Přehledový článek | Review article

Neuregulin-1 and Cardiovascular Diseases

Lutfu Askin[a], Yahya Urkmez[b], Hakan Ozerol[c]

[a] *Department of Cardiology, Gaziantep Islamic Science and Technology University, Gaziantep, Turkey*
[b] *Department of Internal Medicine, Gaziantep City Hospital, Gaziantep, Turkey*
[c] *Department of Emergency Medicine, Gaziantep City Hospital, Gaziantep, Turkey*

ARTICLE INFO

Article history:
Submitted: 21. 2. 2025
Accepted: 24. 3. 2025
Available online: 1. 12. 2025

Klíčová slova:
Funkce levé komory
Kardiovaskulární onemocnění
Neuregulin-1

SOUHRN

Srdeční tkáň exprimuje růstový faktor neuregulin-1 (NRG-1), s jehož pomocí lze léčit srdeční selhání (heart failure, HF), infarkt myokardu, kardiomyopatie i arytmie. Použití NRG-1 při HF zlepšuje angiogenezi, vznik kardiomyocytů a tlumí fibrotizaci srdečního svalu. Tyto účinky zlepšují fungování komor a omezují na minimum vznik srdečních příhod. Protein NRG-1 snižuje rozsah infarktu myokardu a podporuje regeneraci tkáně. Angiogeneze a tlumení zánětu a fibrotizace v infarzované oblasti účinkem NRG-1 minimalizuje incidenci nepříznivých srdečních příhod. Při kardiomyopatii zlepšuje NRG-1 funkci levé komory srdeční a zpomaluje fibrotizaci srdeční tkáně. NRG-1 moduluje iontové kanály a tlumí zánět a fibrotizaci srdeční tkáně, a snižuje tak riziko arytmií. Léky obsahující NRG-1 vyvíjené pro léčbu kardiovaskulárních onemocnění jsou jistým příslibem, nicméně pro jejich maximální využití je třeba pokračovat ve výzkumu. Nicméně použití NRG-1 v léčbě kardiovaskulárních onemocnění představuje nesmírně zajímavou oblast výzkumu, jehož výsledkem mohou být nová a účinnější léčiva pro tato častá a závažná onemocnění.

Keywords:
Cardiovascular diseases
Left ventricular function
Neuregulin-1

ABSTRACT

Cardiac tissue expresses neuregulin-1 (NRG-1), a growth factor. NRG-1 may treat heart failure (HF), myocardial infarction, cardiomyopathy, and arrhythmias. NRG-1 improves angiogenesis, cardiomyocyte development, and cardiac fibrosis in HF. These effects increase left ventricular function and minimise cardiac events (CE). NRG-1 reduces myocardial infarct size and promotes tissue regeneration. Angiogenesis and reduced inflammation and fibrosis in the infarcted region by NRG-1 minimise the incidence of unfavourable CE. NRG-1 improves left ventricular function and cardiac fibrosis in cardiomyopathy. NRG-1 modulates ion channels and reduces cardiac inflammation and fibrosis to lower arrhythmia risk. NRG-1 modulates ion channels and reduces cardiac inflammation and fibrosis in arrhythmias. NRG-1-based therapeutics for cardiovascular diseases (CVDs) are promising, but further research is required to maximise their usage. However, NRG-1 as a therapeutic target for CVDs is an exciting area of research that may lead to new and better treatments for these common and serious conditions.

Introduction

Neuregulin-1 (NRG-1) is another protein from the neuregulin family that has been extensively studied in relation to cardiovascular disease (CVD). NRG-1 is known to play an essential role in the development and maintenance of the CV system, including the regulation of cardiac function, angiogenesis, and the repair of injured tissues. In animal models of heart failure (HF), NRG-1 administration has been shown to attenuate the progression of HF and improve survival. In humans, NRG-1 levels have been found to be lower in individuals with HF and coronary artery disease (CAD). Furthermore, genetic variations in the NRG-1 gene have been associated with an increased risk of developing CVD.

NRG-1 is a growth factor that stimulates heart, mammary gland, and central nervous system cells. NRG-1, a cardiac regeneration growth factor, interests cardiology. NRG-1 promotes cardiomyocyte proliferation, angiogenesis, extracellular matrix remodelling, stem-cell recruitment, and other cardiac activities. These activities improve myocardial repair and function, suggesting a molecular approach to regeneration.[1,2]

NRG-1 boosts heart cell differentiation, proliferation, and expression. NRG-1 signals adult cardiomyocytes to split and replenish myocardium. Outside of NRG-1, NRG-1

Address: Lutfu Askin, MD, Gaziantep Islamic Science and Technology University, 2700 Gaziantep, Turkey, e-mail: lutfuaskin23@gmail.com
DOI: 10.33678/cor.2025.053

