the action of initial stimuli. Secondary alteration results from the conditions that take place in the focus of inflammation. These conditions include: oxygen deficiency, metabolic acidosis, high osmotic pressure, ionic imbalance, toxic effect of cellular enzymes and inflammatory mediators.

INFLAMMATORY MEDIATORS

Inflammatory mediators are soluble, diffusible molecules that act locally at the site of tissue damage and infection, and at more distant sites, and they determine the course and signs of inflammation. Inflammatory mediators may be cellular (histamine, prostaglandins, interleukine-1, tumor necrosis factor and interferons and others) or plasma in origin (complement, kinin, and clotting system factors). The major source of cellular mediators is leukocytes.

In acute inflammation vascular changes have the following order: inconstant and transient ischemia (several seconds), arterial hyperemia, venous hyperemia and stasis.

Arterial hyperemia is caused by inflammatory mediators such as histamine, some complement fragments, bradykinin, platelet-derived factor, lipoxins, prostaglandins, NO.

The mechanism of venous hyperemia and stasis is complex. Inflammatory mediators increase permeability of venules and capillaries for plasma proteins. Plasma proteins leak into interstitial compartment causing fluid retention. It results in the chain of events: increasing in blood viscosity, reduction of the local blood flow, microthrombosis and adhesion of leukocytes to the vessel walls.

Inflammatory mediators and other factors increase vascular permeability by the following ways.

- Histamine, bradykinin, leukotrienes, substance P cause endothelial cell contraction in venules that leads to formation of endothelial gaps.
- Endothelial growth factors stimulate transcytosis.
- Direct endothelial injury may result from the action of toxic oxygen species and proteolytic enzymes derived from leukocytes, bacterial toxins, some components of complement, antibodies and antigen-antibody complexes.

Leukocyte extravasation is a process of leukocytes exit from the lumen to the interstitium. Extravasation consists of intraluminal events, transmigration across the endothelium and of the cells migration into the interstitial compartment.

Intraluminal events, in turn, include margination, rolling, and adhesion. A reduced blood flow promotes white cells to assume a peripheral position along the endothelial surface. This process is called margination. Rolling following margination is a process of tumble and transient adhesion of leukocytes along the endothelial surface. Rolling is mediated through a redistribution of P-selectins to the endothelial cell surface and synthesis of E-selectins de novo. Selectins bind mucin-like glycoproteins located on the surface of leukocytes. Histamine, thrombin and platelet-activating factor induce a redistribution of P-selectin while interleukine-1 and tumor necrosis factor stimulate synthesis of E-selectin. Firm adhesion is mediated via binding integrin molecules that are located on the leukocyte surface with intercellular adhesion molecule 1 (ICAM-1) located on the endothelial surface. Interleukine-8 and other cytokines increase the affinity of integrin molecules to ICAM-1.

After firm adhesion, leukocytes insert pseudopods into the junctions between the endothelial cells, squeeze through endothelial junctions, and assume position between the endothelial cells and the basement membrane. Adhesion molecules such as PECAM-1 and ICAM-1

participate in transmigration. Neutrophils, monocytes, eosiniphils, and various type of lymphocytes use different molecules for rolling and adhesion, and the adhesion can be modulated by the state of leukocytes and endothelium. Neutrophils travel through the basement membrane and in the interstitium by releasing collagenase IV from secondary granules. After enzymatic splitting, collagen molecules are able to restore their structure spontaneously.

In most forms of acute inflammation, neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours, and then are replaced by monocytes in 24 to 48 hours.

CHEMOTAXIS

After extravasation, leukocytes emigrate in tissues toward the site of injury by a process called chemotaxis. The most common exogenous chemoattractants are bacterial peptides or lipids. The most potent endogenous chemoattractants are component of complement system, particularly C5a, leukotriene B4 and interleukine-8. Leukocyte position in the interstitial compartment is determined by the expressed receptors and chemokine gradients.

The role of leukocytes' extravasation and phagocytosis is illustrated in fig. 6.

