Acute cardiac effects of neuregulin-1/ErbB signalling

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Neuregulin1 (Nrg1) is a member of the epidermal growth factor family. Its biological effects are mediated by the ErbB family of receptor tyrosine kinases (ErbB2, ErbB3, and ErbB4). Nrg1/ErbB signalling is an essential paracrine mediator of cell–cell interactions that are indispensable for cardiac development but also play a crucial role in the adult heart.

In the foetal heart, Nrg1 is produced in the endocardial endothelium adjacent to the cardiomyocytes where the ErbB2 and ErbB4 receptors are expressed. In contrast to ErbB2 and ErbB4, the ErbB3 receptor is only expressed in the mesenchymal cells of the endocardial cushions, the structure that forms the valves. The first evidence for a function of the Nrg1/ErbB pathway in cardiac morphogenesis was revealed by studies of mice lacking functional Nrg1, ErbB2, or ErbB4 signalling, which display a similar impairment of cardiac development characterized by a failure to undergo expansion and trabeculation of the primitive ventricles, resulting in embryonic lethality at E10.5. The similar cardiac phenotypes observed between Nrg1-, ErbB2-, and ErbB4-deficient mice demonstrate the requirement of these three proteins in the Nrg1-dependent regulation of ventricular trabeculation. Impairment of the ErbB3 signalling displays less severe heart malformation. ErbB3-null mice exhibit hypoplastic endocardial cushions leading to blood reflux through defective valves and embryonic lethality at day E13.5. In the adult heart Nrg1, ErbB2 and ErbB4 but not ErbB3 continue to be expressed and are essential to maintain ventricular structure and function. Indeed, mice harbouring a conditional deletion of the ErbB2 or ErbB4 receptors develop dilated cardiomyopathy with altered cardiac function.

In vivo and in vitro studies showed that numerous processes are regulated by Nrg1 signalling. During heart development, Nrg1 signalling is implicated in the regulation of cardiomyocyte differentiation, cardiac conduction system specification, proliferation, and foetal cardiac function. In the adult heart, Nrg1 has been shown to modulate cell growth, survival, sarcomere function, myocardial performance, and cardiomyocyte reentry into the cell cycle. Nrg1 downstream signalling pathways have been extensively characterized in other tissues, and multiple signalling molecules, including Erk1/2, PI3K/Akt, FAK, and eNOS, appear to be involved. Nevertheless, how Nrg1 signalling impacts on adult cardiac physiology and on cardiac development is still unknown.

Brero et al. investigated the molecular mechanism involved in the regulation of cardiac function in the adult rat through the Nrg1 pathway. They demonstrated that Nrg1 induces, within minutes, rapidly enhances NO production through a PI3K/Akt-dependent eNOS phosphorylation. Although not measured in this study, NO presumably increases intracellular cGMP levels via activation of the soluble guanylyl cyclase, which in turn activates cGMP-dependent protein kinase (PKG). PKG phosphorylation was previously shown to regulate major components of excitation–contraction coupling, such as the L-type Ca2+ channel (LTCC), phospholamban (PLN), and troponin I. Accordingly, Brero et al. found that Nrg1 induces PKG-dependent phosphorylation of PLN, causing an increased Ca2+ uptake into the sarcoplasmic reticulum and hence a larger Ca2+ transient amplitude. Surprisingly, they found no effect of Nrg1 on the amplitude of the LTCC current (I_{Ca,L}). Although they did not examine whether Nrg1 modifies the amplitude of I_{Ca,L} during β-adrenergic stimulation, as generally observed with NO donors in rat cardiomyocytes, their findings raise an interesting possibility that the pool of cGMP/PKG which is activated by Nrg1 controls exclusively the phosphorylation of PLN without affecting other PKG target proteins. Although this hypothesis needs to be directly tested in future experiments, it would support recent findings in the same preparation demonstrating a high degree of compartmentalization of intracellular cGMP that involves a feedback control by PKG.

While this study provides a complete picture of the molecular events involved in the Nrg1 signalling pathway (Nrg1/PI3K/eNOS/PKG/PLN), it also brings up a temporal issue that was not addressed in prior studies. While most other studies reported long-term effects of Nrg1 on cardiomyocytes, Brero et al. investigated acute Nrg1-dependent regulation of cardiac function and suggested a potential role in the short-term protection of cardiac function during ischaemia.

During heart development, Nrg1-ErbB2/4-Erk1/2 signalling is required for the maintenance of the cardiac transcription program in both trabecular and non-trabecular myocardium, which is essential for cardiac chamber specification. In addition, Nrg1 appears to be...
essential for the establishment of embryonic cardiac contractility, since Nrg1 treatment of E8.5-cultured embryos results in changes in the pattern of electrical activity. Moreover, disruption of Nrg1 leads to altered cardiac function with an abnormal base-to-apex muscular contraction pattern. The PI3K/Akt pathway has been described to be implicated in the regulation of cardiac progenitor and foetal cardiomyocyte proliferation, and thus plays an important role in regulating heart morphogenesis and function. However, its connection with Nrg1 signalling in cardiac development has not yet been established. In this respect, the study of Brero et al. provides a novel hypothesis regarding the role of the PI3K/eNOS pathway in Nrg1-dependent regulation of heart morphogenesis and foetal cardiac function. Indeed, haemodynamic forces are critical for cardiac chamber growth and trabeculation. Therefore, alteration of the foetal cardiac function, as in the Nrg1-deficient animals, may act as an epigenetic input causing the observed cardiac malformations.

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References