From neurotrophins to immunotrophins

NGF 2002: The 7th international conference on NGF and related molecules

Mike Fainzilber⁺ & Bruce D. Carter¹

Laboratory of Molecular Neurobiology, Department of Biological Chemistry, Weizmann Institute of Science, 76100 Rehovot, Israel and ¹Department of Biochemistry and Center for Molecular Neuroscience, Vanderbilt University Medical School, Nashville, TN 37232, USA

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The 7th international conference on NGF and related molecules, organized by Luigi Aloe (CNR, Rome) and Laura Calza (University of Bologna) and their colleagues, was held in Modena, Italy, over the 15–19th of May, 2002; with the active participation of the discoverer of NGF, Dr Rita Levi-Montalcini, now a sprightly 93 and still going strong.

The series of international conferences on nerve growth factor (NGF) and related molecules arose from a meeting held in 1986, to mark Rita Levi-Montalcini's 77th birthday, and in recognition of the fact that her discovery of NGF opened up the field of trophic factors. One of the best characterized families of such trophic factors is the NGF family of neurotrophins, which in mammals also includes BDNF (brain derived neurotrophic factor), NT3 (neurotrophin 3) and NT4 (neurotrophin 4). The meeting has since become a biennial event held in alternating years with the Gordon Conference on neurotrophic factors. This year's meeting, the seventh in the series, was held in the lovely Italian town of Modena and was honored once again by the presence of the Nobel laureate. In accordance with Levi-Montalcini's views on expanding roles for neurotrophins outside the nervous system, the organizers prepared a wide-ranging program encompassing neuronal, non-neuronal and clinical aspects of NGF research. Presentations included some quite striking research topics, such as the effects of increased gravity on tissue levels of neurotrophins (D. Santucci, Rome, Italy), as well as more conventional studies on different aspects of neurotrophic factor biology. In this short report we focus on molecular and mechanistic advances presented at the meeting. We apologize to the many speakers and poster presenters whose data could not be highlighted due to space constraints. For a more thorough discussion of the neurotrophins and their actions, readers are

referred to more comprehensive reviews (Bibel and Barde, 2000; Huang and Reichardt, 2001).

The PNS, not a peripheral topic

The meeting kicked off on the theme of neurotrophin action in the peripheral nervous system (PNS). B. Fritsch (Omaha, NE) described the role of the neurotrophins NT3 and BDNF in sensory neuron innervation of the inner ear. The structure and innervation pattern of this sensory system is highly complex, as is the trophic dependence of the various neurons. Nevertheless, it had been reported previously that mice lacking *bdnf* have a dramatic loss in vestibular neurons while *nt3*^{-/-} mice lack cochlear innervation, although there is some overlap in sensory neuron trophic dependence (reviewed in Huang and Reichardt, 2001). Fritsch demonstrated that although many fibers innervating the inner hair cells (IHC) of the cochlea are dependent on NT3 and those innervating outer hair cells (OHC) on BDNF, this correlation is not strict. In fact, detailed analysis reveals a considerable overlap in the dependence of sensory neurons innervating both IHC and OHC. To further address the role of these neurotrophins in regulating sensory innervation of the inner ear, Fritsch's group used a knock-in mouse created by L. Tessarollo (Frederick, MD), in which *bdnf* replaces *nt3*. Preliminary analysis indicates a complete rescue of the *nt3*^{-/-} phenotype in terms of survival, but a misrouting of some vestibular fibers into the cochlea. Certainly we look forward to 'hearing' more about the role of neurotrophins in the auditory system.

The dependence of peripheral neurons on neurotrophins was a topic further addressed by K. Unsicker (Heidelberg, Germany), who described a role for NT4 in promoting the survival of preganglionic sympathetic neurons. This population of neurons, located in the spinal cord, sends projections to the peripheral ganglia, thus acting as a bridge between the PNS and CNS. Mice lacking *nt4* exhibit a deficit in a subset of preganglionic neurons, specifically those that project to the stellate and prevertebral ganglia, but not those projecting to the superior sympathetic

⁺Corresponding author: Tel: +972 8 934 4266; Fax: +972 8 934 4112; E-mail: mike.fainzilber@weizmann.ac.il

ganglia. It is curious that loss of *nt4* leads to such selective effects, since all preganglionic neurons express TrkB, the tyrosine kinase receptor that binds NT4 and BDNF selectively, and all postganglionic neurons express NT4. Such highly selective effects of *nt4* deletion have also been observed in the sensory neuron population, where a specific class of cutaneous neurons are lost (Stucky *et al.*, 1998). Further studies of how NT4 signals through TrkB in these neurons will be needed to understand how such specificity is achieved.

