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The neurotrophic factors in non-neuronal tissues

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Abstract. Although neurotrophic factors are defined as molecules that maintain neuronal cells, they possess a range of functions outside the nervous system. For example, glial cell line-derived neurotrophic factor is essential for ureteric branching in kidney morphogenesis and for regulating the fate of stem cells during spermatogenesis. Leukemia inhibitory factor, a member of the interleukin-6 (IL-6) ciliary neurotrophic factor family, inhibits differentiation of embryonic stem cells, induces tubulogenesis in the embryonic kidney, and regulates sperm differentiation. Other IL-6 family members are important in cardiac differentiation and they have pleiotropic functions in the hematopoietic and immune systems. Although neurotrophin receptors have been found on a number of non-neuronal tissues, they represent mostly truncated receptor isoforms that are incapable of signal transduction and may have scavenger or dominant negative functions. However, several examples can be presented of essential non-neuronal functions played by neurotrophins in e.g., cardiac, hair follicle, and vascular differentiation, and the maintenance of immune cells.

Key words. Neurotrophic factor; GDNF; neurotrophin; interleukin-6; kidney; testis; lymphocyte; mast cell; liver.

Introduction

Neurotrophic factors are defined as target-derived, antiapoptotic molecules that maintain embryonic or adult neuronal cells. The word ‘trophic’ is derived from Greek ‘trophé’ meaning nourishment or taking up of nutrients. Originally, neurotrophism implied that the target tissues feed the neurones that innervate them [1]. The food is now known to consist of signalling molecules secreted by the target tissues. While evidence is accumulating that a number of multifunctional signalling molecules, such as fibroblast growth factors, transforming growth factors, and bone morphogenetic proteins, act as neurotrophic factors, the class of neurotrophic factors by tradition includes only molecules that preferentially act on neuronal cells or that were originally discovered as antiapoptotic molecules for neuronal cells. However, even these definitions are somewhat arbitrary, because some ‘typical’ neurotrophic factors, such as neurotrophin (NT)-3, glial cell line-derived neurotrophic factor (GDNF), and leukemia inhibitory factor (LIF), affect critical morphogenetic processes outside the nervous system. On the other hand, a GDNF homologue, neurturin, does not maintain neuronal cells, although it promotes their differentiation and acts as a chemoattractant [2]. Ultimately, the use and definition of the term ‘neurotrophic factor’ seems to be based on the perspective of the scientist rather than the actual function and tissue specificity of the signalling molecule. I will briefly review the known non-neuronal effects of the neurotrophin, interleukin-6/ciliary neurotrophic factor (IL-6/CNTF) and GDNF families. Although they are well-known from their functions in central and peripheral nervous systems, they possess several critical roles outside the nervous system, for example, in kidney and cardiac development, spermatogenesis, and maintenance of immune cells. An intriguing question concerns the similarity of functions of IL-6 and GDNF families in spermatogenesis, raising the possibility that these neurotrophic factors could act in concert or on the same downstream signalling pathways. Furthermore, the functions or low- and high-affinity neurotrophin receptors in non-neuronal tissues provide a long-standing dilemma.

Neurotrophins and their receptors

The neurotrophin family consists of four members: nerve growth factor (NGF), brain-derived neurotrophic factor

(BDNF), NT-3 and NT-4/5. They share the same low-affinity neurotrophin receptor $p75^{NTR}$, but use different members of the Trk receptor tyrosine kinase family for high-affinity binding and signal transduction. NGF preferentially activates TrkA, BDNF and NT-4/5 prefer TrkB, and NT-3 uses TrkC. The low- and high-affinity neurotrophin receptors are widely distributed in non-neuronal tissues (table 1).

The Trk receptors outside the nervous system represent mostly truncated isoforms, suggesting that they do not transduce neurotrophin signals but rather act as scavenger or dominant negative receptors [3–8]. Although their role is unknown in most tissues, gene-targeted mice and transgenic mice overexpressing truncated receptor isoforms have shown that TrkC is important in the morphogenesis of the cardiac outflow tract [9]. TrkC is also important in the differentiation, maintenance, and function of lymphocytes, monocytes, and mast cells [10–12]. Targeted disruption of other trk receptor genes has not revealed severe defects outside the nervous system.