Please cite this article as: Askin L, Urkmez Y, Ozerol H. Neuregulin-1 and Cardiovascular Diseases. Cor Vasa 2025;67:751–757.

stimulates work-related gene expression and cardiomyocyte growth in cardiac conduction system cells. Stem cell differentiation into working-type cardiomyocytes improves cardiac tissue function after pathological damage. In experimental and clinical studies, NRG-1 may heal heart tissue.[3,4] NRG-1 signalling mostly affects the ventricular wall, heart valves, conduction system, and microvasculature.[5] To demonstrate NRG-1's crucial involvement in cardiovascular disease development, we summarise its physiological and pathological activities in cellular and cardiovascular tissues. According to new studies, NRG-1 is involved in atherosclerosis, myocardial infarction (MI), HF, cardiotoxicity, and arrhythmia.

Basic structure of neuregulin-1

NRG-1 is a type of protein that is important for the development and function of the nervous system. It is made up of a large extracellular domain and a smaller intracellular domain. The extracellular domain of NRG-1 contains several domains, including an epidermal growth factor (EGF)-like domain, a transmembrane domain, and a cytoplasmic domain. The EGF-like domain is responsible for binding to its receptor, which is known as ErbB. The intracellular domain of NRG-1 contains several sites for phosphorylation, which is a chemical modification that can alter the activity of proteins. These locations are believed to be crucial for the activation of signalling pathways by NRG-1 binding to ErbB. Overall, the basic structure of NRG-1 is a large protein with an extracellular domain that contains an EGF-like domain and a transmembrane domain and an intracellular domain that contains phosphorylation sites.[6,7] The effect of NRG-1β on multiple NRG-1 isotypes in cardiac microvascular endothelial cells in addition to cardiac myocytes is shown in **Figure 1**.[8]

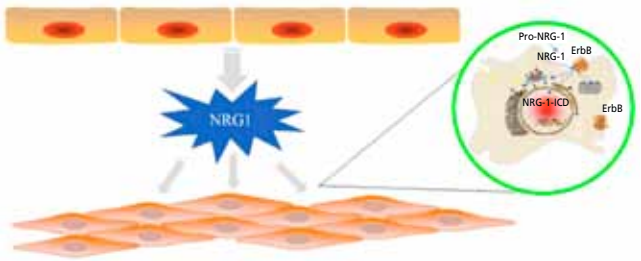

Fig. 1 – Endothelial and cardiomyocyte ErbB proteins activate NRG1. In "reverse signalling", extracellular cleavage releases mature NRG1 and cleaves NRG1-ICD, which travels to the nucleus to regulate gene transcription. In developed cardiomyocytes, NRG1 binds to ErbB3 and ErbB4 ECD and induces conformational changes to improve positive signalling receptor affinity. NRG1 ligand binding homodimerizes ErbB4 and heterodimerizes ErbB2/3, ErbB2/4, and ErbB3/4. Central pathway signalling follows.

Regulation of NRG-1

Post-translational modifications

In "reverse signalling", extracellular cleavage releases mature NRG-1, which is then cleaved by secretase to produce NRG-1 – intracellular structural domains (ICD), which moves to the nucleus to control gene transcription. The heart-expressed pro-NRG-1 transmembrane protein needs protease processing to activate. According to previous investigations, the disintegrin and metalloproteinase (ADAM) family of matrix metalloproteinases (MMPs), notably ADAM17 and ADAM19, release pro-NRG-1 from the endothelium membrane. ADAM17, not ADAM19, releases pro-NRG-1. As the ADAM17-deficient mouse had heart defects in the embryo, other proteins that activate pro-NRG-1 may be involved. Neurohormones (angiotensin II, phenylephrine, and endothelin 1) and mechanical pressure regulate NRG-1 mRNA and protein production. Inhibiting NRG-1 expression stimulates NRG-1 mRNA expression. Recent investigations have demonstrated that when nitric oxide (NO) generation is abolished, endothelial cells increase NRG-1 expression via the paracrine route.[9–11]

NRG-1-ErbB signal pathway

The NRG-1-ErbB signalling pathway is a complex signalling pathway that is involved in various biological processes, including cell proliferation, differentiation, migration, and survival. The ErbB receptors are a family of transmembrane receptor tyrosine kinases that are responsible for activating it. Dysregulation of the NRG-1-ErbB signalling pathway has been implicated in various human diseases, including cancer, schizophrenia, and HF, making it an attractive target for therapeutic intervention.[12–14]