The molecular mechanisms by which peripheral neurons undergo cell death during development have begun to be elucidated over the last decade, in large part, through the work of E. Johnson's group (St Louis, MO). Johnson described the events involved in the 'commitment to die' by sympathetic neurons deprived of NGF, focusing particularly on the role of the mitochondria. These neurons undergo death through two 'commitment' stages. Commitment one involves classic apoptotic mechanisms and can be inhibited by blocking caspases. However, even these rescued neurons die, through commitment two, which depends on mitochondrial depolarization. Intriguingly, inhibiting both the caspases and the mitochondrial permeability transition rescues rat neurons, but not those of mice, perhaps since dying murine neurons appear to run the mitochondrial F_0F_1 -ATPase in reverse during 'commitment two' to deplete the cellular energy pool.

The effects of neurotrophins in the PNS were also covered by S. McMahon (London, UK) who told us 'what a pain' these factors can be. It has long been recognized that tissue injury causes pain at the site of injury, as well as a reduction in the threshold for pain perception (hyperalgesia) and sensitization of nociceptors (the sensory neurons responsive to pain) in the surrounding area. Although it has been shown that the sensitization is partly due to a local increase in NGF, McMahon presented data suggesting that there is a CNS component to BDNF-mediated sensitization. Dorsal root ganglia neurons that express the NGF receptor, TrkA, increase their expression of BDNF after injury. McMahon's group used an *in vitro* slice preparation to demonstrate that stimulation of the dorsal roots caused release of BDNF into the dorsal horn of the spinal cord, resulting in TrkB activation, which is thought to enhance synaptic transmission and increase nociceptive signaling. Moreover, injection of a soluble TrkB-Fc fusion into the spinal cavity to adsorb extracellular BDNF prevented the second phase of formalin-induced hyperalgesia. Thus, the multiple functions of neurotrophins include diverse ways of mediating or modulating multiple pain signals.

To be or not to be ... a neuron

The role of transcription factors in controlling neuronal differentiation was discussed by several speakers. J. Angelastro and L. Greene (New York, NY) presented results from serial analysis of gene expression (SAGE) in PC12 cells induced to differentiate by NGF application. This study found numerous transcription factors to be regulated by NGF. One such factor, ATF-5, was downregulated 26-fold by NGF treatment, and when constitutively overexpressed in PC12 cells or primary neurons, caused an inhibition of neurite extension. Constitutive overexpression of CREB, a transcription factor instructive for neurite outgrowth,

antagonizes the repression observed with ATF-5. In the developing brain this factor is found in regions undergoing neurogenesis, but not in mature neurons. Angelastro's and Greene's presentations culminated in a model suggesting that trophic factor-regulated transcription factors are involved in regulating the transition between proliferating precursor cells and post-mitotic neurons. Complementary data from a different system was presented by J. Kessler (Chicago, IL). In stem cells derived from the subventricular zone (SVZ), bone morphogenetic protein 4 (BMP4) promotes a neuronal and astroglial lineage commitment, while suppressing oligodendroglial lineage (OL) commitment throughout development. Eighteen thousand genes in BMP4-exposed stem cells were subjected to microarray analysis, and BMP4 treatment was found to stimulate the expression of only seven of these. The seven candidates all belonged to either the HEY1 or the Id4 families of transcription factors. Inhibition of their expression blocked the BMP4-mediated suppression of OL development. Conversely, overexpression of the factors blocked OL differentiation. Furthermore, transgenic mice expressing BMP4 under the control of nestin (a promoter expressed in early neural precursor cells), exhibited a large increase in astrocytes and a decrease in OL in the hindbrain. Thus, a shared conclusion from the session was that commitment to a neuronal fate may be regulated in part by suppression of default commitments to other lineages.

