Neurotrophic Factors and Heart Diseases

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Neurotrophic factors are well known for their action on the development, survival and regeneration of neurons. However, new functions have been assigned to those peptides not only during development but also throughout the postnatal life. The searches for new therapeutic strategies have highlighted the role of neurotrophic factors in various phenomena related to pathological and physiological processes. In this review, we will summarize the knowledge of the families of neurotrophic factors as well as other growth factors with known neurotrophic activity. We also aim to provide a synopsis of the involvement of those peptides in cardiac diseases since this knowledge undoubtedly contributes to the development of therapeutic strategies for prevention and treatment of heart diseases.

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Key words: Heart disease; Cardiac disease; Neurotrophic factors

Abbreviations

INTRODUCTION

Different cell types, including fibroblasts, vascular smooth muscle cells, endothelial cells, macrophages, pericytes, and stem cells compose the heart, together with distinct cardiac muscle cell types, whose specialized functions include contraction, generation and conduction of electrical activity, and secretion of different molecules. A network of dynamic interactions between all those cell types and the extracellular matrix as well as soluble factors intensifies the complexity of cardiac functions[1,2]. Overall, the sympathetic and parasympathetic innervation works in a reciprocal way to control heart rate (chronotropy) and conduction velocity (dromotropy) through acting on pacemaker cardiac cells. Also, sympathetic nerves, by innervating cardiomyocytes from atria and ventricles, control cardiac function.
the force of contraction and relaxation (inotropy and lusitropy respectively) of the myocardium\(^{3}\). Afferent nerves can also elicit different physiological responses in the heart\(^{4}\).

Among the factors that control both cardiac development and function are the neurotrophic factors (NF), a group of polypeptides originally known by their ability in promoting development, survival and regeneration of neurons\(^{5,7}\). New functions have been assigned to these substances during embryonic and postnatal development, adulthood and aging, such as cell proliferation and activation\(^{6,10}\), hormonal control\(^{11,12}\), energy balance\(^{13,14}\), gametogenesis\(^{15,16}\), plasticity, learning and memory\(^{17,18}\). The search for novel therapies has also highlighted the role of NF in many pathology-related phenomena like neurodegeneration and regeneration\(^{8,19-21}\), inflammation\(^{22}\), stress\(^{23,24}\), and pain\(^{25-27}\). Accordingly, NF can be secreted not only by neurons and glial cells but also by several other cell types, like endothelial and epithelial cells\(^{28-29}\), muscle cells\(^{30,31}\), adipocytes\(^{32}\), endocrine cells\(^{33,34}\), and immune cells\(^{35-37}\).

In this review, we will gather key information on NF involvement in cardiac diseases. Comprehensive knowledge of the role of these substances may provide subsidies for their use as therapeutic molecules in both the prevention and the treatment of heart diseases.

**NEUROTROPHIC FACTORS (NF)**

NF from mammals can be grouped in 3 families of biochemically related molecules. The Neurotrophin family includes Nerve Growth Factor (NGF), Brain Derived Neurotrophic Factor (BDNF), and the Neurotrophins 3 and 4/5 (NT3 and NT4/5). The Giall cell line-Derived Neurotrophic Factor (GDNF) family includes GDNF itself, Neurturin (NTN), Persephin (PSP), and Artemin (ART)\(^{39}\). More recently, a revolutionary family of NF has been settled with two members, the Cerebral Dopamine Neurotrophic Factor (CDNF) and the Mesencephalic Astrocyte-derived Neurotrophic Factor (MANF)\(^{40}\). The neuropeptide superfamily includes leukemia inhibitory factor (LIF), interleukin-6 (IL-6), interleukin-11 (IL-11), oncostatin M (OSM), and Ciliary Neurotrophic Factor (CNTF), the only one with neurotrophic activity in this family\(^{41}\). Moreover, there are growth factors not produced by neurons and glial cells that show neurotrophic activity, the Insulin-like Growth Factor 1 (IGF-1), Acidic Fibroblast Growth Factor (FGF-a or FGF-1) and Basic Fibroblast Growth Factor (FGF-b or FGF-2)\(^{42}\). A synopsis of NF and growth factors with neurotrophic activity is depicted in the figure 1.