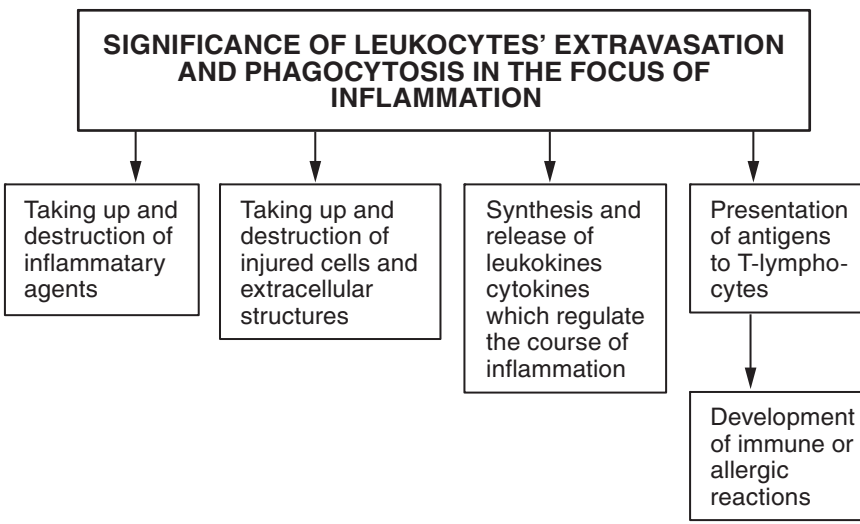

Fig. 6. Role of leukocytes' extravasation and phogocytosis in the focus of inflammation

Phagocytosis involves three steps: a) attachment of particles to the leukocyte and recognition of particles by the leukocyte, b) engulfment, with formation of a phagocytic vacuole and c) killing and degradation of the ingested material.

Recognition and attachment. Most microorganisms cannot be recognized by leukocytes directly. Particles have to be coated by opsonins, which bind to specific receptors on the leukocytes. The major opsonins are: the Fc fragment of immunoglobulin G, component of complement system C3b and lectins.

Binding of opsonized particles to the receptors triggers engulfment. Pseudopods flow around the particles creating phagocytic vacuole. The latter fuses with the membrane of lysosomal granule forming a phagolysosome. At this stage neutrophils become degranulated.

Killing or degradation. Phagocytosis stimulates oxygen consumption, glycolysis, hexose-monophosphate shunt, and the production of reactive oxygen metabolites. As a result HOCL is produced with a help of enzyme myeloperoxidase. HOCL destroys bacteria by oxidation of proteins and lipids. The dead microorganisms are degraded by the action of lysosome hydrolases. Bacterial killing can be also induced by the proteins that increase a permeability of bacterial cell membrane, hydrolyze the muramic acid bonds (lysozyme) and bind iron (lactoferrin).

LOCAL AND SYSTEMIC EFFECTS OF INFLAMMATION

Systemic effects of inflammation include fever, leukocytosis and secretion of C-reactive protein, serum amyloid, globulins, complement, coagulation proteins by liver and behavioral signs such as anorexia, somnolence, and malaise.

Local signs include redness, pain, edema and an increased temperature. An increased local temperature and redness result from arterial hyperemia. Pain is associated with the action of inflammatory mediators and compression of nervous fibers by the oedematic fluid. Edema is caused by an increased permeability for proteins of venules and capillaries and an abnormal lymph outflow.

Outcomes of acute inflammation may be resolution, abscess formation, healing (scarring) and progression to chronic inflammation.

6. TYPICAL DISORDERS OF THERMOREGULATION. FEVER

Disorders of thermoregulation derive from the readjustment of the hypothalamic thermoregulatory center or failure of the thermoregulatory physiological mechanisms to meet the environmental challenges. As a result the normal body temperature may decrease (hypothermic state) or increase (hyperthermic state). Either of these states may take several forms.

Hypothermic states	Hyperthermic states
Hypothermic reaction	Hyperthermic reaction
Hypothermia	Hyperthermia
	Fever

HYPOTHERMIA

Hypothermia is arbitrarily defined as a core body temperature of 35 °C or below.

Causes of hypothermia:

- decreased heat loss, and
- inadequate heat production.

Decreased heat loss may be the result of:

- extreme environmental conditions;
- enhanced blood flow to the skin (burns, psoriasis).

Inadequate heat production may result from:

- decreased metabolism;
- altered thermoregulation;
- ingestion of certain drugs.