A. Vescovi (Milan) also discussed a role for transcriptional regulation of stem cell differentiation. His group obtained stem cells from throughout the adult SVZ and its rostral extension, and showed the existence of regional differences in the isolated cells. The distally derived cells grew more slowly in culture and expressed higher levels of the homeobox protein, *Emx2*, which is also expressed in the SVZ. Vescovi's data suggest that *Emx2* may negatively regulate proliferation and function to drive stem cells to arrest and begin differentiation.

p75—new tricks from an old receptor

Although p75 was the first neurotrophin receptor to be identified, characterization of the Trk gene family placed it 'in the shade' for some years. The inherent tyrosine kinase activities and potent signaling of Trks contrasted starkly with the lack of an identified catalytic activity for p75. Furthermore, even though p75 clearly belongs to the TNF receptor superfamily, it does not share the trimeric ligands or major signaling pathways characterized thus far for TNF receptors. However, p75 has lately returned to center stage (Figure 1), with the definition of pro-neurotrophins as a new category of high affinity ligands for this receptor, and the characterization of drastic neurological and vascular defects in the completely null animal (reviewed by Hempstead, 2002). A series of presentations at this meeting showed that surprises are still in store for the p75 field. B. Hempstead (New York, NY) and S. Yoon (Columbus, OH) both presented data confirming and extending the role of pro-neurotrophins as newly described, specific ligands for p75. Hempstead stressed the sensitivity of pro-neurotrophins to extracellular degradation by matrix metalloproteases as a potential mechanism for regulating the system, but also as a cautionary note for those commencing analyses of these ligands. The data from Yoon's group was especially intriguing, since they show a physiological role for a

Fig. 1. A variety of ligands and proposed signaling modalities for the p75 receptor. Both pro-NTs (pro-neurotrophins) and NTs can bind p75, with processing of pro-NTs potentially occurring extracellularly at multiple cleavage sites. Once activated, p75 may recruit a primary layer of interactors from the MAGE family to form a MAGE-scaffolded complex (MSC). Such a complex might be internalized into a signaling endosome (SE); or the p75 intracellular domain might undergo cleavage to form a nuclear-targeted complex (NTC). Such cleavage may also free the 'Chopper' domain of p75 (Chp) to activate second messenger pathways that modulate potassium channels (KCh).

p75-mediated apoptotic signal induced by pro-NGF and/or pro-BDNF in the removal of oligodendrocytes during the 'Wallerian degeneration' that follows spinal cord injury. W. Friedman (Rutgers, NJ) also presented evidence for p75-induced death in a biologically relevant context, following seizure in the hippocampus; whether pro-neurotrophins are involved here too remains to be determined.

A signaling cascade emanating from the p75 receptor and culminating in the activation of effector death caspases was sketched out by P. Barker (Montreal, Canada). The cascade is initiated by NRAGE, a recently described p75 interactor from the MAGE gene family, and proceeds via the jun kinase (Jnk) pathway to caspase-9 activation and cytochrome c release. New members of the MAGE family that interact with p75 were presented by M. Tcherpakov and M. Fainzilber (Rehovot, Israel). These additional MAGE family members interact with p75 in a ligand-dependent manner to affect differentiation or survival of transfected cells. Taken together with P. Barker's presentation,

these findings suggest that the MAGE gene family figures prominently in p75 signaling pathways.

Two other known p75 intracellular interactors, TRAF6 and NRIF, were shown by J. Gentry and B. Carter (Nashville, TN) to associate with each other and to modulate signaling through Jnk. Curiously, the interaction of TRAF6 and NRIF results in nuclear accumulation of NRIF, perhaps indicating a nuclear target for p75 signaling. This topic was further developed in the intriguing presentation of M. Bothwell (Seattle, WA). He discussed two novel p75 homologs, NRH1 and NRH2, at least one of which is co-expressed in specific tissues together with p75, and is found in certain cases as a cytoplasmic, intracellular domain only form. Inspired by this finding, Bothwell's group went on to examine the possibility that p75 itself might be cleaved to release its intracellular domain. They were able to demonstrate such cleavage upon ligand binding to the extracellular domain in cell lines, and that this was followed by translocation of the intracellular cleavage product to the nucleus. Thus, p75 may send a signaling complex to the nucleus in a manner analogous to that previously demonstrated for a number of other receptors such as Notch, ErbB4 and the amyloid precursor protein (APP) (Ebinu and Yankner, 2002).

