ISSN 2706-6819 Vol.5, Issue 7: 63-69, DOI: 10.25236/IJFM.2023.050710

Research Progress of NRG1/ErbB4 Receptor Signaling Pathway in the Cardiovascular Field

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Abstract: *The NRG1/ErbB4 receptor signaling pathway plays a critical role in the regulation of cardiovascular development, vascular biology, and cardiac injury. This review provides an overview of the NRG/ErbB receptor signaling pathway and its involvement in the regulation of cardiac development, vascular biology, and cardiac injury. We discuss the regulation of NRG on vascular biology and vascular regeneration, the endogenous activation of NRG1/ErbB receptor signaling pathway in alleviating myocardial ischemic injury, and the potential therapeutic value of NRG1 on myocardial injury and heart failure.*

Keywords: *NRG1, ErbB4 Receptor, Cardiovascular Development, Vascular Biology, Myocardial Injury, Heart Failure*

1. Introduction

The NRG1/ErbB4 receptor signaling pathway is a complex signaling pathway that regulates a wide range of biological processes, including cardiovascular development, vascular biology, and cardiac injury. The NRG1/ErbB4 receptor signaling pathway is activated by the binding of neuregulin-1 (NRG1) to the ErbB4 receptor, which leads to the activation of downstream signaling pathways. The NRG1/ErbB4 receptor signaling pathway is essential for the normal development and function of the heart and plays a crucial role in the response to cardiac injury is shown in Figure 1.

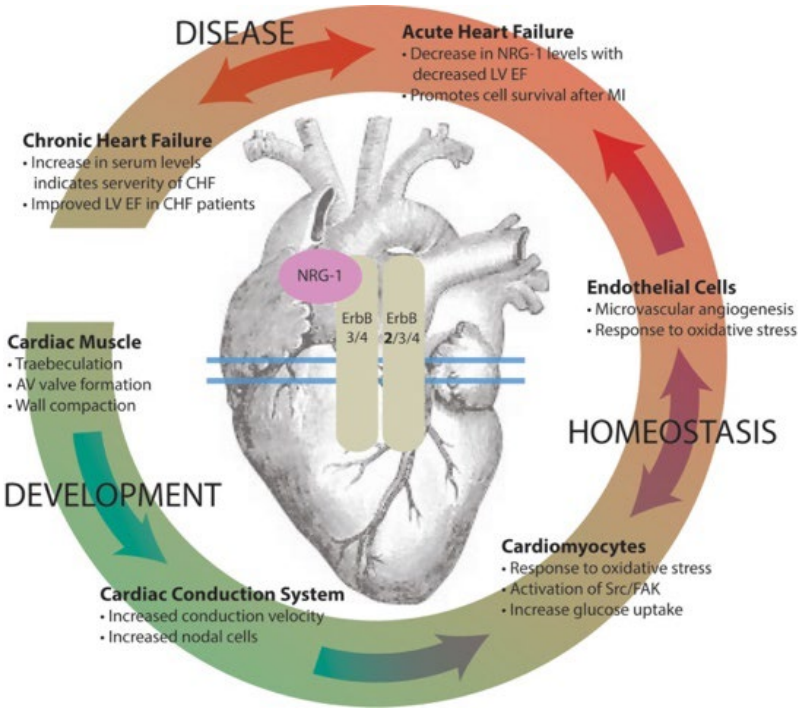

Figure 1: The NRG-1/ErbB signaling pathway exerts diverse effects on various states of the heart

ISSN 2706-6819 Vol.5, Issue 7: 63-69, DOI: 10.25236/IJFM.2023.050710

In the heart, NRG-1/ErbB signaling demonstrates varied, context-sensitive physiological impacts during development, homeostasis, and disease progression.[1]

2. Overview of NRG/ErbB Receptor Signaling Pathway

The NRG/ErbB receptor signaling pathway is a vital pathway that has a significant role in controlling numerous biological processes. NRG ligand binding to the ErbB receptor family triggers a series of signaling events that modulate cell proliferation, differentiation, and survival. The ErbB receptor family contains four members, such as ErbB1 (also referred to as the epidermal growth factor receptor or EGFR), ErbB2, ErbB3, and ErbB4, which function as transmembrane receptor tyrosine kinases [2]. NRG ligands, comprising NRG1, NRG2, NRG3, and NRG4, interact with the extracellular domain of the ErbB receptor family, resulting in receptor dimerization and activation of subsequent signaling pathways [3] is shown in Figure 2.

