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Phylogenetic theory of general pathology.
Atherosclerosis and atheromatosis as two different processes: aphysiological implementation of biological function of trophology and endoecology

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Summary

We believe that seven biological functions have formed during phylogenesis. They are: 1) trophology, 2) homeostasis, 3) endoecology, 4) adaptation, 5) reproduction, 6) locomotion, 7) cognitive function, including intellect. The function of trophology (feeding) is realized via the biological reaction of exotrophy (external feeding) and endotrophy (internal feeding). The function of endoecology provides the maintenance of all vital parameters within physiological range. This function is realized through the reactions of inflammation and excretion. Etiological factors of atherosclerosis are: 1) oleic monounsaturated fatty acid (MFA) that is more actively utilized in biochemical reactions than palmitic fatty acid, 2) in the ocean all animals were carnivorous (fish eating), after millions of years of living on dry land Homo sapiens became herbivorous, 3)insulin plays the major role in transition from

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carnivorous to herbivorous belongs, since this hormone is involved in conversion of endogenous saturated palmitic (SFA) into oleic MFA, 4) phylogenetically insulin does not initiate in vivo conversion of exogenous palmitic SFA into oleic MFA, and 5) in the ocean, biologically active eicosanoids are synthesized from eicosapentaenoic polyenic FA (PFA); on dry land this acid is not available. Excessive eating of meat by herbivorous Homo sapiens provides the basis for atherosclerosis. Blocked bioavailability of PFA leads to their deficiency in cells. Insulin-initiated transport of oleic MFA as oleic triglycerides (TG) in oleic apoE/B-100 very low density lipoproteins (VLDL) occurs without LDL formation; transport of SFA in palmitic apoE/B-100 VLDL is blocked at the stage of nonligand palmitic VLDL→LDL formation, glycolipoprotein formation and high level of LDL-cholesterol. Incomplete utilization of palmitic VLDL→LDL by monocytes leads to atheromatosis in the intima of elastic arteries. Polyenic FA metabolites which were not internalized via apoB-100 endocytosis are the major constituents of atheromas. Atherosclerosis, hyperlipoproteinemia and high content of LDL-cholesterol result from impaired function of trophology, while atheromatosis is associated with impaired biological function of endoecology.

Key words

Atherosclerosis, atheromatosis, insulin, biological functions, LDL-cholesterol, arterial intima.

New epochs, new theories, new concepts of medicine, disease etiology and pathogenesis create thoughts about the necessity of developing a new theory of general pathology after the cellular theory of R. Virchow. These thoughts appear the most often during observation of phylogenesis of difference between etiological factors and pathogenetic unity of metabolic pandemias, the diseases of the civilization that became widespread in populations of developed countries. We select [1] seven metabolic pandemias:

1. Atherosclerosis and atheromatosis;
2. Metabolic essential arterial hypertension (AH);
3. Insulin resistance (IR) syndrome;
4. Metabolic syndrome;
5. Obesity;
6. Non-alcoholic fatty liver disease;
7. Endogenous hyperuricemia. Their differences are determined by the specificity of etiological factors that have formed during phylogenesis of these non-physiological processes. The World Health Organization (WHO) specialists do not consider all metabolic pandemias as nosological forms of diseases, instead only systemic, etiologically specific ones and widespread in vivo metabolic abnormalities can be considered metabolic pandemias.

All metabolic pandemias excluding endogenous hyperuricemia, are characterized by in vivo (at organism level) impairment of fatty acids (FA) metabolism. Simultaneously they affect:

a) functions of cellular structures;

b) regulatory and

c) energetic basics of FA metabolism in phylo- and ontogenesis.

Etiological factors of metabolic pandemias have been consequently formed during the stages of phylogenesis. If the frequency of non-infectious, non-physiological process in population exceeds 5-7%, we suppose that its etiological cause is based on impaired biological functions and reactions. We suggest that the phylogenetic theory of general pathology would become a biologically proved successor of cellular theory of R.Virchow. There is nothing more difficult then changing well-established ideas of people. It is fair even for scientific terminology; sometimes terms start to exist independently from the meaning that the investigators put into them in the beginning. We have been using the term "cardiovascular system" for 400 years, starting from the times of William Garraway, but as soon as we start to discuss the regulation of circulation and in vivo circulatory pathologies we should rationally remember that vasculary-cardiac system has been formed phylogenetically. Similar changes happen with the words atherosclerosis and atheromatosis. We can about the atherosclerosis of coronary arteries as much often as about the atheromatosis of elastic arteries' intima. What is the real difference of ideological, phylogenetic, pathopysiological meaning between the terms "atherosclerosis" and "atheromatosis"? How do the specific different etiological factors and atheromatosis have been formed during the stages of phylogenesis, and in which tissues these non-physiological (physiological?) processes are localized, which is their order of appearance, which is the common part of their pathogenesis? Which term is it more correct to use talking about arterial intima: "atherosclerosis" or "atheromatosis"?