Patterns of fever

On the basis of the extent of temperature elevation:

- subfebrile (<38 °C during axillary measuring);
- febrile (from 38 to 39 °C);

- pyretic (from 39 to 41 °C);
- hyperpyretic (more than 41 °C).

On the basis of temperature fluctuation:

- sustained (circadian fluctuation <10 °C);
- remittent (fluctuation 1–2 °C);
- hectic (fluctuation 3 °C and more);
- intermittent (great fluctuations with falls in the morning up to normal values);
- relapsing (febrile episodes are separated by intervals of normal temperature).

Biological significance of fever:

Positive aspects:	Negative aspects:
the growth and virulence of several bacterial species are impaired	caloric and fluid requirements are increased
the phagocytic and bactericidal activity of neutrophils is increased	increased muscle catabolism leading to negative nitrogen balance
the cytotoxic effects of lymphocytes are increased	fever may produce stupor or delirium
the increase in the liver detoxication activity	stress to the fetuses
	stress to the heart and the respiratory system
	children are prone to fevers
	fever in the first trimester of pregnancy increases the risk of neural tube defects in the fetus

HYPERTHERMIA

Hyperthermia is an elevation of body temperature above the hypothalamic set point due to insufficient heat dissipation (e.g. in association with exercise, perspiration-inhibiting drugs, or a hot environment).

HYPERTHERMIC REACTION

Hyperthermic reactions refer to changes in the hypothalamic set point in the absence of pyrogens.

They are classified as:
- centrogenic;
- psychogenic;
- reflexogenic;
- hormonal;
- drug-induced.

FEVER

Fever is a typical pathological process caused by pyrogens and characterized by an elevation of body temperature above the normal circadian range. Fever is the result of resetting of the thermoregulatory center located in the anterior hypothalamus.

Pyrogens are substances that cause fever. They may be either exogenous or endogenous, primary or secondary. Exogenous pyrogens come from outside the host, whereas endogenous pyrogens are produced in the body. Primary pyrogens induce fever indirectly. Their action is mediated by secondary pyrogens produced and released by the host's cells (monocytes, macrophages, granulocytes, etc.). The majority of exogenous pyrogens are microorganisms, their products, or toxins. One of the most potent exogenous pyrogen is referred to as endotoxin [lipopolysaccharide (LPS)], which is found in the outer membrane of all gram-negative bacteria. Primary pyrogens act by inducing the formation of secondary pyrogens, such as IL-1, TNF-α, IL-6.

Pathogenesis of fever: under the effect of secondary pyrogens endothelial cells of the vascular network in the anterior hypothalamus produce PG E_2. The latter then presumably diffuses into the region of the thermoregulatory center where it activates receptors on the surface of glial cells. Activated glial cells produce cAMP which in turn raises the thermoregulatory set point. With the new, higher «thermostatic setting», signals go to centers of the sympathetic system, which in turn initiate vasoconstriction and promote heat conservation. The thermoregulatory center also sends signals to the cerebral cortex, resulting in behavioral changes such as seeking a warm environment.

7. TYPICAL DERANGEMENTS OF CARBOHYDRATE METABOLISM. DIABETES MELLITUS

Typical forms of derangement of carbohydrate metabolism include:
- hypoglycemia;
- hyperglycemia;
- glycogenoses;
- aglycogenoses;
- pentosemias-, hexosemias.

HYPOGLYCEMIA

Hypoglycemia may be defined as a decrease of blood glucose below the physiological minimal level of 3,3 mmol/L.

Causes of hypoglycemia:
- neurogenic;
- endocrinogenic;
- hepatic;
- renal;
- inadequate substrate supply;
- use of drugs.

Hypoglycemic encephalopathy and coma

In severe cases hypoglycemia typically causes confusion, seizures, stupor, coma, and occasionally hemiparesis or other focal neurological findings. Blood glucose concentrations are typically <1,4 mmol/L (<25 mg/dL). Persistent hypoglycemia depletes cerebral energy supplies and can lead to irreversible neuronal damage. This process has been shown to involve excitotoxic mechanisms in animal studies.

