Nerve growth factor: Does this have the potential to become a miraculous treatment for diabetic heart?

Diabetic heart, which includes any condition causing pathological changes in blood vessels, cardiac muscle or valves and cardiac rhythm in diabetic patients, such as diabetic cardiomyopathy and ischemic heart disease, is an important cause of mortality in diabetic patients. However, strategies for the treatment of diabetic heart have not been well documented. Recent, large, clinical trials, the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT), failed to show glucose lowering effects on mortality in diabetic patients, suggesting the need for safer ways to lower glucose, as well as specific strategies for the treatment of diabetic heart.

Diabetic cardiomyopathy is characterized by the presence of myocardial damage, a disturbance in the management of the metabolic cardiovascular load, and cardiac autonomic neuropathy. A recent study by Meloni *et al.*[1] evaluated the impact of nerve growth factor (NGF) gene therapy on the prevention of cardiomyopathy in type 1 diabetic mice. They used a gene transfer technique and investigated whether NGF gene transfer can prevent diabetic cardiomyopathy in mice, using two types of adeno-associated viral vectors (AAV) injected in mice in two different ways – by a direct intramyocardial injection or a systemic delivery by venous injection. Both methods of NGF gene delivery reduced the deterioration of cardiac function and showed additional protective effects on myocardial microvascular rarefaction, interstitial fibrosis, and apoptosis of endothelial cells and cardiomyocytes (Figure 1).

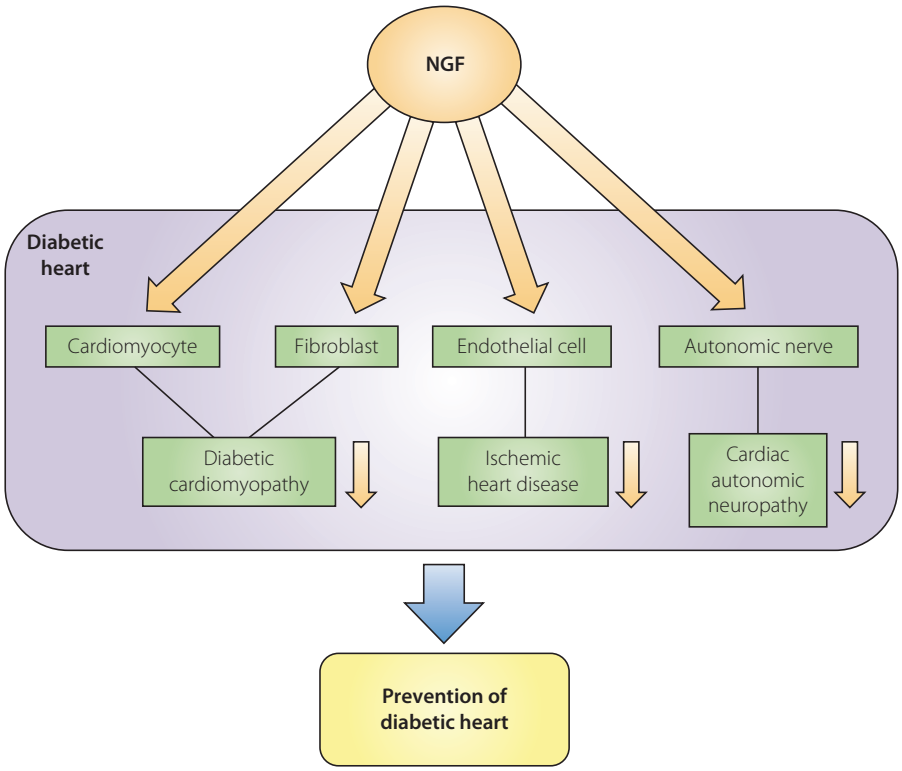

Figure 1 | Therapeutic potential of nerve growth factor (NGF) on diabetic heart. Diabetic heart includes any condition causing pathological changes in blood vessels, cardiac muscle or valves and cardiac rhythm in diabetic patients. NGF has prosurvival effects in heart cells, such as cardiomyocytes and endothelial cells, as well as protective effects in cardiac autonomic neuropathy and interstitial fibrosis, which result in the prevention of diabetic cardiomyopathy, ischemic heart disease and cardiac autonomic neuropathy in diabetic patients.