NGF, the prototype NF, was firstly described as a diffusible factor acting on sensory and sympathetic neurons\(^{43-45}\), but further proved to act also on the cholinergic neurons of the basal forebrain\(^{36,47}\). The discovery of other chemically related molecules, BDNF\(^{48}\), NT-3\(^{49}\), and NT-4/5\(^{50-52}\) led to the establishment of the neurotrophin family. In the Peripheral Nervous System (PNS) neurotrophins act in the regulation of the survival and differentiation of neurons, and can influence many processes, including cell body size, innervation density, axonal terminal sprouting, dendrite arborization, and neurotransmitter synthesis. In the Central Nervous System (CNS) neurotrophins have effects mostly on differentiation and modulation of neuronal function\(^{53}\). Neurotrophins are likewise important for protection of PNS and CNS neurons in different conditions such as excitotoxicity\(^{54,55}\), hypoxia\(^{16,57}\), and hypoglycemia\(^{18}\). Not less important are the neurotrophins functions that extend beyond the nervous system, including inflammation\(^{22,17}\), gametogenesis\(^{15}\), stress\(^{34}\), learning, and memory\(^{19}\). In the heart, neurotrophins have important functions during development, postnatal life and in pathological conditions. It is demonstrated that the actions of neurotrophins on heart have exceeded the neural control of cardiac function, and these factors can affect different processes such as angiogenesis and cell survival\(^{49}\).

The biological effects of neurotrophins are mediated through activation of two kinds of membrane receptors, the tropomyosin-related Tyrosine Kinase (Trk) receptors and the p75 neurotrophin receptor (p75NTR). Binding of neurotrophin to Trk receptors causes their dimerization and phosphorylation of tyrosine residues. These residues form docking sites for adaptor proteins and enzymes that couple the receptors to intracellular signaling cascades, which ultimately regulate cell growth and survival\(^{55,62}\). The specificity of each neurotrophin is supposed to be achieved by its selective interaction with members of the Trk receptor family. NGF binds specifically to TrkA\(^{63,64}\), BDNF and NT 4/5 bind to TrkB and NT3 to TrkC\(^{65,66}\). NT-3 can also interact through a low-affinity binding with TrkA and TrkB\(^{67}\). In addition, all neurotrophins bind with a similar affinity to the p75 neurotrophin receptor, a member of the tumor necrosis factor receptor superfamily. Interesting, p75 signaling depends on the cell type, cell differentiation status, neurotrophin binding, and availability of intracellular adaptor molecules. This unrestrained signaling leads to diverse and even divergent cellular responses, like cell survival or apoptosis, neurite outgrowth or retraction, myelination, cell cycle regulation, and cell migration\(^{68}\). A same cell often expresses both neurotrophin receptors Trk and p75, and the signals generated by them can either augment or oppose each other. The cellular responses to neurotrophins are modulated by this dual action, and several studies focuses on the signal transduction pathways used by these receptors to promote neurotrophin actions. Details of these signaling pathways will not be explored here since reviews dealing elegantly with this subject can be found elsewhere\(^{22,68,70}\).
Typically neurotrophins are target tissue-derived molecules sustaining the innervating neurons\cite{71,72}. After binding to Trk or p75 receptor in the axonema the neurotrophin is endocytosed and retrogradely transported to the cell soma to promote cell signaling\cite{73}. However, anterograde routes have been proposed as a pathway for interneuronal signaling\cite{74}.