Careful investigation of etiological factors of metabolic pandemias that include:

a) hyperlipoproteinemia (HLP);

b) plasma concentration of non-esterified FA (NEFA);

c) clinical manifestations of coronary heart disease (CHD);

d) variants of abnormal lipoprotein (LP) metabolism;

e) difference of topological variants of coronary sclerosis, may help to establish a reasonable point of view that inhabited terms "atherosclerosis" and "atheromatosis" for real express two FA metabolism abnormalities with different etiology and equal pathogenesis.

It is possible to understand the difference of etiological factors of atherosclerosis and atheromatosis if we start to observe them from the positions of our phylogenetic theory of general pathology [2].

We suppose that impaired regulatory activity of insulin underlies atherosclerosis pathogenesis; atherosclerosis is a non-physiological reaction of HLP formation, impaired metabolism of FA, lipids, triglycerids (TG, esters of triatomic alcohol glycerol and insulin-dependent phylogenetically young ApoE/B-100 very low density lipoproteins (VLDL)) at first. Being expressed as the target of insulin, they started to transfer ω-9 C18:1 oleic acid, monounsaturated FA (MFA) endogenously synthesized in hepatocytes from exogenous glucose in the form of oleic TG phylogenetically late.

When ApoE/B-100 LP start to transfer to cells big amounts of exogenous C16:0 palmitic saturated FA (SFA) derived from food in case of impaired biological function of trophology (feeding), it blocks the bioavailability and cell uptake of polyunsaturated FA (PUFA) as part of low density LP (LDL). PUFA are the substrate for the synthesis of biologically active phylogenetically old humoral mediators eicosanoids, that include prostacyclines, prostaglandines, thromboxanes and leukotriens. This is atherosclerosis and it is initiated by impaired biological function of trophology (feeding), biological reaction of exotrophy (external feeding), by excessive amounts of consumed and present in vivo palmitic SFA and impaired biological activity of insulin.

From the point of view of phylogenetic theory of general pathology, biological role of insulin consists at first of FA metabolism regulation and at second of mediating the regulation of glucose metabolism.

Atheromatosis is a generally physiological process of compensation of abnormal FA metabolism, in particular HLP, realization of biological function of endoecology, unfortunately in vivo conditions it often does not reach its functional ending. In this condition it leads to formation of inflammatory-destructive non-physiological process called atheromatosis of elastic (or mixed type) arteries' intima in phylogenetically late part of arterial system. Atheromatous masses of arterial intima are consisted of palmitic ligandless ApoE/B-100 VLDL→LDL impossible to be absorbed by cells by ApoE/B-100 endocytosis due to excess of exogenous palmitic SFA.

The main part of atheromatous masses of intima is made of PUFA esters of cholysterol (PUSChE) that cells were unable to take together with ligandless palmitic VLDL→LDL via ApoE/B-100 endocytosis.

Phylogenetic theory of general pathology

The main approaches of general biology and medicine include:

1. Unity of structure and function;

2. Unity of the main stages of phylo- and ontogenesis;

3. The same technology of functional systems formation in ontogenesis;

4. Use of systemic approach of general biology for explanation of events happening in vivo. We suggest completing this list with other two biological approaches;

5. Continuity of formation of biological functions and reactions in phylogenesis, and 6. Methodological approach of biological subordination.

Development of biological functions and reactions during phylogenesis occurs not as creation of something principally new, this way is more characteristic for mutations, of high or low significance or neutral by now. According to biological subordination, newly formed humoral (hormonal) mediator in vivo is organically built upon earlier ones, it interacts with them functionally, but no new mediator, even more perfect one, can change the action of phylogenetically older mediators.

If the frequency of non-infectious disease in population exceeds 5-7% we suggest that:

a) this metabolic pandemia is etiologically based on impaired biological functions and reactions;

b) it is necessary to build rational pathogenesis in the aspect of phylogenesis; and

c) these abnormalities should undergo pharmacological correction only in case of development of complications. We suggest rational estimating all that has happened and is happening in vivo from the point of biological functions and reactions. We suppose that seven biological functions have been formed during

phylogenesis not simultaneously millions of years ago. These seven functions include:

1. Biological function of trophology;
2. Biological function of homeostasis;
3. Biological function of endoecology;
4. Biological function of adaptation;
5. Biological function of continuation of the species;
6. Biological function of locomotion, and
7. Cognitive biological function, and intellect is its upper point.

Biological function of homeostasis is aimed to fulfill the following position: intercellular medium in vivo should contain enough of everything for all cells at any point of time. The function of homeostasis should not allow the reduction of analytes (physical and chemical parameters) concentration in intercellular medium below the lower limit of physiological interval. Dozens of biological reactions fulfill the function of homeostasis according to the number of biochemical (physical-chemical) analytes in intercellular medium.

