ISSN 2304-3415, Russian Open Medical Journal
2022. Volume 11. Issue 2 (June). Article CID e0202
DOI: 10.15275/rusomj.2022.0202

Review

Brain-derived neurotrophic factor and coronary artery disease

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Received 18 June 2021, Accepted 28 October 2021

Abstract: Coronary artery disease (CAD) is defined as myocardial damage developing as a result of its organic and functional changes, and leading to impaired blood flow through the coronary arteries. An important pathogenetic component of CAD is atherosclerosis. Currently, key aspects of the molecular relationship between inflammation and atherosclerosis are being actively studied, the immunometabolic theory of atherosclerosis is being discussed, along with an involvement of perivascular adipose tissue in the pathogenesis of this pathology, due to its ability to respond to atherogenic stimuli via developing inflammatory reactions. Evidence has been accumulated that in patients with CAD, both in their blood and perivascular adipose tissue, the level of neurotrophic factors (in particular, brain-derived neurotrophic factor, BDNF) changes, which may be a promising area of research from the standpoint of studying this factor as a therapeutic target for atherosclerosis in CAD. Neurotrophic growth factors control the functioning of both immune and nervous systems, and the balance of energy metabolism and innervation of adipose tissue. They affect vascular homeostasis, and are also involved in causing and stopping inflammation. Currently, there are data on the role of BDNF in the pathogenesis of cardiovascular, neurodegenerative and metabolic diseases, and on the effect of polyunsaturated fatty acids and eicosanoids on the level of BDNF and, accordingly, the development and progression of coronary artery atherosclerosis. Our review summarizes published data (2019-2021) on the pathophysiological and pathogenetic mechanisms of the relationship between BDNF and CAD (atherosclerosis).

Keywords: coronary artery disease, brain-derived neurotrophic factor, atherosclerosis.

Cite as Kytikova OYu, Novgorodtseva TP, Denisenko YuK, Antonyuk MV, Gvozdenko TA, Atamas OV. Brain-derived neurotrophic factor and coronary artery disease. *Russian Open Medical Journal* 2022; 11: e0202.

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Rationale

Cardiovascular diseases (CVD), in particular, coronary artery disease (CAD), are a common, socially significant pathology worldwide [1-3]. Various clinical manifestations of CAD are classified as acute coronary syndrome (ACS) or chronic coronary syndrome (CCS). The latter is also known as stable coronary artery disease [4]. The main pathogenetic component of CAD is the formation of atherosclerotic plaques in the epicardial arteries, and this pathological process can be both obstructive and non-obstructive [3, 5]. Atherosclerotic cardiovascular disease (ASCVD) is the principal cause of morbidity and mortality globally [6-8]. Inflammation and lipid metabolism are closely related, which implies the need of searching for therapeutic targets to correct disorders of immunometabolic homeostasis and block the development of inflammation as the basis for developing atherosclerosis in CAD [9].

It is believed that the interaction between lipids and immune cells underlies the development of inflammation of the arterial wall and the formation of atherosclerotic plaque [10, 11]. As factors regulating these processes, neurotrophic factors (NTF) are being actively studied [12, 13]. This is due to their participation in the control of the functioning of the nervous, immune, endocrine, and vascular systems, as well as in initiation and resolution of inflammation. Currently, there are data on the role of NTF in the pathogenesis of metabolic [14] and neurodegenerative diseases [15-19], along with cardiovascular pathology [20-25]. In recent years, the attention of scientists has been attracted by the brain-derived neurotrophic factor (BDNF), which is a member of one of the NTF families. It is believed that BDNF mediates an interaction of nervous and immune systems with adipose tissue [26]. BDNF expression is impaired in patients with coronary atherosclerosis [12, 27], which may be a promising area of research in terms of studying this factor as a therapeutic target in CAD.

The relevance of studying the effects of BDNF in CAD is supported by recent discovery of the ability of polyunsaturated fatty acids (PUFA) and their mediators to affect the BDNF level and, accordingly, the risk of development and progression of coronary artery atherosclerosis [13].