The low-affinity neurotrophin receptor p75 ($p75^{NTR}$) is widely expressed in embryonic and adult tissues [13–16], and has been suggested to affect spermatogenesis [17], nephrogenesis [18–19] and the length of the hair follicle cycle [20]. However, not all of these functions are supported by the phenotype of $p75^{NTR}$-deficient mice that are fertile and develop normal kidneys [21]. $p75^{NTR}$ is expressed in hair follicles, and mice deficient for $p75^{NTR}$ show significantly accelerated hair follicle morphogenesis with an early progression to the regression (catagen) stage characterized by extensive apoptosis in the hair root [20]. $p75^{NTR}$ is also expressed by the hepatic stellate cells that secrete interstitial collagens, a critical process in the pathogenesis of liver cirrhosis. The stellate cells undergo massive apoptosis in vitro when exposed to NGF, raising the possibility that NGF must be considered in the therapy of liver cirrhosis [22].

Table 1. Distribution of high- and low-affinity neurotrophin receptors in non-neuronal tissues.

Tissue/cell type	TrkA	TrkB	TrkC	p75
B lymphocyte	+			+
T lymphocyte, monocyte, granulocyte, mast cell	+ +			
Spleen		+		+
Astrocyte, oligodendrocyte, Schwann cell		+		
Tooth		+	+	+
Salivary gland		+	+	+
Fat tissue			+	
Lung	+	+	+	+
Heart		+	+	+
Pericardium			+	
Thyroid gland	+	+	+	+
Kidney	+	+	+	+
Aorta		+	+	+
Muscle	+	+	+	+
Liver				+
Testis	+	+	+	+
Hair follicle		+	+	+

Expression in the peripheral nervous system is not included [9]. The data were mainly collected from mRNA expression studies either by in situ hybridization or Northern blotting.

The most striking defect outside the nervous system in neurotrophin-deficient mice has been found in mice lacking NT-3 [23, 24]. They exhibit a series of cardiac defects that appear to be related to abnormal neural crest development. The variety of cardiac defects range from pulmonary stenosis, tetralogy of Fallot, persistent truncus arteriosus to ventricular septal defects that are typically caused by a defect in the migrating neural crest cells that contribute to the development of the cardiac outflow tract [25]. Furthermore, NT-3 shows a highly stage-specific expression pattern during the hair follicle cycle, and transgenic mice with either increased or reduced NT-3 expression display either precocious or delayed hair follicle regression, respectively [26]. A similar function has also been ascribed to BDNF and NT-4/5 [27]. Several neurotrophins are expressed by vascular smooth muscle cells (SMCs): they act as chemoattractants in vitro for SMCs, and both they and their receptors are highly upregulated in vessel walls in experimentally induced endothelial damage [28].

NGF promotes the differentiation of B lymphocytes [29]. It maintains memory B lymphocytes [30], neutrophils, and peritoneal mast cells [31, 32]. Furthermore, NGF is expressed by testis and epididymis in rat and mouse, and its expression is downregulated by testosterone, but its function in spermatogenesis has remained unresolved [33].

GDNF family factors and their receptors

GDNF and the related molecules, neurturin, artemin, and persephin, signal via the same high-affinity receptor, the Ret receptor tyrosine kinase [2]. The signalling receptor complex also includes phosphatidylinositol-linked co-receptors, the GDNF family receptor αs (GFRα1–4). GDNF-, Ret- and GFRα1-deficient mice show relatively similar phenotypes. They all die during the first postnatal day [34–39], because of the lack of enteric innervation below the stomach as well as renal aplasia or hypodysplasia [2, 40].

Kidney differentiation is regulated by an inductive tissue interaction between the ureteric bud and the nephrogenic mesenchyme [41]. The ureteric bud induces epithelial differentiation of the nephrogenic mesenchyme which, in

turn, reciprocally promotes branching of the bud. GDNF is expressed by the nephrogenic mesenchyme and Ret by the adjacent epithelial cells, the tips of the ureteric bud [42, 43]. The co-receptor GFRα1 is expressed by both the nephrogenic mesenchyme and the ureteric bud [44]. Thus, this ligand-receptor pair was considered a good candidate to regulate ureteric branching. Indeed, organ culture experiments and transgenic approaches have now shown that GDNF is an essential signal to trigger the initial ureteric budding and subsequent branching [35–37, 44, 46] (fig. 1). Neurturin is expressed by the tips of the ureteric bud, by the same cells that express Ret, and it promotes ureteric budding in organ culture, suggesting that cell-autonomous signalling is also involved in the regulation of ureteric branching morphogenesis [47]. However, neurturin-deficient mice do not show renal defects, indicating that neurturin is not important in normal kidney differentiation [48]. In addition, pharmacological doses of persephin promote small ureteric buds. However, mRNA levels of persephin are very low in the embryonic kidney and transgenic mice lacking persephin do not show renal defects, suggesting that it is not essential in kidney differentiation [49].

