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Brain-derived Neurotrophic Factor: Significance in the Physiology and Pathology of the Cardiovascular System

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ABSTRACT

The lecture provides an analysis of literature data on the role of brain-derived neurotrophic factor (BDNF) in the development and functioning of the cardiovascular system and its involvement in the heart and blood vessels pathogenesis. The information is structured according to the multifunctional properties and effects of BDNF allowing for the BDNF to be considered as a therapeutic target for attenuating myocardial dysfunction and restoring cardiac function during ischemia/reperfusion.

The lecture contains data on the ability of neurokine to exert a cardioprotective effect by activating angiogenesis and neovascularization of ischemic myocardial tissue via increasing endotheliocyte viability. It is known that vegetative tone is the most important indicator of the state of the cardiovascular system. The nature of BDNF affecting the activity of sympathetic and parasympathetic neurons is yet to be determined. However, the current prevailing view is that BDNF regulates heart rate by enhancing parasympathetic activity of the brainstem structures. Based on experimental and clinical data, the prospects for the use of neurokine analogs in cardiology practice are considered.

Keywords*:* brain-derived neurotrophic factor, heart, blood vessels, angiogenesis, cardioprotection, autonomic regulation of heart

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Нейротрофический фактор мозга: значение в физиологии и патологии сердечно-сосудистой системы

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РЕЗЮМЕ

В лекции проведен анализ литературных данных о роли нейротрофического фактора мозга (BDNF) в развитии и функционировании сердечно-сосудистой системы и его участии в патогенезе сердца и сосу-

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дов. Информация структурирована в соответствии с многофункциональными свойствами и эффектами BDNF, позволяющими рассматривать нейротрофический фактор мозга в качестве терапевтической мишени для ослабления миокардиальной дисфункции и восстановления деятельности сердца при ишемии/реперфузии.

Приведены данные о способности нейрокина оказывать кардиопротекторное действие посредством активации ангиогенеза и неоваскуляризации ишемизированной ткани миокарда путем повышения жизнеспособности эндотелиоцитов. Известно, что вегетативный тонус является важнейшим показателем состояния сердечно-сосудистой системы. Вопрос о характере влияния нейротрофического фактора мозга на активность симпатических и парасимпатических нейронов остается открытым. Однако в настоящее время преобладает мнение о том, что BDNF регулирует частоту сердечных сокращений, усиливая парасимпатическую активность стволовых структур головного мозга. На основании экспериментальных и клинических сведений рассматриваются перспективы применения аналогов нейрокина в кардиологической практике.

Ключевые слова: нейротрофический фактор мозга, сердце, сосуды, ангиогенез, кардиопротекция, вегетативная регуляция сердца

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

The key representative of the neurotrophin/neurokine family is brain-derived neurotrophic factor (BDNF) [1, 2]. The scientific literature provides extensive information on the neuroprotective effects of BDNF including its positive influence on the growth, development, and regeneration of the nervous system. There is substantial evidence that, in addition to regulating neuroplasticity, BDNF is involved in the pathogenesis of many immune, inflammatory, and metabolic reactions in the body [3–5]. Neurotrophin acts through tyrosine kinase receptors associated with tropomyosin-related kinase (TrkB-type) receptors, which are also synthesized in non-neuronal tissues [3–5], including the heart and blood vessels [6].

Studying the role of BDNF in the physiology and pathology of the cardiovascular system is of particular interest due to its involvement in nervous regulation of heart function [7–10]. It is known that TrkB-type BDNF receptors are localized in neurons of the hypothalamus and brainstem, where the control centers of the cardiovascular system are situated [11, 12]. Neurokine also influences the development and metabolism of the sympathetic nervous system (SNS), acting as a trophic factor and regulator of cardiac nerve growth and axon branches [13]. Accordingly, alterations in sympathetic regulation of cardiac activity may be associated with dysfunctions in BDNF signaling mechanisms [6]. Evidence suggests that BDNF modulates heart rate by enhancing parasympathetic activity within brainstem structures [14].

In many cases, disorders or alterations in BDNF synthesis are associated with cardiovascular diseases, such as high blood pressure (BP), arrhythmias, myocardial infarction (MI), and atherogenesis [6]. An analysis of recent scientific data indicates that BDNF plays a fundamental role in assessing the risk of cardiovascular diseases, since lower concentrations of BDNF are often linked to these conditions [15].