Biological function of trophology (feeding) is realized via two biological reactions: a) biological reaction of exotrophy — exogenous feeding (hydrolysis, absorption of exogenous nutrients, complicated process of nutrients' deposition) and b) biological reaction of endotrophy that provides cells with all necessary substrates during food deprivation at night, during hibernation and forced fasting. It is more difficult to release FA from adipose cells rather than to deposit them. Trophology is the science about food, feeding, trophic connections in vivo and food assimilation [3]. It seems to be interesting for researchers that pathogenesis of non-physiological processes in vivo can be based on impaired biological function of trophology and feeding.

Biological function of endoecology is aimed to prevent analytes from exceeding upper limits of normal (physiological) intervals in physiological (non-physiological) conditions. Biological function of endoecology considers elevated amounts of analytes as lack of "cleanness" of intercellular environment, its "pollution" with endogenous phlogogens with high molecular weight (>70 kDa, big phlogogens) initiating biological reaction of inflammation. Glucose and Na+ can become small molecular weight phlogogens (<70 kDa, small phlogogens) in case of hyperglycemia and hypernatremia. Palmitic VLDL→LDL can act as big phlogogens n vivo when they don't form ApoE/B-100 ligand and cannot be absorbed by all insulin-dependent cells via physiological ApoE/B-100 endocytosis.

Two non-specific biological reactions are responsible for the function of endoecology: a) biological reaction of excretion and b) biological reaction of inflammation. If molecular weight of small endogenous phlogogens in intercellular environment is not higher than molecular weight of albumin their excretion goes through realization of biological reaction of excretion in kidney nephrons and urine formation. If endogenous phlogogens are big as exogenous ones or can be infectionally pathogenic (lipopolysaccharide + specific binding protein) and have higher molecular weight than albumin, their collection and utilization occur in vivo and in situ through the realization of biological reaction of inflammation. Main function of biological reaction of inflammation is to maintain "cleanness" of intercellular environment in vivo, collection and utilization of big endogenous phlogogens and exogenous pathogens in situ. The meaning of biological function of endoecology is that "intercellular environment should be always clean". Accumulation of big endogenous phlogogens is the main condition for activation of biological function of endoecology in vivo. Realization of biological function of endoecology does not depend on etiological factors, from the character of endogenous phlogogens: apoptotic bodies, products of cellular autophagy, antigen/antibody complexes, exogenous infectious pathogens like polysaccharides of Gram-negative bacteries [4]. Excretion is determined by the size of fenestrae on the membrane of glomerulus between the feet of podocytes on the basal membrane.

The main tests that detect abnormalities of biological function of endoecology are microalbuminuria and C-reactive protein (CRP) — monomer and pentamer. The test for microalbuminuria can demonstrate:

a) "pollution" of intercellular environment with small phlogogens;

b) prevalence of active glomerular filtration over passive reabsorption in proximal tubules of nephrons, and

c) activation of angiotensin-II secretion by the cells of juxtaglomerular cluster of nephron via the mechanism of reverse feedback and decreased filtration after compensatory spasm of afferent arteriole.

Increased urinary excretion of microquantities of albumin often goes along with increased plasma levels of:

a) pro- and anti-inflammatory interleukins;

b) increased oxidation of proteins with reactive oxygen species (ROS) (physiological process of protein denaturation) [5].

Increased concentration of CRP monomers and pentamers is a sign of "pollution" of intercellular environment with big endogenous phlogogens, apoptotic bodies, products of biological reaction of autophagy and inflammatory reactions [5]. Biological role of CRP consists from formation of vector, directed FA transfer, providing substrates for production of energy (FA in the form of TG as part of VLDL) just in the cells that should fulfill biological reaction of inflammation.

Biological reactions that participated in realization of biological function of endoecology include also:

1. Reaction of hydrodynamic arterial pressure (BP);

2 Physiological denaturation of endogenous proteins with ROS;

3. Biological reaction of transcytosis throw endothelial monolayer;

4. Reaction of hyperthermia;

5. Biological reaction of apoptosis;

6.Reaction of opsonization by complement components;

7. Biological reaction of innate and

8. Acquired immunity;

9. Reaction of systemic inflammatory response, and

10. Biological reaction of autophagy.

To activate biological reaction of excretion it is necessary to increase hydrodynamic (hydraulic) pressure on basal membrane of glomerules. That's why accumulation of small endogenous phlogogens in intercellular environment initiates BP elevation and increases filtration in glomerules of nephrons independently of phlogogens' etiology, and these abnormalities can occur in physiological range for a long time.

After formation of closed circulatory system cells continued to excrete big phlogogens from cytoplasm into the bloodstream, in the local pool of intravascular intercellular environment as it used to be millions of years before. In this case evolutionally late pull of collection and utilization of big phlogogens from intravascular pull of intercellular environment is located directly after the endothelial monolayer in elastic arteries' intima.