The downstream signaling pathways of the NRG/ErbB receptor signaling pathway are varied and intricate, encompassing multiple intracellular signaling cascades. The PI3K/Akt and MAPK/ERK pathways are the most thoroughly investigated downstream signaling pathways of the NRG/ErbB receptor signaling pathway [4]. PI3K/Akt pathway activation contributes to the enhancement of cell survival and the suppression of apoptosis, whereas MAPK/ERK pathway activation promotes cell proliferation, differentiation, and survival [5].

In conclusion, the NRG/ErbB receptor signaling pathway is an intricate signaling pathway that governs various biological processes, such as cell proliferation, differentiation, and survival. The activation of the NRG/ErbB receptor signaling pathway results in the initiation of downstream signaling pathways, including the PI3K/Akt and MAPK/ERK pathways, which modulate cell survival, proliferation, and differentiation.

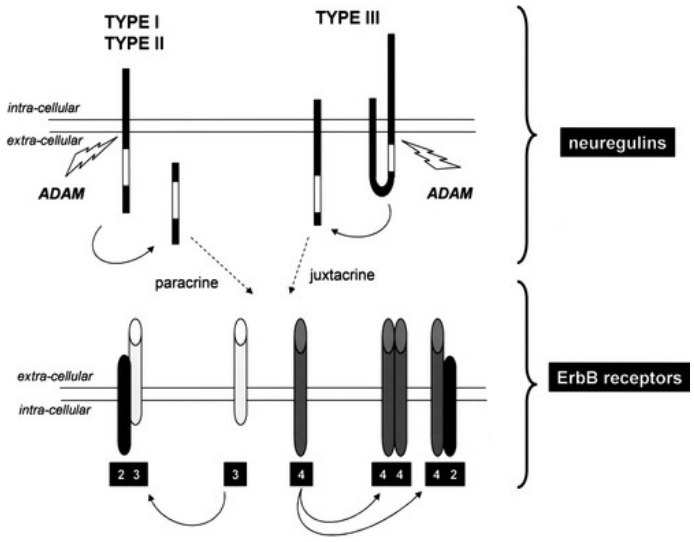

Figure 2: The NRG-1/ErbB signaling pathway and its subtypes

Figure 2. NRG-1/ErbB signaling involves three types of NRG-1 isoforms. Type I and II are single-pass transmembrane proteins, while type III is a 2-pass transmembrane protein with a cysteine-rich domain. Proteolytic cleavage produces bioactive fragments with EGF-like receptor binding domains. Type I and II isoforms enable paracrine signaling, and type III serves as juxtacrine signals. Type I NRGs are most common in the heart. NRG-1 binds to ErbB3 and ErbB4 receptors, forming homodimers and heterodimers. ErbB3 homodimers are functionally defective, while ErbB2 is the favored heterodimerization partner. Dimerization activates the kinase domain, leading to phosphorylation and downstream signaling [6].

3. Involvement of NRG1/ErbB4 Receptor Signaling Pathway in the Regulation of Cardiac Development

Moreover, NRG1/ErbB4 signaling is essential for maintaining cardiac function in adulthood. Conditional ErbB4 deletion in mice hearts leads to cardiac dysfunction, dilated cardiomyopathy,

ISSN 2706-6819 Vol.5, Issue 7: 63-69, DOI: 10.25236/IJFM.2023.050710

enlarged ventricles, and impaired contractility [7]. Similarly, NRG1 gene mutations are linked to an increased risk of dilated cardiomyopathy and heart failure in humans [8].

NRG1/ErbB4 signaling also controls the heart's response to stress and injury. It protects the heart against ischemia-reperfusion injury by promoting cardiomyocyte survival and reducing apoptosis [9]. Additionally, NRG1/ErbB4 signaling regulates angiogenesis, crucial for maintaining cardiac function under stress [10].