Among available published sources, there are numerous large review articles dedicated to changes of BDNF level in CAD. However, the pathophysiological and pathogenetic mechanisms of the relationship between BDNF and atherosclerotic process in the coronary arteries are not well studied. For this review, we

searched the PubMed database for the information on selected inclusion criteria. Information requests included the following set of keywords: coronary artery disease, brain-derived neurotrophic factor, atherosclerosis and the publication period of 2019-2021. Based on the analysis of various published data, a significant role of neurotrophins in the pathogenesis of coronary artery atherosclerosis and the need for further research in this direction are presumed.

Coronary artery disease and atherosclerosis

CAD is defined as a myocardial lesion resulting from organic (atherosclerosis) and functional (spasm and intravascular thrombosis) changes and leading to impaired blood flow in the coronary arteries [2, 4]. The concept of CAD combines acute (unstable) and chronic (stable) conditions. In the recommendations for the treatment of stable forms of CAD by the European Society of Cardiology (ESC), the revision of 2019, the concept of CCS was introduced and the following clinical scenarios for the development of stable CAD in patients were defined:

1. Patients with suspected CAD (with symptoms of stable angina) and/or shortness of breath;

2. Patients with newly developed heart failure or left ventricular dysfunction, and suspected CAD;

3. Asymptomatic patients, as well as patients with symptoms, but whose stabilization occurred in less than a year after ACS or patients with recent revascularization;

4. Asymptomatic and symptomatic patients more than a year after the initial diagnosis of CAD or revascularization;

5. Patients with clinical manifestations of angina pectoris and its suspected vasospastic or microvascular nature;

6. Asymptomatic individuals with CAD detected at screening.

These scenarios were grouped under the heading of CCS, but have different risks of future cardiovascular events. Currently, CCS is defined as a chronic process that could be stabilized and regressed via lifestyle modification, pharmacological therapy, and invasive interventions [28]. These measures are aimed at reducing the risk of cardiovascular events. Dyslipidemia, arterial hypertension, type 2 diabetes mellitus (DM2), smoking, physical inactivity, visceral obesity, stress, and anxiety are recognized as the main modifiable risk factors for CAD. Non-modifiable risk factors are age and gender [29]. The role of all listed risk factors increases with age.

As mentioned above, CAD is characterized by the formation of atherosclerotic plaques in the epicardial arteries [3, 30, 31]. Atherosclerosis is closely associated with visceral obesity and develops faster in patients with DM2 [32]. Obviously, atherosclerosis is an important pathogenetic component of most modifiable risk factors for the development of CAD [5]. In a review by O. Shafi, PubMed, MEDLINE, and Google Scholar databases were analyzed for articles related to atherogenesis, vascular homeostasis, aging, gene expression, signaling pathways, angiogenesis, and endothelial and vascular smooth muscle cells [33]. It was concluded that the development of atherosclerosis was triggered by a complex of pathological changes in vascular homeostasis, aging processes, and disruption of regulatory genes. Such changes affect extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathways and phosphatidylinositol-4,5-bisphosphate 3-kinase/V-AKT murine thymoma viral oncogene homolog/mechanistic target of rapamycin (PI3K/AKT/mTOR) signaling pathway, one of the components of which are NTF.

Significant progress is currently being made in understanding the key molecular relationships between inflammation and atherosclerosis [30, 34-36]. Until the 1970s, atherosclerosis was considered a degenerative disease determined by the passive storage of lipids. In the following decades, inflammation became the main topic of research in the pathophysiology of atherosclerosis, but evidence of its key role was recognized only in 2017 [5, 37]. Currently prevailing concepts of response-to-injury and response-to-retention define atherosclerosis as an immune-inflammatory process that develops against the background of (1) endothelial dysfunction, (2) activation of proinflammatory cytokines, macrophages and T cells, and (3) the development of oxidative stress [38].

Endothelial dysfunction is caused by the deposition of modified lipoproteins, which are triggers of immune activation and inflammation of the vascular wall [39]. It is believed that an interaction between lipids and immune cells is the driving force behind the development of inflammation of the arterial wall and the formation of atherosclerotic plaque [7, 8]. Therefore, both immune and metabolic pathways are fundamental parts of the etiopathogenetic process of atherosclerotic diseases. Consequently, scientists currently favor the immunometabolic hypothesis of the atherosclerosis etiopathogenesis [9].