Activation of biological reaction of inflammation for excretion of big phlogogens from the local pool of intravascular intercellular environment to elastic arteries' intima requires activation of biological reaction of transcytosis (pinocytosis, endo- + exocytosis) through endothelial cells monolayer. Since the formation of closed circulatory system was evolutionally late, the only way of transcytosis activation is the increase of hydrodynamic pressure in the distal part of arterial system made of precapillary muscular arterioles. And if a patient has increased plasma levels of CRP monomers or pentamers for a long time it is always accompanied with elevated BP, it occurs within physiological values of BP more frequently, but constantly and during long time periods. It is followed by impairment of biological function of endoecology and slow formation of essential metabolic AH.

Biological function of adaptation is realized through the following mechanisms:

1. Biological reaction of stress;

2. Reaction of compensation;

3. Biological reaction of compensatory anti-inflammatory protection, and

4. Reaction of innate and acquired immunity. Biological stress reaction is evolutionally old, it is realized even at autocrine level (inside cells) through the synthesis of chaperone proteins [6].

Chaperones are the heat shock proteins, the "clips" synthesized by each and every cell for realization of biological stress reaction in order to preserve functional conformation (ternary and quaternary structure) of the most functionally important proteins through physical-chemical interaction with chaperones [6].

Biological reactions of compensation in vivo are various, and they are realized as at cellular level as at the level of paracrine regulation of cellular communities. The syndrome of compensatory anti-inflammatory response also participates in the realization of biological function of adaptation; it controls in vivo the consistency between biological inflammatory reactions and action of initiating factors like endogenous phlogogens or exogenous pathogens.

After each biological reaction of stress, even after emotional one, intercellular environment contains many chaperons including the ones with high molecular weight (65-130 kDa). Loose connective tissue (LCT) cells utilize chaperons in vivo through realization of biological reaction of inflammation, and this is the function of "sedentary", resident macrophages. Each episode of any stress including emotional one is followed by biological reaction of inflammation:

a) synthesis of chaperone family proteins;

b) their collection and elimination from intercellular environment, and

c) their utilization via inflammatory reaction in elastic arteries' intima. Due to this even emotional AH is always accompanied with biological reactions of BP and inflammation.

From functional point of view arterial intima is a single pool that collects and utilizes in vivo multiple endogenous phlogogens, exogenous infectious pathogens and various xenobiotics, alien substances that enter circulation during pharmacological treatment; intima also regulates utilization — the final step of generalized biological function of endoecology and inflammatory reaction. Biological function of endoecology, reaction of inflammation occurs in vivo every minute and second, as it happens with biological reaction of excretion in glomerules of nephrons.

Independently from etiology, every disease is based on initial or acquired impairment of biological functions. Only the therapy that overcomes (eradicates) undesirable endogenous and exogenous influences and brings back the processes to their natural course can be called effective. Adaptation of organism to non-physiological conditions can be considered as the unity of adaptation mechanisms (formation of optimal changes) and compensation of physiological processes. It is necessary to note that compensation can be physiological and non-physiological.

Biological function of locomotion

Realization of locomotion during phylogenesis that requires movement due to reciprocal contraction of evolutionally late skeletal myocytes was accompanied with formation of: a) closed circulatory system; b) heart started to work as the central pump in the proximal part of arterial system; c) differentiated function of millions of local peristaltic pumps like muscular arterioles, formation of "peripheral" heart in the distal part of arterial system. The system of insulin-dependent cellular pools has been formed: striated myocytes, cardiomyocytes' syncytium, subcutaneous insulin-dependent adipocytes, periportal hepatocytes, specialized Kupffer cells in liver, ß-cells of Langerhans islets in pancreas; d) vector transfer of oleic MFA synthesized in situ de novo from glucose in hepatocytes in the form of oleic TG as the part of oleic ApoE/B-100 VLDL that do not turn to LDL. They are absorbed by insulin-dependent cells via vector ApoE/B-100-dependent endocytosis of ligand oleic VLDL.

Cognitive biological function

The term "cognitive function" arises from Latin word "cognition" — knowledge; cognosere – to know, to estimate the environment, to look around. The terms like recognition of abnormalities, estimation (of metabolism) and outer condition (environment) have the same etymology [7]. As we suppose, cognitive function includes: a) the ability of an individual to focus on metabolism regulation in vivo and combine regulation of all cellular community function in vivo in all three levels of relative biological "perfection" [7]. It can be related to:

1) Autocrine regulation of each cell;
2) All cellular communities, organs, organ system s receiving paracrine regulation;
3) Organism in general [8] in vivo, and
4) Microbiota that lives together with organism during all its life [9].

Realization of cognitive function means adequate self-positioning in outer environment, space and being surrounded by other individuals in conditions of constantly changing, severe, not always positive influences of environmental factors. This can be also applied to physiology of organism that is an optimal combination between dominating multicellular system and local bacterial ecosystem of facultative anaerobic organisms of the large intestine [9].