NRG-1-Hippo-YAP pathway

The NRG-1-Hippo-YAP pathway is a signalling pathway that is involved in the regulation of cell growth, proliferation, and survival. The activation of downstream signalling pathways, including the Hippo pathway, results from the binding of the protein NRG-1 to the ErbB receptor. Activation of the NRG-1-Hippo-YAP pathway has been shown to promote cell growth and proliferation in various cell types, including cancer cells. Dysregulation of this pathway has been implicated in the development and progression of several types of cancer, making it an attractive target for cancer therapy.[15–17]

NRG-1-PI3K-AKT pathway

The NRG-1-PI3K-AKT pathway is a signalling pathway that is involved in the regulation of cell growth, proliferation, and survival. The PI3K-AKT pathway and other downstream signalling pathways, including the binding of the protein NRG-1 to the ErbB receptor, activate it. The PI3K--AKT pathway is a conserved signalling pathway that plays a critical role in regulating cell survival, growth, and metabolism. Upon activation, PI3K phosphorylates the membrane phospholipid PIP2 to produce PIP3, which recruits and activates downstream signalling molecules, including AKT. Activation of the NRG-1-PI3K-AKT pathway has been shown to promote cell growth, proliferation, and survival in various cell types, including cancer cells.[18–20]

NRG-1 and atherosclerosis

NRG-1 and cell aging

There is currently limited research on the direct effects of NRG-1 on cell ageing. However, some studies suggest that

the NRG-1-ErbB signalling pathway may play a role in the regulation of cellular senescence, which is a key aspect of cell ageing. Cellular senescence is a process which leads to irreversible growth arrest and altered cellular function. The process is thought to play a critical role in the ageing process and the development of age-related diseases, such as cancer and neurodegenerative disorders. Several studies have shown that the NRG-1-ErbB signalling pathway can regulate the cellular senescence process in various cell types. For example, one study found that the activation of the ErbB2 receptor by NRG-1 can induce cellular senescence in breast cancer cells. NRG-1 can promote the senescence of human cardiac fibroblasts by activating the ErbB2 receptor. Overall, while there is still much to be understood about the role of NRG-1 in cell ageing, current research suggests that it may play a role in regulating cellular senescence and could have potential implications for the development of therapies for age-related diseases.[21,22]

NRG-1 and endothelial cell damage

NRG-1 may play a role in the regulation of endothelial cell damage, which is a key factor in the development and progression of cardiovascular diseases (CVDs) such as atherosclerosis. Damage to these cells can lead to the dysfunction of the endothelium and the development of CVDs. NRG-1 can protect endothelial cells against various forms of damage, such as oxidative stress and inflammation. For example, one study found that NRG-1 can protect endothelial cells against oxidative stress-induced damage by activating the PI3K-Akt signalling pathway. Another study showed that NRG-1 can protect endothelial cells against inflammation-induced damage by inhibiting the NF-kB signalling pathway.[23,24]

NRG-1 and MI

NRG-1 and oxidative stress

NRG-1 can protect cells against oxidative stress-induced damage. For example, one study found that NRG-1 can protect cardiomyocytes against oxidative stress-induced apoptosis by activating the PI3K-Akt signalling pathway. Another study showed that NRG-1 can protect vascular smooth muscle cells against oxidative stress-induced damage by inhibiting the expression of inflammatory cytokines. The protective effects of NRG-1 against oxidative stress-induced damage are thought to be mediated through the activation of the ErbB receptors and downstream signalling pathways. These signalling pathways regulate the expression of genes involved in cell survival, antioxidant defence, and DNA repair. Overall, the ability of NRG-1 to protect cells against oxidative stress-induced damage suggests that it may have potential therapeutic applications in the prevention and treatment of diseases associated with oxidative stress.[25,26]

NRG-1 and myocardial inflammatory injury

NRG-1 can reduce the severity of myocardial inflammation and fibrosis in a rat model of MI. NRG-1 can reduce the expression of inflammatory cytokines and adhesion molecules in cardiac cells treated with lipopolysaccharides, which are known to induce inflammation. In addition to its anti-inflammatory effects, NRG-1 has also been shown to promote the proliferation and differentiation of cardiac progenitor cells, which could potentially aid in the regeneration of damaged heart tissue. Current evidence suggests that it may have protective effects against this condition through its anti-inflammatory and regenerative effects on cardiac cells.[27,28]

NRG-1 and energy metabolism

NRG-1 is involved in energy metabolism via the PI3K-Akt signalling pathway. NRG-1 can increase the expression of genes involved in fatty acid oxidation in adipocytes. In the liver, NRG-1 has been shown to regulate the expression of genes involved in glucose and lipid metabolism. NRG-1 can increase the expression of genes involved in gluconeogenesis and fatty acid oxidation in hepatocytes, which suggests that NRG-1 may play a role in the regulation of hepatic glucose and lipid metabolism. Current evidence suggests that it may have potential therapeutic applications in the treatment of metabolic disorders, such as diabetes and obesity, by modulating glucose and lipid metabolism in various tissues.[29–31]