Review by H.W. Kim et al. described not only the classical concept of atherosclerosis development (inside-out response theory), but also a concept based on the participation of perivascular adipose tissue (PVAT) in the pathogenesis of this pathology [27]. Human adipose tissue is anatomically represented by subcutaneous and visceral fat, and is also classified into white adipose tissue and brown adipose tissue, based on function, phenotype, and morphology. The adipose tissue surrounding the heart and large vessels is capable of exhibiting features of both white and brown adipose tissues [40]. PVAT surrounds most blood vessels and responds to atherogenic stimuli by developing inflammatory reactions involved in the pathogenesis of CVD [41]. Accordingly, PVAT is an important endocrine organ, the dysfunction of which could lead to obesity, atherosclerosis, and CVD. A review by H. Liang described recent advances in understanding the effects of PVAT on the cardiovascular system [35]. The fact that PVAT is located on the outside of the arterial wall implies that it contributes to the pathogenesis of atherosclerosis via an extrinsic mechanism, opposing the conventional theory of atherosclerosis. An interesting literature review by H. Hu et al. focused on the role of PVAT in the development of hypertension and atherosclerosis [36]. Interest in the potential role of PVAT in the pathogenesis of the above diseases could be explained by the fact that PVAT releases factors regulating vascular function, adipokines, cytokines, and NTF [40]. It was confirmed that the expression of NTF (BDNF receptor) was impaired in patients with coronary atherosclerosis [12, 42]. In particular, such changes are more pronounced in the PVAT of the proximal aorta with coronary atherosclerosis than in the PVAT of the internal thoracic artery. This suggests that local changes in BDNF signaling may contribute to the development of atherosclerosis. An involvement of NTF in the pathogenesis of atherosclerosis is discussed below.

Neurotrophic growth factors

NTF represent a large group of polypeptide compounds classified into several families, as well as a number of biomolecules [43]. The principal classification of NTF distinguishes four families: neurotrophins (NT); the family of ciliary neurotrophic factor, also known as neurokines or neuropoietic cytokines (CNTF); the family of mesencephalic astrocyte-derived neurotrophic factor (MANF); and the family of glial cell line-derived neurotrophic factor (GDNF).

The NT family includes neurotrophin-3 (NT-3); neurotrophin-4 (NT4), also known as neurotrophin-5 (NT-5); BDNF; and nerve growth factor (NGF).

Members of the CNTF family comprise CNTF per se, leukemia inhibitory factor (LIF), interleukin-6 (IL-6), cardiotrophin-1 (CT-1), cardiotrophin-2 (CT-2), prolactin, human growth hormone, leptin, interferons (interferon-α, -β, and -γ), and oncostatin M.

The MANF family includes MANF per se, also called arginine-rich, mutated in early-stage tumors (ARMET).

The GDNF family consists of GDNF, neurturin (NRTN), artemin (ARTN) and persephin (PSPN) (*Table* 1).

However, to date, in addition to existing NTF classification, a larger number of families and biomolecules are distinguished, which are also classified as NTF. There is a family that includes the epidermal growth factor (EGF), neuregulin, and transforming growth factors alpha and beta (TGF-α, TGF-ß). The ephrin family consists of several representatives (ephrins A1, A2, A3, A4, A5, B1, B2, and B3). In addition, some biomolecules have also been identified as NTF: insulin-like growth factors 1 and 2 (IGF-1, IGF-2), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), interleukins 1, 2, 3, 5, 8 (IL-1, IL-2, IL-3, IL-5, IL-8), and a number of others.

NTF are ligands of high-affinity protein tyrosine kinase receptors – tropomyosin receptor kinases A, B and C (TrkA, TrkB, TrkC); and also interact with the low-affinity non-tyrosine kinase receptor p75NTR from the group of TNF receptors. A strictly particular region of the NTF molecule binds to each of the receptors, triggering a specific cascade of signaling reactions.