These findings indicate the NRG1/ErbB4 receptor signaling pathway's importance in heart development, maintenance, and function. Dysregulation contributes to various cardiac disorders, including dilated cardiomyopathy and heart failure, making it a promising therapeutic target.

4. Involvement of NRG1/ErbB4 Receptor Signaling Pathway in the Regulation of Cardiac Function

The NRG1/ErbB4 receptor signaling pathway has been shown to be involved in the regulation of cardiac contractility. Activation of NRG1/ErbB4 signaling has been shown to increase contractility in isolated cardiomyocytes and in intact hearts of mice and rats, both in vitro and in vivo studies [11,12]. This effect is believed to be mediated by the activation of the PI3K/Akt and MAPK/ERK signaling pathways, which stimulate the production of calcium ions in cardiomyocytes and enhance contractility [13].

In addition to its role in regulating cardiac contractility, NRG1/ErbB4 signaling also regulates heart rate. Studies have shown that NRG1/ErbB4 signaling plays a crucial role in regulating the intrinsic heart rate and pacemaker activity of the sinoatrial node (SAN), the natural pacemaker of the heart [14,15]. Activation of NRG1/ErbB4 signaling has been shown to increase the spontaneous firing rate of SAN cells, which is believed to be mediated by the activation of the cyclic AMP (cAMP) signaling pathway [16,17].

Moreover, the NRG1/ErbB4 receptor signaling pathway is also involved in the regulation of the heart's response to stress, including pressure overload and myocardial ischemia. Studies have shown that NRG1/ErbB4 signaling can protect the heart from hypertrophy and heart failure induced by pressure overload [18,19]. In addition, activation of NRG1/ErbB4 signaling has been shown to protect the heart from myocardial ischemia-reperfusion injury, a common cause of myocardial infarction [20,21]. The protective effect of NRG1/ErbB4 signaling in the heart is believed to be mediated by the activation of anti-apoptotic and pro-survival signaling pathways, such as the PI3K/Akt and MAPK/ERK pathways [22].

Overall, the NRG1/ErbB4 receptor signaling pathway plays a crucial role in the regulation of cardiac function, including cardiac contractility, heart rate, and response to stress. Dysregulation of NRG1/ErbB4 signaling has been implicated in the pathogenesis of various cardiovascular diseases, such as heart failure and myocardial infarction, highlighting the importance of this signaling pathway in maintaining cardiovascular homeostasis.

Furthermore, studies have also shown that the NRG1/ErbB4 signaling pathway is involved in the regulation of cardiac metabolism. In a study by Zhang et al., it was demonstrated that activation of the NRG1/ErbB4 signaling pathway enhances glucose uptake and utilization in cardiomyocytes, which is important for maintaining cardiac function under stress conditions such as myocardial ischemia [23].

The NRG1/ErbB4 signaling pathway has also been implicated in the regulation of cardiac fibrosis, a common pathological feature of various cardiac diseases including heart failure. A study by Wang et al. showed that activation of the NRG1/ErbB4 signaling pathway attenuated cardiac fibrosis in a mouse model of pressure overload-induced heart failure [24]. This effect was attributed to the inhibition of the TGF-β1/Smad signaling pathway by NRG1/ErbB4 signaling.

Taken together, these studies demonstrate the crucial role of the NRG1/ErbB4 receptor signaling pathway in the regulation of cardiac function and pathology. The NRG1/ErbB4 signaling pathway regulates various aspects of cardiac function including contractility, heart rate, stress response, metabolism, and fibrosis. Targeting this pathway may hold therapeutic potential for various cardiac diseases.

ISSN 2706-6819 Vol.5, Issue 7: 63-69, DOI: 10.25236/IJFM.2023.050710

5. Regulation of NRG on Vascular Biology and Vascular Regeneration

The NRG1/ErbB4 receptor signaling pathway regulates cardiac contractility. Activation increases contractility in isolated cardiomyocytes and intact mouse and rat hearts in vitro and in vivo [11,12]. This is mediated by PI3K/Akt and MAPK/ERK pathways, stimulating calcium ion production in cardiomyocytes [13].