The lecture focuses on the analysis of data regarding the role of BDNF in the physiology and pathology of the cardiovascular system, highlighting its potential as a promising therapeutic target for reducing myocardial dysfunction and restoring cardiac activity.

THE ROLE OF THE BDNF/TRKB AXIS IN THE PHYSIOLOGY OF THE HEART AND BLOOD VESSELS

BDNF is directly involved in the formation and development of the cardiovascular system during the prenatal period [1, 16]. Primarily, this pertains to BDNF's role in angiogenesis: increased expression of BDNF/TrkB receptors occurs in the coronary artery endothelium [1], contributing to capillary development in heart tissue during late pregnancy [17–19]. During embryogenesis, neurotrophin participates in forming the coronary vessel wall through direct angiogenic action on endothelial cells expressing tropomyosin receptor kinase B (TrkB) [1]. BDNF deficiency leads to endotheliocyte apoptosis, a lack of significant intramyocardial blood vessels, ventricular wall hemorrhage, atrial septal defects, decreased cardiac contractility, and early postnatal death in mice [20–23].

The critical role of neurotrophin in cardiac physiology is confirmed by pioneering experiments conducted by a large group of Chinese researchers [24]. These studies involved cardiomyocytes from the developing mouse heart with suppressed BDNF expression under the control of the myosin heavy chain 6 (MYH6) promoter. It was found that removing BDNF from cardiomyocytes did not affect heart growth and development. However, subsequent pathological changes were observed in young animals, including cardiomyocyte death, myocardial degeneration, thrombosis of the left atrial appendage, reduced cardiac function, increased inflammation, and reactive oxygen species (ROS) generation, as well as metabolic disturbances [24].

Furthermore, suppression of BDNF expression at the stage of cardiomyocyte development impaired regenerative processes after MI in hearts of adult animals. The authors concluded that BDNF synthesized in cardiomyocytes is essential for maintaining structural and functional integrity of adult cardiac muscle and for regeneration following MI [24].

During embryogenesis, BDNF stimulates the development of the cholinergic phenotype in autonomic brainstem neurons and enhances their viability [14]. Its involvement in the neurogenesis of sensory and sympathetic neurons has also been demonstrated [25, 26].

In adult mammals, BDNF participates in the autonomic regulation of cardiac activity and exhibits significant angiogenic and angioprotective effects [1, 22, 23]. M. Cefis et al. provided evidence that endothelial-derived BDNF functions as a nitric oxide-dependent autocrine factor produced by endothelium that influences the vessel wall condition [27]. Research by B.L.Wang et al. showed that rats engaged in regular physical activity exhibited increased myocardial angiogenesis and improved cardiac function; these effects were attenuated by the BDNF K252a blocker [28].

Experiments involving BDNF microinjections into the subfornical organ of rats revealed a significant decrease in blood pressure without notable changes in heart rate [7], suggesting that this brain region is a site where circulating BDNF can influence the cardiovascular system state [7]. However, direct involvement of BDNF in blood pressure regulation has been demonstrated [29] at the level of catecholaminergic signaling between neurons of the nucleus tractus solitarius and the paraventricular hypothalamic nuclei (PVN).

The authors observed decreased sensitivity of PVN neurons to inhibitory beta-adrenergic hypotensive input from the nucleus tractus solitarius — a phenomenon attributed to BDNF-mediated downregulation of β1-adrenergic receptor expression in PVN, resulting in increased blood pressure [29]. Research by N. Feng et al. highlighted BDNF's role in calcium ion (Ca^{2+}) circulation within cardiomyocytes [23]. It was established that myocardial contraction and relaxation mediated by Ca2+/calmodulin-dependent protein kinase II involve this neurokine and TrkB receptors [23].

Experiments on TrkB knockout mice revealed impaired inotropic processes within the heart [23]. The authors believe that the BDNF/TrkB signaling pathway includes a previously unrecognized mechanism whereby the peripheral nervous system directly influences myocardial function alongside beta-adrenergic control. In hippocampal neuron cultures, activation of the BDNF–TrkB complex via PLCγ/IP3 signaling led to increased intracellular calcium levels [30]. This calcium rise promotes myosin II activation and facilitates translocation of cytoplasmic protein Drp1 (dynamin-related protein 1) from cytoplasm to mitochondria, accelerating mitochondrial fission and ATP synthesis [30].