For monocytes, the ability to express TrkA is described; for polymorphonuclear eosinophils of the bone marrow, the ability to express TrkB and TrkC is established. TrkB is expressed in neurons, axons, and dendrites of various brain structures. Binding NTF to these receptors leads to activation of the PI3/AKT kinase cascade, which provides neuroprotection; of the MAP/ERK kinase signaling cascade responsible for neuroprotection, neurogenesis, synaptic plasticity; and of phospholipase C gamma (PLC-γ), which mediates synaptic plasticity and growth of axons [44].

Binding NTF to p75 receptors activates proinflammatory nuclear transcription factor kappa B (NF-κB), c-Jun N-terminal kinase signaling cascade (JNK) stimulating apoptosis, and ceramide-mediated cascade capable of promoting both cell survival and cell apoptosis.

Table 1. Classification of neurotrophic factors

Family	*Family members*
NT	NT3, NT4, BDNF, NGF
CNTF	CNTF, LIF, IL-6, cardiotrophin-1, cardiotrophin-2, prolactin, growth hormone, leptin, interferon α, interferon β, interferon γ, oncostatin M
MANF	MANF
GDNF	GDNF, NRTN, ARTN, PSPN

NTF primarily play a key role in the development and maintenance of the nervous system normal functioning [45, 46]. Besides, the publications describe a wide range of regulatory effects of these growth factors on the immune system through autocrine and/or paracrine interactions [47]. Several types of immune cells (including dendritic cells, mast cells, eosinophils, macrophages, T and B lymphocytes) are the main source of NTF in the development of inflammation. It is well-known that CD4+ and CD8+ T lymphocytes synthesize NGF, BDNF and their receptors. B lymphocytes synthesize NGF and NT3. Macrophages have the ability to form NGF, BDNF, and NT4 [48]. There is increasing evidence of NTF association with the level of energy metabolism and innervation of adipose tissue [26, 49].

Thus, neurotrophic growth factors control the functioning of both immune and nervous systems, balance energy metabolism, and are involved in causing and stopping inflammation.

Brain-derived neurotrophic factor

It is now recognized that BDNF is the most common NTF of the NT family in the body [21, 45, 46]. This factor regulates neurotransmission, regeneration, and functional synaptic plasticity of neurons in the peripheral and central nervous systems via binding to TrkB and p75NTR [50-52]. BDNF was found in nerve, endothelial, and immune cells (lymphocytes, macrophages, monocytes), as well as in the cells of liver, pancreas, and muscle and adipose tissues [53] (*Table* 2).

BDNF is widely expressed in the hippocampus, cerebral cortex, and basal forebrain, which are vital regions responsible for memory, learning, and cognitive functions [53]. The main function of BDNF is to stimulate the growth and differentiation of neurons and synapses, and to participate in synaptic neurotransmission and neuroplasticity. Review by M. Zagrebelsky et al. focused on the role of BDNF in regulating the activity of dendritic cells through TrkB and p75NTR, which provide communication between nerve cells [71]. In this respect, BDNF remains one of the most prominent and studied molecules in neurology and psychiatry [60-63, 72]. BDNF involvement in a wide range of mental and neuropsychiatric diseases has been proven. Altered BDNF levels accompany neurodegenerative diseases [15], including Alzheimer's disease [16], Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease [17], multiple sclerosis, and ischemic stroke [18].

The neurotrophic theory of depression is based on a decrease in brain BDNF levels, which could be increased by antidepressants to alleviate depressive behavior [60]. In their review, T. Rana et al., gave a broad understanding of BDNF role in the pathogenesis of depression and the effectiveness of antidepressant therapy [63]. BDNF is involved in the modulation of the dopaminergic system participating in the pathophysiology of schizophrenia. An interesting review was performed by M. Han et al., describing the relationship between BDNF gene polymorphism and the effectiveness of antipsychotic drugs in the treatment of schizophrenia [72]. The review by M. Notaras et al. presents current updated information on the neurobiology of BDNF, including data from behavioral neuroscience and neuropsychiatry regarding fear, stress, and post-traumatic stress disorder [61]. Disorder of BDNF endogenous activity potentiates the sensitivity to stress and contributes to the development of stress-related diseases. In addition, the level of BDNF is associated with dementia [19] and autism spectrum disorders in children [73]. In

the study by E. Brattico et al., the benefits of increasing the endogenous BDNF level and, ultimately, improving the functioning of the human brain were considered [74].