E. Coulson and P. Bartlett (Melbourne, Australia) presented another possible mechanism for p75-induced cell death. This was based on studies of another intracellular fragment of the receptor, the juxtamembrane portion, which is referred to as 'Chopper'. Chopper-induced neuronal cell death was found to be dependent on extracellular K⁺, suggesting the involvement of a specific channel. The channel has now been identified, and does not appear to interact directly with the Chopper domain, indicating that K⁺ channel activation by p75 may occur *in trans* via second messenger pathways.

Studies by A. Kruttgen (Bern, Switzerland) and F. Bronfman (Rehovot, Israel) examined the possibility that p75 signaling might utilize endosomes. Both presented data showing ligand-induced internalization of p75, and suggested that p75 may contribute significantly to neurotrophin internalization in neurons. Thus, an embarrassing richness of potential ligands, interactors and signaling modalities are available for the p75 neurotrophin receptor (Figure 1). Clearly the immediate challenge will be to delineate those that are of physiological significance in the organism.

Trk receptor signaling—endosomes away!

The subcellular location and trafficking of signaling complexes centered around the NGF receptor tyrosine kinase, TrkA, has been a hot topic of late (Heerssen and Segal, 2002; see also Figure 2), and was addressed in the presentation of W. Mobley (Stanford, CA). He reviewed a series of studies aimed at identifying a TrkA signaling endosome and defining its components. Analyses conducted in both cultured cells and in sciatic nerves suggest that TrkA signaling complexes are activated in conjunction with their transport from the axonal surface to early endosomes, and that they are subsequently retrogradely transported to the cell body. The importance of an intracellular signaling platform for TrkA was also emphasized by M. Chao (New York, NY) and B. Rudkin (Lyon, France). The Chao group studied TrkA receptors trans-activated by G-protein-coupled receptor signaling, and

found that the activated TrkA pool was exclusively intracellular. Rudkin presented data from studies in PC12 cells, in which the kinetics of internalization were compared with the kinetics of receptor activation. These indicated that signaling was mediated mainly by internalized receptors. Continuing on this theme, B. Lu (Bethesda, MD) presented studies examining activity-dependent internalization of BDNF–TrkB complexes under conditions similar to those used previously to study the modulation of long term potentiation (LTP) or long term depression (LTD) by these molecules. In one case, neuronal activity in hippocampal neurons was shown to facilitate BDNF receptor internalization. In another, performed at neuromuscular synapses in *Xenopus*, blocking TrkC internalization with dominant-negative dynamin inhibited the long-term, but not the acute, effects of NT-3. These findings emphasize the importance of the subcellular localization of the signaling platform for specific effects of the neurotrophins.

Further studies on Trk signaling mechanisms were presented by D. Kaplan (Montreal, Canada) who, in collaboration with F. Miller (Montreal, Canada), has elucidated a role for the p53 family of cell cycle checkpoint proteins (which includes p53, p73 and p63) in regulating neuronal survival. Both p73 and p63 can exist as either full-length transcripts or N-terminal truncated forms (DN). The latter lack the transactivation domain and thus act as dominant repressors, inhibiting the pro-apoptotic function of the full-length proteins. In the presence of NGF, both DNp73 and DNp63 are expressed in sympathetic and cortical neurons, but are downregulated upon loss of trophic signaling (e.g. by NGF removal). Ectopic expression of either truncated protein can prevent cell death following NGF withdrawal, whereas deletion of the *p73* gene results in a massive loss in sympathetic neurons and cells of the developing cortex. Interestingly, Nakagawa *et al.* (2002) recently demonstrated that there is an alternative promoter located in intron 3 of the *p73* gene, and that this drives the expression of DNp73. In future, it will be interesting to determine how NGF signaling regulates the transcription of these suppressors of apoptosis.