We suppose that cognitive biological function is the combined, single, neurohumoral vegetative regulation of metabolism at the third level of relative biological perfection, at the level of organism. It occurs during:

a) combined function of all organs [10] and systems;

b) dynamic formation of metabolic unity in vivo;

c) changes of the environment [11].

Whatever were the parameters (1), however fast the environmental changes occurred (2), cognitive biological function of subcortical brain structures would be responsible for optimal changes of metabolism [12]. During phylogenesis imperfection of cognitive biological function sometimes used to create so imperfect in vivo conditions even for Homo sapiens ancestors that the majority of population members died [13].

Impaired cognitive function during the formation of metabolic pandemias that are tightly connected with each other from pathogenetic point of view includes pathology of biological functions of trophology, homeostasis, endoecology and adaptation. Restricted pool of cells independent from insulin action that includes visceral omental adipose cells and unlimited number of insulin-dependent subcutaneous adipocytes participate in the formation of pathology and lo-

cal abnormalities of paracrine communities, tissues and organs in vivo [14].

In psychology "cognition" means the ability to acquire and fulfill knowledge, perception, thinking, speech, conscience and memory [15]. The terms "cognitive skills" and "cognitive capacities" usually characterize individual capacities through realization of which person can perceive knowledge, information and successfully fulfill them. During evolution the action of leptin, adiponectin, and acetyl-CoA [16] and biological cognitive function have not created in vivo system [17] that would have informed subcortical nuclei of hypothalamic area of the brain about the end of physiological food intake and aphysiological continuation of meal using the mechanism of reverse negative feedback [18].

The unity of pathogenesis of atherosclerosis, impaired biological function of trophology and endoecology

Etiological factors of atherosclerosis that have been formed during the early stages of phylogenesis include the following ones:

1. Oleic MFA is more active in chemical reactions than palmitic FA [19];

2. When animals used to live in the ocean, they were carnivorous (they used to eat fish). After the reduction of the ocean level, forced life on the ground during millions of years and adaptation to new environmental conditions made Homo sapiens become herbivorous [20].

3. Biological role of insulin consists of providing substrates for energy production, first of all, for biological function of locomotion, to provide organism with energy (ATP) through combined use of two substrates: FA and glucose. Insulin expresses transformation of C 16:0 palmitic SFA endogenously synthesized from glucose to ϕ-9 C18:1 oleic MFA. Insulin expression increased kinetic parameters in vivo [21].

4. At the same time evolutionally late insulin cannot initiate in vivo transformation of all exogenous palmitic SFA of meat (carnivorous food) to oleic MFA. Herbivorous organisms realize oleic variant of FA metabolism under the action of insulin, and after meat food consumption they shift to palmitic variant of FA metabolism.

5. During the life in the ocean all animals used to synthesize biologically active mediators eicosanoids from the fish fat, from ϕ-3 C20:5 eicosapentaenoic PUFA (eicosa) [22]. There was no PUFA synthesis system on the ground.

High consumption of carnivorous food (meat) by evolutionally herbivorous Homo sapiens is the most frequent pathogenetic factor of atherosclerosis. It leads to formation of:

a) alimentary deficiency of PUFA [23] due to its blocked bioavailability and its absorption by cells in the form of polyunsaturated cholesteryl ester (PUSChE) activates biological reaction of compensation and in vivo synthesis of non-physiological eicosanoids that impairs in vivo regulation of many aspects of metabolism [24];

b) evolutionally late insulin is unable to transform exogenous palmitic SFA to oleic MFA; in this case palmitic variant of FA metabolism starts to prevail in vivo and it impairs providing cells with energy comparing with oleic variant; meat contains several times more palmitic SFA than fish [25];

c) Vector transfer of oleic MFA in the form of oleic TG as part of oleic ApoE/B-100 VLDL initiated by insulin does not lead to LDL formation, and ligand oleic VLDL are directly consumed by insulin-dependent cells via ApoE/B-100 endocytosis.

d) Phylogenetically late ApoE/B-100 FA transport cannot transfer palmitic SFA in the form of palmitic TG as part of palmitic VLDL, the blockade occurs at the stage of formation of ligandless palmitic VLDL→LDL. Cells cannot absorb ligandless VLDL in receptor-mediated way, and these particles become big endogenous phlogogens forming retention HLP and high levels of LDL-cholesterol [26].

Increase of LDL cholesterol occurs first of all due to increased concentration of non-esterified cholesterol in polar monolayer of palmitic VLDL→LDL. They block cellular absorption of PUFA as part of physiological linoleic and linolenic LDL in the form of PUSChE via ApoB-100 endocytosis. Instead of highly effective oleic variant of energy production by cells blocked action of insulin leads to non optimal palmitic variant of FA metabolism that is characterized with constant deficiency of energy in the form of ATP in vivo.