Furthermore, binding of BDNF to its TrkB receptor activates PI3K and Akt kinases within the brain [31], leading to mechanistic target of rapamycin (mTOR) activation — a key regulator of cell growth and metabolism. The latter stimulates translation of mRNAs encoding glucose transporter GLUT3 and monocarboxylate transporter 2, thereby enhancing cellular uptake of glucose and lactate [31]. Based on these findings, the authors assume that a similar mechanism may operate in cardiomyocytes, where activation of downstream signaling pathways by the BDNF–TrkB complex promotes mitochondrial fission and ATP production, supporting energy supply to cardiomyocytes and exerting a protective effect on the heart [30].

Thus, these data support the notion that neurokine BDNF largely governs processes related to heart and vascular system development and functioning. Its key effects include angiogenic and angioprotective actions, improved energy supply to cardiomyocytes, participation in maintaining intracellular homeostasis of calcium ions, ultimately contributing to enhanced cardiac contractility.

The main aspects of BDNF's multifunctional activity under cardiovascular pathology are discussed further in subsequent sections.

THE ROLE OF BDNF IN THE PATHOLOGY OF THE CARDIOVASCULAR SYSTEM

Numerous data indicate that BDNF plays a significant role not only in physiological processes but also in the pathology of the cardiovascular system [2, 30]. The BDNF/TrkB complex is known to be expressed within the cardiovascular system and is closely associated with the development and outcomes of cardiovascular diseases (CVD) including coronary heart disease, heart failure, cardiomyopathy, hypertension, and metabolic disorders [32]. In this regard, considerable efforts by researchers are focused on studying the contribution of BDNF to the pathogenesis of heart diseases and exploring the potential use of neurokine analogs in cardiological practice [2, 30].

CORONARY HEART DISEASE

Endothelial dysfunction is considered as an initiating factor in the formation of atherosclerotic lesions and is associated with all stages of atherosclerosis. The vascular endothelium lines the luminal surface of blood vessels and functions as a physical barrier that regulates the movement of plasma proteins and circulating cells through the blood vessel. Dysfunction of this barrier leads to lipoprotein leakage and extravasation of monocytes into the vascular walls, thereby accelerating atherosclerosis [33]. ROS play a crucial role in the pathogenesis of coronary artery disease and plaque instability [34].

Studies by J. Ejiri et al. have shown that macrophages, smooth muscle cells, and fibroblasts are the main sources of BDNF within human atherosclerotic plaques [34]. In this context, BDNF can contribute to plaque instability due to its ability to induce oxidative stress and promote superoxide radical formation [34–36] by activating the NAD(P)H oxidase system in coronary vessels [34]. Elevated BDNF levels in coronary vessels are also associated with platelet activation and an inflammatory response [2, 37]. Consequently, increased neurotrophin levels may exacerbate this pathology under these conditions.

However, other studies have found that plasma BDNF concentrations are inversely correlated with levels of triglycerides, LDL cholesterol, and fibrinogen [2, 38]. Interestingly, plasma BDNF levels have been identified as an independent predictor of both coronary and overall mortality [2]. Furthermore, serum BDNF concentrations in patients with coronary heart disease have been linked to inflammatory biomarkers, such as soluble P-selectin and procoagulant platelets [37].

Experimental studies demonstrate that mice lacking BDNF exhibit impaired survival of coronary artery and capillary endotheliocytes, whereas overexpression of BDNF in cardiac tissues promotes increased capillary density [19]. There are reports indicating that BDNF levels decrease in blood samples from patients with acute coronary syndrome [2, 39].

Finally, according to H. Jiang et al., activation of TrkB receptors can stimulate vascular endothelial cadherin synthesis and restore endothelial barrier integrity during atherogenesis in coronary heart disease [20].

Thus, most authors agree about the protective role of BDNF in coronary heart disease, while elevated serum BDNF levels are associated with a reduced risk of coronary heart disease and mortality [36, 38, 40, 41].

ISCHEMIC INJURIES AND MYOCARDIAL INFARCTION

It is well established that myocardial ischemia/reperfusion (I/R) injury manifests primarily through cardiomyocyte necrosis and apoptosis, reperfusion-induced contractile dysfunction of the heart, arrhythmias, and endothelial dysfunction of the coronary artery, which can lead to incomplete restoration of coronary perfusion [42, 43]. Signaling pathways associated with BDNF play a crucial role in cardioprotection mechanisms during the development of myocardial infarction or hypoxia accompanied by reoxygenation [44].