Hypoglycemic encephalopathy is typically caused by accidental or deliberate overdoses of insulin or antidiabetic agents, insulin-secreting islet

cell tumors or retroperitoneal sarcoma, protracted ethanol intoxication (in rare cases), or the Reye's syndrome (in childhood).

HYPERGLYCEMIA

Hyperglycemia is defined as an increase of capillary blood glucose levels above 5.6 mmol/L (or 120 mg/dl).

Causes of hyperglycemia:

- neurogenic;
- endocrinogenic;
- alimentary;
- hepatogenic.

GLYCOGENOSES

Glycogenoses are inherited disorders that affect glycogen metabolism. Disorders in virtually every enzyme involved in the synthesis or degradation of glycogen and its regulation cause some type of glycogen storage disease in which glycogen is abnormal in quantity, quality, or both.

Hepatic glycogen storage disease:

I group (hepatomegaly and hypoglycemia)	**II group (cirrhosis and hepatomegaly)**
Glucose-6-phosphatase deficiency (type I)	Branching enzyme deficiency (type IV)
Debranching enzyme deficiency (type III)	Debranching enzyme deficiency (type III)
Liver phosphorylase deficiency (type VI)	

Muscle glycogen storage disease:

I group (muscle pain, exercise intolerance, myoglobinuria, susceptibility to fatigue, i.e. muscle-energy disorder)	**II group (progressive skeletal muscle weakness and atrophy and/or cardiomyopathy)**
Muscle glycogen phosphorylase deficiency (type V, McArdle disease)	Lysosomal α-glucosidase deficiency (type II)
Deficiency of phosphofructokinase (type VII)	Muscle debranching enzyme deficiency (type IIIa)

AGLYCOGENOSES

Aglycogenoses are inherited disorders characterized by low levels or absence of glycogen in the cell. Aglycogenoses are caused by mutations in genes coding the enzymes of glycogen synthetic pathway, for example glycogen synthetase.

PENTOSEMIAS. HEXOSEMIAS

These disease states are characterized by inherited derangements of pentose and hexose metabolism and utilization.

Galactosemia

Biochemical pathway of galactose utilization:

galactose + ATP → galactose-1-P + ADP

galactose-1-P + UDP-glucose → UDP-galactose + glucose-1-P

UDP-galactose → UDP-glucose.

The first reaction is catalysed by galactokinase, the second by galactose-1-phosphate uridyl transferase (GALT), and the third by UDP-galactose-4-epimerase.

Galactosemia refers to any of three inborn errors of galactose metabolism. Classic galactosemia is due to the deficiency of GALT and is typically associated with cataract formation, mental retardation, and cirrhosis. The second disorder, galactokinase deficiency, leads primarily to cataract formation.

Fructosemia (fructose intolerance)

This pathology is due to deficiency of various enzymes of fructose metabolism. It is characterized by increased concentration of fructose in blood and urine.

Deficiency of phosphofructoaldolase

The disease is transmitted as autosome-recessive trait; pathology results from accumulation of fructose-1-phosphate causing inhibition of glycogenolysis and glyconeogenesis. Consumption of fructose or cane sugar, even in moderate quantities, provokes hypoglycemia with tremor, sweating, confusion, nausea, and abdominal pains.

Deficiency of fructokinase

This state is characterized by excretion of fructose with no signs of pathology.

DIABETES MELLITUS

Diabetes mellitus is a systemic illness caused by absolute or relative insulin deficiency and characterized by derangements of carbohydrate, lipid and protein metabolism (fig. 7).