Overweight and obnoxious? Try some TrkB

Moving to *in vivo* physiology of neurotrophins in the CNS, B. Xu and L. Reichardt (San Francisco, CA) presented data on the *trkB* hypomorph mouse. This animal, which expresses TrkB at 25% of normal levels, is aggressive, hyperactive and severely obese. Since this phenotype mirrors that observed in certain hypothalamic lesions, Xu and Reichardt looked at BDNF and TrkB expression in the ventral medial hypothalamus (VMH), a region known to regulate feeding behavior. No clear colocalization of TrkB with peptides such as leptin, orexin or NPY, all of which are associated with the regulation of food intake, was apparent in the hypothalamus, but BDNF was highly expressed in the VMH and decreased dramatically during fasting. Although it is not yet clear how BDNF regulates caloric homeostasis, Reichardt demonstrated that BDNF expression is under the control of α MSH, a peptide known to regulate food intake.

L. Parada (Dallas, TX) continued on the theme of the roles of neurotrophins in the CNS, describing a conditional knock-out of *nt3* specifically in the cerebral cortex. Strikingly, although these

mice have an anatomically intact visual system, they are cortically blind in behavioral tests, and have inappropriate thalamo-cortical innervation, suggesting a novel role for NT3 in regulating synaptic strength in the cortex. The role of neurotrophins in regulating the visual cortex was also highlighted by L. Maffei (Pisa, Italy). His group, and others, have elucidated an essential role for the neurotrophins in the activity-dependent formation of ocular dominance columns during the critical

Fig. 2. Different modalities for TrkA signaling. Ligand-induced activation and internalization of TrkA can be complemented or modulated by transactivation of internalized receptor by a G-protein coupled receptor (GPCR). Recruitment of adaptor molecules such as phospholipase Cγ (PLCγ) creates a functional signaling endosome (SE) that may be retrogradely transported from axon to cell body. PI3K, phosphatidylinositol-3' kinase.

period of development in rats. Maffei's group has begun to investigate the molecular changes responsible for these effects on visual plasticity, and has shown that the activation of Erks downstream of the Trk receptors is required for mediating the effects initiated by monocular deprivation. Maffei described the group's most recent findings, which implicate Erk activation of the transcription factor CREB in this system.

Finally, although several of the clinical trials using neurotrophins to treat peripheral neurodegenerative conditions such as diabetic neuropathy and amyotrophic lateral sclerosis have proved unsuccessful, there are still several pathologies for which neurotrophins are being considered as potential therapeutics. M. Tuszynski (San Diego, CA) presented the example of Alzheimer's disease, for which a clinical trial is ongoing. This trial follows up on very promising data in monkeys, where transplantation of NGF-secreting cells rescued cholinergic neurons following either a transection of the fimbria-fornix or normal aging. Importantly, the graft size remained stable and continued NGF secretion for at least one year, and the treated monkeys showed no adverse side effects. Thus, there is still some promise for using neurotrophins to treat a disease afflicting millions worldwide.

Reports from the other side— GDNFRs *in cis* and *trans*

Two speakers at the meeting presented updates on the GDNF family of trophic factors, highlighting different approaches to the question of whether signaling *in trans* by the GDNF co-receptors, GRF α 1 and c-Ret, is a requirement for pathway activation. Members of the GDNF family bind to the glycosyl phosphatidylinositol-anchored α -subunits (GRF α), which then couple to the tyrosine kinase c-Ret. GDNF signaling through this receptor complex promotes the survival of a variety of neuronal populations, including midbrain dopaminergic, motor, sensory and enteric neurons. In addition, GDNF activation of c-Ret is essential for normal kidney morphogenesis (Airaksinen and Saarma, 2002). Curiously, the GFR α co-receptors are more widely expressed in the nervous system than c-Ret, suggesting that GDNF may be presented by GRF α on one cell to c-Ret on the surface of another cell, i.e. signaling *in trans*. In support of such *trans* signaling, C. Ibanez (Stockholm, Sweden) showed subcellular partitioning of c-Ret and GFR α 1 in cultured neurons. Whereas GFR α 1 appears restricted to the cell bodies in cultures of dissociated sympathetic neurons, and is less apparent on axons or growth cones, c-Ret is also expressed robustly along axons. Moreover, soluble GFR α 1 potentiates neurite outgrowth in the presence of saturating levels of GDNF. Thus, GFR α 1 applied *in trans* can apparently present GDNF to c-Ret on the axon, providing a neurite outgrowth/guidance signal. An *in vivo* approach to this question was presented by J. Milbrandt (St Louis, MO), who engineered a transgenic mouse to co-express GFR α 1 exclusively in Ret-expressing cells. The kidney morphology and the innervation pattern of enteric and motor neurons in the transgenic animals appeared identical to those of wild-type mice, indicating that interactions *in trans* are not required for normal development of these tissues. It will be interesting to see how the sensory and sympathetic systems are affected in these '*cis*-only' animals, both developmentally and