NRG-1 and cell multiplication

Studies have shown that NRG-1 can promote cell multiplication in various cell types, including neurons, glial cells, and cancer cells. NRG-1 binds to and activates a family of receptors known as ErbB receptors, which are protein tyrosine kinase receptors. The activation of ErbB receptors triggers a signalling cascade that promotes cell growth and division. In addition to promoting cell multiplication, NRG-1 has also been shown to regulate cell survival, migration, and differentiation. The specific effects of NRG-1 on cells depend on various factors, including the type of cells, the isoforms of NRG-1, and the context of the cellular environment. Overall, NRG-1 plays an important role in the regulation of cell multiplication and other cellular processes, and its dysregulation has been implicated in various diseases, including cancer and schizophrenia.[32]

NRG-1 and angiogenesis

Studies have shown that NRG-1 can regulate angiogenesis by promoting the proliferation and migration of endothelial cells, which are the cells that line the inner surface of blood vessels. NRG-1 exerts its angiogenic effects by binding to ErbB receptors on endothelial cells and activating downstream signalling pathways that promote cell proliferation and migration. In addition to promoting angiogenesis, NRG-1 has role in the maintenance and stability of blood vessels. For example, NRG-1 has been shown to enhance the expression of vascular endothelial growth factor (VEGF), a potent angiogenic factor, and to promote the recruitment of pericytes, which are cells that help stabilise blood vessels. The role of NRG-1 in angiogenesis is complex, and its effects on blood vessels depend on various factors, including the isoforms of NRG-1, the context of the cellular environment, and the presence of other angiogenic factors. Nonetheless, NRG-1 is considered a promising target for the development of angiogenesis-based therapies for various diseases, including cancer and cardiovascular disorders.[33]

NRG-1 and ischemia reperfusion

Ischemia-reperfusion injury occurs when blood flow to an organ or tissue is interrupted, leading to a lack of oxygen and nutrients. Reperfusion, which is the restoration of blood flow, can exacerbate tissue damage by triggering a cascade of inflammatory and oxidative stress responses. The protective effects of NRG-1 are thought to be mediated by its ability to modulate various signalling pathways that are involved in cell survival, inflammation, and oxidative stress. For example, NRG-1 can activate the PI3K/Akt pathway, which promotes cell survival and reduces oxidative stress. NRG-1 has also been shown to reduce the expression of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-alpha), and to increase the expression of anti-inflammatory cytokines, such as interleukin-10 (IL-10). In addition to its direct effects on cells, NRG-1 has been shown to promote the recruitment and differentiation of various cell types, including stem cells and immune cells, which can contribute to tissue repair and regeneration following ischemia-reperfusion injury. Overall, the protective effects of NRG-1 against ischemia-reperfusion injury make it a promising therapeutic target for the prevention and treatment of various diseases, including MI, stroke, and organ transplantation.[34–36]

NRG-1 and HF

NRG-1 with myocardial hypertrophy and myocardial fibrosis

NRG-1 has been shown to have potential therapeutic effects in the context of myocardial hypertrophy and fibrosis. NRG-1 can attenuate the pathological hypertrophic response of the heart to various stimuli, including pressure overload and ischemia-reperfusion injury. The cardioprotective effects of NRG-1 are thought to be mediated by its ability to activate the ErbB family of receptors, which are expressed on cardiomyocytes, fibroblasts, and endothelial cells in the heart. Activation of ErbB receptors by NRG-1 can stimulate various signalling pathways that promote cell survival, inhibit apoptosis, and modulate the expression of genes involved in hypertrophy and fibrosis. In addition to its direct effects on cardiomyocytes and fibroblasts, NRG-1 has been shown to modulate the activity of immune cells, including macrophages and T cells, which can contribute to the development of myocardial fibrosis.[37,38]

NRG-1 with left ventricular function

NRG-1 has potential therapeutic effects on left ventricular function in the context of these diseases. NRG-1 has been shown to stimulate the growth and survival of cardiomyocytes, the cells that make up the majority of the left ventricle. In addition, NRG-1 has been shown to have anti-apoptotic effects on cardiomyocytes, which can contribute to the preservation of left ventricular function. Furthermore, NRG-1 has been shown to enhance angiogenesis in the heart, which can improve blood flow to the left ventricle and promote tissue repair and regeneration. NRG-1 has also been shown to modulate the activity of immune cells in the heart, which can contribute to the development of left ventricular dysfunction. In animal studies, administration of NRG-1 has been shown to improve left ventricular function in various models of HF and MI. However, the clinical efficacy of NRG-1-based therapies in humans remains to be fully established, and further studies are needed to optimise the use of NRG-1 for the treatment of left ventricular dysfunction.[39]