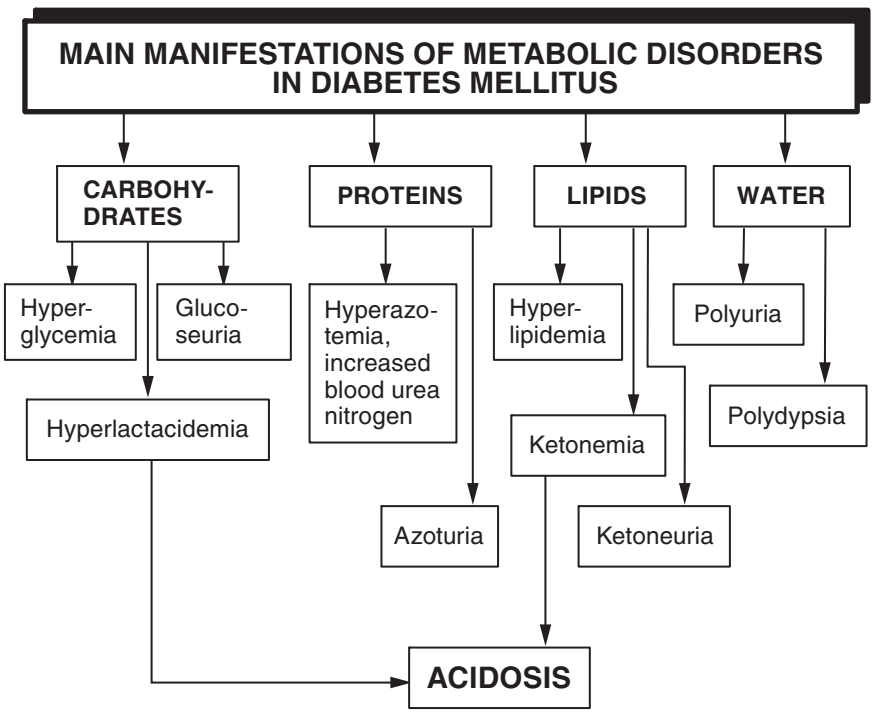

Fig. 7. Metabolic disorders in diabetes mellitus

Two main forms of diabetes mellitus are distinguished based on the nature of insulin deficit — absolute or relative: type I and type II. The term «type I diabetes» is often used as a synonym for insulin-dependent diabetes mellitus (IDDM), and type II diabetes is considered equivalent to non-insulin-dependent diabetes mellitus (NIDDM).

Acute metabolic complications of diabetes mellitus

Patients with diabetes are susceptible to two major acute metabolic omplications: diabetic ketoacidosis and hyperosmolar, nonketotic coma.

The former is a complication of IDDM, while the latter usually occurs in the setting of NIDDM.

Late complications of diabetes mellitus

- Circulatory abnormalities:
  – atherosclerosis;
  – cardiomyopathy (with no apparent coronary arteries pathology).
- Retinopathy.
- Diabetic nephropathy.
- Diabetic neuropathy (peripheral polyneuropathy, radiculopathy, autonomic neuropathy).
- Diabetic foot ulcers.

8. TYPICAL DISORDERS OF LIPID METABOLISM. ATHEROSCLEROSIS

Typical disorders of lipid metabolism include:
- hyperlipidemia;
- hypolipidemia;
- dyslipidemia;
- obesity;
- lipodystrophy, wasting, cachexia;
- lipidoses.

HYPERLIPIDEMIA

Hyperlipidemia is an increase in the plasma lipids concentration above 8 g/L.

Types of hyperlipoproteinemia (Fredrickson, 1967):

Type	Plasma cholesterol levels	Plasma TGs levels
I Hyperchylomicronemia	↑	↑↑
IIa Hyper-β-lipoproteinemia	↑	N
IIb Hyper-β + pre-β-lipoproteinemia	↑	↑
III Dys-β-lipoproteinemia	↑	↑
IV Hyperpre-β-lipoproteinemia	↑	↑
V Hyperpre-β-lipoproteinemia + hyperchylomicronemia	↑ or N	↑↑

Lipoproteins can be classified by their ability to cause atherosclerosis (fig. 8).

Mechanisms of hyperlipoproteinemia:
- Abnormal structure of receptors for lipoproteins on the cell's surface (e.g. familial hypercholesterolemia).
- Defective structure or synthesis of apoproteins (e.g. defective synthesis of apo-B100, apo-E, apo-CII).