NRG1/ErbB4 signaling also regulates heart rate, playing a crucial role in intrinsic heart rate and pacemaker activity of the sinoatrial node (SAN) [14,15]. Activation increases SAN cell firing rate, mediated by the cyclic AMP (cAMP) signaling pathway [16,17].

Furthermore, the NRG1/ErbB4 pathway regulates the heart's stress response, including pressure overload and myocardial ischemia. It protects the heart from hypertrophy and heart failure induced by pressure overload [18,19]. Additionally, NRG1/ErbB4 activation protects against myocardial ischemia-reperfusion injury, a common myocardial infarction cause [20,21], through PI3K/Akt and MAPK/ERK pathways [22].

Overall, the NRG1/ErbB4 pathway is crucial for cardiac function regulation, including contractility, heart rate, and stress response. Dysregulation contributes to various cardiovascular diseases, emphasizing this pathway's importance in maintaining cardiovascular homeostasis.

Furthermore, NRG1/ErbB4 signaling regulates cardiac metabolism. Zhang et al. demonstrated that pathway activation enhances glucose uptake and utilization in cardiomyocytes, critical for maintaining cardiac function under stress like myocardial ischemia [23].

The NRG1/ErbB4 pathway is also involved in cardiac fibrosis regulation, a common pathological feature in heart failure. Wang et al. showed that activation attenuated cardiac fibrosis in a mouse model of pressure overload-induced heart failure [24] by inhibiting the TGF-β1/Smad signaling pathway.

These studies highlight the NRG1/ErbB4 receptor signaling pathway's essential role in regulating cardiac function and pathology. It regulates contractility, heart rate, stress response, metabolism, and fibrosis, making it a potential therapeutic target for various cardiac diseases [25-29].

6. Endogenous Activation of NRG1/ErbB Receptor Signaling Pathway Alleviates Myocardial Ischemic Injury

Endogenous activation of the NRG1/ErbB receptor signaling pathway has been shown to protect against myocardial ischemic injury. NRG1, expressed in the heart, can be released following ischemic injury and activate the ErbB receptor family, leading to downstream signaling pathways that promote cardioprotection and tissue repair. Research indicates that NRG1/ErbB signaling pathway activation enhances cardiomyocyte survival and reduces myocardial damage in animal models of myocardial ischemia [30,31]. Furthermore, NRG1/ErbB signaling encourages angiogenesis and collateral blood vessel formation, improving blood flow and tissue oxygenation following ischemic injury [32,33]. These findings suggest that endogenous activation of the NRG1/ErbB receptor signaling pathway may be a potential therapeutic strategy for myocardial ischemic injury treatment.

Exogenous Activation of NRG1/ErbB Receptor Signaling Pathway Reduces Myocardial Ischemic Injury:

Exogenous activation of the NRG1/ErbB receptor signaling pathway has been investigated as a potential therapeutic approach for myocardial ischemic injury treatment. Preclinical studies have shown that exogenous NRG1 administration can improve cardiac function and reduce myocardial damage following ischemic injury. For example, a rat model of myocardial infarction study demonstrated that recombinant NRG1 protein treatment significantly improved cardiac function and reduced infarct size compared to the control group [34]. Similarly, another study using a mouse model of myocardial ischemia-reperfusion injury found that NRG1 treatment reduced myocardial damage and improved cardiac function by enhancing angiogenesis and promoting cardiomyocyte survival [35].

The cardioprotective effects of exogenous NRG1 administration involve complex and multifaceted mechanisms. NRG1 activates multiple signaling pathways related to cardiac function and angiogenesis, including the PI3K/Akt and MAPK/ERK pathways [36]. These pathways play a crucial role in promoting cell survival, proliferation, and angiogenesis in response to ischemic injury. Additionally, NRG1 promotes the secretion of growth factors and cytokines that can further enhance angiogenesis and tissue repair [37].