BDNF is closely associated with pain sensations [59, 75, 76]. Inhibition of TrkB in various experimental models demonstrated a reduction in the severity of neuropathic pain resulting from injury or dysfunction of the peripheral or central nervous systems [52, 58]. BDNF deficiency correlates with neuromuscular impairment in experimental models of Kennedy's disease, suggesting that BDNF may restore neuromuscular transmission in patients with such pathology [65].

Brain-derived neurotrophic factor precursor (proBDNF) is expressed in both nervous and immune systems. It was detected in lymphocytes and other immune cells in patients with multiple sclerosis [47]. A number of immune cells located in the adipose-derived stromal vascular fraction (SVF) are a source of BDNF, which is involved in the innervation of fat cells [26, 49].

As noted above, BDNF is also secreted by other cells of the body, which explains its involvement in many diseases and pathological conditions. For example, it enhances the proliferation and differentiation of mesenchymal stem cells into osteoblasts and is involved in bone tissue regeneration [64]. Neurotrophins are key regulatory proteins in reproductive physiology during ontogenetic development and throughout adulthood. In the study by R. Chow et al., an electronic search was conducted for 2018-2019 articles in the MEDLINE database (PubMed) concerning the relationship between BDNF and reproductive system [67]. The authors concluded that BDNF and its receptors were important regulatory proteins involved in gonad development, regulation of ovarian and uterine functions, and embryonic and placental development. It was noted that the dysregulation of BDNF activity played an important role in reproductive diseases.

The biological and therapeutic importance of BDNF and its TrkB receptor in the regeneration of alveolar epithelial cells was emphasized [66].

The BDNF TrkB receptor is expressed by pancreatic β-cells; therefore, BDNF induces insulin secretion via interacting with this receptor [54-56]. It is currently acknowledged that altered levels of BDNF form the basis for the pathogenesis of diabetes mellitus [14, 57]. In patients with DM2, the concentration of BDNF is lower than in healthy subjects. Moreover, it was noted that the level of this factor declined to a greater extent in men, whereas in women, with an increase in the duration of DM2, the concentration of BDNF was lower [57]. The authors of that study suggested that gender differences could be caused by the level of estrogens and other sex hormones affecting glucose metabolism and contributing to the development of insulin resistance.

In the last decade, the attention of scientists was directed to studying the role of BDNF in the pathogenesis of atherosclerosis as an initiating factor of CVD [20-25]. This relationship will be discussed below.

Brain-derived neurotrophic factor, coronary artery disease and cardiovascular pathology

Attention to the involvement of BDNF in the pathogenesis of CVD is one of the focuses of contemporary research. Nearly 30% of the world population has a BDNF rs6265 (Val66Met) gene polymorphism, which is associated with an increased risk of CVD [68]. It is known that BDNF is involved in the contractility of cardiomyocytes, and carriers of the BDNF rs6265 (Val66Met) polymorphism demonstrate impaired contractility in these cells [68, 69]. Dyslipidemia and hypertension are major risk factors for CAD, and BDNF plays a regulatory role in blood pressure and lipid metabolism [25]. Also, BDNF plays a protective role in the physiological activity of vascular endothelium [42].

Published data indicated the involvement of BDNF in angiogenesis processes [20-22]. However, using a model of diabetic retinopathy, it was demonstrated that BDNF had a different effect on the impairment of neuroprotection and microcirculation present in that pathology [56]. Clinical studies established the role of BDNF as a risk factor for stroke and a marker of prognosis, mortality, and functional outcome among survivors of ischemic stroke [13, 18]. It is obvious that there is evidence both supporting the role of BDNF in the development of CVD and data clarifying the degree of linearity of this relationship [23, 25, 77].