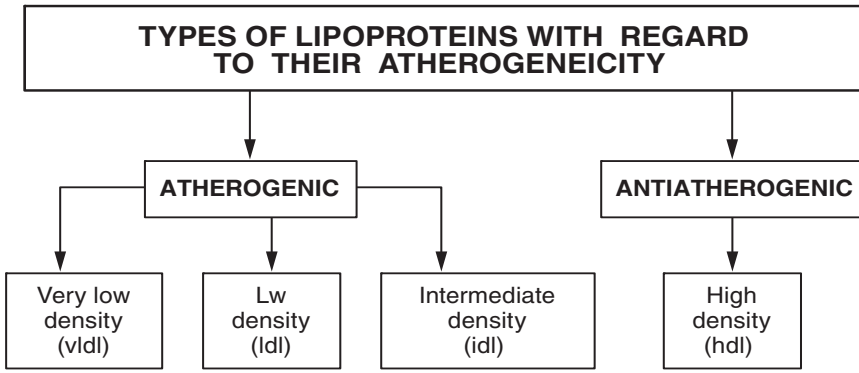

Fig. 8. Atherogeneicity of lipoproteins

- Deficient activity of plasma lipoproteinlipase.
- Increased mobilization of lipids from the lipid stores.

HYPOLIPIDEMIA

Hypolipidemia is a decrease in the plasma lipids concentration below 4 g/L. Mechanisms of hypolipoproteinemia.

- Abnormal synthesis of apo-B.
- Defective formation of VLDL (the absence of the microsomal triglyceride transfer protein). For example, abetalipoproteinemia.
- Abnormal synthesis of apo-A (e.g. hypoalphalipoproteinemia — Tangier's disease).

DYSLIPIDEMIA

Dyslipidemia is manifested as changes in the normal ratio between different classes of lipoproteins, or formation of abnormal lipoproteins.

OBESITY

Obesity can be defined as an increase in body weight above the standard values, designated as «ideal weight», by 20% or more due to accumulation of fat in the adipose tissue.

Body mass index (BMI) = weight in kg / height in m^2.
Good weight: BMI = 20–24.9 kg/m^2.
Overweight: BMI = 25–30 kg/m^2.
Obesity: BMI >30 kg/m^2.
Types of obesity based on their pathogenesis.
- Central (cortical).
- Hypothalamic.
- Endocrine.
- Metabolic.

The central (cortical) factors of obesity: disorders of eating behavior occur in various psychiatric conditions: depressive disorder, schizophrenia, eating disorders (bulimia nevrosa).

Hypothalamic obesity: hypothalamic injury from trauma or surgery and destructive lesions in the region of the ventromedial or the paraventricular nucleus in the hypothalamus can produce obesity.

Endocrine obesity: the endocrine dysbalances associated with obesity include hypothyroid state (myxedema) and hypercortisolism (Cushing's disease).

Metabolic obesity: physiologically the adaptation to a high-fat diet requires a decrease in carbohydrate oxidation to preserve carbohydrate stores. If carbohydrate oxidation is reduced, the oxidation of fat increases to provide for nutrient needs. If the body is unable to reduce carbohydrate oxidation, the compensatory mechanism is increased by food intake to provide needed carbohydrate with increasing fat storage.

LIPODYSTROPHY

Lipodystrophies are characterized by generalized or partial loss of body fat and metabolic abnormalities, including insulin resistance, hyperglycemia, and hypertriglyceridemia. In generalized lipodystrophy essentially all body fat is lost, in partial lipodystrophy fat atrophy is limited.

LIPIDOSES

Lipidoses are characterized by intracellular accumulation of lipids in nonadipose tissues. The accumulated lipids may have normal or abnormal structure.

Hereditary lipidoses: glucocerebrosidosis, sphingomyelinosis.

Typical examples of the acquired lipidoses include fatty liver developed as a result of intoxication by organic solvents (ethanol, carbon tetrachloride, etc.), phosphorus or arsenic compounds.

ATHEROSCLEROSIS

Atherosclerosis may be defined as chronic focal deterioration of the large and medium size arteries, characterized by accumulation of VLDL and LDL, complex carbohydrates, blood plasma proteins, fibrous tissue, and calcium salts in the intimal layer, and alteration of the medial layer.

Stages of atherogenesis.

I. Initiation (formation of «fatty streak»).
- Lipoprotein accumulation and modification.
- Leukocyte recruitment and foam-cell formation.

II. Formation and evolution of atheroma.
- Involvement of arterial smooth muscle cells (SMC).
- Development of plexi of microvessels in atheroma.
- Ruptures of the atheroma's microvessels and production of focal hemorrhages.

III. Complication of atheroma.
- Accumulation of calcium salts.

The main pathogenic events in atherogenesis are illustrated in fig. 9.