GDNF as well as its related members NTN, PSP and ART are dimeric proteins with a cysteine knot structure, which identify them as members of the Transforming Growth Factor b (TGF-b) superfamily\cite{75}. The GDNF family members act through the common receptor tyrosine kinase Ret, and their specificity is determined by the GDNF family co-receptor α (GFRα), a class of glycosylphosphatidylinositol (GPI)-anchored proteins. GDNF binds preferentially to GFRα1, NTN to GFRα2, ART to GFRα3, and PSP to GFRα4. According to the receptor-activating model, a dimer of the ligand first binds two identical GFRα molecules, and this complex interacts with two RET molecules, resulting in tyrosine autophosphorylation and then cell signalization\cite{76,77}.

The GDNF family members are responsible for the development and maintenance of several neuronal populations. In the CNS, they are potent survival factors for midbrain dopaminergic neurons\cite{77,78}, noradrenergic neurons of the locus coeruleus\cite{79,80}, and for spinal motor neurons\cite{81,82}. The factors have also effects in the peripheral nervous system, including autonomic, sensory and enteric neurons\cite{83,84}. In the heart GDNF is a candidate to promote sympathetic innervation during both development and recovery after denervation\cite{30,31,84}. In addition, GDNF family is known to have important roles outside the nervous system as GDNF promotes uterine branching during kidney morphogenesis\cite{85}, and participates from spermatogenesis\cite{86}.

CNTF was isolated from chick eye tissue as a survival factor for ciliary ganglionic neurons\cite{86}. CNTF is synthesized mostly by astrocytes and Schwann cells and stimulates the survival of a variety of neurons, including motor, sensory, sympathetic, and parasympathetic ones. The high-affinity biological actions of CNTF require binding to CNTF receptor complex CNTFRα, followed by the recruitment of gp130 and LIFRb membrane signal transducing units. Administration of CNTF has been shown to rescue different populations of neurons aside from photoreceptors and oligodendrocytes. Expression of both CNTF mRNA and protein is intensely altered by injury to the CNS or PNS. Although CNTF itself lacks a classical signal peptide sequence for secretion, altogether these facts suggest that CNTF has a neurotrophic role in response to nervous system injury, and it is believed that their protective effects occur by some mechanism induced by lesion\cite{87,88}. In the heart, CNTF seems to be protective for the cardiac muscle cells during heart failure\cite{89,90}.

IGF-1 is a well-known peptide involved mainly in cell metabolism and growth. Nowadays its neurotrophic activity is recognized both in central and peripheral nervous system. Concerning the CNS, the synthesis of IGF-1 is restricted to a few brain regions and in very low quantities. However, circulating IGF-1 appears to be an important source for the adult brain. IGF-1 exhibits high affinity binding to the tyrosine kinase type 1 IGF receptor (IGF-1R). This receptor has a distinctive structural feature since it functions as a tetramer of two covalently linked- α and β subunits. IGF-1 has been revealed to have effects on brain neuron and glial cells, acting as an important modulator in neurogenesis, and neuronal plasticity and excitability. Recently IGF-1 has been related to some neuropathologies like Alzheimer and diabetes\cite{90,91}. About the neurotrophic activity of IGF-1 in the PNS, the factor promotes survival, growth and regeneration of nerves\cite{92}. Regarding the heart, the effects of IGF-1 are more related to cardiomyocyte protection from apoptosis and promotion of neovascularization\cite{93,94}.

Fibroblast growth factors (FGFs) and their receptors are expressed in virtually all-mammalian tissues. This family includes 23 FGF different members, ten of them being identified in the brain. Four FGF receptor genes, FGRFR-1–4, have been identified, and their protein isoforms display distinct specificities for the FGF subtypes. FGF-1 and FGF-2 are considered to have neurotrophic activity\cite{95}. FGF-2 (or basic FGF – bFGF) is highly expressed in cardiomyocytes endothelial cells, smooth muscle cells, and fibroblasts in all stages of heart development, suggesting that this factor has important effects in cardiac functions\cite{96}.

CDNF and MANF have been described as neurotrophic factors with potent effects on adult midbrain dopaminergic system\cite{97,98} and on cortical neurons during brain ischemic model\cite{99}. Different studies suggest both a secretion-based neuroprotective and an endoplasmic reticulum stress-induced cytoprotective roles for these factors, but the relation between these functions are not yet established\cite{100,101,102}. Cardioprotective actions were recently attributed to MANF\cite{102-104}.