P. Hang et al. demonstrated that BDNF significantly inhibited cardiomyocyte apoptosis by upregulating the expression and activity of Bcl-2 and decreasing the expression and activity of caspase-3 in ischemic myocardium [45]. In another study, P. Hang et al. also demonstrated that BDNF exerted a cardioprotective effect by reducing the pro-apoptotic influence of miRNA-195 in rat cardiomyocytes following myocardial ischemia/reoxygenation [46].

Recent studies indicate that TrkB receptor expression in myocardial cells decreases after cardiac ischemia, with BDNF binding to another subtype of NT receptors, p75NTR [30]. Under hypoxic conditions, BDNF activates p75NTR and converts it into the TrkB receptor, thereby promoting myocardial cell proliferation. Reactivation of p75NTR after hypoxia enhances BDNF activity. Consequently, increased BDNF expression under hypoxic conditions can be achieved through p75NTR activation [30]. The authors conclude that BDNF protects the heart, likely by suppressing apoptosis through reduced expression of caspase-3 and cleaved caspase-9 [30].

The anti-apoptotic effect of the neurotrophic factor was confirmed by other Chinese researchers in experiments involving a model of left coronary artery occlusion in rats [47]. These researchers succeeded in stimulating BDNF synthesis by upregulating sirtuin deacetylase 1 (SIRT1), which ultimately improved cardiac inotropic function and decreased cardiomyocyte apoptosis [47].

It has been established that BDNF promotes neovascularization in ischemic tissue by recruiting endotheliocytes [48]. Mice lacking BDNF exhibit high mortality in postnatal ontogenesis due to impaired endothelial adhesion, accompanied by numerous hemorrhages in cardiomyocytes [3], which indicates BDNF's involvement in angiogenic processes [21]. Some authors suggest that BDNF's pro-angiogenic role is realized through two mechanisms: (a) local activation of TrkB receptors expressed on endotheliocytes; and (b) involvement of bone marrow-derived cells that facilitate neovascularization [1, 21, 48].

Thus, BDNF activates factors that stimulate cardiomyocyte survival and angiogenesis following MI [21, 22]. Both *in vitro* and *in vivo* models have demonstrated that BDNF triggers anti-ischemic protective mechanisms in the myocardium via signaling pathways involving vascular endothelial growth factor [21, 49], protein kinase B (Akt) [50], transient receptor potential channels (TRPC) [42, 51], and macrophage activation [19, 52].

Studies have shown that exogenous delivery of BDNF improves angiogenesis and enhances contractile function of the left ventricle [22]. It has been observed that myocardial BDNF levels decrease in models of heart failure in mice and humans with heart failure [53]. According to these researchers, mice with TrkB receptor knockouts exhibit a reduced adaptive cardiac response to exercise, accompanied by diminished activation of transcription factor networks that regulate mitochondrial biogenesis and metabolism, including the coactivator of the 1-alpha gamma receptor PGC-1a [53].

Following pathological stress, such as transaortic constriction (TAC), mice with the *cTrkB* gene knockout experienced progression of heart failure. Additionally, these scientists observed a decrease in PGC-1α levels in *cTrkB* knockout mice, which is one of the key regulators of mitochondrial biogenesis in striated muscles [53]. Consequently, under conditions of physical exertion or stress (TAC), there is a significant reduction in energy supply processes to the heart in experimental animals lacking the *cTrkB* gene. Furthermore, these researchers identified that BDNF induced an increase in PGC-1α and bioenergetic levels via a novel signaling pathway involving the pleiotropic transcription factor Yin Yang 1 [53].

Further studies confirm that BDNF plays a crucial role in regulating cellular energy in an ischemic heart [53, 54]. The findings of another research team also suggest that neurotrophic factor can improve the condition of ischemic myocardium by reducing mitochondrial dysfunction in cardiomyocytes and thereby increasing ATP production [54]. As an *in vitro* model of mitochondrial dysfunction, P. Hang et al. employed rotenone (Rot), a specific inhibitor of mitochondrial respiratory complexes.