NRG-1 and cardiotoxicity

Cardiotoxicity is a side effect of many chemotherapeutic agents, including anthracyclines, which are commonly used to treat various types of cancer. Cardiotoxicity can lead to impaired cardiac function, HF, and other adverse cardiac events (CE), which can limit the use of these drugs and compromise the overall effectiveness of cancer treatment. NRG-1 has been shown to have potential cardioprotective effects against chemotherapy-induced cardiotoxicity. NRG-1 can attenuate the cardiotoxic effects of anthracyclines by promoting the survival and regeneration of cardiomyocytes as well as reducing oxidative stress and inflammation in the heart. The cardioprotective effects of NRG-1 are thought to be mediated by its ability to activate the ErbB family of receptors, which are expressed on cardiomyocytes, fibroblasts, and endothelial cells in the heart. Activation of ErbB receptors by NRG-1 can stimulate various signalling pathways that promote cell survival, inhibit apoptosis, and reduce oxidative stress and inflammation.[40]

NRG-1 and arrhythmia

NRG-1 has been shown to have potential anti-arrhythmic effects by modulating various signalling pathways and ion channels in the heart. NRG-1 can modulate the activity of ion channels that are involved in the generation and propagation of electrical signals in the heart, including the inward rectifier potassium channel (Kir2.1) and the L-type calcium channel (LTCC). NRG-1 has been shown to increase the activity of Kir2.1 channels, which can stabilise the resting membrane potential and reduce the likelihood of abnormal electrical activity in the heart. NRG-1 has also been shown to reduce the activity of LTCCs, which can reduce calcium overload and the risk of arrhythmias. In addition to its effects on ion channels, NRG-1 has been shown to have anti-inflammatory and anti-fibrotic effects in the heart, which can reduce the risk of arrhythmias associated with inflammation and fibrosis.[8]

Recent studies

Haller et al.[41] found that MI may independently impact NRG-1. Fibrin and NRG-1 may be viable MI treatments.[42] Right ventricular pressure load (RV-PL) expansion momentarily boosts cardiomyocyte cell cycle activity (CCA). CCA stimulation improves cardiac function and delays fibrosis. CCA stimulation increases RV adaptation to PL in the postnatally growing heart and may help congenital heart dise-

ase patients retain RV function.[43] In a male mouse model of ischemic stroke, NRG-1 restores neuronal proliferation, differentiation, and oligodendrogliogenesis to improve acute and long-term neurological functioning.[44]

HF with preserved ejection fraction (HFpEF) patients exhibited elevated NRG-1β. NRG-1β levels predicted hospitalisation for decompensated chronic HF.[45] Shakeri et al. found that endothelium-derived NRG-1 can compensate for cardiac and kidney endothelial nitric oxide synthase (eNOS) impairment.[46] During cardiac pressure overload, left atrial ETS translocation variant 1 (ETV1) downregulation causes electrical and structural remodelling.[47] NRG-1 may enhance energy metabolism after MI by stimulating cardiac ErbB4 receptor phosphorylation.[48] Plasma NRG-1 increases coronary collateral circulation in CAD patients. NRG-1 independently and consistently predicted good CC development and may reduce myocardial ischemia damage.[49] Vascular dementia (VaD) patients had elevated blood NRG-1, which may be an independent risk factor for cognitive impairment.[50] The main topic points of recent studies were shown in **Table 1**.

Conclusion

NRG-1 is a growth factor that is expressed in various tissues, including the heart. NRG-1 has been shown to have potential therapeutic effects on various CVDs, including HF, MI, cardiomyopathy, and arrhythmias. In HF, NRG-1 stimulate the growth and survival of cardiomyocytes, as