### HEART DISEASES AND NF

This section describes the main studies showing the participation of neurotrophic factors in phenomena related to heart diseases, in order to provide an overview on the importance of these molecules and their potential as therapeutic tools in these conditions.

#### Ischemia

Myocardial ischemia or myocardial infarction occurs when the cells of the myocardium are deprived from oxygen supply, mostly as a consequence of coronary artery disease. Besides the death of cardiomyocytes in the ischemic area, there is a heterogeneous sympathetic innervation that contributes to arrhythmias and sudden cardiac death\cite{105-107}.

NGF is a key factor in the myocardial response to ischemia. In this condition, the expression of NGF and its high affinity receptor TrkA is elevated in human heart\cite{108}, and in rat experimental models, mainly in the viable border zone of infarcted area\cite{109}. Besides its role in promoting sympathetic hyperinnervation (issue to be discussed in the next section), NGF promotes angiogenesis and cell survival\cite{108}. In mice, NGF gene transfer to infarcted myocardium improved the survival of both endothelial cells and cardiomyocytes, stimulating neovascularization and ameliorating myocardial blood flow\cite{108}.

Cardiomyocyte itself is a source of NGF\cite{31,110}, produced and released in a stress-regulated manner\cite{101}. Myofibroblasts and macrophages were also described as source of NGF in the post infarction heart, confirming the contribution of inflammatory cells to elevation of NGF levels in this condition\cite{111}. One of the mechanisms by which NGF protects the heart from ischemia is the P38/Akt pathway activation that leads to attenuation of endoplasmic reticulum stress-induced apoptosis in cardiomyocytes\cite{112}.

Other neurotrophin, BDNF, might also be involved in the overall protection of the heart since ischemic insults transmitted to CNS by cardiac afferent nerve fibers appears to be able to increase neuronal BDNF secretion and its elevation in the peripheral blood\cite{113}. Circulating BDNF could then promote the protection of cardiac tissue by stimulating expression of prosurvival and proangiogenic factors. By the other hand, Halade and collaborators\cite{114} demonstrated a decrease of myocardium BDNF in the ischemic early inflammatory phase that could be important for both cell survival improvement.
and attenuation of ventricular remodeling by its effect on the kinetics of leukocyte infiltration as well as on the angiogenic response. Interestingly, p75, the low affinity receptor for neurotrophins can be involved in the heterogeneity of innervation process that occurs after infarction. Lorentz and collaborators\(^\text{[105]}\) observed that in the viable myocardium beyond the infarcted area there are not only areas of hyperinnervation but also areas presenting denervation process. The authors hypothesized that while binding of NGF to its high affinity TrkA receptor stimulates sympathetic hyperinnervation, binding of proNGF and BDNF to the p75 receptor could stimulate the denervation of peri-infarcted area.

Besides neurotrophins, other growth factors have been implicated in cardiac protection post infarction. FGF-2 has been proved to be an important factor for cell survival, angiogenesis, recovery of infarcted area, and contractile function in this condition\(^\text{[17,18]}\). In rat, the administration of exogenous FGF-2 after the onset of ischemia was protective against injury, and the factor was suggested for acute local therapeutic treatment\(^\text{[19,20]}\). MANF is another NF recently implicated in cardiac protection after ischemia. Studies have demonstrated that myocardial ischemia is capable of activate the endoplasmic reticulum stress response (ERSR) in cardiomyocytes. In this condition, the sarcoplasmic reticulum suffers a calcium depletion that can induce the secretion of MANF that in turn can protect cardiomyocytes from death by an autocrine or paracrine mechanism\(^\text{[21,22]}\). Finally, a role for IGF-1 in the ischemic heart is considered, although it effects are indirect. It is demonstrated that mesenchymal stem cells treated with IGF-1 and transplanted to infarcted heart are able to attenuate both cell apoptosis and inflammatory cytokines expression\(^\text{[23]}\).\n
Arrhythmia