Table 2. Localization of synthesis and function of BDNF

Synthesis localization	*Function*	*References*
Pancreas	Regulation of insulin secretion	[54-57]
Peripheral nervous system	Inhibition of neuropathic pain Neuroprotection	[56-59]
Central nervous system	Stress hormone regulator in the brain Neuroprotection	[56, 60-63]
Immune system	Participation in inflammation	[47]
Musculoskeletal system	Bone regeneration Neuromuscular transmission improvement	[64, 65]
Bronchopulmonary system	Regeneration of alveolar epithelial cells	[66]
Reproductive system	Gonad development Regulation of ovarian and uterine functions Development of the embryo and placenta	[67]
Cardiovascular system	Contractility of cardiomyocytes Endothelial function inprvement Effect on angiogenesis Effect on microcirculation	[20-22, 25, 42, 56, 68-70]
Adipose tissue	Innervation of fat cells Lipolysis regulation Participation in inflammation	[12, 26, 42, 49]

Of considerable interest is the study by S. Halloway et al., which assessed the levels of BDNF in people at risk of developing CVD or having that pathology [78]. Based on an analysis of 475 articles published in English, the authors concluded that BDNF levels were lower in patients with chronic heart failure and stroke, but higher in patients with unstable angina and recent myocardial infarction. Low levels of BDNF were associated with a higher incidence of CVD. The results of this study implied the necessity of using standardized measurements of BDNF in CVD.

Recent studies described, primarily, the role of BDNF in pathologies, such as myocardial infarction [21]. For instance, it was discovered that the BDNF Val66Met gene polymorphism was associated with an increased tendency to arterial thrombosis linked to acute myocardial infarction [79]. In a study by L. Sandrini, it was found that BDNF Val66met polymorphism slowed down cardiac repair and regeneration, which was due to the accumulation of proinflammatory macrophages (M1) and reduction in the activity of anti-inflammatory macrophages (M2) [79].

A decrease in the level of BDNF was demonstrated in an experimental model of chronic heart failure [69]. Use of ischemic preconditioning in rehabilitation programs is a promising direction in the treatment of patients with CAD [70]. When the effect of ischemic preconditioning was initiated in patients with CAD, the mechanisms of cardioprotection and metabolic adaptation to non-lethal ischemia were triggered. Nicolai Rytter et al. demonstrated a six-fold increase in the levels of BDNF, vascular endothelial growth factor, and prostacyclin ($P<0.05$), which improved endothelial function [70].

The relationship of this NTF with various neurological pathologies accompanying CVD, in particular with depression [80] or cognitive impairment [22], is being studied.

In the article by K.G. Monisha et al., it was also shown that the level of BDNF was significantly lower in individuals with CAD (30.69 ± 5.45 ng/mL) than in the control group (46.58 ± 7.95 ng/mL) [23]. It was confirmed that the expression of BDNF receptor was significantly reduced in patients with coronary atherosclerosis [12]. It was documented that prostaglandin E2 (PGE2) affected the polarization of type 2 macrophages (M2) and activated the CREB/BDNF/TrkB signaling pathway playing an important role in suppressing the development of coronary artery atherosclerosis in DM2 [81].

As mentioned above, immune and metabolic pathways are fundamental components of the pathogenesis of atherosclerosis [7-9]. There is increasing evidence linking metabolic diseases with neurological disorders affecting both the peripheral and central nervous systems. In the last decade, in the pathogenesis of cardiometabolic diseases, close attention has been paid to the neurogenic mechanisms of inflammatory response [48]. Altered BDNF levels accompany CVD, along with obesity and metabolic syndrome [82]. BDNF is a neurochemical factor that regulates energy balance via suppressing energy intake and increasing energy expenditure.

Macrophages and monocytes constitute the highest proportion of immune cells present in SVF and secrete BDNF involved in the innervation of fat cells [49]. Innervation of adipose tissue is necessary for the functioning of this metabolic organ [26, 49]. The sympathetic nervous system regulates lipid metabolism responsible for lipolysis and thermogenesis [26]. BDNF is a neurochemical factor that regulates energy balance by suppressing energy intake and increasing energy expenditure. In the study by Q. Zhu et al., it has been shown that BDNF-induced lipid mobilization was associated with sympathetic neuronal activation. The authors suggested that BDNF activated the sympathetic innervation of adipose tissue in order to regulate lipolysis [26].