Table 1 – The main topic points of recent studies

Reference no.	Authors	Subjects	Main theme
2	Arora et al.	Mice	A novel explant culture method maintains three-dimensional newborn mouse hearts and mammals neonatal cardiac regeneration *ex vivo*. Epicardial cells multiply and move to the injury site, recruiting putative cardiomyocytes.
12	Ding et al.	Rats	PI3K-AKT-mTOR pathway transdifferentiation of reactive astrocytes to oligodendrocytes by Nrg1 heals SCI. Remyelination using NRG-1 may repair spinal cords.
25	Haller et al.	Patients with ST-elevation myocardial infarction	MI may independently impact NRG-1. Additional extensive clinical trials are necessary to elucidate this hypothesis.
38	De Keulenaer et al.	Heart failure patients	Due to the intricacy of pathways and the difficulty of generating tyrosine kinase receptor medicines (proteins, peptides, small molecules, and RNA-based therapies), NRG-1's compensatory and positive effects on heart failure are difficult to convert into therapies.
41	Haller et al.	Patients with ST-elevation myocardial infarction	MI may independently impact NRG-1. Fibrin and NRG-1 may be viable MI treatments.
42	Chang et al.	Patients with myocardial infarction	Fibrin and NRG-1 may be viable MI treatments.
43	Bossers et al.	Rats	Right ventricular pressure load (RV-PL) expansion momentarily boosts cardiomyocyte cell cycle activity (CCA). CCA stimulation improves cardiac function and delays fibrosis.
44	Cui et al.	A male mouse model	In a male mouse model of ischemic stroke, NRG-1 restores neuronal proliferation, differentiation, and oligodendrogliogenesis to improve acute and long-term neurological functioning.
45	Zhbanov et al.	Heart failure patients with preserved ejection fraction	HF with preserved ejection fraction (HFpEF) patients exhibited elevated NRG-1β. NRG-1β levels predicted hospitalisation for decompensated chronic HF.
46	Shakeri et al.	Mice	Endothelium-derived NRG-1 can compensate for cardiac and kidney endothelial nitric oxide synthase (eNOS) impairment.
47	Yamaguchi et al.	Patients who underwent cardiac surgery	During cardiac pressure overload, left atrial ETS translocation variant 1 (ETV1) downregulation causes electrical and structural remodelling.
48	Wang et al.	Rats	NRG-1 may enhance energy metabolism after MI by stimulating cardiac ErbB4 receptor phosphorylation.
49	Huang et al.	Patients with coronary artery disease	Plasma NRG-1 increases coronary collateral circulation in CAD patients. NRG-1 independently and consistently predicted good CC development and may reduce myocardial ischemia damage.
50	Wang et al.	Vascular dementia patients	Vascular dementia (VaD) patients had elevated blood NRG-1, which may be an independent risk factor for cognitive impairment.

well as enhance angiogenesis and reduce fibrosis in the heart. These effects can improve left ventricular function and reduce the risk of adverse CE (ACE). NRG-1 can also reduce the risk of ACE by enhancing angiogenesis and reducing inflammation and fibrosis in the infarcted area. In cardiomyopathy, NRG-1 may improve left ventricular function and reduce fibrosis in the heart. NRG-1 can also reduce the risk of arrhythmias by modulating ion channels and reducing inflammation and fibrosis in the heart. In arrhythmias, NRG-1 has been shown to have potential anti-arrhythmic effects by modulating ion channels and reducing inflammation and fibrosis in the heart. Despite the promising results from preclinical studies, the clinical efficacy of NRG-1-based therapies in humans remains to be fully established, and further studies are needed to optimise the use of NRG-1 for the treatment of CVDs. However, the potential of NRG-1 as a therapeutic target for CVDs represents an exciting area of research that may lead to new and improved treatments for these common and serious conditions.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding

The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

Ethical statement

The work was written in accordance with the Declaration of Helsinki.