ISSN 2706-6819 Vol.5, Issue 7: 63-69, DOI: 10.25236/IJFM.2023.050710

Despite promising preclinical results, translating exogenous NRG1 administration to clinical practice remains in early stages. Clinical trials investigating NRG1 therapy's safety and efficacy in heart failure patients have produced mixed results, and further studies are necessary [36,37]. However, NRG1's potential as a therapeutic agent for myocardial ischemic injury highlights the NRG1/ErbB receptor signaling pathway's importance in cardiovascular biology and disease.

7. The Potential Therapeutic Value of NRG1 on Myocardial Injury and Heart Failure

The therapeutic potential of NRG1 for myocardial injury and heart failure has been extensively studied. NRG1 administration has demonstrated beneficial effects on cardiac function and myocardial damage in animal models of myocardial injury and heart failure. For instance, a study by Huang et al. showed that NRG1 administration improved cardiac function and reduced myocardial damage in a rat model of myocardial infarction [38]. Additionally, a study by Gao et al. demonstrated that NRG1 administration improved cardiac function and reduced fibrosis in a rat model of heart failure induced by myocardial infarction [39].

Several mechanisms have been proposed to explain NRG1's beneficial effects on myocardial injury and heart failure. One possible mechanism is promoting cardiomyocyte survival and proliferation. Studies have shown that NRG1/ErbB4 signaling promotes cardiomyocyte survival and proliferation, potentially restoring cardiac function following myocardial injury and heart failure [40,41]. Another mechanism involves promoting angiogenesis and collateral blood vessel formation, improving blood flow and tissue oxygenation in damaged myocardium [42,43].

Clinical trials are currently underway to evaluate the safety and efficacy of NRG1 administration in patients with heart failure. A phase I clinical trial conducted by Bersellini-Farinotti et al. demonstrated that NRG1 administration was well-tolerated in patients with heart failure and showed potential to improve cardiac function [44]. A phase II clinical trial is currently underway to evaluate the efficacy of NRG1 administration in patients with heart failure [45].

Overall, the NRG1/ErbB4 receptor signaling pathway has emerged as a promising therapeutic target for treating myocardial injury and heart failure. Further studies are needed to fully elucidate the mechanisms of NRG1 action and to determine the optimal dosing and administration strategies for NRG1 therapy.

In conclusion, the NRG1/ErbB4 receptor signaling pathway is an important regulator of cardiovascular development, vascular biology, and cardiac injury. Its potential therapeutic value in treating myocardial injury and heart failure has been demonstrated in preclinical studies and is currently being evaluated in clinical trials. The regulation of NRG on vascular biology and vascular regeneration suggests that NRG1 may have applications in treating vascular diseases as well. However, further research is needed to fully elucidate the mechanisms underlying the effects of NRG1 on the cardiovascular system and to develop effective therapies based on this pathway.

In the field of cardiac surgery, using NRG1 as a therapeutic agent holds significant potential. One study showed that delivering NRG1 directly into the myocardium improved cardiac function and reduced myocardial damage following acute myocardial infarction in a rat model, suggesting that NRG1 may be useful as an adjunct to reperfusion therapy in treating acute myocardial infarction. Additionally, NRG1's use in the context of heart failure surgery, such as left ventricular assist device (LVAD) implantation or heart transplantation, may also be beneficial. LVAD implantation is a treatment option for patients with end-stage heart failure, and NRG1 has been shown to improve myocardial function and reduce ventricular remodeling in animal models of LVAD implantation. NRG1 may also have potential as a protective agent during heart transplantation, as ischemia-reperfusion injury is a common complication of transplantation that can lead to graft dysfunction and rejection.

In summary, the NRG1/ErbB4 receptor signaling pathway holds significant therapeutic potential in the field of cardiovascular medicine and surgery. Continued research and development of NRG1-based therapies may lead to improved outcomes for patients with cardiovascular disease.

Acknowledgement

Funding: This work was supported by the first batch of Shandong Provincial Natural Science Foundation. Project Number: ZR202111180081.

ISSN 2706-6819 Vol.5, Issue 7: 63-69, DOI: 10.25236/IJFM.2023.050710

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