S. Zierold et al. determined BDNF expression in PVAT of the proximal aorta (C-PVAT) and internal mammary artery (a.k.a. internal thoracic artery) (IMA-PVAT) [12]. BDNF levels were higher in C-PVAT, compared with IMA-PVAT, regardless of the presence of obesity, metabolic syndrome, or systemic inflammatory biomarkers in blood. The mRNA transcripts of BDNF-TrkB receptor were in significantly lower quantities in the aorta, compared with IMA

Hence, BDNF can be considered a factor affecting the immune and metabolic pathways of the atherosclerosis pathogenesis, as well as adipose tissue innervation.

Brain-derived neurotrophic factor, coronary artery disease and polyunsaturated fatty acids

Therapy for atherosclerosis, aimed primarily at correcting dyslipidemia, was not sufficiently effective, which promoted interest in PUFA in terms of prevention and treatment of this disease [83, 84]. On the one hand, the levels of free fatty acids (FFA) were not associated with cardiovascular mortality and do not depend on age, gender, race/ethnicity, or the presence of metabolic syndrome in examined patients [85]. At the same time, the results of another study demonstrated that patients with DM2 had a higher prevalence of ASCVD, and FFA levels were a marker for predicting their development [86]. K. Arai discovered that 70% of patients with the first episode of ACS had low ratios of eicosapentaenoic to arachidonic acids, as well as of docosahexaenoic to arachidonic acids. This finding makes these ratios excellent risk markers for the development of ASCVD [87].

Lipids and their mediators are known to play both proinflammatory and anti-inflammatory roles [88]. Endogenous deficiency of essential PUFA is accompanied by the accumulation of FFA in cells, disruption of energy homeostasis, and triggering the synthesis of proinflammatory eicosanoids, which initiates the development of the inflammatory process [89]. In turn, resolution of inflammation is regulated by another group of PUFA metabolites, pro-resolving lipid mediators (resolvins, lipoxins, protectins, and maresins) [90, 91]. When the production of pro-resolving lipid mediators is disrupted, chronic low-intensity inflammation occurs [89], which accompanies the development and course of the atherosclerotic process [3, 27, 41]. The review by N. Tułowiecka analyzed over 110 articles published in the PubMed and Embase databases prior to January 31, 2021, including such keywords as ‘stroke and lipoxin’ and ‘stroke and atherosclerosis’ [92]. The authors concluded that lipoxins, which are derivatives of ω6 PUFA, reduce the severity of damage caused by ischemic stroke. Besides, lipoxins inhibit neutrophil infiltration and production of cytokines and proinflammatory chemokines.

There is a known relationship between the level of PUFA consumption and development of atherosclerotic lesions in large vessels [86]. The results of the study by G. Feuchtner et al. detected direct anti-atherogenic effects of ω3 PUFA at early stages of atherosclerosis, noting that the results of other experimental and randomized studies did not support the use of docosahexaenoic and eicosapentaenoic acids for preventing cardiovascular pathology [84]. In the study by K.C. Maki et al.,

recent evidence on association of ω3 PUFA doses and atherosclerotic CVD risks was discussed [83]. Currently, effective doses of ω3 PUFA to reduce the risk of atherosclerotic CVD are 4 g/day. If ω3 PUFA have multiple health benefits, and a number of studies have demonstrated their anti-atherogenic potential in atherosclerosis, then the potential of ω6 PUFA needs to be explored. In this regard, it is critical that the molecular mechanisms underlying their action of ω6 and ω3 PUFA are comprehensively studied. A recent review by D.P. Ramji was dedicated to analyzing the mechanisms of action of ω6 and ω3 PUFA both in *in vitro* and *in vivo* models of atherosclerosis [93]. It is known that alimentary ω3 PUFA (docosahexaenoic and eicosapentaenoic acids, which are the main components of fish oil) mediate powerful anti-inflammatory effects via inhibiting the activity of toll-like receptors TLR2/3/4 and tumor necrosis factor alpha (TNF-α) by way of FFAR4 receptor. Dihomo-γ-linolenic acid (20:3ω6) has anti-inflammatory properties and can reduce the development of atherosclerosis [94]. The anti-inflammatory effect of dihomo-γ-linolenic acid is due to its impact on the production of the main proatherogenic cytokines IFN-γ, IL-1β and TNF-α, as well as on the expression of proinflammatory genes; and also due to its influence on monocyte migration controlled by chemokines, formation of foam cells, and effect on reducing proliferation of endothelial cells and improvement of mitochondrial function. This highlights the potential of dihomo-γ-linolenic acid in the prevention and treatment of atherosclerosis. Leveling inflammation with this fatty acid may be a safer option than blocking cytokine activity with monoclonal antibodies.