References

1. Lin Y, Liu H, Wang X. Neuregulin-1, a microvascular endothelialderived protein, protects against myocardial ischemia-reperfusion injury (Review). Int J Mol Med 2020;46:925–935.
2. Arora H, Lavin AC, Balkan W, et al. Neuregulin-1, in a conducive milieu with Wnt/BMP/retinoic acid, prolongs the epicardial-mediated cardiac regeneration capacity of neonatal heart explants. J Stem Cells Regen Med 2021;17:18–27.
3. Kundumani-Sridharan V, Subramani J, Owens C, Das KC. Nrg-1β released in remote ischemic preconditioning improves myocardial perfusion and decreases ischemia/reperfusion injury via ErbB2-mediated rescue of endothelial nitric oxide synthase and abrogation of Trx2 autophagy. Arterioscler Thromb Vasc Biol 2021;418:2293–2314.
4. Sun K, Li YY, Jin J. A double-edged sword of immunomicroenvironment in cardiac homeostasis and injury repair. Signal Transduct Target Ther 2021;6:79.
5. Rupert C E, Coulombe KL. The roles of neuregulin-1 in cardiac development, homeostasis, and disease. Biomark Insights 2015;10:1–9.
6. Chou CF, Ozaki M. In silico analysis of neuregulin 1 evolution in vertebrates. Biosci Rep 2010;30:267–275.
7. Yin DM, Chen YJ, Liu S, et al. Calcyon stimulates neuregulin 1 maturation and signaling. Mol. Psychiatry 2015;20:1251–1260.
8. Wang Y, Wei J, Zhang P, et al. Neuregulin-1, a potential therapeutic target for cardiac repair. Front Pharmacol 2022;13:945206.
9. Lemmens K, Doggen K, De Keulenaer GW. Role of neuregulin-1/ErbB signaling in cardiovascular physiology and disease: Implications for therapy of heart failure. Circulation 200;116:954–960.
10. Lemmens K, Fransen P, Sys SU, et al. Neuregulin-1 induces a negative inotropic effect in cardiac muscle: Role of nitric oxide synthase. Circulation 2004;109:324–326.
11. Shakeri H, Gevaert AB, Schrijvers DM, et al. Neuregulin-1 attenuates stress-induced vascular senescence. Cardiovasc Res 2018;114:1041–1051.
12. Ding Z, Dai C, Zhong L, et al. Neuregulin1 converts reactive astrocytes toward oligodendrocyte lineage cells via upregulating the PI3K-AKT-mTOR pathway to repair spinal cord injury. Biomed Pharmacother 2021;134:111168.
13. Kataria H, Alizadeh A, Karimi-Abdolrezaee S. Neuregulin-1/ErbB network: An emerging modulator of nervous system injury and repair. Prog Neurobiol 2019;180:101643.
14. Dugaucquier L, Feyen E, Mateiu L, et al. The role of endothelial autocrine NRG-1/ERBB4 signaling in cardiac remodeling. Am J Physiol Heart Circ Physiol 2020;319:443–455.
15. D'Uva G, Aharonov A, Lauriola M, et al. ERBB2 triggers mammalian heart regeneration by promoting cardiomyocyte dedifferentiation and proliferation. Nat Cell Biol 2015;17:627–638.
16. Dey A, Varelas X, Guan KL. Targeting the Hippo pathway in cancer, fibrosis, wound healing and regenerative medicine. Nat Rev Drug Discov 2020;19:480–494.
17. Zhang Y, Re DD. A growing role for the Hippo signaling pathway in the heart. J Mol Med 2017;95:465–472.
18. Mahiny-Shahmohammady D, Hauck L, Billia F. Defining the molecular underpinnings controlling cardiomyocyte proliferation. Clin Sci 2022;136:911–934.
19. Meng D, Pan H, Chen Y, et al. Roles and mechanisms of NRG-1 in modulating the pathogenesis of NAFLD through ErbB3 signaling in hepatocytes (NRG-1 modulates NAFLD through ErbB3 signaling). Obes Res Clin Pract 2021;15:145–151.
20. Zhang J, Ji JY, Yu M, et al. YAP-dependent induction of amphiregulin identifies a non-cell-autonomous component of the Hippo pathway. Nat Cell Biol 2009;11:1444–1450.
21. Wang F, Wang H, Liu X, et al. Neuregulin-1 alleviate oxidative stress and mitigate inflammation by suppressing NOX4 and NLRP3/caspase-1 in myocardial ischaemia-reperfusion injury. J Cell Mol Med 2021;25:1783–1795.
22. Shakeri H, Gevaert AB, Schrijvers DM, et al. Neuregulin-1 attenuates stress-induced vascular senescence. Cardiovasc Res 2018;114:1041–1051.
23. Xu G, Watanabe T, Iso Y, et al. Preventive effects of heregulin-beta1 on macrophage foam cell formation and atherosclerosis. Circ Res 2009;105:500–510.
24. Clement CM, Thomas LK, Mou Y, et al. Neuregulin-1 attenuates neointimal formation following vascular injury and inhibits the proliferation of vascular smooth muscle cells. J Vasc Res 2007;44:303–312.
25. Haller P M, Goncalves IF, Acar E, et al. Relationship between plasma Neuregulin-1 and cardiac function in patients with ST-elevation. Rev Cardiovasc Med 2022;23:63.
26. Belmonte F, Das S, Sysa-Shah P, et al. ErbB2 overexpression upregulates antioxidant enzymes, reduces basal levels of reactive oxygen species, and protects against doxorubicin cardiotoxicity. Am J Physiol Heart Circ Physiol 2015;309:1271–1280.
27. Wang F, Wang H, Liu X, et al. Neuregulin-1 alleviate oxidative stress and mitigate inflammation by suppressing NOX4 and NLRP3/caspase-1 in myocardial ischaemia-reperfusion injury. J Cell Mol Med 2021;25:1783–1795.
28. Wu L, Walas S, Leung W, et al. Neuregulin1-β decreases IL-1β-induced neutrophil adhesion to human brain microvascular endothelial cells. Transl Stroke Res 2015;6:116–124.
29. Szablewski L. Glucose transporters in healthy heart and in cardiac disease. Int. J. Cardiol 2017;230:70–75.
30. Honkoop H, de Bakker DE, Aharonov A, et al. Single-cell analysis uncovers that metabolic reprogramming by ErbB2 signaling is essential for cardiomyocyte proliferation in the regenerating heart. Elife 2019;8:e50163.
31. Pentassuglia L, Heim P, Lebboukh S, et al. Neuregulin-1β promotes glucose uptake via PI3K/Akt in neonatal rat cardiomyocytes. Am J Physiol Endocrinol Metab 2016;310:782–794.