They found that the neurotrophic factor mimetic 7,8-dihydroxyflavone (7,8-DHF) dose-dependently prevented Rot-induced cell death [54]. In this context, treatment with 7,8-DHF resulted in decreased lactate dehydrogenase release and mitochondrial ROS production, as well as restoration of mitochondrial membrane potential [54]. The authors suggest that one possible molecular mechanism underlying the mitoprotective effect of 7,8-DHF involves a signaling pathway mediated by the cardiomyocyte protein p-STAT3 [54]. In experiments conducted by the same team of Chinese scientists, the mitoprotective effects of neurotrophic factor analogs – 7,8-DHF and 7,8,3’-trihydroxyflavone (THF) – were demonstrated on another model of mitochondrial dysfunction [55]. Collectively, these data suggest that BDNF plays a vital role in regulating cellular energy in an ischemic heart [53–55].

Italian researchers conducted experiments to investigate the effects of ischemia on cardiomyocytes in wild-type mice knocked out by both the β_3-adrenergic receptor gene and the *BDNF* gene. They found that in wild-type hearts, BDNF levels sharply decreased four weeks after MI, coinciding with the development of left ventricular (LV) dysfunction and impaired angiogenesis. The administration of the LM22A-4 TrkB receptor agonist in BDNF knockout animals attenuated the progression of LV dysfunction and impaired angiogenesis [56]. The authors also observed that the β_3-adrenergic receptor agonist BRL-37344 increased BDNF content in cardiomyocytes.

Therefore, the use of TrkB receptor agonists may mitigate LV ischemic dysfunction by restoring BDNF levels in the myocardium, and stimulation of the heart’s β_3-adrenergic receptors represents a potential strategy to prevent chronic post-ischemic heart failure through upregulation of BDNF [56].

There are isolated reports indicating the antiarrhythmic effect of neurotrophin [57, 58]. The authors observed a significant reduction in the average monthly duration of atrial fibrillation (AF) episodes – by more than sixfold – following administration of a low dose of BDNF [58]. In the study by F. Rahman et al., a correlation was identified between low BDNF concentrations and risk factors for AF [57].

Thus, a substantial body of evidence suggests that BDNF plays a protective and beneficial role in ischemia–reperfusion injury and/or MI. However, the opposite activity of neurokine in some experimental models remains unexplained [51].

THE ROLE OF BDNF IN SYMPATHETIC AND PARASYMPATHETIC REGULATION OF HEART RHYTHM

The rostral ventrolateral medulla (RVLM) is a key integrative region involved in heart rate regulation, containing sympatho-excitatory neurons that play a crucial role in modulating sympathetic nerve activity [59]. These sympatho-excitatory neurons tonically regulate the activity of sympathetic neurons by transmitting excitatory signals to preganglionic sympathetic neurons located in the intermediolateral cell column of the spinal cord [59].

It has been demonstrated that BDNF is expressed in several neural groups within this pathway, indicating its potential role in cardiovascular regulation [60]. The neurotrophic factor is involved in the development and functioning of the arterial baroreceptor system [61], and its injection into the RVLM results in increased blood pressure [60]. Additionally, BDNF and its TrkB receptors are localized in neurons within the hypothalamus and brainstem, regions that house autonomic control centers of the cardiovascular system [11, 12, 60].

BDNF is an unusual neurotrophin that acts not only as a classical neurotrophic factor promoting neuronal survival and differentiation but also as a neurotransmitter [60]. Two lines of evidence have been proposed to explain BDNF-dependent synaptic transmission as a key component of heart rate regulation:

Physical exercise and intermittent fasting, which increase BDNF expression in various brain regions

[14, 62], can reduce resting heart rate by enhancing parasympathetic activity [14, 63];

BDNF induces the expression of choline acetyltransferase and promotes the synthesis and release of acetylcholine (ACh) in developing autonomic neurons cultured *in vitro* [14].

Vagal cardioinhibitory preganglionic cholinergic neurons of the brainstem project their axons via the vagus nerve to the heart where they release ACh onto cardiac ganglion cells, thereby reducing heart rate [14]. Vagal preganglionic neurons in the brainstem express the high-affinity TrkB receptor [14] and produce BDNF [14]. A study by R. Wan et al. demonstrated that intracerebroventricular administration of BDNF to haplon-deficient (BDNF+/-) mice enhanced the activity of parasympathetic nuclei in the nucleus ambiguus, resulting in a decreased heart rate. Collectively, these findings suggest that BDNF signaling is essential for normal cardioinhibitory parasympathetic regulation of the heart at rest [14].

