Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 2557–2558, April 1993

Commentary

A central role for ciliary neurotrophic factor?

Donald C. Lo

Department of Neurobiology, Duke University Medical Center, Box 3209, Durham, NC 27710

The study of the molecular basis of neurotrophic interactions has progressed by leaps and bounds in recent years with the discovery of several novel neurotrophic factors belonging to the nerve growth factor (NGF) family of neurotrophins (1), the identification of the *trk* family of protooncogenes as receptors for the neurotrophins (2), and the solving of the long-elusive crystal structure of NGF (3). Equally exciting has been progress in research on ciliary neurotrophic factor (CNTF), its purification and cloning (4, 5), and the identification of its receptor as a member of a "neural" cytokine family of receptors (6). Most recently, in research reported by Ip *et al.* (7) and by Clatterbuck, Price, and Koliatsos in the previous issue of the *Proceedings* (8), much impetus has been added for considering the sites of action of CNTF—previously thought to be primarily in the periphery—to include the central nervous system.

The existence of CNTF was originally inferred from the ability of eye and sciatic nerve extracts to support the survival of parasympathetic neurons of the ciliary ganglion, which innervate the iris (for review, see ref. 9). Its subsequent purification and cloning identified CNTF as molecularly distinct from the neurotrophins and "traditional" growth factors such as the fibroblast growth factors. The identification of the α receptor for CNTF as a relative of the interleukin 6 α receptor indicated that CNTF might, instead, belong to the cytokine family of factors (6). Indeed, subsequent analysis of similarities in secondary and tertiary structure strongly suggested that CNTF is part of a subfamily of hematopoietic cytokines that includes interleukin 6, granulocyte colony-stimulating factor, oncostatin M, and, notably, leukemia inhibitory factor (LIF; also known as cholinergic differentiation factor, or CDF) (10). This and the great degree of overlap between the cellular targets and effects of CNTF and LIF/CDF have led to the consideration of CNTF and CDF/LIF as "neurokines" or "neuropoietic" factors (11, 12). Much of this overlap results from the sharing of two signal-transducing receptor subunits, gp130 and the LIF β receptor, by CNTF and LIF/CDF (7, 13–15).

The isolation of the α receptor for CNTF provides a powerful tool with which to identify cells that are potentially responsive to CNTF. Ip *et al.* (7) have used this approach to identify neurons in the nervous system that express the CNTF receptor by using Northern analysis and *in situ* hybridization. As expected, peripheral targets such as the ciliary, dorsal root, and sympathetic ganglia that had previously been shown to contain CNTF-responsive neurons did indeed express the CNTF α receptor. In the central nervous system, lower motor neurons, whose survival is supported by CNTF (16, 17), showed strong expression of the CNTF receptor. Surprisingly, expression was also found in many other regions of the central nervous system, including the neocortex (in layer V), the hippocampus, the thalamus, the subependymal zone of the lateral ventricle, the substantia nigra pars reticula, and several brainstem nuclei. In all of these regions, expression was found exclusively in neurons.

The particularly high level of expression of CNTF receptor found in the anterior nuclei of the thalamus correlates well with the findings of Clatterbuck *et al.* (8). In these experiments, the degeneration of neurons in the anterodorsal (AD) and anteroventral (AV) thalamic nuclei was induced by the transection of their axonal projections to the cingulate and retrosplenial cortex via the cingulum bundle, providing a model for "retrograde" degeneration of central neurons. Such degeneration of neurons is thought to occur through the deprivation of trophic factors normally provided in a retrograde fashion by axonal projections. Rescue of axotomized neurons is well documented for cholinergic neurons of the basal forebrain nuclei—both NGF (18, 19) and brain-derived neurotrophic factor (20) can prevent the degeneration of these neurons after fimbrial transection of their projections to the hippocampus. CNTF has also been shown to prevent the degeneration of medial septal neurons after such lesions; its effect, in fact, is broader and not limited to cholinergic neurons (21).

Could the degeneration of thalamic neurons be similarly prevented by trophic factors such as CNTF? In control experiments, axotomy led to the degeneration of 56% (AD) and 75% (AV) of the neurons in the anterior thalamic nuclei. Provision of CNTF to the anterior thalamus, through implantation of a miniosmotic pump, reduced the losses of neurons in the anterior nuclei to 20% (AD) and 34% (AV). Clatterbuck *et al.* (8) further presented evidence for the molecular basis of the trophic action of CNTF, using PCR analysis to demonstrate the expression of CNTF receptor mRNA in the anterior thalamus, and the expression of CNTF in the retrosplenial cortex. Whether other neurotrophic factors can support the survival of the axotomized thalamic neurons in these experiments remains to be tested.

These and other experiments are beginning to implicate CNTF in the trophic support of a broad range of peripheral and central neurons, broader, in fact, than that of the neurotrophins. Particularly intriguing is the strong expression of CNTF receptor in both upper and lower motor neurons and other regions involved in motor system function (7). However, many uncertainties remain concerning the trophic action of CNTF. For example, in what cells is CNTF normally produced, and how is its release regulated? In the periphery, very high levels of CNTF are found in the cytoplasm of Schwann cells, but there is little evidence of its release. The primary structure of CNTF shows that it lacks a signal sequence, suggesting that it cannot be secreted through conventional pathways; cell culture and transfection experiments have not demonstrated the release of CNTF (see ref. 9 for review). CNTF shares this property with the fibroblast growth factors, which also do not contain signal sequences. Thus, it has been suggested that the trophic role of CNTF is primarily pathophysiological—namely, that CNTF is released only upon nerve injury that causes the rupture of Schwann cells. Release of CNTF can, in fact, be detected after nerve (9) and central nervous system (22) injury, and application of CNTF to nerve stumps supports the survival of denervated motor neurons (17).