Atherosclerosis, alimentary deficiency of PUFA in cells and compensatory synthesis of non-physiological eicosanoids

Eicosapentaenoic and docosahexaenoic PUFA, so called Omega-3 FA (and this name is normally applied just to them and not to all ω-3 FA) are biologically active components of fish fat, substrates for synthesis of evolutionally early humoral mediators eicosanoids in humans [27]. Plasma concentrations of

docosahexaenoic PUFA is several times higher than eicosapentaenoic PUFA; the first one is the form of PUFA for PUFA deposing in phospholipids (PL) of intracellular membranes. ϖ-3 C20:5 eicosapentaenoic acid (name is derived from a Greek word "eikosa" that means twenty) is the only biologically active predecessor for synthesis of eicosanoids-3 (three double bonds in eicosanoid molecule) (Figure 1).

When animals entered the ground environment that lacked of eicosapentaenoic PUFA cells started to produce less active eicosanoids of the second group from such physiological predecessor like ω6 C20:4 arachidonic PUFA. During the life in the ocean cells started to produce evolutionally early highly active prostaglandins belonging the group of prostacyclins, thromboxans, and leukotriens of the third groups that have three double bonds in the molecule from C20:5 PUFA. During the life on the ground animals started to synthesize less active humoral mediators from C20:4 arachidonic PUFA; these eicosanoids have two double bonds in their molecules. In case of atherosclerosis cells lack both C20:5 eicosapentaenoic and C20:4 arachidonic PUFA and start to produce eicosanoids not from PUFA, but from endogenously synthesized C20:3 dihomo-γ-linolenic UFA, mead acid; these non-physiological eicosanoids have one double bond in their molecules.

Synthesis of non-physiological eicosanoids of the first group is the cause of many metabolic abnormalities in vivo in atherosclerosis:

a) non-physiological role of prostacyclins of the first group in regulation of biological reactions of endothelium-dependent vasorelaxation and impaired circulation in distant parts of arterial system, dysfunction of biological reaction metabolism↔microcirculation; all this creates conditions for metabolic AH;

b) absence of PUFA in the structure of aminophospholipids causes the change of function of all integral proteins of cell membrane including glucose trasporters, Na^+/K^+ ATPase, various receptors, acyltransferases, and biological reaction of endo-exocytosis (transcytosis) [28];

c) synthesis of thromboxanes of the first group from endogenous predecessors instead of its inhibition activates adhesion of all cells including platelets in vivo [29];

d) synthesis of non-physiological leukotrienes of the first group is the condition for activation of synthesis of mostly proinflammatory cytokines that augment biological reaction of inflammation in vivo [30], thus initiating impairment of biological reaction metabolism↔micrucirculation.

Atheromatosis is the impairment of biological function of endoecology, collection from circulation and utilization of palmitic VLDL→LDL in arterial intima

Etiological factors of atheromatosis include:

a) evolutionally late pool of collection and utilization of big endogenous phlogogens (exogenous pathogens) from circulation for realization of biological function of endoecology was localized directly behind endothelial monolayer in elastic arteries' intima [31];

b) when too many endogenous phlogogens are concentrated in the collection pool of arterial intima, a restricted number of polyfunctional resident macrophages of LCT in situ are responsible for utilization

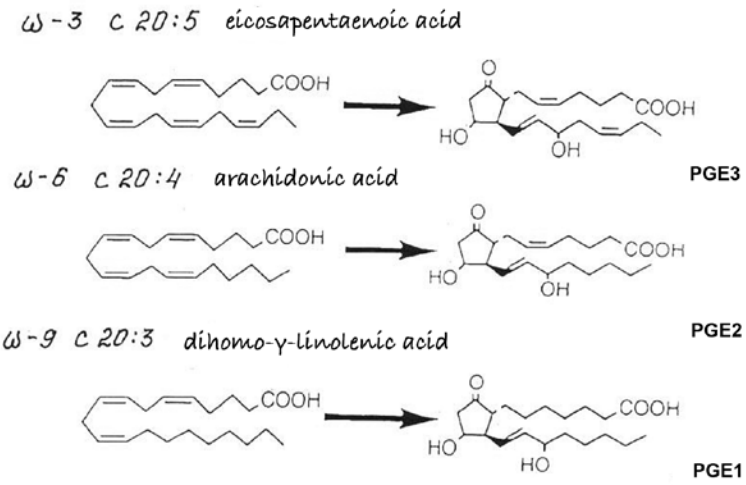

Figure 1. Structural formulas of FA – substrates and highly active prostaglandins PGE3, less active PGE2, and absolutely non-physiological PGE1.

of phlogogens, and numerous recruited monocytes of hematogenous origin [32];

c) bone marrow-derived monocytes have less expression of PUSChE than resident macrophages [33].