after nerve injury. Moreover, although interactions *in cis* appear to be sufficient for most functions, '*trans*-only' animal models would be interesting to complete the picture.

Milbrandt also presented a novel role for artemin, a GDNF family member, as an attractant or tropic (as opposed to a survival or trophic) factor. Artemin is expressed along the pathways of sympathetic projections in vascular smooth muscle cells. In the knock-out mice, sympathetic neurons are generated but fail to migrate normally and their axonal projection pattern is aberrant. Implantation of artemin-soaked beads into early embryos demonstrated the tropic effect of this factor, as the sympathetic axons were directed toward the bead, indicating that artemin acts as a chemoattractant.

And finally, immunotrophins!

A role for neurotrophins in the immune system has long been hypothesized by R. Levi-Montalcini and colleagues (reviewed in Aloe *et al.*, 2001; Serafeim and Gordon, 2001), and work addressing this hypothesis was highlighted extensively at the meeting. L. Bracci-Laudiero (Rome, Italy) is interested in whether NGF can upregulate calcitonin-gene-related peptide (CGRP) production in B-cells and monocytes/macrophages, as it does in sensory neurons, since these immune cells express TrkA. Her group found that B-cells increase expression of NGF when activated *in vivo* and that this leads to upregulation of CGRP. The receptor for this peptide is also expressed on B- and T-cells, as well as on macrophages where it acts to dampen the immune response. Thus, NGF may be capable of acting as an immune suppressant. In agreement with these findings, C. Genain (San Francisco, CA) presented data that NGF, injected into the brain ventricles, upregulates the anti-inflammatory cytokine IL-10 in glial cells and suppresses interferon- γ expression by infiltrating T-cells in both normal white matter and inflammatory lesions of marmoset EAE (experimental allergic encephalomyelitis), a model for human multiple sclerosis. The administration of NGF dramatically reduced the number and size of lesions produced in this model. This finding supports work from L. Aloe (Rome, Italy) who showed that anti-NGF treatment of rats resulted in more severe EAE pathology. H. Wekerle (Martinsried, Germany) also investigated the role of NGF in the EAE model and found that any of the neurotrophins could suppress the upregulation of MHC class II by tetrodotoxin and interferon- γ on microglia. Since MHC class II protein expression would increase T-cell activation and cytokine production, this inhibition would likely prevent the development of lesions; indeed, Wekerle observed such protective effects of NGF. Taken together, these reports suggest that NGF can have profound effects on the immune system, primarily acting to repress inflammatory responses.

Despite these interesting findings, the role of neurotrophins during normal development of the immune system remains mysterious. An exciting new mouse that could be used to address this issue was unveiled by L. Tessarollo (Frederick, MD). His group used an ingenious 'reverse conditional' strategy to rescue expression of TrkA in neurons in a *trkA* knock-out mouse, while retaining the null phenotype in all non-neuronal tissues. The mice thus survive to adulthood and do not exhibit gross morphological or anatomical defects. Careful analyses of their immune systems reveal highly specific and subtle changes and

defects in the levels of specific cell types and certain immunoglobulin subtypes. Tessarollo's presentation thus provided definitive evidence of a role for TrkA in normal development of the immune system, and will undoubtedly stimulate increased interest in neurotrophins as immunotrophins. This was truly a fitting ending to a meeting held once again in honor of Rita Levi-Montalcini.

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