GDNF was recently implicated in sperm differentiation. GDNF is expressed by Sertoli cells that are known to regulate spermatogenesis, and its receptors are displayed by a subset of spermatogonia including the stem cells for spermatogenesis [50]. Gene-targeted mice with one GDNF-null allele show depletion of spermatogenic stem cells, whereas mice overexpressing GDNF accumulate undifferentiated spermatogonia [50]. Thus, GDNF contributes to the paracrine regulation of spermatogonial self-renewal and differentiation (fig. 2). GDNF-overexpressing mice are infertile and develop testicular tumors in adulthood, which makes GDNF signalling a promising target for therapeutic intervention for men suffering from infertility or testicular cancer. In accordance with this proposal, testicular cancers express both Ret and GFRα1 [51].

The regulatory functions of GDNF in spermatogenesis and kidney morphogenesis clearly show the haploinsufficiency of the GDNF gene. The dosage of GDNF has dose-dependent effects in the target tissue, and these are not only quantitative, such as the dose-dependent increase in the number of branches from the ureteric bud [35, 44], but also qualitative, such as the dose-dependent cell lineage determination of spermatogonia [50]. Thus, the expression of the GDNF receptors on a cell obviously defines the target cell type for GDNF, but both the quantity and nature of the response are regulated by the dosage of the ligand. This mode of action is very similar to that of neurotrophins that act as rate-limiting, target tissue-derived molecules [1].

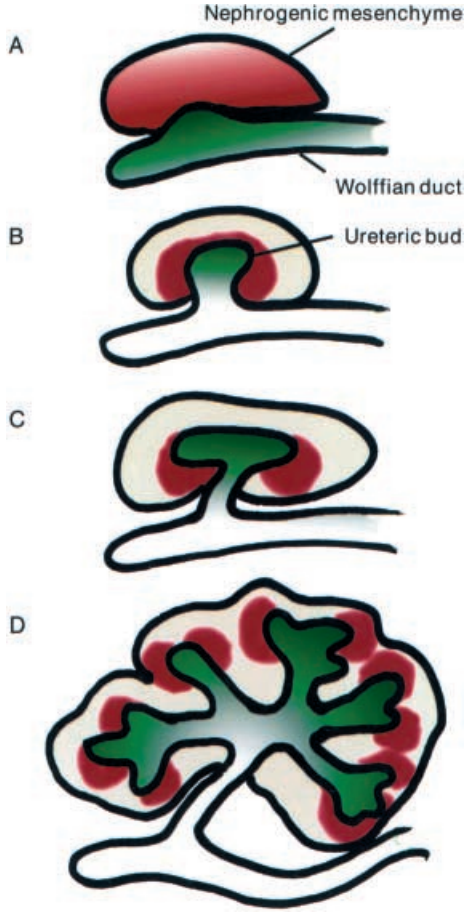

Figure 1. Interplay between GDNF (red) and Ret (green) in the ureteric branching during nephrogenesis. (*A*) In the undifferentiated kidney rudiment, the entire nephrogenic mesenchyme expresses GDNF which promotes budding from the Wolffian duct (expressing Ret and GFRα1). (*B*) This so-called ureteric bud invades the mesenchyme and induces two pretubular condensates that upregulate their GDNF expression. (*C*) The double-gradient created by the formation of the condensates triggers branching of the bud. (*D*) The same event is repeated at all subsequent steps of nephrogenesis. The ureteric bud will ultimately form the collecting duct network, and the pretubular condensates, the nephrons. After epithelial transformation of the nephrons, GDNF expression is downregulated.