Atheromatous masses of elastic arteries' intima are partially catabolized physiological ϖ-3, ϖ-6 and non-physiological ϖ-9 PUFA in the form of non-polar PUSChE. Cells were unable to absorb these PUFA from blood in the form of PUSChE as part of linoleic and linolenic LDL via ApoB-100 mediated endocytosis in physiological way. The more severe is PUFA and physiological eicosanoids synthesis deficiency in cells, the more evident is atheromatosis in intima of phylogenetically late mixed type and elastic arterioles in the proximal part of arterial system. Therefore, a) atherosclerosis is the impairment of biological function of trophology and biological reaction of exotrophy, the pathology of PUFA and SFA transport as part of LP and their metabolism; b) atheromatosis is a non-physiological realization of compensatory function of endoecology and biological reaction of inflammation in the pool of collection and utilization of palmitic VLDL→LDL from the local pool of intravascular system in elastic arteries' intima.

Insulin is required to provide all cells responsible for locomotion function with substrates for energy production. The systems of FA transport in non-polar TG have been consequently developed in vivo during phylogenesis:

a) in carnivorous animals consuming meat food it looked like: enterocytes →ApoE/B-48 chylomicrons →lymphatic vessels→hepatocytes→ApoB-100 VLDL →ApoB-100 LDL→ApoB-100 receptor-mediated endocytosis;

b) in herbivorous animals consuming plant food: transport was much shorter in case of endogenous synthesis of oleic MFA and insulin action: hepatocytes→ligand oleic VLDL — ApoE/B-100 endocytosis by insulin-dependent cells; herbivorous animals do not form oleic LDL if they consume mostly vegetal and fish food.

c) Insulin cannot transform palmitic SFA into oleic MFA in herbivorous animals consuming meat food and big amounts of exogenous palmitic SFA; many ligandless palmitic VLDL→LDL are accumulated in blood during transport, cells do not absorb them, and these particles pollute intravascular pool of intercellular environment forming HLP.

If we start to compare phylogenetic variants of FA transport in carnivorous animals (1), in herbivorous animals consuming vegetal food (2), and in herbivorous animals on carnivorous diet (3), we can observe the following mechanisms:

1) enterocytes→chylomicrons→hepatocytes→VLDL→LDL→ApoB-100 endocytosis;

2) hepatocytes — VLDL→ApoE/B-100, and

3) hepatocytes — palmitic VLDL→LDL→ApoB-100 endocytosis blockade→HLP→increased concentration of TG and LDL cholesterol.

In this case all steps of HLP formation after impairment of biological function of trophology start to look clear. We can see why the system of oleic UFA as part of oleic VLDL transport cannot be functional with palmitic VLDL.

It leads us to understanding that herbivorous animals producing mostly oleic MFA, oleic TG and oleic VLDL from glucose in hepatocytes form physiologically minimal amounts of palmitic LDL and LDL cholesterol in blood. The more animal food evolutionally herbivorous Homo sapiens consumes, the more palmitic TG, palmitic VLD and non-physiological VLDL→LDL he has in blood. Excessive consumption of non-physiological amount of meat food and excess of palmitic UFA are the main reasons of elevated concentration of LDL cholesterol [20].

Palmitic ligandless VLDL→LDL that haven't been absorbed by cells via insulin-dependent ApoE/B-100 endocytosis become the substrate for atheromatosis of intima [34]. Non-physiological palmitic VLDL→LDL unite pathogenesis of atherosclerosis and atheromatosis [35]. Palmitic VLDL→LDL are formed during realization of atherosclerosis as non-physiological process, in case of atheromatosis ligandless palmitic LP are removed from blood, unfortunately it occurs in not absolutely physiological [36] or in non-physiological way [37]. Palmitic VLDL→LDL induce atheromatosis in elastic arteries' intima [38]. Excessive amount of palmitic SFA in food is the main cause of lipoidosis in all insulin-dependent cells: sceletary myocytes, cardiomyocytes, periportal hepatocytes, Kupffer cells and ß-cells of Langerhans islets.

Phylogenesis and biological bases of atherosclerosis and atheromatosis primary prevention

Biological action of insulin determined the transformation of carnivorous animals to herbivorous ones. At first it required the expression of insulin-like growth factor, then glucagon was added, and in the end of phylogenesis humoral mediator insulin appeared. And if during phylogenesis every cell synthesized just palmitic UFA from acetyl-CoA before the appearance

of insulin, this hormone has added two biochemical reactions to FA synthesis: C16:0 palmitic UFA→C18:0 stearic UFA→ ω-9 C18:1 oleic UFA. It accompanied the development of herbivorous animals on the ground, since previously carnivorous animals started to be herbivorous after leaving ocean for ground. The same thing happened with Homo sapiens.

Insulin initiated formation of functionally new cells in vivo. These cells were:

1. Striated myocytes;
2. Syncytium of cardiomyocytes;
3. Pool of subcutaneous adipocytes;
4. Periportal hepatocytes, and
5. Resident liver macrophages – Kupffer cells, and
6. Pancreatic β-cells of Langerhans islets.