32. Hotham WE, Henson FMD. The use of large animals to facilitate the process of MSC going from laboratory to patient-'bench to bedside. Cell Biol Toxicol 2020;36:103–114.
33. Hedhli N, Dobrucki LW, Kalinowski A, et al. Endothelial-derived neuregulin is an important mediator of ischaemia induced angiogenesis and arteriogenesis. Cardiovasc Res 2012;93:516–524.
34. Steffens S, Van Linthout S, Sluijter JPG, et al. Stimulating pro-reparative immune responses to prevent adverse cardiac remodelling: Consensus document from the joint 2019 meeting of the ESC working groups of cellular biology of the heart and myocardial function. Cardiovasc Res 2020;116:1850–1862.
35. Fang SJ, Li PY, Wang CM., et al. Inhibition of endoplasmic reticulum stress by neuregulin-1 protects against myocardial ischemia/reperfusion injury. Peptides 2017;88:196–207.
36. Hong X, Oh N, Wang K, et al. Human endothelial colony-forming cells provide trophic support for pluripotent stem cell-derived cardiomyocytes via distinctively high expression of neuregulin-1. Angiogenesis 2021;24:327–344.
37. Gupte M, Lal H, Ahmad F, et al. Chronic neuregulin-1β treatment mitigates the progression of postmyocardial infarction heart failure in the setting of type 1 diabetes mellitus by suppressing myocardial apoptosis, fibrosis, and key oxidant-producing enzymes. J Card Fail 2017;23:887–899.
38. De Keulenaer GW, Feyen E, Dugaucquier L, et al. Mechanisms of the multitasking endothelial protein NRG-1 as a compensatory factor during chronic heart failure. Circ Heart Fail 2019;12:e006288.
39. Zurek M, Johansson E, Palmer M, et al. Neuregulin-1 induces cardiac hypertrophy and impairs cardiac performance in post-myocardial infarction rats. Circulation 2020;142:1308–1311.
40. Bian Y, Sun M, Silver M, et al. Neuregulin-1 attenuated doxorubicin-induced decrease in cardiac troponins. Am J Physiol Heart Circ Physiol 2009;297:1974–1983.
41. Haller PM, Gonçalves IF, Acar E, et al. Relationship between plasma Neuregulin-1 and cardiac function in patients with ST-elevation myocardial infarction. Rev Cardiovasc Med 2022;23:63.
42. Chang T, Liu C, Yang H, et al. Fibrin-based cardiac patch containing neuregulin-1 for heart repair after myocardial infarction. Colloids Surf B Biointerfaces 2022;220:112936.
43. Bossers GPL, Günthel M, van der Feen DE, et al. Neuregulin-1 enhances cell-cycle activity, delays cardiac fibrosis, and improves cardiac performance in rat pups with right ventricular pressure load. J Thorac Cardiovasc Surg 2022;164:493–510.
44. Cui MY, Fu YQ, Li ZL, et al. Neuregulin-1/PI3K signaling effects on oligodendrocyte proliferation, remyelination and behaviors deficit in a male mouse model of ischemic stroke. Exp Neurol 2023;362:114323.
45. Zhbanov KA, Shchendrygina AA, Salakheeva EY, et al. The Prognostic Value of Neuregulin-1β in Heart Failure Patients With Preserved Ejection Fraction. Kardiologiia 2022;62:3–8.
46. Shakeri H, Boen JRA, De Moudt S, et al. Neuregulin-1 compensates for endothelial nitric oxide synthase deficiency. Am J Physiol Heart Circ Physiol 2021;320:2416–2428.
47. Yamaguchi N, Xiao J, Narke D, et al. Cardiac Pressure Overload Decreases ETV1 Expression in the Left Atrium, Contributing to Atrial Electrical and Structural Remodeling. Circulation 2021;143:805–820.
48. Wang JF, Li FH, Shen DL, et al. [Effect of neuregulin-1 on cardiac glucose metabolism in rats with experimental myocardial infarction]. Zhonghua Xin Xue Guan Bing Za Zhi 2021;49:912–919.
49. Huang M, Zheng J, Chen Z, et al. The Relationship Between Circulating Neuregulin-1 and Coronary Collateral Circulation in Patients with Coronary Artery Disease. Int Heart J 2020;61:115–120.
50. Wang X, Zhang F, Ma W, et al. Increased Levels of Serum Neuregulin 1 Associated with Cognitive Impairment in Vascular Dementia. Biomed Res Int 2020;2020:6683747.