Arrhythmia is an important phenomenon in cardiac patients and one of the main causes of sudden death\(^\text{[24]}\). The autonomic nervous system plays an important role in the pathophysiology of arrhythmogenesis. The contributions of the sympathetic and parasympathetic components are complex and may vary depending on the type of arrhythmia. The identification of specific autonomic triggers is of great interest since modulation of autonomic activities either by stimulation or ablation can control a wide spectrum of cardiac arrhythmias\(^\text{[25]}\).

Experimental data have confirmed NGF as a key factor in triggering the sympathetic hyperinnervation that appears in this condition. The ischemic model is the model of choice for studying NF involvement in the arrhythmogenesis. NGF both protein and mRNA are increased in the heart of different animal models of myocardial infarction\(^\text{[10,14,15]}\). In transgenic mice the overexpression of NGF induces hyperinnervation followed by an augment in the catecholamine production in the heart\(^\text{[26]}\). In dogs, the NGF infusion to the left stellate ganglion is capable of producing nerve sprouting and then cardiac arrhythmogenesis after myocardial ischemia\(^\text{[27]}\). Accordingly, high levels of catecholamine provoke a prolongation of the cardiac action potential that could contribute to the occurrence of ventricular arrhythmias\(^\text{[28]}\). The TrkA receptor is considered the principal target for NGF during sympathetic nerve regeneration in the heart, as its prosurvival and prodifferentiation actions are well established\(^\text{[29,30]}\). Nonetheless, the p75NTR receptor has been also implicated in the establishment of arrhythmias since it influences both the density and distribution of cardiac sympathetic nerves\(^\text{[31,32,33]}\). While the data support a relation between the NGF upregulation and the sympathetic hyperinnervation after myocardial infarction, the molecular mechanisms regulating cardiac NGF expression during arrhythmia are not fully understood. Some studies point for a role of the endothelin (ET-1)/NGF pathway in nerve regeneration after myocardial infarction. ET-1 was capable of stimulate the NGF expression by cardiomyocytes, that in turn induced PC2 cells differentiation in culture. In ET-1-deficient mice hearts, it was observed a reduction in NGF expression, followed by decrease in the sympathetic innervation and norepinephrine levels. Moreover, cardiac overexpression of NGF could rescue the heart from the effects of ET-1 deficiency\(^\text{[34,35]}\).

The participation of other NF in arrhythmogenesis is considered, but data on it are still scarce. Mabs and Hoover\(^\text{[36]}\) observed significant both structural and functional cholinergic deficits in the heart of mice deficient in NTN, among them a lower heart rate. The authors considered that this condition could make these animals more prone to cardiac diseases including arrhythmias. About IGF-1, some studies showed an inverse association between its levels in the serum and QTc intervals, and suggested that individuals with low IGF-1 present higher risk for cardiac arrhythmias\(^\text{[37,38]}\). More, the antiarrhythmic properties of IGF-1 were demonstrated in rat models of myocardial infarction. The injection of IGF-1 in the heart improved intercellular coupling through a higher connexin43 expression that in turn prolonged the effective refractory period (ERP). This effect resulted in attenuation of unfavorable remodeling and subsequent arrhythmia\(^\text{[39]}\).

Hypertrophy

Hypertrophy is a heart response to an imbalance in the contractile activity, and is associated with increased volume of cardiomyocytes. When induced by stimulus like exercise training hypertrophy is called physiological, and consists of an induced beneficial adaptive heart response. By the other hand, stimulus like hypertension and cardiac valvular disease can lead to a pathological hypertrophy due to pressure overload\(^\text{[40,41]}\). While initially pathological hypertrophy can preserve the pumping function and reduce ventricular wall stress, chronically hypertrophy can lead to the development of arrhythmias, heart failure and sudden death\(^\text{[42]}\).