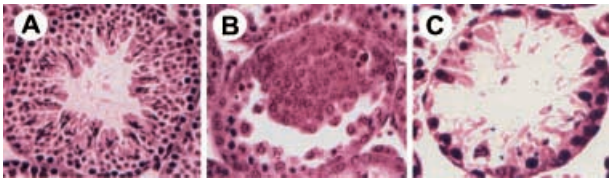

Figure 2. Regulation of spermatogonial cell fate decision by GDNF, as shown by gain- and loss-of-function in transgenic mice. (*A*) In normal seminiferous tubules, the dosage of GDNF allows balanced differention and self-renewal of spermatogonia, the stem cells of spermatogenesis. (*B*) If GDNF dosage is high, the spermatogonia form clusters in the tubules but do not differentiate (targeted overexpression). (*C*) When the GDNF dosage is low, the stem cells differentiate in excess and are depleted (heterozygotes of GDFN-deficient mice). The end result is a seminiferous tubule without germ line cells, called the Sertoli-cell-only syndrome in human [50].

Mutations in the Ret gene leading to the constitutive activation of the receptor cause two multiple endocrine neoplasia syndromes, MEN2A and MEN2B [52–54]. These syndromes are characterized by medullary thyroid carcinoma, pheochromocytomas and parathyroid adenomas. Mutations inactivating the Ret gene lead to variable defects in the enteric innervation causing congenital megacolon (Hirschsprung's disease, OMIM 171400). It is puzzling that the predisposition to renal and testicular malignancies is not increased in MEN2 patients, although GDNF signalling affects both kidney morphogenesis and spermatogenesis, and testicular tumors develop upon GDNF overstimulation. A plausible explanation could be the tissue-specific distribution of the GFRαs that may modulate the oncogenic potential of the MEN2 mutations in the Ret gene [55].

Sertoli cells also express neurturin [56]. The primary coreceptor for neurturin, GFRα2, is expressed later than GFRα1 on differentiating sperm cells, indicating different functions for GDNF and neurturin during spermatogenesis. Indeed, unlike the GDNF-overexpressing mice, the testis-targeted mice overexpressing neurturin are fertile and show only segmental defects in spermatogenesis [50].

IL-6 family and its shared gp130 receptor

gp130 is the common signal-transducing component of the functional receptor complexes for the IL-6/CNTF family of 'neuropoietic cytokines,' including IL-6, IL-11, LIF, oncostatin M, CNTF, and cardiotrophin-1 (CT-1). These cytokines exhibit pleiotropic biological activities in immune, hematopoietic, and neural systems, and function in a redundant manner owing to the shared usage of gp130 [57]. CT-1 was originally isolated for its hypertrophy-inducing effects on cardiac myocytes, whereas IL-11 was identified due to its ability to stimulate an IL-6-dependent plasmocytoma cell line [58]. Oncostatin M protects stellate cells from apoptosis in the liver [59].

LIF was recently shown to induce differentiation of kidney tubules in organ culture after priming of the nephrogenic mesenchyme with fibroblast growth factor-2 [60]. All IL-6 family members are potent inhibitors of embryonic stem cell differentiation and LIF, at least, is critical for blastocyst implantation [61, 62]. In embryonic stem cells, LIF activates Janus kinases and STAT-3 that may be responsible for the maintenance of the undifferentiated state [63].

Conclusions

The non-neuronal functions of neurotrophic factors share some common and maybe educational similarities. GDNF and IL-6 families seem to affect at least some overlapping processes, such as kidney morphogenesis and spermatogenesis. The neurotrophins play different roles outside the nervous system, functioning in cardiac morphogenesis, maintenance of immune cells, control of hair follicle cycle, and angiogenesis. Common to all three classes of signalling molecule seems to be their obvious dose-dependent mode of action. Despite the well-defined non-neuronal functions for neurotrophins, the widespread distribution of truncated Trk isoforms has in most cases remained enigmatic, and the role of $p75^{NTR}$ inside and outside the nervous system is still highly controversial.

The term neurotrophic factor seems to be a historical misnomer. When one tries to classify certain signalling molecules into this category and exclude others, one easily gets lost. This term is obviously a scientific relict of little justification after the identification of the neurotrophic activities of most if not all families of signalling molecules, and because the neurotrophic factors have various activities outside the nervous system. Ip and Yancopoulos [64] stated in 1994: 'As the actions of neurotrophic factors appear so strikingly different from those of growth factors and cytokines operating elsewhere in the body, it was long thought that neurotrophic factors might in some way be fundamentally different from traditional growth factors and cytokines. Recent advances in the understanding of the structure of the receptors for neurotrophic factors reveals them to be much more like the receptors used by other cytokines and growth factors than was perhaps first anticipated. These findings suggest that neurotrophic factors display distinctive actions not because they utilize novel receptor systems, but rather because they activate these receptors in neurons.'

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