Risk factors of atherosclerosis:
- hyperlipidemia;
- arterial hypertension;
- smoking;
- diabetes mellitus;
- obesity;
- age, male sex;
- psychological stress, hypodynamia.

Clinical manifestations of the atherosclerosis:
- aneurysm of the aorta, dissection and rupture of the aortic wall;
- acute and chronic ischemic heart disease;
- transient cerebral ischemia and strokes;
- intermittent claudication, gangrene of the lower extremities;
- mesenteric ischemia and bowel infarction;
- renal artery stenosis, renal atheroembolic disease.

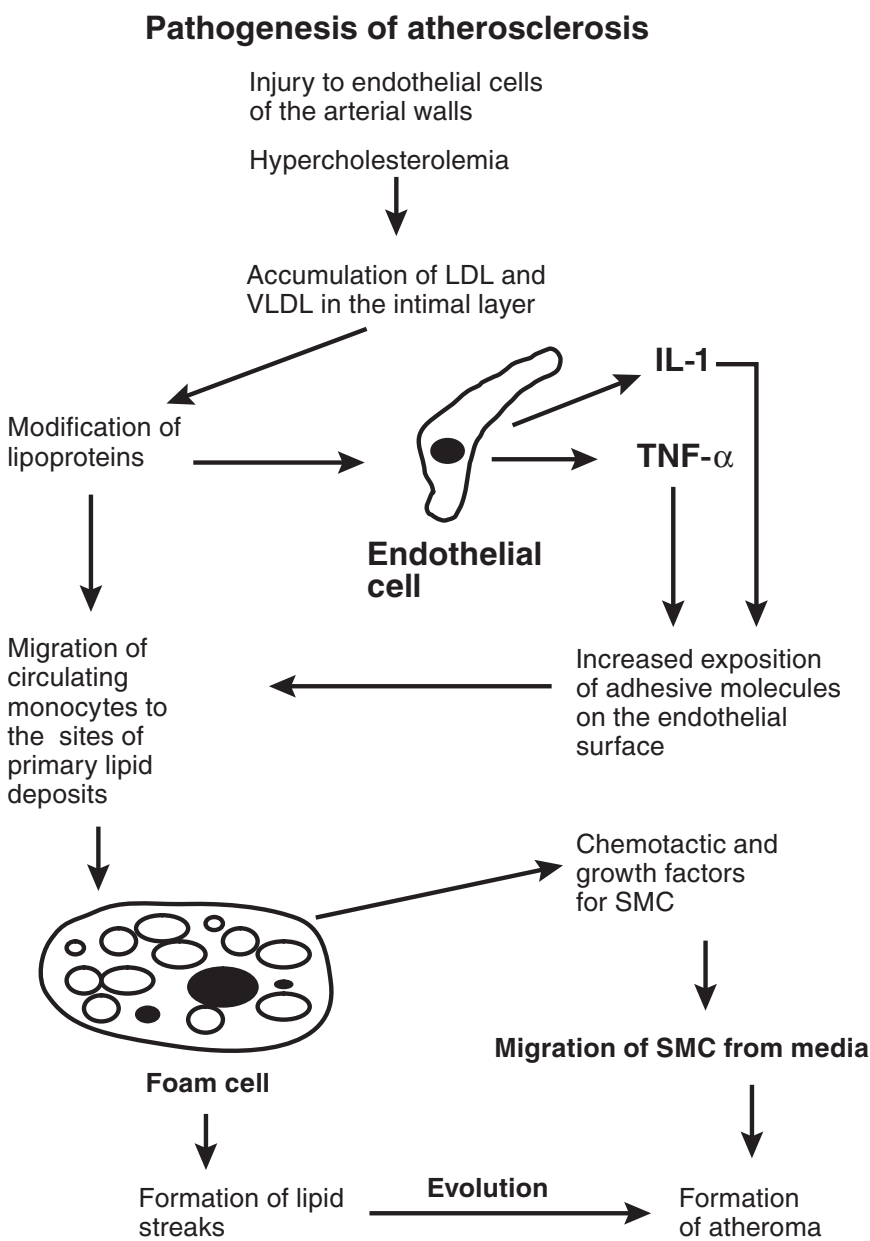

Fig. 9. Factors of atherogenesis