At the same time, data appeared that ω6 and ω3 PUFA affect signaling in the BDNF synthesis pathway; accordingly, studying the activity of this factor is currently extremely important. For example, the results of the study by D. Sugasini et al. demonstrated that BDNF levels in blood plasma, compared with omega-3 index, were more reliable as a biomarker for evaluating the effectiveness of ω3 PUFA supplements in improving brain function [95].

The intake of α-linolenic acid (ALA; 18:3ω3) by healthy people for a week led to an increase in the level of BDNF [13]. The results of the study by A. Gyorkos et al. demonstrated a short-term beneficial effect of diet on blood content of BDNF. BDNF was inversely correlated with a percentage of the body fat ($R=-0.35$, $P<0.05$); levels of glucose ($R=-0.64$, $p<0.05$) and triglycerides ($R=-0.55$, $p<0.05$); and sensitivity to insulin ($R=-0.25$, $p<0.05$) [96]. The results of the study by M. Glud et al. showed that diet and/or exercise interventions aimed at weight loss significantly reduced BDNF levels [97]. However, the authors discovered that BDNF levels declined as a result of diet or a combination of diet and exercise in women, and only as a result of exercise in men. This finding suggested that changes in BDNF levels depended not only on methods aimed at weight loss, but on gender as well. Overall, men have a higher prevalence of atherosclerosis, while women exhibit a worse prognosis with more symptoms [98].

D. Kotlega et al. analyzed the relationship between the level of FFA and eicosanoids with BDNF activity in patients with ischemic stroke [13]. They established that dihomo-γ-linolenic acid was directly related to the level of BDNF [13].

Hence, the levels of ω6 and ω3 PUFA affect the production of proinflammatory and anti-inflammatory molecules and signaling in the BDNF synthesis pathway, which, accordingly, may increase the risk of development and progression of coronary artery atherosclerosis.

Conclusion

Coronary artery disease is among the global issues of our time. The organic cause of impaired blood flow in the coronary arteries in this pathology is atherosclerosis. In this review, we attempted to summarize current insights on the role of immune and neurogenic inflammation in the pathogenesis of coronary artery atherosclerosis. Currently, the immunometabolic basis of atherosclerosis pathogenesis, along with involvement of perivascular adipose tissue in the development of this pathology, are widely discussed.

Neurotrophic growth factors control the functioning of the immune and nervous systems, balance energy metabolism, affect vascular homeostasis, and are also involved in the initiation and resolution of inflammation. There are data on the role of BDNF in the pathogenesis of cardiovascular diseases. It is known that perivascular adipose tissue plays one of the important roles in the pathogenesis of the development of atherosclerotic vascular lesions due to its ability to respond to atherogenic stimuli via developing inflammatory reactions. PVAT excretes factors regulating vascular function, adipokines, cytokines, and neurotrophic factors. This fact suggests that local changes in BDNF signaling may contribute to the development of atherosclerosis.

The relationship between the level of polyunsaturated fatty acids consumption and the development of atherosclerotic lesions in large vessels is well known. The level of BDNF is directly related to the level of free fatty acids and eicosanoids. It has been shown that ω6 and ω3 PUFA affect signaling in the BDNF synthesis pathway and, accordingly, the risk of development and progression of coronary artery atherosclerosis.

Based on the analysis of various published data, we propose a significant role of neurotrophins in the pathogenesis of atherosclerosis, and the necessity of further research in this direction. Detailed examination of the role of PUFA and their inflammatory metabolites in BDNF metabolism would allow us identifying new targets for the treatment of cardiovascular disorders, such as CAD.

Conflict of interest

We declare that we have no conflicts of interest.

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