The involvement of IGF-1 in cardiac hypertrophy has long been recognized\(^\text{[43,44]}\). A relation between IGF-1 levels and ventricular mass was established in patients with abnormal left ventricular diastolic function caused by hypopituitarism\(^\text{[45]}\). Moreover, Toyozaki and collaborators\(^\text{[46]}\) demonstrated that the expression of the receptor IGF-1R was augmented in the myocardium of patients with hypertrophic cardiomyopathy. A number of experimental studies have also demonstrated the role of IGF-1 in heart hypertrophy. The administration of IGF-1 provoked an augment in size of cultured rat cardiomyocytes via IGF-1R associated to an elevation in the expression of muscle specific contractile proteins\(^\text{[47]}\). Furthermore, it was observed that ventricular myocytes of rat hypertrophic hearts not only increase the expression of IGF1-R, but also the binding of IGF-1 can stimulate re-entry of these cells into the cell cycle\(^\text{[48]}\). More recently, in dog hypertrophic hearts, it was showed that the expression of the cell cycle regulatory molecules cyclins is correlated with the IGF-1 and its receptor\(^\text{[49]}\). However, it is discussed the way in which IGF acts on the growth of cardiomyocytes. In mice with overexpression of IGF-1R and experiencing exercise it was observed that IGF-1 caused a physiological cardiac hypertrophy through the phosphoinositide 3-kinase (PI3K)-Akt pathway, since the factor promoted the translation of key proteins for an adaptive response but did not activate the expression of cardiac genes related to a pathological response\(^\text{[50]}\). In this way, it was suggested that the IGF-1/IGFIR/AKT pathway regulates cardiomyocyte growth only in physiological conditions, while in the pathological conditions there is...
FGF-2 and IGF-1 appear to be the main factor with neurotrophic activity involved in the fibrosis process. Data on the role of FGF-2 in fibrosis are conflicting. Prior studies suggest that FGF-2 could have a pro-fibrotic action. Virag and collaborators[157] observed that the deletion of FGF-2 provoked a reduced proliferation of fibroblasts and ECM deposition in the heart of a mouse model of infarct. By the other hand the authors verified that the overexpression of FGF-2 induced an augment in these processes. The induction of fibrosis by FGF-2 was also strongly suggested in a mouse model of pressure overload[158]. More recently, it was demonstrated that FGF-2 is able to promote atrial fibrosis in the myocardium of patients with atrial fibrillation and rheumatic heart disease[159]. In contrast, others studies point to an anti-fibrotic effect of FGF-2. In Dahl salt-sensitive rats FGF-2 inhibited interstitial fibrosis and then the progression of ventricular remodeling[160]. Moreover, it was observed that lo-FGF-2 was able to attenuating ECM remodeling by myofibroblasts cultured within a 3D collagen matrix[170]. Additional studies may be provided in order to clarify the different aspects of FGF-2 activities in fibrosis. Concerning IGF-1 the studies are scarcer but they point to a role of this factor in protecting the myocardium against fibrosis. IGF-1 administrated or expressed locally in heart resulted in the blockade of fibroblast proliferation and resultant fibrosis[171,172].

CONCLUSION

Considerable research to date has implicated the NF in ameliorating heart function in many heart diseases. NGF and BDNF are able to induce angiogenesis, nerve sprouting and endothelial and cardiac muscle cell survival in the ischemic heart. These effects are evoked by conventional TrK signaling and the PI3K/Akt pathway to attenuate the endoplasmic reticulum stress-induced death. NGF and BDNF binding to p75 receptor can act on reducing the density of autonomic innervation in the ischemic area. MANF and FGF have also been implicated in cardiac muscle cell survival during ischemia. FGF and IGF are the main growth factors implicated in the cardiac hypertrophy. Distinct neurotrophic peptides are involved in a same pathophysiological condition, indicating that might have complementary, additive or opposite effects.

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CONFICT OF INTEREST

There are no conflicts of interest with regard to the present study.

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