Since hepatocytes and not enterocytes were the starting point for FA transport in vivo in herbivorous animals, insulin can be considered phylogenetically late. The transport of oleic MFA, first of all, in the form of oleic TG as part of oleic VLDL was the shortest vector way. Hepatocytes→oleic VLDL→lypolysis and ligand oleic VLDL→ApoE/B-100 endocytosis without formation of oleic LDL. Only palmitic VLDL→LDL are accumulated in blood, and they lead to increased concentration of LDL cholesterol in blood.

Unwillingness of patients to consume animal (fish) food is non-physiological [39]. For millions of years ancestors of human used to be carnivorous. From this period people inherited: a) every animal cell synthesizes just palmitic UFA from acetyl-CoA; b) biological functions and reactions are regulated with highly active humoral mediators that cells synthesize from exogenous essential PUFA [40] from the components of fish fat; c) many herbivorous animals feed their children with animal food milk. Milk consists ov of palmitic, saturated animal fat, we call it butter without any reasonable background. Without any reasonable background doctors recommend animal palmitic butter for eating and prevent patients from consuming vegetal oleic palm oil [41]. From the position of atherosclerosis and atheromatosis prevention, vegetal oils are better than any animal fat, including butter [42].

Refusal of fish consumption and alimentary deficiency of essential eicosapentaenoic and docosahexaenoic PUFA always lead to atherosclerosis; and atheromatosis in this case will not be so evident [43]. We can reasonably suppose that atherosclerosis formation in vivo depends on cellular deficiency of ω-3 PUFA. Atheromatosis of arterial intima occurs in parallel with excess of meat with high contents of palmitic UfA, cholesterol and palmitic VLDL→LDL (LDL cholesterol) in food consumed by herbivorous animals.

Exogenous hypercholesterolemia in the experiments of S.S. Khalatov and N.N. Anichkov is a particular case of general law of biology: rabbit is a herbivorous animal, and exogenous alcohol cholesterol represents excess of animal food. By now it was impossible to reproduce aorta atheromatosis in exogenous hypercholesterolemia in carnivorous rats [44]. Every single excess of animal food in the diet of herbivorous human (animals) leads to formation of locus minoris resistentia. Palmitic ApoE/B-100 VLDL form ligands very slowly, ligandless palmitic VLDL→LDL are accumulated in blood, and they increase the concentration of LDL cholesterol.

Ligandless palmitic VLDL→LDL that have not been absorbed by cells are transported via biological reaction of transcytocis through endothelium of proximal part of arterial system to the pool of collection and utilization of big endogenous phlogogens in arterial intima. Since utilization of palmitic VLDL→LDL in intima is performed not by polyfunctional resident intima macrophages, but by functionally overloaded monocytes originated from peripheral blood, realization of inflammation leads to intima atheromatosis [45]. Oleic MFA prevents the action of palmitic UFA excess and impaired mitochondrial function during IR. It has been shown that C16:1 palmitoleic MFA can influence the function of resident macrophages [46].

Physical and chemical properties of oleic MFA, oleic TG, and oleic VLDL are very different from palmitic UFA, palmitic TG, and palmitic VLDL [47]. Etiological factors of atherosclerosis incude:

a) excessive, non-physiological consumption of animal food by herbivorous Homo sapiens, and

b) lower involvement of C16:0 palmitic UFA in all biochemical reaction in vivo comparing with high parameters of C 18:1 oleic MFA.

Atheromatosis is in vivo catabolism (utilization) of PUFA that were not absorbed by cells from blood being part of palmitic LDL; they are PUFA in the form of non-polar PUSChE. PUFA collection and utilization from LDL occurs in arterial intima, only partial catabolism of PUSChE under the action of hematogenous monocytes [48] forms atheromatous lipid depositions (plaques), and leads to stenosis of elastic arteries with CHD manifestations and brain ischemia. If together with high levels of LDL cholesterol blood plasm has elevated concentrations of TG, atherothrombosis occurs simultaneously in arterial intima;

it is characterized with formation of soft plaques that contain much TG and have high risk of rupture.

Conclusion

We said nothing about such etiological factors of atherosclerosis and atheromatosis like innate disorders of metabolism, familiar HLP [49], pathologies of ApoE isoforms, and formation of HLP, III type [50]. Etiologically different abnormalities of primary structure of apoproteins are characterized with low affinity to non-polar lipids. Abnormal activity of hydrolases and esterases of glycerol and cholesterol esters, blockage of palmitic SFA transport through inner mitochondrial membrane promote the formation of atherosclerosis. In the situations difficult for our metabolism it is necessary to follow optimal diet since it is the most effective way to prevent atheromatosis complications and atheromatosis of elastic arteries in the proximal part of arterial system, formation of AH, acute coronary system and ischemic circulatory disorders of the brain. We have no other alternative for phylogenesis; it is important to remember that Homo sapiens is phylogenetically herbivorous.

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