Nevertheless, the experiments reviewed here add to a growing body of evidence that CNTF is important for the normal development and functioning of the nervous system (9). That CNTF

seems not to be a "classical" target-derived neurotrophic factor suggests that our notions of neurotrophic support and regulation may have to be revised (1, 23). Indeed, neurotrophins such as NGF and brain-derived neurotrophic factor appear to be much more than "survival" factors; they play important roles in the differentiation of neurons and in the maintenance of their phenotype in maturity (24). Similarly, CNTF has been shown to be a differentiation factor as well as a survival factor, with the ability, for example, to induce the differentiation of O-2A progenitor cells into type-2 astrocytes (25) and to promote the differentiation of sympathetic neurons and their precursors (13, 26–28). Findings such as these emphasize the multiplicity of neurotrophic regulatory pathways that operate in development and in the adult that are critical for the continual regulation of neuronal function and connectivity.

I would like to thank Drs. Andy Goodearl and Nancy Ip for their very helpful comments.

1. Thoenen, H. (1991) *Trends Neurosci.* **14,** 165–170.
2. Chao, M. V. (1992) *Neuron* **9,** 583–593.
3. McDonald, N. Q., Lapatto, R., Murray-Rust, J., Gunning, J., Wlodawer, A. & Blundell, T. L. (1991) *Nature (London)* **354,** 411–414.
4. Lin, L.-F. H., Mismer, D., Lile, J. D., Armes, L. G., Butler, E. T., III, Vannive, J. L. & Collins, F. (1989) *Science* **246,** 1023–1025.
5. Stockli, K. A., Lottspeich, F., Sendtner, M., Masiakowski, P., Carroll, P., Gotz, R., Lindholm, D. & Thoenen, H. (1989) *Nature (London)* **342,** 920–923.
6. Davis, S., Aldrich, T. H., Valenzuela, D. M., Wong, V., Furth, M. E., Squinto, S. P. & Yancopoulos, G. D. (1991) *Science* **253,** 59–63.
7. Ip, N. Y., McClain, J., Barrezueta, N. X., Aldrich, T. H., Pan, L., Li, Y., Wiegand, S. J., Friedman, B., Davis, S. & Yancopoulos, G. D. (1993) *Neuron* **10,** 89–102.
8. Clatterbuck, R. E., Price, D. L. & Koliatsos, V. E. (1993) *Proc. Natl. Acad. Sci. USA* **90,** 2222–2226.
9. Manthorpe, M., Louis, J.-C., Hagg, T. & Varon, S. (1993) in *Neurotrophic Factors*, eds. Loughlin, S. E. & Fallon, J. H. (Academic, New York), pp. 443–473.
10. Bazan, J. F. (1991) *Neuron* **7,** 197–208.
11. Hall, A. K. & Rao, M. S. (1992) *Trends Neurosci.* **15,** 35–37.
12. Patterson, P. H. (1992) *Curr. Opin. Neurobiol.* **2,** 94–97.
13. Ip, N. Y., Nye, S. H., Boulton, T. G., Davis, S., Taga, T., Li, Y., Birren, S. J., Yasukawa, K., Kishimoto, T., Anderson, D. J., Stahl, N. & Yancopoulos, G. D. (1992) *Cell* **69,** 1121–1132.
14. Ip, N. Y. & Yancopoulos, G. D. (1992) *Prog. Growth Factor Res.* **4,** 139–155.
15. Stahl, N., Davis, S., Wong, V., Taga, T., Kishimoto, T., Ip, N. Y. & Yancopoulos, G. D. (1993) *J. Biol. Chem.*, in press.
16. Arakawa, Y., Sendtner, M. & Thoenen, H. (1990) *J. Neurosci.* **10,** 3507–3515.
17. Sendtner, M., Kreutzberg, G. W. & Thoenen, H. (1990) *Nature (London)* **345,** 440–441.
18. Hefti, F. (1986) *J. Neurosci.* **6,** 2155–2162.
19. Williams, L. R., Varon, S., Peterson, G. M., Wictorin, K., Fischer, W., Bjorklund, A. & Gage, F. H. (1986) *Proc. Natl. Acad. Sci. USA* **83,** 9231–9235.
20. Knusel, B., Beck, K. D., Winslow, J. W., Rosenthal, A., Burton, L. E., Widmer, H. R., Nikolics, K. & Hefti, F. (1992) *J. Neurosci.* **12,** 4391–4402.
21. Hagg, T., Quon, D., Higaki, J. & Varon, S. (1992) *Neuron* **8,** 145–158.
22. Ip, N. Y., Wiegand, S. J., Morse, J. & Rudge, J. S. (1993) *Eur. J. Neurosci.* **5,** 25–33.
23. Barde, Y.-A. (1988) *Trends Neurosci.* **11,** 343–346.
24. Loughlin, S. E. & Fallon, J. H. (1993) *Neurotrophic Factors* (Academic, New York).
25. Lillien, L. E. & Raff, M. C. (1990) *Neuron* **5,** 111–119.
26. Ernsberger, U., Sendtner, M. & Rohrer, H. (1989) *Neuron* **2,** 1275–1284.
27. Saadat, S., Sendtner, M. & Rohrer, H. (1989) *J. Cell Biol.* **108,** 1807–1816.
28. Rao, M. S., Tyrrell, S., Landis, S. C. & Patterson, P. H. (1992) *Dev. Biol.* **150,** 281–293.