Research on bimodal neonatal sympathetic neurons capable of maintaining both adrenergic and cholinergic neurotransmitter status in co-culture with cardiomyocytes [64] has shown that BDNF acting through the panneurotrophin receptor p75NTR induces a rapid switch toward ACh release [64, 65], leading to a slowdown in spontaneous cardiomyocyte contractions [14]. Sympathetic neurons express TrkA and Trkc receptors, which are not activated by BDNF and do not express BDNF-specific TrkB; instead, they express p75NTR [66]. It appears that BDNF functions as an agonist for p75NTR in sympathetic neurons [66].

It is also noteworthy that BDNF likely influences neurons providing glutamatergic or GABAergic input to the CNS. Indeed, BDNF enhances glutamate release from presynaptic terminals of hippocampal and visual cortex neurons [14], and modulates activity in GABAergic synapses [14]. These findings highlight a novel background and potential role for altered BDNF signaling in disorders associated with autonomic dysregulation. Accordingly, mice with Huntington's disease mutations exhibit increased heart rates associated with a significant decrease in brainstem BDNF levels [14]. Elevated BDNF levels have also been observed in patients with Chagas disease, a phenomenon attributed to both inflammatory processes and cardiac autonomic dysfunction [67].

A group of researchers evaluated the effect of BDNF on the autonomic tone of the heart using heart rate variability (HRV) [68]. A comparative analysis of HRV parameters and serum BDNF levels was performed in patients diagnosed with generalized anxiety disorder (GAD) and healthy individuals. The authors observed a significant decrease in HRV in these patients compared to the control group. Additionally, significantly higher levels of BDNF in blood plasma were detected in healthy individuals relative to patients with GAD at the initial stage of the study [68]. Following pharmacological treatment with paroxetine, an increase in HRV and BDNF levels was noted [68].

Based on our own studies involving 28 healthy volunteers aged 20 to 22 years, HRV indicators also demonstrate a close relationship with blood plasma levels of BDNF. A statistically significant negative correlation was established between BDNF content and the absolute power of the VLF parameters. This finding may serve as evidence of the cerebral ergotropic effects of neurotrophin on underlying autonomic regulation and suggests a relationship between BDNF content in blood plasma, psychoemotional stress, and the functional state of the cerebral cortex.

The NT content in tissues innervated by the SNS changes with age, and these changes are associated with altered sympathetic function during heart diseases [66]. There is evidence that nerve growth factor (NGF) and BDNF exert functionally antagonistic effects on sympathetic neuron growth. BDNF has been shown to inhibit sympathetic nerve growth via p75NTR [69] and is necessary for normal programmed cell death and regulation of neuronal numbers during development [70]. Additionally, BDNF promotes local axonal degeneration and suppresses NGF-stimulated TrkA signaling *in vitro* [70].

CONCLUSION

Neurotrophins have been extensively studied in relation to their effects on the development and functioning of the nervous system and have historically been investigated exclusively within the field of neuroscience. In the lecture, we focused on highlighting the significance of the most well-studied representative of this class of neurokines, BDNF, in maintaining a cardiovascular phenotype and homeostasis. We discussed the multifunctional properties of BDNF and its potential role in conditions characterized by resistance or heart failure.

Beyond its critical role in neurobiology, increasing evidence suggests that BDNF is also involved in the development and pathophysiology of the cardiovascular system. It is known that BDNF promotes cardioprotection by activating angiogenesis and neovascularization in ischemic tissue through the recruitment of endotheliocytes and regulation of their survival. Studies have demonstrated that BDNF and its receptors are expressed in various tissues, including the heart, endothelium, macrophages, vascular smooth muscle cells, and atherosclerotic coronary arteries [6, 53, 71, 72].

According to R. Samal et al., BDNF-mediated effects are not limited solely to neurons or endotheliocytes but can also exert regulatory influence on cardiac progenitor cells, promote cardiac recovery, and mitigate myocardial dysfunction [16]. Over the past decade, cell therapy has emerged as a potential alternative approach. Data indicate that a subset of undifferentiated progenitor cells resides in the adult heart and can stimulate regeneration of damaged myocardium, thereby offering new opportunities for endogenous heart repair mechanisms [16]. Additionally, circulating BDNF has been identified as a promising biomarker for both the diagnosis and prognosis of cardiovascular disease (CVD) [32].

Therefore, further research on neurotrophins is essential to develop new effective therapeutic strategies for the treatment and prevention of cardiovascular diseases.

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