The content of NGF in the heart is altered by heart disease. Reduced myocardial expression of NGF is reported in heart failure. Several reports have described that diabetes reduces cardiac NGF expression. Ieda *et al.*[2] showed that the levels of NGF messenger ribonucleic acid (mRNA) did not change in hearts of 8 weeks' streptozotocin (STZ) rats, but were significantly downregulated in 16 weeks' STZ hearts. Meloni *et al.*[3] also showed reduced NGF mRNA levels in the heart at 12 weeks of diabetes in their study. There is emerging evidence that NGF showed protective effects in heart

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disease, including diabetic heart. NGF has prosurvival effects in heart cells, including cardiomyocytes and endothelial cells, as well as protective effects in cardiac autonomic neuropathy. The findings of Meloni *et al.*[1] showed that NGF gene transfer prevented diabetes-associated left ventricular dysfunction, such as reduced left ventricle ejection fraction (LVEF) and left ventricle fractional shortening (LVFS), dilatation of the left ventricle chamber, and increase in the left ventricle internal diameter (LVID). NGF gene transfer also preserved the microvascular density and cardiac perfusion in diabetic mice. Transferase-mediated dUTP-biotin nick end labeling (TUNEL)-positive apoptotic endothelial cells and cardiomyocytes are increased in diabetic heart, which was reduced by NGF gene transfer. In addition, NGF gene transfer reduced diabetes-associated cardiac interstitial fibrosis. From the viewpoint of signal transduction, Meloni *et al.*[1]showed that the phosphorylation of Akt and Forkhead transcription factor Forkhead box class O (Foxo) 3a, one of the downsteam pathways of Akt, was reduced in the diabetic heart, but preserved by NGF gene transfer. The same group has previously shown that NGF activates the Akt/Foxo3a signaling in cultured cardiomyocytes and in the mouse infarcted heart, and that Akt/Foxo3a signaling plays a functional role in NGF-induced cardiomyocyte survival and myocardial angiogenesis.

Cardiac autonomic neuropathy (CAN), which is an autonomic imbalance between the sympathetic and parasympathetic nervous systems in cardiovascular function, contributes to significant morbidity and mortality in individuals with diabetes. A recent subanalysis of the ACCORD trial confirmed the importance of CAN, and showed that the presence of CAN at baseline was an independent risk factor for higher cardiovascular mortality in both the intensive and standard glycemic treatment group[4]. The development of cardiac sensory nerves parallels the production of NGF in the heart. Cardiac nociceptive sensory nerves are markedly impaired in NGF-deficient mice and rescued in mice overexpressing NGF, specifically in the heart[5]. Direct gene transfer of NGF into diabetic rat hearts improved cardiac sensory innervation and function during myocardial ischemia[2]. These results show the crucial role of NGF in the cardiac nerve system.

NGF is one of the neurotrophins that has a high affinity to tropomyosin kinase receptor A (trkA) and a low affinity to receptor of 75 kDa MW ($p75^{NTR}$). TrkA mainly binds to mature neurotrophins, including NGF, and promotes cell growth and survival[6]. In contrast, $p75^{NTR}$ mainly binds to proneurotrophins, which are an uncleaved form of neurotrophins, increases apoptosis and negatively regulates cells. TrkA is expressed not only in neural cells, but also in non-neural cells, such as cardiomyocytes and endothelial cells. As mature NGF genes are transferred by the gene transfer technique, NGF by gene transfer is assumed to bind to trkA.

Phase I and phase II clinical trials of systemic administration of recombinant NGF for the treatment of diabetic polyneuropathy showed its safety and potential efficacy, although a phase III trial showed no beneficial effects, possibly because the dosage and method of administration were suboptimal. So far, NGF is thought to be a promising tool to treat diabetic heart. The findings of Meloni *et al.*[1] showed that both direct intramyocardial injection and systemic delivery of NGF gene by AAV vector prevented cardiomyopathy in type 1 diabetic mice, although increased expression of NGF was observed in non-cardial tissues, by AAV-systemic administration for NGF gene delivery. Emerging studies support the protective effects of NGF in the heart. Now, validated clinical trials of NGF gene therapy in patients with diabetic heart are expected to lead to new strategies.

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